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Addition of Organolithium Reagents to Some Carbohydrate Enones

Osman Achmatowicz* and Barbara Szechner

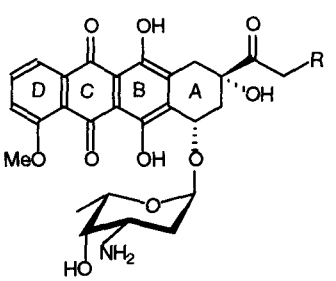
Pharmaceutical Research Institute, 8 Rydygiera Str., 01-793 Warszawa, Poland

Jan K. Maurin

Institute of Atomic Energy, 05-400 Otwock-Świerk, Poland

Abstract: Addition of organolithium reagents to the sugar enones: alkyl 2,3,6-trideoxy-α-L- and 2,3-dideoxy-α-D-hex-2-enopyranosid-4-ulose has been examined. Butyl, benzyl and 2,5-dimethoxy-4--methylphenyllithium add, with increasing stereoselectivity, to the carbonyl group of the α,β-unsaturated ketosugars, whereas 2,5--dimethoxybenzyllithium undergoes stereospecific conjugate addition and 1,2-addition in the ratio of 1.7:1. The structure of the resultant carbinols is based on X-ray crystallographic evidence. © 1997 Published by Elsevier Science Ltd.

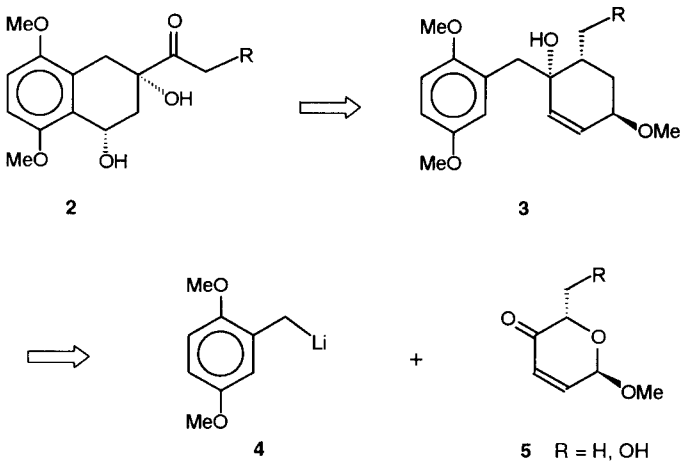
One of the general methodologies for the total synthesis of anthracycline antibiotics[1] *e.g.* daunomycin (**1a**) or adriamycin (**1b**), relies upon construction of the chiral building block of rings AB comprising stereogenic centers with the absolute configuration corresponding to those appearing in the target antibiotic[2].



1a R = H
1b R = OH

In a project aimed at the development of a novel route to the anthracycline antibiotics **1a,b** we envisage the dihydropyran derivative **3** as an advanced intermediate for the preparation of the chiral AB precursor **2** (Scheme 1). The retroanalysis shown in Scheme 1 reveals that intermediate **3** (R = H or OH) could be obtained by a 1,2-addition reaction of 2,5-dimethoxybenzyllithium (**4**) to the 2,3-unsaturated ketosugar **5** (R = H or OH). The versatile reactivity of α,β-unsaturated ketosugars has provided an excellent opportunity for devising new synthetic routes to various aminodeoxy and branched-chain sugars as well as other natural products[3]. In pursuit of these objectives

Scheme 1



the stereo- and regioselectivity of the addition reactions of carbanions to α,β-unsaturated pyranosiduloses **11** (R = H, Bz, Ac, Tr) (Scheme 2) have been examined[4,5]. 1,2- or 1,4-addition products were obtained depending on the reagent used. Thus reaction with lithium dialkyl cuprate gave only conjugate addition products with none or only traces of 1,2-adducts[4]. However, when only catalytic amounts (0.02 mole) of the copper salt complex (Bu_3PrCuI) were used a mixture of 1,2- and 1,4- adducts was obtained[4b]. The same regioselectivity was also reported for the addition of the 1,3-dithiane anion to the α,β-unsaturated sugars **12a** or **12b** (Scheme 3), carried out in the presence of a copper catalyst[6]. On the other hand reaction of methyllithium with ketosugar **11** (R = Bz) yielded the 1,2-adduct as the exclusive product[6] , in accord with general rule of the reactivity of organolithium compounds towards α,β-unsaturated carbonyl compounds[7].

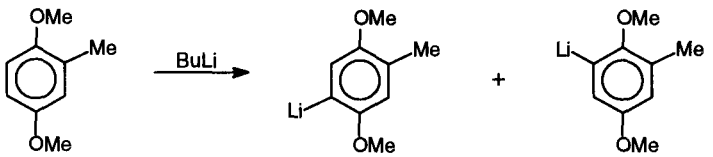
In the present paper we report on the regio- and stereochemical course of the addition of butyl-, benzyl-, 2,5-dimethoxy-4-methylphenyl- (7) and 2,5-dimethoxybenzyllithium (**4**) with sugar enones **11a,b** and **12a,b**.

RESULTS AND DISCUSSION

Organolithium compounds

Benzyllithium and 2,5-dimethoxybenzyllithium (**4**) were prepared immediately before use by reductive lithiation, with metallic lithium, of benzyl ethyl and 2,5-dimethoxybenzyl ethyl ether, respectively[8]. A complex of benzyllithium with diazabicyclooctane (DABCO) was obtained by treatment of toluene with butyllithium[9]. Promoted by the methoxy groups lithiation of 2,5-dimethoxytoluene (**6**) by butyllithium, unlike a similar reaction with 2-methoxytoluene which gives both products of metallation: on the *ortho* position and on the methyl group, led almost exclusively to metalation on the phenyl ring. As could be inferred from the structure of resulting adducts, (*vide*

infra) a mixture of 2,5-dimethoxy-4-methylphenyllithium (7) and the 3-methyl isomer **8** was obtained[10]. The course of the lithiation did not appear to change upon addition of DABCO or TMEDA.



6 **7** **8**

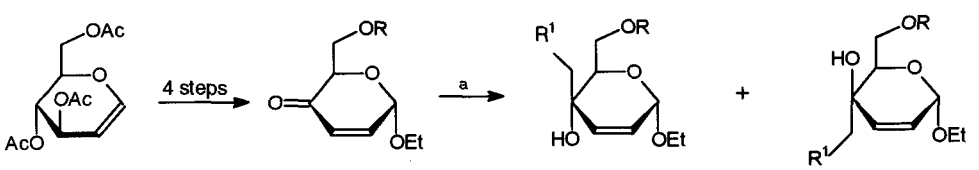
Sugar enones

α,β-Unsaturated ketosugars **11** and **12** were obtained in 4 and 3 steps from D-glucal (**9**) and L-rhamnal (**10**), respectively, according to literature procedures[11]. Addition of lithium reagents to the sugar enones was carried out in ether/THF at -70°C and after the usual work up products were separated by flash chromatography on a silica gel column. The results are collected in Table 1.

Structure of adducts

Gross structures of 1,2- and 1,4-adducts were evident from their spectroscopic (^{1}H NMR, IR, HRMS) and analytical data. The assigned configuration at C-2 in the 1,4-adduct **20** was based on the H-2 proton coupling constant values: $J_{1,2}$ = 3.95 Hz, $J_{2,3}$ = 8.0 Hz and $J_{2,3'}$ = 4.9 Hz, which are similar to those reported for the analogous ketopyranosides[4c] and which indicate a *trans* relationship of the substituents at C-1 and C-2. The configuration of the new stereogenic center at C-4 in the 1,2-adducts could not be deduced from their ^{1}H NMR spectra. For compound **13a**, a major product of benzyllithium addition to ketosugar **11a** the α-*erythro* configuration

Scheme 2



9

11a R = TBDMS
11b R = Tr

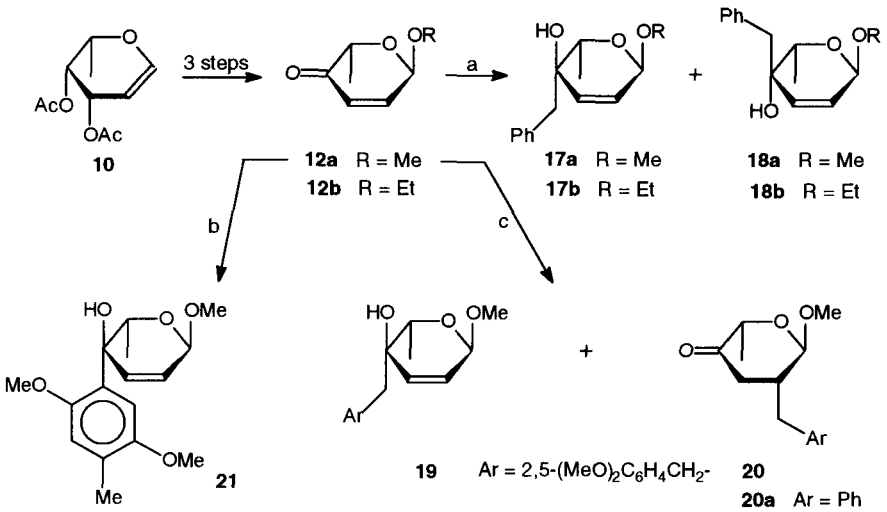
13a R = TBDMS, R^1 = Pr
13b R = Tr, R^1 = Pr
15 R = TBDMS, R^1 = Ph

14a R = TBDMS, R^1 = Pr
14b R = Tr, R^1 = Pr
16 R = TBDMS, R^1 = Ph

a. BuLi (or $PhCH_2Li$)/THF, -70°C

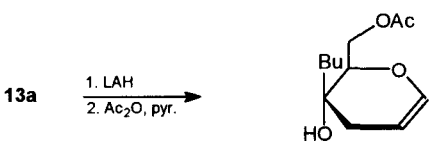
has been demonstrated by single crystal X-ray analysis[12] and consequently the α-*threo* configuration followed for the minor product **14a**. The configurations at C-4 in other adducts with 4-C benzyl and 2,5-dimethoxybenzyl groups

Scheme 3



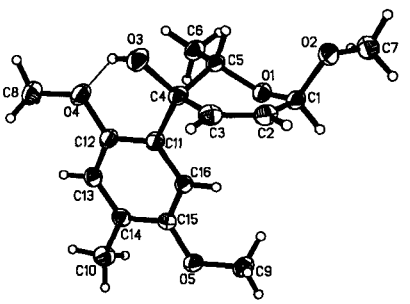
a. $PhCH_2OEt$, Li, THF/ether, -15°C, then - 70°C, **12** or $PhCH_3$, BuLi, DABCO, 85°C, then -70°C, **12**, *ether*; *b*. 2,5-$(OMe)_2C_6H_3CH_3$, THF, BuLi, 80°C, *then* -70°C, *ether*, **12**; *c*. 2,5-$(OMe)_2C_6H_3CH_2C$ Li, THF/ether, -20°C, then -70°C, **12.**

were assigned on the basis of their ^{1}H NMR spectra. The chemical shift of H-3 is of particular diagnostic value. In the α-*erythro* stereoisomers H-3 appeared at δ 5.4, whereas a downfield shift of about 0.5 ppm to δ 5.9 indicated the α-*threo* configuration. α-*Erythro* (**13a**) and α-*threo* (**14a**) adducts with C-4 butyl substituents have been differentiated chemically. The facile reductive rearrangement of **13a** by treatment with LAH in ether at rt to the 3-deoxyglycal **22**, in contrast to the unreactivity of **14a** under these conditions, was taken as indicative[13] of α-*erythro* configuration.



The structure and α-*erythro* configuration of the 1,2-adduct **21**, obtained in the reaction of the 2,3-unsaturated pyranosid-4-ulose **12a** with 2,5-dimethoxy-4-methylphenyllithium (**7**), was also determined by single crystal X-ray analysis. The ORTEP drawing of **21** with the numbering scheme is shown in Fig. 1. From the torsion angles of the pyranoside moiety (Table 2) asymmetry parameters $\Delta C_2^{23} = 9.67$ and $\Delta C_s^2 = 28.16$ have been calculated[14]. Their values show that conformation of the sugar ring could be described as a non-ideal half-chair distorted towards a sofa. The plane of the phenyl ring which occupies a pseudoaxial position is almost perpendicular to the best plane defined by the sugar ring atoms O1 through C5 (the dihedral angle between both planes is 87.30(8)°). It is held in this position by a strong intramolecular hydrogen bond, the only one observed in the crystal structure, between the C-4 hydroxyl group and the *ortho* methoxy group. It has following dimensions: O3-H3' 0.82; H3'....O4 1.890(9); O3....O4 2.603(3) Å and angle O3-H3'....O4 145°. All C-C and O-C bonds have acceptable dimensions.

Fig. 1. ORTEP drawing of **21** showing numbering of atoms.



Regio- and stereoselectivity of addition

The reaction of butyllithium with ketosugars **11a** and **11b** was regiospecific affording, as in the case of the addition of methyllithium[5] mentioned above, exclusively 1,2-adducts, albeit with almost no stereoselection (ratio 1.76:1, Table 1, entry 1)[15].

In case of benzyllithium addition to sugar enones **11a** and **12a,b** was also highly regioselective, yielding almost solely 1,2-adducts. Products of conjugate addition were detected (^{1}H NMR) in crude reaction mixtures in minute amounts. Reaction of this lithium reagent proceeded with a modicum of stereoselectivity affording the C-4 epimeric alcohols in the ratios 3.6 - 2.5:1 (Table 1, entries 3, 4 and 5), with a predominance of the α-*erythro* stereoisomers resulting from an axial approach of the nucleophile to the C-4 carbonyl group. Using the benzyllithium complex with DABCO did not improve stereoselectivity but led, as could be expected[16], to the increased formation of 1,4-adduct (Table 1, entry 6).

The reaction of 2,5-dimethoxybenzyllithium (**4**) with sugar enone **12a** (Scheme 3), which was of interest for our synthetic plan, took a different course. The addition was not regioselective and yielded both 1,4- (**19**) and

1,2-adducts (**20**) in a ratio 1.7:1 (Table 1, entry 7). However the reaction was virtualy stereospecific. Both adducts **19** and **20** arose from an axial attack of the nucleophile at the C=O and C=C double bond, respectively. Attempts to improve regioselectivity in favour of 1,2-addition, either by reacting **4** *prior* to addition with anhydrous cerium(III) chloride or by treating ketosugar **12a** with the same salt[17], led to essentially the same results as obtained when using **4** without additives. Possibly the presence of stoichiometric amounts of lithium ethoxide had detrimental effects on the formation of organocerium compounds.

Table 1

Entry	Substrate	Lithium reagent	Adducts, yield (%)[a] (1,2)				(1,4)	
1	**11a**	C_4H_9Li	**13a**	41.4	**14a**	23.7	-	
2	**11b**	C_4H_9Li	**13b**	47.4	**14b**	29.6	-	
3	**11a**	$PhCH_2Li$	**15**	51.5	**16**	21.2	-	
4	**12a**	$PhCH_2Li$	**17a**	59.5	**18a**	16.6	-	
5	**12b**	$PhCH_2Li$	**17b**	57.5	**18b**	20.6		
6	**12a**	$PhCH_2Li$·DABCO	**17a**	41.2	**18a**	21.3	**20a**	12
7	**12a**	$2,5\text{-}(MeO)_2C_6H_3CH_2Li$	**19**	14.3	-		**20**	24.1
8	**12a**	2,5-dimethoxy-4-methylphenyl-lithium	**21**[18]	45.8	-		-	

[a]Isolated yields.

CONCLUSION

Formation of a single stereoisomer **20** with the substituent at C-2 *trans* to the aglycon is consistent with the literature precedent for conjugate addition to sugar enones[4,6]. It appears that stereoselectivity of the 1,2-addition improves with the increasing bulk of the carbanion residue in the order: C_4H_9- < $PhCH_2$- << $(CH_3O)_2C_6H_3CH_2$- ≈ $(CH_3O)_2(CH_3)C_6H_2$-. The most significant finding is the difference in regioselectivity between 2,5-dimethoxybenzyllithium (**4**) and benzyllithium. The favoured conjugate addition in case of **4** can be explained by the effect of complex formation with an intramolecular donor (*ortho* methoxy group), similar to one exerted by solvents like hexametapol or TMEDA[19] on the 1,2- *versus* 1,4-selectivity.

EXPERIMENTAL

General procedures

^1H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 or Brucker AM 500 spectrometer using TMS as internal reference. IR spectra were recorded for $CHCl_3$ solution with Nicolet FT-IR Impact 400 or Perkin Elmer FT IR, 1725X spectrophotometer. Chromatography refers to column chromatography on Merck Kieselgel 60 (230-400 mesh). Analytical thin layer chromatography was performed using pre-coated aluminum plates (Merck Kieselgel 60

F_{254}) and visualized with UV light or acidic ammonium molybdate (IV)-cerium sulfate reagent. Butyllithium (2.5 M in hexane) was obtained from Aldrich. All reactions were conducted in oven-dried glassware under an atmosphere of dry argon. Air sensitive solutions were transferred by syringe or canula and introduced to reaction flasks through rubber septum. Solvents and reagents were purified before use according to standard procedures[20].

Crystallographic Measurements and Structure Analysis of **21**[21].

A columnar crystal of dimensions 0.3x0.3x0.4 mm, obtained from hexane-ether solution, was mounted on the KM-4 K-axis single crystal diffractometer. CuKα radiation (λ=1.54178Å) was used to collect the data. Cell parameters a=7.9780(6), b=12.0384(9), c=16.567(1)Å, α=β=γ=90°, V=1591.1(2) Å^3 in an orthorombic system were obtained by the least squares treatment of 25 reflections with 40≤2θ≤50°. 1706 reflections with 0≤h≤9, -14≤k≤4 and -19≤l≤5 were collected up to 2θ=130° (R_{int}=0.0637). Systematic absences (h00, h=2n; 0k0, k=2n; 00l, l=2n) led to the choice of the $P2_12_12_1$ space group (Z=4, M_r=294.34, D_x=1.229 mg m^{-3}, μ(CuKα)=0.747 mm^{-1}, F(000)=632). The structure was solved using direct methods from *SHELXS86*[22] program and then refined basing on F^2 by application of *SHELXL93*[23]. All non-hydrogen atoms were located from the E-map. All hydrogen atoms were located after anisotropic refinement using standard geometrical criteria. In the last cycles of the full matrix refinement all non-hydrogen atoms positions together with their anisotropic displacement parameters and the isotropic thermal coefficients for hydrogen atoms were refined. Isotopic displacement parameters being 1.5 times larger than the respective parameters of the adjacent carbon atoms were ascribed to the idealized methyl group hydrogens.The final R, wR(F^2) and S were 0.0376, 0.1012 and 1.059, respectively, for 1452 observed, independent reflections with I≥2σ(I). Weights used were w=1/[σ(Fo^2)+(0.0742P)^2+0.1179P] where P=(Fo^2+2Fc^2)/3. The number of data per refined parameter was 1452/204=7.11, and the Δ/σ ratios in the last cycle was less than 0.001. The peaks on the final Δρ map were in the range -0.124 and 0.226 eÅ^{-3}. The absolute configuration of **21** was verified basing on the Flack parameter[24] which was -0.05(31).

Table 2. Selected torsion angles in the solid state structure of **21**[a].

C(5)-O(1)-C(1)-C(2)	42.2(2)
O(1)-C(1)-C(2)-C(3)	-6.0(3)
C(1)-C(2)-C (3)-C(4)	-5.6(4)
C(2)-C(3)-C(4)-C(5)	-16.8(3)
C(3)-C(4)-C(5)-O(1)	50.6(2)
C(4)-C(5)-O(1)-C(1)	-66.3(2)

[a]Atom numbering as in Fig.1.

Addition of organolithium compounds to enones 11a, 11b, 12a and 12b. Typical procedure.

To a finely cut lithium wire (160 mg, 22.2 mmol) suspended in THF (1 mL) cooled to -10°C was added slowly, with stirring, benzyl ethyl ether (410 mg, 3 mmol) dissolved in ether (1 mL) and the mixture was stirred for 1 h at -10°C. The benzyllthium solution was added dropwise *via* syringe to a cold (-70°C) solution of enone **12a** (150 mg, 1.1.mmol) in ether (2.5 mL). After stirring at -70°C for 30 min the reaction mixture was diluted with ether (25 mL), quenched with sat. aq. NH_4Cl, washed with water, brine, dried ($MgSO_4$), filtered and evaporated. Flash chromatography of the residue on a silica gel column in a hexane - ethyl acetate (4:1) gave homogenous (tlc) adducts **17a** and **18a**. Yields of products obtained in particular reactions are collected in Table 1.

Ethyl 4-*C*-butyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3,6-trideoxy-α-D-*erythro*-hex-2-enopyranoside (13a):

^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.91 (dd, $J_{2,3}$ = 10.3, $J_{1,3}$ = 1.2 Hz, H-3); 5.67 (dd, $J_{1,2}$ = 2.5 Hz, H-2); 4.93 (ddd, $J_{1,5}$ =0.6 Hz, 1H, H-1); 4.02 - 3.73 (m, 3H, H-5, H-6, H-6'); 3.82 and 3.57 (2xdq, J_d =9.6, J_q = 7.0 Hz, 2H, -OCH_2-); 1.75 - 1.25 (m, 6H, -$[CH_2]_3$-); 1.22 (t, 3H, -CH_3); 0.90 (s, 9H, $SiC(CH_3)_3$); 0.12 (s, 3H, $SiCH_3$); 0.11 (s, 3H, $SiCH_3$). IR ($CHCl_3$) ν_{max} 3495, 1083, 841 cm^{-1}. HRMS calcd. for $C_{16}H_{31}O_3Si$ (M - OC_2H_5): 299.20425. Found: 299.20381.

Ethyl 4-*C*-butyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3,6-trideoxy-α-D-*threo*-hex-2-enopyranoside (14a):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.92 (dd, $J_{2,3}$ = 10.1, $J_{1,3}$ = 0.7 Hz, 1H, H-3); 5.83 (dd, $J_{1,2}$ = 2.8 Hz, 1H, H-2); 5.02 (m, 1H, H-1); 4.01 - 3.78 (m, 3H, H-5, H-6, H-6'); 3.90 and 3.55 (2xdq, J_d = 9.6, J_q = 7.1 Hz, 2H, -OCH_2-); 1.63 - 1.56 (m, 2H, C4-CH_2-); 1.36 - 1.27 (m, 4H, -CH_2-CH_2-); 1.24 (t, 3H, -CH_3); 0.91 (s, 9H, $SiC(CH_3)_3$); 0.10 (s, 6H, $Si(CH_3)_2$). IR ($CHCl_3$) ν_{max} 3579, 3442, 1099, 1004, 840 cm^{-1}. HRMS calcd. for $C_{16}H_{31}O_3Si$ (M - OC_2H_5): 299.20425. Found: 299.20411.

Ethyl 4-*C*-butyl-6-*O*-trityl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (13b)[25]:
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.49 - 7.43 (m, 6H, aromatic); 7.36 - 7.24 (m, 9H, aromatic); 5.89 (dd, $J_{2,3}$ = 10.3, $J_{1,3}$ = 1.1 Hz, 1H, H-3); 5.68 (dd, $J_{1,2}$ = 2.5 Hz, 1H, H-2); 4.93 (m, 1H, H-1); 4.12 (t, 1H, H-5); 3.94 and 3.54 (2xdq, J_d = 9.5, J_q = 7.1 Hz, 2H, -OCH_2-); 3.46 (dd, $J_{6,6'}$ = 9.6, $J_{5,6}$ = 6.6 Hz, 1H, H-6); 3.24 (dd, $J_{5,6'}$ = 6.8 Hz, 1H, H-6'); 1.50 - 1.05 (m, 6H, -CH_2-CH_2-CH_2-); 1.27 (t, J = 7.0 Hz, 3H, -CH_3); 0.80 (t, J = 6.8 Hz, -CH_3).

Ethyl 4-*C*-butyl-6-*O*-trityl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (14b)[25]:
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.52 - 7.47 (m, 6H, aromatic); 7.34 - 7.18 (m, 9H, aromatic); 5.91 - 5.80 (m, 2H, H-2, H-3); 5.08 (bd, $J_{1,2}$ = 2.5 Hz, 1H, H-1); 4.16 (dd, $J_{5,6}$ = 5.4, $J_{5,6'}$ = 4.2 Hz, 1H, H-5); 4.10 and 3.62 (2xdq, J_d = 9.5, J_q = 7.1 Hz, 2H, -OCH_2-); 3.42 - 3.35 (m, 2H, H-6, H-6'); 1.33 (t, 3H, -CH_3); 1.40 - 1.10 (m, 6H, -CH_2-CH_2-CH_2-); 0.83 (t, J = 6.5 Hz, 3H, -CH_3).

Ethyl 4-*C*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3,6-trideoxy-a-D-*erythro*-hex-2-enopyranoside (15):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28 - 7.20 (m, 5H, -C_6H_5); 5.62 (dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 2.5 Hz,1H, H-2); 5.42 (dd, $J_{1,3}$ = 1.1 Hz, 1H, H-3); 5.01 (dd, 1H, H-1); 4.12 - 3.83 (m, 3H, H-5, H-6, H-6'); 3.86 and 3.55 (2xdq, J_d = 9.6, J_q = 7.1 Hz, 2H, -OCH_2-); 2.39 (AB, J_{gem} = 13.3 , Δ_{AB} = 6.9 Hz, 2H, C4-CH_2-); 1.21 (t, 3H, -CH_3); 0.96 (s, 9H, $SiC(CH_3)_3$); 0.16 (s, 3H, $SiCH_3$); 0.15 (s, 3H, CH_3). IR ($CHCl_3$) ν_{max} 3494, 3006, 2929, 1085, 1010, 841 cm^{-1}. HRMS calcd. for $C_{15}H_{20}O_3Si$ (M - OC_2H_5 - C_4H_9): 276.11817. Found: 276.11746.

Ethyl 4-*C*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3,6-trideoxy-α-D-*threo*-hex-2-enopyranoside (16):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.32 - 7.23 (m, 5H, -C_6H_5); 5.92 (dd, $J_{2,3}$ = 10.3, $J_{1,3}$ = 1.1 Hz, 1H, H-3); 5.67 (dd, $J_{1,2}$ = 2.5 Hz, 1H, H-2); 5.02 (dd, 1H, H-1); 4.1 - 3.75 (m, 4H, H-5, H-6, H-6', O-CH<); 3.54 (dq, J_d = 9.7, Jd = 7.1 Hz, 1H, -OCH<); 3.12 (d, J_{gem} = 13.8 Hz, 1H, C4-CH<); 2.63 (d, 1H, C4-CH'<); 1.29 (t, 3H, -CH_3); 0.92 (s, 9H, $SiC(CH_3)_3$); 0.11 (s, 6H, $Si(CH_3)_2$). HRMS calcd. for $C_{15}H_{20}O_3Si$ (M - OC_2H_5 - C_4H_9): 276.11817. Found: 276.11862.

Methyl 4-*C*-benzyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (17a):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.40 - 7.15 (m, 5H, aromatic); 5.65 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 2.5 Hz, 1H, H-2); 5.44 (d, $J_{1,3}$ = 1.0 Hz, 1H, H-3); 4.90 (m, 1H, H-1); 4.03 (q, $J_{5,6}$ = 6.6 Hz, 1H, H-5); 3.46 (s, 3H, OCH_3); 2.86 (s, 2H, C4-CH_2-); 1.35 (d, 3H, -CH_3). IR ($CHCl_3$) ν_{max} 3581, 1052, 1009 cm^{-1}. HRMS calcd. for $C_{13}H_{15}O_2$ (M - OCH_3) 203.10720. Found: 203.10701.

Methyl 4-*C*-benzyl-2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranoside (18a):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.35 - 7.15 (m, 5H, aromatic); 5.90 (dd, $J_{2,3}$ = 10.1, $J_{1,3}$ = 2.9 Hz, 1H, H-2); 4.82 (m, 1H, H-1); 4.20 (q, $J_{5,6}$ = 6.6 Hz, 1H, H-5); 3.42 (s, 3H, OCH_3); 2.96 and 2.53 (AB, J_{gem} = 14.7 Hz, 2H, C4-CH_2-); 1.33 (d, 3H, -CH_3). IR ($CHCl_3$) ν_{max} 3577, 1062, 1004 cm^{-1}. HRMS calcd. for $C_{13}H_{15}O_2$ (M - OCH_3) 203.10720. Found: 203.10736.

Ethyl 4-*C*-benzyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (17b):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.35 - 7.17 (m, 5H, aromatic); 5.65 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 2.6 Hz, 1H, H-2); 5.44 (dd, $J_{1,3}$ = 1.0 Hz, 1H, H-3); 5.01 (m, 1H, H-1); 4.06 (q, $J_{5,6}$ = 6.6 Hz, 1H, H-5); 3.86 and 3.57(2xdq, J_d = 9.6, J_q = 7.1 Hz, 1H, -OCH_2-); 2.86 (s, 2H, C4-CH_2-); 1.43 (s, 1H, OH); 1.33 (d, 3H, C5-CH_3); 1.25 (t, 3H, -CH_3).
IR($CHCl_3$) ν_{max} 3580, 1046, 1010 cm^{-1}. HRMS calcd. for $C_{13}H_{15}O_2$ (M - OC_2H_5) 203.10720. Found: 203.10741.

Ethyl 4-*C*-benzyl-2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranoside (18b):
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38 - 7.13 (m, 5H, aromatic); 5.88 (dd, $J_{2,3}$ = 10.1, $J_{1,3}$ = 0.7 Hz, 1H, H-3); 5.76 (dd, $J_{1,2}$ = 2.9 Hz, 1H, H-2); 4.94 (d, J1H, H-1); 4.06 (q, $J_{5,6}$ = 6.5 Hz, 1H, H-5); 3.83 and 3.58 (2xq, J_d = 9.7, J_q = 7.1 Hz, 2H, -OCH_2-); 2.75 (AB, J_{gem} = 13.8 Hz, 2H, C4-CH_2-); 1.26 (d, 3H, C5-CH_3); 1.23 (t, 3H, -CH_3). IR ($CHCl_3$) ν_{max}: 3579, 1064, 1006 cm^{-1}. HRMS calcd. for $C_{13}H_{15}O_2$ (M - OC_2H_5) 203.10720. Found: 203.10719.

Methyl 4-*C*-(2,5-dimethoxybenzyl)-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (19)[26]:
^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.85 - 6.71 (m, 3H, aromatic); 5.58 (dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 2.4 Hz, 1H, H-2); 5.46 (dd, $J_{1,3}$ = 0.9 Hz, 1H, H-3); 4.88 (dd, 1H, H-1); 4.05 (q, $J_{5,6}$ = 6.50 Hz, H-5); 3.78, 3.76 and 3.45 (3xs, 3x3H, 3xOCH_3); 2.93 (AB, J_{gem} = 13.7 Hz, 2H, C4-CH_2); 1.35 (d, 3H, -CH_3). IR ($CHCl_3$) ν_{max} 3486, 1500, 1465, 1055 cm^{-1}. Anal. calc. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53%; Found: C, 65.42, H, 7.63%.

Methyl 2-*C*-(2,5-dimethoxybenzyl)-2,3,6-trideoxy-α-L-*threo*-hexopyranosid-4-ulose (20):
^{1}H NMR (500 MHz; $CDCl_3$) δ: 6.76 (d, $J_{3',4'}$ = 8.84 Hz, 1H, H-3'); 6.72 (dd, $J_{4',6'}$ = 3.0 Hz, 1H, H-4'), 6.66 (d, $J_{4',6'}$ = 2.95 Hz, 1H, H-6'); 4.62 (d, $J_{1,2}$ = 3.95 Hz, 1H, H-1); 4.19 (q, $J_{5,6}$ = 6.75 Hz, 1H, H-5); 3.76, 3.75 and 3.42 (3*x*s, 3*x*3H, 3*x*OCH_3); 2.77 (dd, $J_{2a,2'a}$ = 13.26, $J_{2,2a}$ = 6.32 Hz, 1H, H-2a), 2.66 (dd, $J_{2,2'a}$ = 8.32 Hz, 1H, H-2'a); 2.47 (dd, $J_{3,3'}$ = 15.18, $J_{2,3}$ = 4.88 Hz, 1H, H-3); 2.41 (m, 1H, H-2); 2.29 (dd, $J_{2,3'}$ = 7.98 Hz, 1H, H-3'); 1.31 (d, $J_{5,6}$ = 6.77 Hz, 3H, -CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.2 (C-4), 153.3 (C-2'); 151.9 (C-5'); 128.0 (C-1'), 117.3 (C-6'); 111.9 (C-4'); 111.2 (C-3'); 102.2 (C-1); 71.0 (C-5); 55.7 (2*x*OCH_3); 55.4 (OCH_3); 40.1 (C-2); 39.1 (C-3); 33.5 (C-2a), 15.0 (C-6). IR ($CHCl_3$) ν_{max} 1725, 1500, 1067 cm^{-1}. Anal. calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53%; Found: C, 65.29, H, 7.51%. HRMS: Calc. for $C_{16}H_{22}O_5$ (M^+): 294.14672. Found: 294.146352

Methyl 4-*C*-(2,5-dimethoxy-4-methylphenyl)-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (21):
^{1}H NMR (200 MHz, $CDCl_3$)) δ: 6.76 and 6.71 (2xs, 2H, aromatic); 6.05 (dd, $J_{2,3}$ = 10.0 Hz, $J_{1,3}$ = 1.0 Hz, 1H, H-3); 5.91 (dd, $J_{1,2}$ = 2.5 Hz, 1H, H-2); 4.96 (m, 1H, H-1); 4.16 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5); 3.86, 3.74 and 3.45 (3*x*s, 3*x*3H, 3*x*OCH_3); 2.20 (s, 3H, -CH_3); 1.08 (d, 3H, CH_3).

1,5-Anhydro-6-*O*-acetyl-4-*C*-butyl-2,3-dideoxy-D-*erythro*-hex-1-enitol (22):
To a solution of **13a** (100 mg, 3 mmol) in ether (5 mL) was added lithium aluminum hydride (50 mg, 1.3 mmol) and the mixture was stirred overnight at rt. After standard work-up reduction product, treated with acetic anhydride - pyridine mixture at rt, after work-up and flash chromatography afforded acetate **22** (58 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.31 (dt, $J_{1,2}$ = 6.0, $J_{1,3} \approx J_{1,3'}$ = 2.0 Hz, 1H, H-1); 4.71 (dt, $J_{2,3} \approx J_{2,3'}$ = 3.8 Hz, 1H, H-2); 4.21 (dd, $J_{6,6'}$ = 11.4, $J_{5,6}$ = 2.7 Hz, 1H, H-6); 4.10 (dd, $J_{5,6'}$ = 8.1 Hz, 1H, H-6'); 4.00 (dd, 1H, H-5); 2.10 (s, 3H, OAc); 2.01 (m, 2H, H-3, H-3'); 1.60 - 1.25 (m, 6H, -$[CH_2]_3$-); 0.90 (t, 3H, CH_3). HRMS calcd. for $C_{12}H_{20}O_4$ (M^+) 228.13616. Found: 228.13594.

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18. Flash chromatography of **21** afforded also small quantity of methyl 4-*C*-(2,5-dimethoxy-3-methylphenyl)-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.00 and 6.70 (2*x*s, 2*x*1H, aromatic); 6.04 (dd, $J_{2,3}$ = 10.0, $J_{1,3}$ = 1.0 Hz, 1H, H-3); 5.82 (dd, $J_{1,2}$ = 3.0 Hz, 1H, H-2); 4.97 (m, 1H, H-1), 4.49 (q, $J_{5,6}$ = 6.5 Hz, 1H, H-5); 3.80, 3.76 and 3.47 (3*x*s, 3*x*3H, 3*x*OCH_3); 2.21 (s, 3H, CH_3); 1.07 (d, 3H, CH_3).
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25. Characterized only by the ^{1}H NMR spectrum.
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