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A convenient route to enantiomerically pure, conjugated dienes from sugar allyltin derivatives

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Abstract

The transformation of sugar allyltin derivatives into enantiomerically pure dienes (R*–CH=CH–CH=CH_2) is presented. The internal double bond with the *trans*-configuration is formed regardless of the configuration of the starting sugar allyltin.

1. Introduction

The Diels–Alder reaction is one of the most important processes in the creation of carbon–carbon bonds.[1] Application of chiral, enantiomerically pure dienes allows preparation of carbocyclic compounds in enantiomerically pure form. Simple monosaccharides are convenient starting materials for the preparation of such compounds, since most transformations of sugar molecules can be performed with high regio- and stereoselectivity.

Many useful methods for the preparation of conjugated diene systems from sugars are reported in the literature.[2] Recently, we elaborated a convenient method for the synthesis of such molecules—dienoaldehydes **2**—from sugar allyltins[3] **1** (Fig. 1).

Treatment of organometallic products **1** with a mild Lewis acid (e.g. zinc chloride) caused their conversion into the *trans*-dienes[3] **2**—useful synthons in the stereoselective preparation of enantiomerically pure bicyclo[4.3.0]nonene[4] and bicyclo[4.4.0]decene[5] derivatives (Fig. 1; **3** and **4**, respectively).

2. Results and discussion

The method of conversion of the allyltin derivatives into the diene system is based on a rearrangement–elimination procedure which requires the presence of an alkoxy function at the δ

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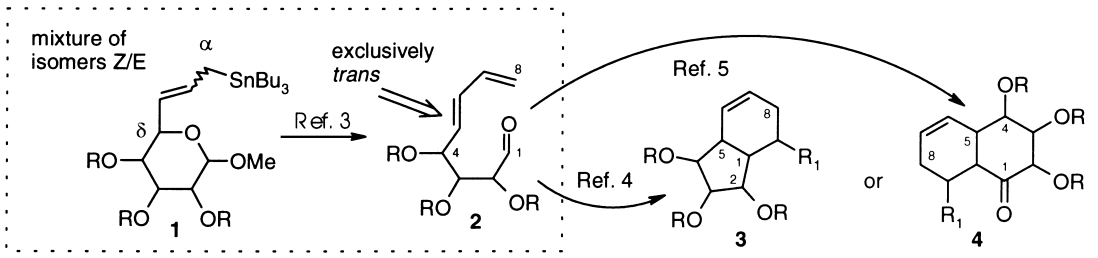
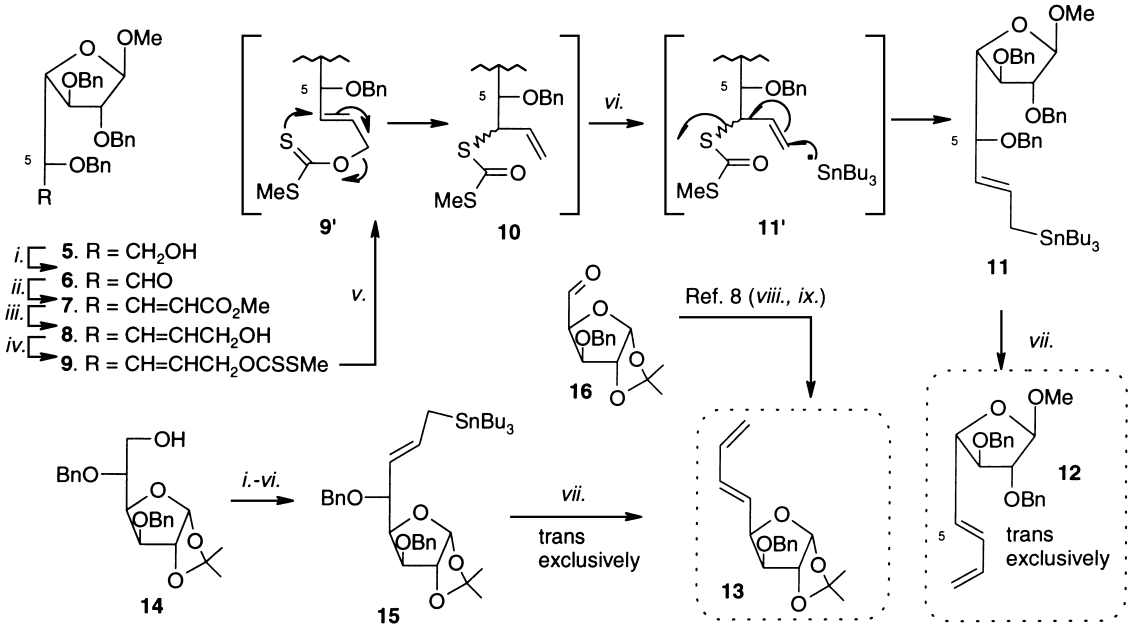


Figure 1. Synthesis of chiral dienes from allyltin pyranosides and their application in synthesis

position. We have observed that this process affords the *trans*-dienes exclusively, regardless of the configuration of starting allyltin derivative.[6] Extension of this methodology for the preparation of other types of sugar-derived dienes is presented.

2.1. Synthesis of the dienes substituted with the furanose ring

The preparation of chiral dienes substituted with a furanose ring consists of two steps: (i) transformation of a simple monosaccharide into the allyltin derivative; and (ii) treatment of the latter with a Lewis acid that should provide title compounds via a rearrangement–elimination sequence. The methodology is outlined in Scheme 1.



Scheme 1. (i) $(COCl)_2$, DMSO, Et_3N; (ii) $Ph_3P{=}CHCO_2Me$; (iii) DIBAL-H; (iv) (a) NaH, THF, 30 min; (b) CS_2, 30 min; (c) MeI, 2 h; (v) toluene, reflux, 3 h; (vi) Bu_3SnH, AIBN, 110°C; (vii) $ZnCl_2$, CH_2Cl_2, rt; (viii) $Ph_3P{=}CHCHO$; (ix) $Ph_3P{=}CH_2$

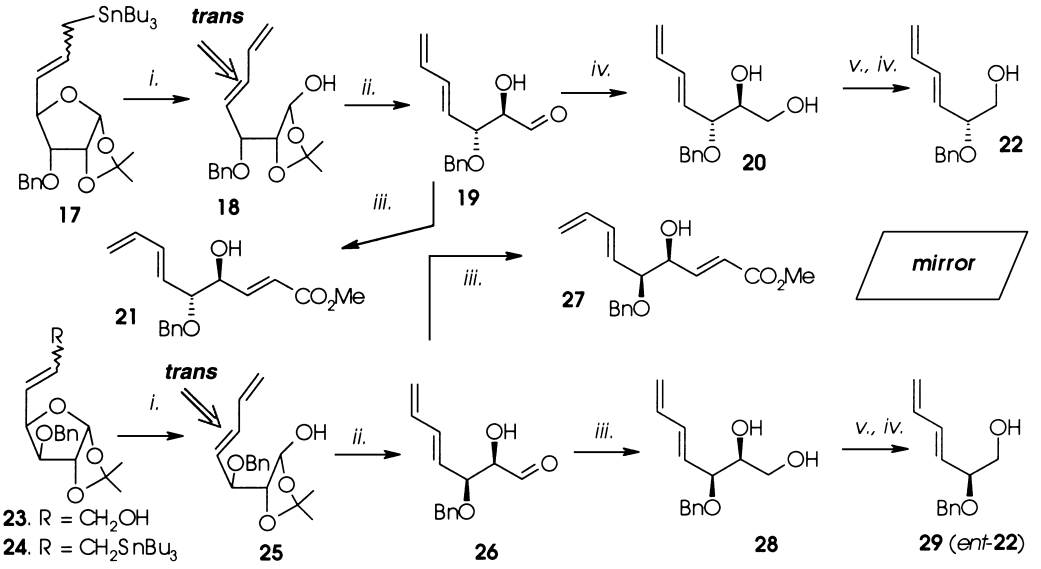
Thus, methyl 2,3,5-tri-*O*-benzyl-β-D-galactofuranoside[7] (**5**) was converted into aldehyde **6** with the Swern reagent and further to α,β-unsaturated ester† **7** by reaction with carbomethoxymethylenetriphenylphosphorane ($Ph_3P{=}CH{-}CO_2Me$). Reduction of the ester function with DIBAL-H gave allylic alcohol **8**, which was transformed into xanthate **9** by standard methodology. Thermal [3,3] rearrangement of the latter afforded thiocarbonate **10**, which, upon reaction with tributyltin hydride, gave the desired organometallic product **11** as a single *trans*-isomer.

As expected, the configuration of the allyltin derivative (ca. 85:15 *trans*:*cis*) did not depend on the configuration of the starting allylic alcohol (since the xanthate–thiocarbonate rearrangement: **9′**→**10** was not selective); however, treatment of the organometallic derivative with zinc chloride exclusively furnished the *trans*-diene **12** in good yield.

Similarly, isomerically pure *trans*-diene **13** (D-*xylo*-configurated)[8] was prepared from allyltin derivative **15**, which was in turn prepared from the known 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-D-glucofuranose.[9]

2.2. Synthesis of the open-chain dienes from furanose derivatives

Application of the methodology presented in Scheme 1 to derivatives of furanoses should result in similar transformations and provide dienes shorter by one carbon atom as compared to **2**. Conversion of 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6,7-trideoxy-7-tributylstannyl-oct-6-ene-α-D-*ribo*-1,4-furanose[3] **17** and its D-*xylo*- analog **24** into such valuable synthons is presented in Scheme 2.



Scheme 2. (i) $ZnCl_2$, CH_2Cl_2, rt; (ii) Et_3N, C_6H_6, MeOH, H_2O; (iii) $Ph_3P{=}CHCO_2Me$; (iv) $NaBH_4$; (v) $NaIO_4$

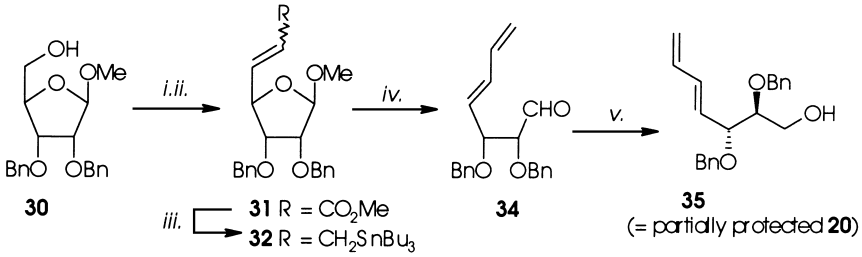
Treatment of **17** with zinc chloride afforded hemiacetal **18**; this product was relatively stable and its conversion into hydroxyaldehyde **19** was achieved by mild basic hydrolysis. Aldehyde **19**

† Configuration of the double bond in such α,β-unsaturated esters is not important for the stereochemical outcome of the process leading to sugar allyltins. As we proved earlier (Ref. 3) the *trans*/*cis* mixture of the latter (with the same—~6:1—proportion of the *trans*:*cis*-isomers) is obtained regardless of the geometry of the double bond in the α,β-unsaturated ester.

may serve as starting material for the preparation of a variety of differently substituted chiral dienes with the *E*-configuration of the internal double bond (assigned from the coupling constant $J_{4,5}$ ~14.5 Hz, observed on the H-5 resonance at δ ca. 5.6 ppm). Reduction of the carbonyl group in **19** with sodium borohydride gave diol **20**, whilst the Wittig reaction with a stabilized ylide afforded triene **21**. Periodic cleavage of diol **20** followed by reduction of resulting aldehyde with $NaBH_4$ provided alcohol **23** with only one stereogenic center.

A similar reaction sequence performed on the D-*xylo*-organometallic analog **24**, prepared from the corresponding allylic alcohol **23**[10] according to the methodology shown in Scheme 1, furnished dienes **25**–**29** in good yields. The configuration at the stereogenic center in **29** was, of course, opposite to that in **22**; thus, both enantiomers of this compound are available.

The methodology presented in Scheme 2 allows for facile preparation of α-hydroxyaldehydes **19** and **26** or the diols derived from them—diols **20** and **28**. However, it is not very useful for the simple preparation of fully protected dienoaldehydes, since the protection of the free hydroxy group in α-hydroxyaldehydes is troublesome. Application of other (fully protected) sugar stannanes may solve this problem (Scheme 3).



Scheme 3. (i) Swern oxidation; (ii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; (iii) (1) DIBAL-H; (2) NaH, THF, CS_2, then MeI; (3) toluene, 110°C, 2 h; (4) Bu_3SnH, AIBN, toluene, reflux; (iv) $ZnCl_2$; (v) $NaBH_4$

Methyl 2,3-di-*O*-benzyl-β-D-ribofuranoside[11] **30** was converted into unsaturated ester **31** as a ca. 4:1 mixture of *E*:*Z*-isomers and then into allyltin derivative **32** according to a method shown in Scheme 2. Treatment of the latter with a Lewis acid induced a rearrangement with elimination of tri-*n*-butyltin moiety and formation of the aldehyde **34**, which was characterized further as alcohol **35**.

3. Conclusion

The synthesis of differently substituted chiral, highly oxygenated dienes was realized by a mild Lewis acid induced, controlled decomposition of sugar allyltins. This procedure gives mono-substituted dienes with the *trans*-configuration of the internal double bond exclusively. The convenient synthesis of unsaturated α-hydroxyaldehydes can also be realized by this methodology.

4. Experimental

4.1. General

NMR spectra were recorded with a Varian Gemini 200 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Mass spectra [LSIMS (*m*-nitrobenzyl alcohol was used as a matrix to which

sodium acetate was added) or EI] were recorded with an AMD-604 (AMD Intectra GmbH, Germany) mass spectrometer. Specific rotations were measured with a JASCO DIP Digital Polarimeter in chloroform solution (c ~1) at room temperature. Column chromatography was performed on silica gel (Merck, 70–230 mesh). Organic solutions were dried over anhydrous magnesium or sodium sulfate.

4.2. Preparation of sugar allyltin derivatives

The sugar allyltin derivatives were prepared from the corresponding alcohols **5**, **14**, and **30** according to our previously published methods[3] involving (cf. Scheme 1):

(i) oxidation of a sugar alcohol to an aldehyde;
(ii) reaction with the stabilized Wittig reagent (to α,β-unsaturated ester);
(iii) reduction of the ester function with DIBAL-H;
(iv) formation of a xanthate;
(v) its thermal rearrangement into thiocarbonate;
(vi) reaction with tri-*n*-butyltin hydride under radical conditions.

The procedure for the preparation of **11** is representative.

4.2.1. Methyl 2,3,5-tri-O-benzyl-6,7,8-trideoxy-8-tributylstannyl-β-D-galacto-oct-6-eno-1,4-furanoside **11**

To a solution of the Swern reagent[12] (prepared from 1 mL of oxalyl chloride and 3 mL of DMSO in 30 mL of CH_2Cl_2) a solution of alcohol **5**[7] (2.3 g, 5 mmol) in CH_2Cl_2 (15 mL) was added at –78°C, and the mixture was stirred for 30 min at this temperature. Triethylamine (4 mL) was added, the mixture was stirred at –78°C for another 30 min and partitioned between ether (100 mL) and water (30 mL). The organic layer was separated, washed with water, dried and concentrated, and the crude aldehyde **6** was dissolved in benzene (50 mL) containing $Ph_3P{=}CHCO_2Me$ (2.34 g, 7 mmol). After 16 h at room temperature, the solvent was evaporated in vacuum and the product ester **7** (*trans*:*cis* = 2.5:1) was isolated by column chromatography (hexane:ethyl acetate, 6:1→3:1); yield 82%.

trans-**7**: ^{1}H NMR δ: 6.94 (dd, $J_{5,6}$ = 5.7, $J_{6,7}$ = 15.8, H-6), 6.09 (d, H-7), 4.95 ($J_{1,2}$ = ~0, H-1), 3.69 (CO_2CH_3), 3.35 (OCH_3); ^{13}C NMR δ: 166.2 (C=O), 144.4 and 123.1 (C-6,7), 107.1 (C-1), 87.7, 82.7, 82.6 and 76.7 (C-2,3,4,5), 72.1, 71.7 and 71.6 (3×CH_2Ph), 54.9 and 51.6 (OCH_3 and CO_2CH_3); HRMS *m*/*z*: 541.2202 [$C_{31}H_{34}O_7Na$ ($M+Na^+$) requires 541.2202].

cis-**7**: ^{1}H NMR δ: 6.35 (dd, $J_{5,6}$ = 8.8, $J_{6,7}$ = 11.7, H-6), 5.94 (dd, $J_{5,7}$ = 0.87, H-7), 4.98 (d, $J_{1,2}$ = 1.1, H-1), 3.67 (CO_2CH_3), 3.33 (OCH_3); ^{13}C NMR δ: 165.9 (C=O), 146.9 and 121.9 (C-6,7), 107.2 (C-1), 87.9, 83.5 and 82.5 (C-2,3,4), 73.2, 72.0 and ~71 (3×CH_2Ph), 54.9 and 51.4 (OCH_3 and CO_2CH_3).

To a cooled –78°C solution of **7** (5 g, 9.7 mmol) in dry methylene chloride a 1 M solution of DIBAL-H in hexane (20 mL, 20 mmol) was added and the mixture was stirred for 2 h at –78°C. The excess of hydride was decomposed by addition of ethyl acetate (2 mL) and, after warming to room temperature, water (10 mL). Insoluble material was filtered off by suction, the filtrate was dried, concentrated, and the product—alcohol **8**—was isolated by column chromatography (hexane:ethyl acetate, 4:1→2:1); yield 86%. HRMS *m*/*z*: 513.2252 [$C_{31}H_{34}O_7Na$ ($M+Na^+$) requires 513.2253].

(*Caution: The next sequence of reactions must be performed in a well-ventilated fume hood*). To a solution of alcohol **8** (4.02 g, 8.2 mmol) in dry THF (30 mL) sodium hydride (ca. 60% suspension in mineral oil, 0.5 g) was added followed by a catalytic amount of imidazole (ca. 50 mg). The mixture was stirred at room temperature under an argon atmosphere for 1 h. Carbon disulfide (neat, 1 mL) was added and the mixture was stirred for another 30 min. MeI (1.5 mL) was then added, the mixture was stirred for 2 h at room temperature, and partitioned between ether (50 mL) and brine (20 mL). The organic layer was separated, washed with water, dried, and concentrated.

A solution of crude xanthate **9** in dry toluene was purged with argon and heated under reflux until TLC (hexane:ethyl acetate, 5:1) indicated disappearance of the starting material and formation of a new slightly less polar product thiocarbonate **10** (2–3 h, two stereoisomers of very similar polarity were seen by TLC). Tri-*n*-butyltin hydride (2.9 mL, 11 mmol) in toluene (5 mL) was added dropwise over 5 min (*caution:* reaction is very exothermic), and heating was continued until TLC (hexane:ethyl acetate, 6:1) indicated disappearance of starting material and formation of a new less polar product (ca. 30 min). The solvent was evaporated under vacuum and the product was purified by column chromatography (hexane:diethyl ether, 20:1→9:1) to afford **11** as colorless syrup, yield 53%.

Compound **11** (pure *trans*-isomer). ^{1}H NMR δ: 5.82 (ddd, $J_{6,7}=15.2$, $J_{7,8a}=8.6$, $J_{7,8b}=6.7$, H-7), 5.34 (dd, $J_{5,6}=8.8$, H-6), 4.96 (d, $J_{1,2}=\sim1$, H-1), 3.79 (dd, $J_{4,5}=3$, H-4), 3.35 (OCH_3); ^{13}C NMR δ: 136.0 and 121.6 (C-6,7), 107.0 (C-1), 88.3, 84.0, 83.3 and 78.7 (C-2,3,4,5), 72.2, 71.7 and 69.4 ($3\times CH_2$Ph), 54.7 (OCH_3), 29.8, 27.3 and 9.9 [$3\times$Sn(CH_2)$_3$CH$_3$], 14.5 (C-8), 13.7 [Sn(CH$_2$)CH_3]; HRMS m/z: 707.2743 [$C_{38}H_{51}O_5^{120}$Sn (M–57) requires 707.2759].

4.2.2. 3,5-Di-O-benzyl-1,2-O-isopropylidene-6,7,8-trideoxy-8-tributylstannyl-α-D-gluco-oct-6-eno-1,4-furanose **15**

This compound was prepared as a 9:1 *trans*:*cis* mixture from known 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[9] according to the above procedure. Overall yield: 45%. MS-EI m/z: [643, M–57]; ^{1}H NMR for *trans*-**15** δ: 5.98 (ddd, $J_{6,7}=15.2$, $J_{7,8a}=8.0$, $J_{7,8b}=5.9$, H-7), 5.89 (d, $J_{1,2}=3.7$, H-1), 5.29 (m, H-6), 1.83 (m, H-8a,b), 1.47 and 1.29 [C(CH$_3$)$_2$]; ^{13}C NMR δ: 136.5 and 123.0 (C-6,7), 111.4 [C(CH$_3$)$_2$], 104.9 (H-1), 82.2, 81.9, 81.7 and 77.6 (C-2,3,4,5), 72.2 and 69.5 ($2\times CH_2$Ph), 29.1, 27.3 and 13.7 [Sn(CH_2)$_3$CH$_3$], 26.7 and 26.3 [C(CH_3)$_2$], 14.6 (C-8), 9.2 [Sn(CH$_2$)$_3CH_3$].

4.2.3. 3-O-Benzyl-1,2-O-isopropylidene-5,6,7-trideoxy-7-tributylstannyl-α-D-xylo-hept-5-eno-1,4-furanose **24**

This compound was prepared as a ca. 4:1 mixture of *trans*:*cis*-isomers from known *3*-O-benzyl-1,2-*O*-isopropylidene-5,6-di-deoxy-α-D-*xylo*-hept-5(*E*/*Z*)-eno-1,4-furanose according to the procedure described in Section 4.2.1.

HRMS m/z: 523.1880 [$C_{25}H_{39}O_4^{120}$Sn (M–57) requires 523.1870]; ^{1}H NMR data for the *trans*-*isomer* δ: 5.99 (m, H-6), 5.85 (d, $J_{1,2}=4.0$, H-1), 5.45 (m, H-5), 3.71 ($J_{2,3}=\sim0$, $J_{3,4}=2.9$, H-3), 1.50 and 1.30 [C(CH$_3$)$_2$]; ^{13}C NMR δ: 136.9 and 118.2 (C-5,6), 111.0 [C(CH$_3$)$_2$], 104.4 (C-1), 83.9, 82.8 and 82.1 (C-2,3,4), 72.1 (CH_2Ph), 29.1, 27.3 and 13.7 [$3\times$Sn(CH_2)$_3$CH$_3$], 26.7 and 26.1, [C(CH_3)$_2$], 14.8 (C-7), 9.3 [Sn(CH$_2$)$_3CH_3$].

4.2.4. Methyl 2,3-di-O-benzyl-5,6,7-trideoxy-7-tributylstannyl-β-D-ribo-hept-5-eno-1,4-furanoside **32**

This compound was prepared from known[11] alcohol **30**, via unsaturated ester **31** {ca. 4:1 *trans*:*cis* mixture. HRMS m/z: 421.1625 [$C_{23}H_{26}O_6$Na (M+Na$^+$) requires 421.1627]; data for the

main *trans-isomer*: ^{1}H NMR δ: 6.94 (dd, $J_{4,5}=5.5$, $J_{5,6}=15.8$, H-5), 6.10 (dd, $J_{4,6}=1.5$, H-6), 4.92 ($J_{1,2}=\sim 0$, H-1), 3.74 (CO_2CH_3), 3.36 (OCH_3); ^{13}C NMR δ: 146.6 and 121.2 (C=O), 106.4 (C-1), 81.8, 79.8 and 79.5 (C-2,3,4), 72.8 and 72.4 ($2\times CH_2$Ph), 55.6 and 51.6 (OCH_3 and CO_2CH_3)} according to the procedure described in Section 4.2.1.

Compound **32** (only *trans*). ^{1}H NMR δ: 5.92 (ddd, $J_{5,6}=14.9$, $J_{6,7a}=8.8$, $J_{6,7b}=8.5$, H-6), 5.21 (dd, $J_{4,5}=8.3$, H-5), 4.86 ($J_{1,2}=\sim 0$, H-1), 3.34 (OCH_3); ^{13}C NMR δ: 135.2 and 124.4 (C-5,6), 105.6 (C-1), 82.8, 82.3 and 80.1 (C-2,3,4), 72.5 and 72.2 ($2\times CH_2$Ph), 54.9 (OCH_3), 29.1, 27.3 and 9.2 [$Sn(CH_2)_3CH_3$], 14.6 (C-7), 13.8 [$Sn(CH_2)_3CH_3$]; HRMS *m/z*: 667.2789 [$C_{34}H_{52}O_4Na^{120}Sn$ ($M+Na^+$) requires 667.2785].

4.3. Reaction of sugar allyltin derivatives with Lewis acids

The corresponding allyltin derivative (**11**, **15**, **17**, **24** or **32**; 3 mmol each) was dissolved in anhydrous methylene chloride (30 mL). A 2.0 M solution of $ZnCl_2$ etherate in methylene chloride (3 mL, 6 mmol) was added, the mixture was stirred at room temperature for 20 min, and partitioned between ether (50 mL) and brine (30 mL). The organic layer was separated, washed with water, dried and concentrated and the products were isolated by column chromatography (hexane:diethyl ether, 7:1). Dienes **18** and **25** were characterized as acetates.

4.3.1. Methyl 2,3-di-O-benzyl-5,6,7,8-tetradeoxy-β-L-arabino-oct-5(E),7-dieno-1,4-furanoside **12**

^{1}H NMR δ: 6.33 (m, H-6,7), 5.72 (dd, $J_{4,5}=7.8$, $J_{5,6}=14.1$, H-5), 5.19 (m, both H-8), 4.91 (d, $J_{1,2}=1.3$, H-1), 4.44 (m, $J_{3,4}=7.1$, H-4), 4.00 (dd, $J_{2,3}=3.5$, H-2), 3.78 (dd, H-3), 3.37 (OCH_3); ^{13}C NMR δ: 136.0, 133.8 and 130.8 (C-5,6,7), 118.4 (C-8), 88.6, 87.5 and 81.3 (C-2,3,4), 72.3 and 72.0 ($2\times CH_2$Ph), 54.8 (OCH_3); HRMS *m/z*: 389.1752 [$C_{23}H_{26}O_4Na$ ($M+Na^+$) requires 389.1729].

4.3.2. 3-O-Benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-α-D-xylo-oct-5(E),7-dieno-1,4-furanose[8] **13**

When this compound was prepared by controlled decomposition of allyltin **15** only the *trans*-isomer was detected in the NMR spectra.

^{1}H NMR δ: 6.36 (m, H-6,7), 5.95 (d, $J_{1,2}=3.8$, H-1), 5.85 (dd, $J_{4,5}=7.5$, $J_{5,6}=14.8$, H-5), 5.20 (m, both H-8), 3.85 (dd, $J_{3,4}=3.1$, H-3), 1.50 and 1.31 [$C(CH_3)_2$]; ^{13}C NMR δ: 136.1, 134.6, 127.1 (C-5,6,7), 118.2 (C-8), 111.4 [$C(CH_3)_2$], 104.7 (C-1), 83.4, 82.9, 80.8 (C-2,3,4), 72.0 (CH_2Ph), 26.7, 26.1 [$C(CH_3)_2$].

When this product was obtained according to Narkunan and Nagarajan[8] (see also Scheme 1) additional signals, that could be connected with the *cis*-isomer, were seen in the ^{13}C NMR spectrum at δ: 133.0, 131.7, 125.0 (C-5,6,7), 119.8 (C-8), and 112.1 [$C(CH_3)_2$]. Also, in the ^{1}H NMR spectrum the H-3 resonance split into two signals at δ: 3.89 (the minor *cis*-isomer) and 3.85 (the main *trans*-isomer). Integration of these signals allowed us to estimate the *trans*:*cis* ratio at 9:1.

4.3.3. 1-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-4,5,6,7-tetradeoxy-4(E),6-dieno-D-erythro-heptose **18-Ac**

^{1}H NMR δ: 6.36 (m, H-5,6), 6.22 (d, $J_{1,2}=2.3$, H-1), 5.65 (dd, $J_{3,4}=7.7$, $J_{4,5}=14.5$, H-4), 5.21 (m, H-7), 4.23 (dd, $J_{2,3}=6.2$, H-2), 3.87 (dd, H-3), 2.07 ($COCH_3$), 1.47 and 1.46 [$C(CH_3)_2$]; ^{13}C NMR δ: 170.1 (C=O), 135.9, 135.8 and 129.0 (C-4,5,6), 118.7 (C-7), 112.9 [$C(CH_3)_2$], 96.6 (C-1), 83.6 and 78.8 (C-2,3), 70.5 (CH_2Ph), 27.2 and 26.7 [$C(CH_3)_2$], 21.2 ($COCH_3$).

4.3.4. 1-O-*Acetyl-3*-O-*benzyl-1,2*-O-*isopropylidene-4,5,6,7-tetradeoxy-4*(E),*6-dieno-D*-threo-*heptose* ***25-Ac***

^{1}H NMR δ: 6.34 (m, H-5,6), 6.17 (d, $J_{1,2}=2.3$, H-1), 5.63 (dd, $J_{3,4}=8.2$, $J_{4,5}=14.6$, H-4), 5.20 (m, both H-7), 4.30 (dd, $J_{2,3}=5.5$, H-2), 3.95 (dd, H-3), 2.06 ($COCH_3$), 1.48 and 1.44 [$C(CH_3)_2$]; ^{13}C NMR δ: 170.2 (C=O), 136.2, 135.5 and 128.7 (C-4,5,6), 118.9 (C-7), 113.1 [$C(CH_3)_2$], 96.4 (C-1), 83.8 and 78.3 (C-2,3), 70.2 (CH_2Ph), 27.0 and 26.9 [$C(CH_3)_2$], 21.2 ($COCH_3$); HRMS *m*/*z*: 355.1521 [$C_{19}H_{24}O_5Na$ (M+Na$^+$) requires 355.1521].

4.4. Basic hydrolysis of dioxolanes ***18*** *and* ***25***

To a solution of **18** or **25** (3 mmol) in benzene (30 mL), triethylamine (1 mL), methanol (1 mL) and water (1 mL) were added and the mixture was stirred at room temperature for 3 h. Toluene (20 mL) was added, and the solution was concentrated to ca. half volume, dried and concentrated to give in almost quantitative yield 2(*R*)-hydroxy-3(*R*)-benzyloxy-hepta-4(*E*),6-dienal **19** and 2(*R*)-hydroxy-3(*S*)-benzyloxy-hepta-4(*E*),6-dienal **26**. These hydroxyaldehydes were rather unstable and should be prepared directly before use in the next step.

4.5. Reaction of hydroxyaldehydes with the stabilized Wittig reagent

Freshly prepared aldehyde (**19** or **26**; 1 mmol) was dissolved in dry benzene (10 mL) to which Ph_3P=CH–CO_2Me (0.5 g, 1.5 mmol) was added. The mixture was stirred for 3 h at room temperature, concentrated, and the product was isolated by column chromatography (hexane:ethyl acetate, 6:1).

4.5.1. Methyl 4(R)*-hydroxy-5*(R)*-benzyloxy-nona-2*(E),*6*(E),*8-trienoate* ***21***

$[\alpha]_D$ –87.7. ^{1}H NMR δ: 6.95 (dd, $J_{2,3}=15.8$, $J_{3,4}=4.6$, H-3), 6.33 (m, H-7,8), 6.11 (dd, $J_{2,4}=1.7$, H-2), 5.62 (dd, $J_{5,6}=8.1$, $J_{6,7}=14.5$, H-6), 5.22 (m, both H-9), 4.36 (H-4), 3.93 (dd, $J_{4,5}=4.4$, H-5), 3.72 (CO_2CH_3); ^{13}C NMR δ: 166.7 (C=O), 145.7 and 121.6 (C-2,3), 136.2, 135.7 and 128.7 (C-6,7,8), 118.9 (C-9), 81.6 (C-5), 72.9 (C-4), 70.4 (CH_2Ph), 51.5 (CO_2CH_3); HRMS *m*/*z*: 311.1280 [$C_{17}H_{20}O_4Na$ (M+Na$^+$) requires 311.1259].

4.5.2. Methyl 4(R)*-hydroxy-5*(S)*-benzyloxy-nona-2*(E),*6*(E),*8-trienoate* ***27***

$[\alpha]_D$ +116.0. ^{1}H NMR δ: 6.89 (dd, $J_{2,3}=15.6$, $J_{3,4}=4.2$, H-3), 6.36 (m, H-7,8), 6.16 (dd, $J_{2,4}=1.9$, H-2), 5.61 (dd, $J_{5,6}=8.4$, $J_{6,7}=14.3$, H-6), 5.24 (m, both H-9), 4.27 (m, H-4), 3.73 (H-5, CO_2CH_3); ^{13}C NMR δ: 166.7 (C=O), 145.6 and 121.6 (C-2,3), 136.6, 135.6 and 128.8 (C-6,7,8), 119.3 (C-9), 82.2 (C-5), 73.1 (C-4), 70.4 (CH_2Ph), 51.6 (CO_2CH_3); HRMS *m*/*z*: 311.1289 [$C_{17}H_{20}O_4Na$ (M+Na$^+$) requires 311.1259].

4.6. Reduction of hydroxyaldehydes ***19***, ***26*** *and alkoxyaldehyde* ***34***

Freshly prepared aldehyde **19** or **26** (1 mmol; obtained by hydrolysis of the corresponding dioxolanes, **18** and **25**) or **34** (obtained by the controlled decomposition of 1 mmol of allyltin **32** according to Section 4.3) was dissolved in a THF:methanol mixture (1:1 v/v, 20 mL), to which sodium borohydride (0.1 g) was added. The mixture was stirred for 1 h, concentrated, then the product was extracted with ether, acetylated under standard conditions and purified by column chromatography (hexane:ethyl acetate, 2:1).

*4.6.1. 1,2(*R*)-Di-acetoxy-3(*R*)-benzyloxy-hepta-4(*E*),6-diene **20-Ac***

$[\alpha]_D$ –88.9. ^{1}H NMR δ: 6.33 (m, H-5,6), 5.60 (dd, $J_{3,4}=8.1$, $J_{4,5}=14.3$, H-4), 5.20 (m, H-2, both H-7), 3.96 (dd, $J_{2,3}=6.2$, H-3), 2.01 and 1.99 (2×$COCH_3$); ^{13}C NMR δ: 170.5 and 170.0 (2×C=O), 135.7, 135.6 and 129.3 (C-4,5,6), 118.7 (C-7), 77.6 and 72.4 (C-2,3), 70.3 (CH_2Ph), 62.4 (C-1), 20.8 and 20.7 (2×COCH_3); HRMS *m*/*z*: 341.1362 [$C_{18}H_{22}O_5Na$ (M+Na$^+$) requires 341.1365].

*4.6.2. 1,2(*R*)-Di-acetoxy-3(*S*)-benzyloxy-hepta-4(*E*),6-diene **28-Ac***

$[\alpha]_D$ +26.6. ^{1}H NMR δ: 6.34 (m, H-5,6), 5.59 (dd, $J_{3,4}=7.8$, $J_{4,5}=14.5$, H-4), 5.22 (m, H-2, both H-7), 4.31 and 4.10 (2×dd, $J_{1a,1b}=11.8$, $J_{1a,2}=3.7$, $J_{1b,2}=7.0$, both H-1), 4.01 (dd, $J_{2,3}=5.3$, H-3), 2.08 and 1.99 (2×$COCH_3$); ^{13}C NMR δ: 170.5 and 170.2 (2×C=O), 135.7, 135.5 and ~128 (C-4,5,6), 118.9 (C-7), 77.2 and 72.5 (C-2,3), 70.4 (CH_2Ph), 62.8 (C-1), 20.9 and 20.7 (2×COCH_3); HRMS *m*/*z*: 341.1350 [$C_{18}H_{22}O_5Na$ (M+Na$^+$) requires 341.1365].

*4.6.3. 1-Acetoxy-2(*R*),3(*S*)-di-benzyloxy-hepta-4(*E*),6-diene **35-Ac***

^{1}H NMR δ: 6.35 (m, H-5,6), 5.68 (dd, $J_{3,4}=8.1$, $J_{4,5}=14.5$, H-4), 5.21 (m, both H-7), 4.32 (dd, $J_{1a,1b}=11.8$, $J_{1a,2}=3.7$, H-1a), 4.19 (dd, $J_{1b,2}=5.7$, H-1b), 3.95 (dd, $J_{2,3}=5.7$, H-3), 3.68 (m, H-2), 1.98 ($COCH_3$); ^{13}C NMR δ: 170.8 (C=O), 136.0, 135.2 and 130.6 (C-4,5,6), 118.1 (C-7), 79.0 and 78.8 (C-2,3), 72.8 and 70.4 (2×CH_2Ph), 63.4 (C-1), 20.9 (COCH_3); HRMS *m*/*z*: 389.1725 [$C_{23}H_{26}O_4Na$ (M+Na$^+$) requires 389.1729].

*4.7. Synthesis of dienes **22** and **29***

Diol **20** or **28** (1 mmol) was dissolved in ether (20 mL) and added to a solution of sodium periodate (0.7 g) in water (10 mL). The heterogeneous mixture was stirred for 30 min, the organic layer was separated, dried and concentrated, and the crude aldehyde was reduced with sodium borohydride as described in Section 4.6. For better characterization, products alcohols **22** and **29** were acetylated and these derivatives were purified by column chromatography (hexane:ethyl acetate, 4:1)

*4.7.1. 1-Acetoxy-2(*R*)-benzyloxy-hexa-3(*E*),5-diene **22-Ac***

$[\alpha]_D$ –87.9. ^{1}H NMR δ: 6.35 (m, H-4,5), 5.61 (dd, $J_{2,3}=6.8$, $J_{3,4}=14.3$, H-3), 5.19 (m, both H-6), 4.11 (m, H-2, both H-1), 2.05 ($COCH_3$); ^{13}C NMR δ: 170.8 (C=O), 135.8, 134.8 and 129.6 (C-3,4,4), 118.6 (C-6), 76.9 (C-2), 70.4 (CH_2Ph), 66.2 (C-1), 20.8 (COCH_3); HRMS *m*/*z*: 269.1165 [$C_{15}H_{18}O_3Na$ (M+Na$^+$) requires 269.1154].

*4.7.2. 1-Acetoxy-2(*S*)-benzyloxy-hexa-3(*E*),5-diene **29-Ac** (=ent-**22-Ac**)*

$[\alpha]_D$ +85.5. HRMS *m*/*z*: 269.1153 [$C_{15}H_{18}O_3Na$ (M+Na$^+$) requires 269.1154]. The NMR spectra of this compound were identical in all respects with the spectra of **22-Ac**.

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