New Access to *C*-Branched Sugars and *C*-Disaccharides under Indium Promoted Barbier-type Allylations in Aqueous Media

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The efficient formation of carbon−carbon bonds with good, and preferably predictable, stereocontrol is still a synthetic challenge in organic chemistry. In carbohydrate chemistry, *C*-branched sugars which represent a very attractive class of compounds because of their occurrence in nature,[1] or because they are found as subunits in many natural products,[2] require such a stereoselective C−C bond creation onto generally base- or acid-sensitive compounds due to their multifunctional character. Interest in *C*-branched sugars also comes from the fact that they are extensively used as a starting point in the total synthesis of natural products.[3]

Among the many methods developed for the synthesis of *C*-glycosides[4] or *C*-branched sugars during the last 20 years, some have been efficient, although they still remain relatively complex, generally requiring many steps[5] and sometimes the use of toxic tin and mercury compounds.[6] Furthermore, problems are frequently encountered with the stereochemical control at the *C*-branching point.[7]

Recently, organic reactions in water have received much attention, not only because water is an economical and environmentally friendly solvent[8] but more especially because unique reactivities and selectivities are often exhibited in water. Among them, organometallic reactions in aqueous media have been developed and their application in organic synthesis has been increasingly explored.[9] From this perspective, indium chemistry has captured much recent attention largely due to the discovery that indium can mediate the smooth coupling of allylic halides with aldehydes to give the corresponding homoallylic alcohols in aqueous media.[10] This reaction has been applied to the synthesis of carbohydrates[11] and many natural products.[12]

We wish to report here a very convenient protocol for the preparation of 2-*C*-branched sugars and *C*-disaccharides under indium-promoted Barbier-type allylations in aqueous media.

Results and Discussion

The construction of the key compound for the allylation reaction, 4-bromo-2-enopyranoside **2**, is described in Scheme 1. We started from the 2-enopyranoside **1** obtained by Ferrier rearrangement of 3,4,6-tri-*O*-acetyl-D-glucal with ethanol in 80% yield.[13]

After *O*-deacetylation of **1**, selective *tert*-butyldimethylsilylation at *O*-6 was carried out in 90% yield.[14] The intermediate 4-bromoderivative prepared by inversion of the 4-hydroxyl group under standard bromination conditions (triphenylphosphine, carbon tetrabromide), was then treated by tetrabutylammonium fluoride to give the desired 4-bromo-2-enopyranoside **2** in 69% overall yield. As expected, only the diastereoisomer with the bromine atom in a C-4 axial position was isolated.

We then tested the allylation reactions with several aldehydes whose results are shown in Table 1. First, we examined the reaction of the bromo-derivative **2** with benzaldehyde under indium-promoted Barbier-type conditions.

The reaction took place in H_2O at room temperature in 2 h to give **3** in 95% yield as a unique stereoisomer

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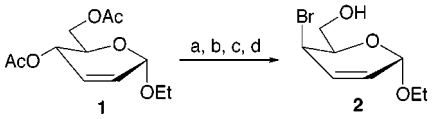
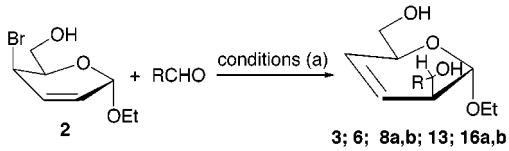
Scheme 1[a]



[a] Conditions: (a) Et_3N, CH_3OH, H_2O, 96%; (b) TBSCl, pyridine, 90%; (c) CBr_4, $(C_6H_5)_3P$, CH_2Cl_2, 75%; (d) $(C_4H_9)N^+F^-$, THF, 92%.

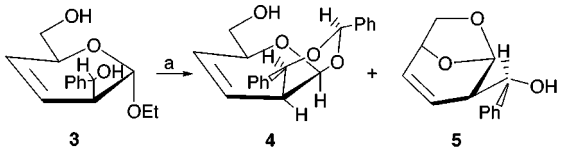
Table 1



entry	RCHO[a]	products	solvents[b]	cond[c]	yield[d] (%)	dr: S/R[e]
1	PhCHO	**3**	A	2; RT	95	1/0
2	HCHO	**6**	A	1; RT	97	
3	$CH_3(CH_2)_2CHO$	**8a,b**	A	4; RT	71	1/1
4	**12**	**13**	B	4; RT	94	0/1
5	**15**	**16a,b**	B	12; RT	55	1/1

[a] RCHO (2 equiv), In (2 equiv). [b] Solvent system: A, H_2O; B, H_2O/THF (1/1). [c] Conditions: reaction time (h); temperature (°C). [d] Isolated yields. [e] Diastereomeric ratio calculated by ^1H and ^{13}C NMR.

Scheme 2[a]



[a] Conditions: (a) C_6H_5CHO, $ZnCl_2$, CH_2Cl_2.

resulting from complete regio- and diastereoselectivity (Table 1, entry 1). The structure of **3** was deduced from an ^1H NMR analysis which exhibited a singlet for the H-1 signal, indicating an axial alkylation at C-2.[15] Furthermore, the presence of a 3,4-double bond was supported by an allylic coupling between H-3 and H-5. These data indicate alkylation at the γ position with syn stereochemistry relative to the bromine atom. The configuration of the second new stereogenic center at the C-7 position was deduced as (S) after introducing a benzylidene group to the C-1 and C-7 hydroxyl groups to give compound **4** (Scheme 2). In this reaction and under these experimental conditions, it is interesting to note the predominant formation of the unsaturated 2-*C*-anhydro-derivative **5** to be used later (vide infra).

In compound **4**, the bulky substituent (phenyl group at C-7) is ideally oriented away from the pyranosidic ring in an equatorial position. This is supported by the $J_{1,2} =$ 2.9 Hz value indicating a cis relationship between the two six-membered cycles and the $J_{2,7} =$ 10.7 Hz value showing a transdiaxial antiperiplanar orientation of the C-2 and C-7 hydrogen atoms.

From a mechanistic point of view, our results can be explained by the formation of the currently accepted six-membered cyclic transition state between the carbonyl compound and the allylindium sugar moiety,[8−10] with the phenyl group in an equatorial position as depicted in Figure 1. The C-7 (S) configuration in **3** was further supported by X-ray crystallography.

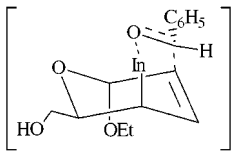
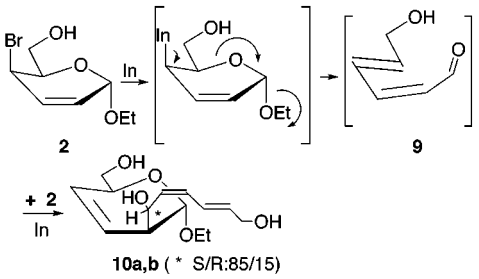


Figure 1.

Scheme 3



This reaction was extended to other aldehydes. In the case of formaldehyde (Table 1, entry 2), the C-2 axial product **6** was obtained in the same conditions and in quantitative yield as a single compound, with the reaction being only faster (1 h). With butyraldehyde (Table 1, entry 3), two new products, **8a,b**, were formed in equal amounts and both correspond to the expected C-2 axial adduct. However, poor selectivity at C-7 was observed, probably due to lower reactivity and a decrease in the steric hindrance around the carbonyl group. In this case, using butyraldehyde, two minor compounds were obtained, **10a,b** (85:15, 8%), whose structures were determined by spectroscopic analysis. For both compounds, the ^1H NMR spectra exhibited a singlet for the H-1 signals, indicating axial alkylation at C-2 and showing the presence of the following three double bonds: the expected 3,4-double bond, a double bond with cis geometry, and another with trans geometry. In fact, they result from the condensation of the aldehyde **9** onto the starting 4-bromo-2-enopyranoside **2**. Aldehyde **9** comes from the elimination of the ethoxy group on the intermediate allyl indium as shown in Scheme 3. In the transition state leading to the major diastereoisomer **10a**, the bulky substituent is, as expected, oriented away from the pyranosidic ring in an equatorial position (C-7, S), whereas it must be in an unfavorable axial position for the minor isomer (C-7, R). This is supported by a large coupling constant ($J_{2,7}$ 9.5 Hz) for the major diastereoisomer. The formation of these two minor compounds **10a,b** comes from a lower reactivity of butyraldehyde in comparison to that of benzaldehyde and formaldehyde, which allow the allyl indium intermediate to decompose to aldehyde **9** before reacting with butyraldehyde. Furthermore, when the 4-bromo-2-enopyranoside **2** was treated with indium alone without any aldehyde, the C-2 axial adducts **10a,b**, epimers at C-7, were obtained in near quantitative yields (45% isolated, theoretical 50%) in an identical 85:15 ratio.

Next, we examined the reaction between the 4-bromo-2-enopyranoside **2** and the 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-dialdose **12**.[16] The reaction was conducted

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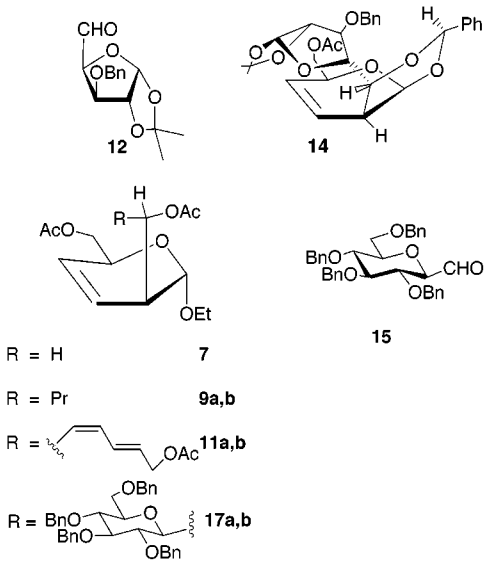


in an H_2O/THF mixture because of the poor solubility of the aldehyde in pure water. In this case, the reaction was as efficient as with benzaldehyde and the C-2 axial adduct **13** was obtained as a single diastereoisomer in 94% yield (Table 1, entry 4). Formation of the benzylidene derivative **14** onto the C-1 and C-7 hydroxyl groups showed that the configuration of new stereogenic center C-7 (R) was opposite to that observed in the case of the reaction with benzaldehyde. Indeed, the very small coupling constant between H-2 and H-7 ($J_{2,7}$ < 1 Hz) in the benzylidene derivative **14,** indicating a cis relationship, confirms this attribution. In this case, a chelated transition state has taken place, with the bulky substituent (sugar moiety) oriented toward the pyranosidic ring in an axial position. At this stage, it is worth pointing out that in product **3** (C-7, S) whose structure was assigned by X-ray and on the basis of the formation of the benzylidene derivative **4**, the $J_{2,7}$ value was greater than that in compound **13** (C-7, R). Considering these criteria, it is therefore possible to assign the C-7 configuration of other similar adducts as it has already been postulated.[17]

The formation of **13** in which C-7 has an (R) configuration could be explained by a chelation of the indium atom with the aldehyde carbonyl and an oxygen atom in **12** either via a six-membered cyclic chair transition state (C-3′ oxygen) or a five-membered cyclic transition state (endocyclic oxygen) which both favored the formation of the C-2 axial adduct with C-7 (R) configuration (Figure 2). In this case, the chelating factor overrides the steric effects, since the bulky substituent (sugar moiety) is in an unfavorable axial position in the cyclic chair transition state.

Finally, to obtain the analogues of the *C*-oligosaccharides, we turned our attention to the reaction between the 4-bromo-2-enopyranoside **2** and the *β*-*C*-linked 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucosyl aldehyde **15**.[18] The reaction, conducted in an H_2O/THF mixture at room temperature (Table 1, entry 5), was slower than with previous aldehydes and required 12 h. As before, only the C-2 axial

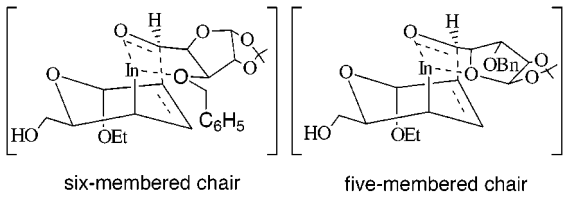
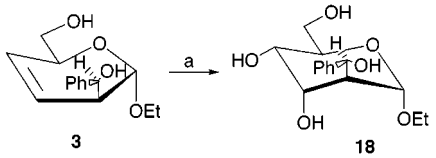


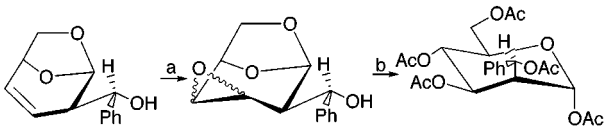
Figure 2.

Scheme 4[a]



[a] Conditions: (a) OsO_4, NMO, CH_3COCH_3/H_2O, 88%.

Scheme 5[a]



[a] Conditions: (a) *m*-CPBA, CH_2Cl_2, 89%; (b) CH_3COOH, Ac_2O, $BF_3.OEt_2$, 65%.

adduct was obtained but with no diastereoselectivity at C-7, and a mixture of the two corresponding diastereoisomers **16a,b** (50/50) was isolated in 55% yield. The moderate value of this yield can be explained by the lower reactivity of the *β*-*C*-linked 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucosyl aldehyde **15** in comparison to that with previous aldehydes, as well as by the enhanced formation of the adducts **10a,b** (85:15, 29%) in the reaction. This lower reactivity in Barbier-type allylation was further demonstrated through the reaction with the simple allyl bromide which required 24 h (66% yield) with aldehyde **15** compared to 2 h (98% yield) when aldehyde **12** was used (data not shown).

As mentioned previously, the formation of the two diastereoisomers **16a,b** was obtained from a six-membered cyclic chair transition state between the carbonyl compound and the allylindium sugar moiety with both the chelating and steric effects operating at the same time to give the C-7 (R) and C-7 (S) diastereoisomers, respectively. Compounds **6**, **8a,b**, **10a,b**, and **16a,b** were acetylated respectively to **7**, **9a,b**, **11a**,**b**, and **17a,b** for full characterization including elemental analyses.

In fact, all these allylation reactions led to unsaturated analogues of *C*-branched sugars or *C*-disaccharides which need to be further elaborated to real sugars. Accordingly, cis-hydroxylation with osmium tetroxide of the *C*-branched sugar **3** gave, with complete stereoselectivity, the 2-*C*-altrose **18** in 88% yield (Scheme 4).

More interestingly, as shown in Scheme 5, treatment of the unsaturated 2-*C*-anhydro-derivative **5** with 3-chloroperoxy-benzoic acid led to a mixture of epoxides **19**, which under acetolysis conditions (Ac_2O, BF_3-Et_2O) led to the opening of both the anhydro and the epoxide rings to give the 2-*C*-mannose, **20**, as a single diastereoisomer (58% overall yield).

In conclusion, the above results show that *C*-branched sugars or *C*-oligosaccharides are obtainable through

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indium-promoted Barbier-type allylations in aqueous media. Alkylation always occurs at the γ position, with syn stereochemistry relative to the bromine atom via a cyclic six-membered chair transition state.

Work is currently in progress in our laboratory to extend this methodology to other bromo-enopyranosides and *C*-formyl-glycosides. This method seems very general and should open the door to interesting prospects for the synthesis of many different *C*-oligosaccharides.

Experimental Section

General Methods and Materials. All moisture sensitive reactions were performed under argon using oven-dried glassware. If necessary, solvents were dried and distilled prior to use. Reactions were monitored on silica gel 60 F_{254}. Detection was performed using UV light, iodine, and/or 5% sulfuric acid in ethanol, followed by heating. Flash chromatography was performed on silica gel 6−35μm. ^{1}H and ^{13}C NMR spectra were recorded at room temperature with Bruker AC 200, 250 or AM 400 spectrometers. Chemical shifts are reported in δ vs Me_4Si for ^{1}H NMR spectra (external reference for D_2O) and relative to the $CDCl_3$ resonance at 77.00 ppm for ^{13}C NMR spectra in $CDCl_3$ and relative to Me_4Si for ^{13}C NMR spectra in D_2O. Melting points were measured on a Reichert apparatus and were uncorrected. Optical rotations were measured on an Electronic Digital Jasco DIP-370 Polarimeter. Mass spectra were recorded in positive mode on a Finnigan MAT 95 S spectrometer using electrospray ionization. Elemental analyses were performed at the Service Central de Microanalyses du CNRS (Gif-sur-Yvette, France).

Acetylation was performed in pyridine with Ac_2O (2:1, v/v) and kept at room-temperature overnight. After several coevaporations with toluene, the crude product was purified by flash chromatography (petroleum ether/ethyl acetate).

Ethyl 4-Bromo-2,3,4-trideoxy-α-D-threo-hex-2-enopyranoside (2). To a solution of ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside[14] (750 mg, 2.6 mmol) in CH_2Cl_2 (10 mL) maintained under argon at −78 °C were added $(C_6H_5)_3P$ (1.02 g, 3.9 mmol) and CBr_4 (948 mg, 2.86 mmol). The suspension was stirred at 0 °C for 2 h then quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) then concentrated. The crude residue was dissolved in THF (10 mL) and then treated at 0 °C with a solution of $NBu_4^+F^-$ (1M in THF, 3.12 mL). The mixture was stirred at room temperature for 3h and then quenched with water and extracted with Et_2O. The organic phase was washed several times with saturated aqueous NH_4Cl solution, dried ($MgSO_4$), and then concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate: 3/1 to 1/1) gave **2** (425 mg, 69%).White crystals, mp 92−93 °C (CH_2Cl_2). $[\alpha]_D^{27}$: −283° (c 1.05, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 2.00 (brs, 1H), 3.57 (dq, J = 7.1, 9.5 Hz, 1H), 3.74 (dd, J = 5.4, 11.2 Hz, 1H), 3.80−3.95 (m, 2H), 4.09 (m, 1H), 4.48 (dd, J = 1.9, 5.4 Hz, 1H), 5.14 (d, J = 3.1 Hz, 1H), 5.83 (dd, J = 10.0 Hz, 1H), 6.22 (dd, J = 5.6 Hz, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 15.2, 44.4, 63.9, 65.0, 68.5, 93.9, 127.4, 129.3. Anal. Calcd for $C_8H_{13}O_3Br$: C, 40.53; H, 5.53; O, 20.24. Found: C, 40.99; H, 5.46; O, 20.21.

General Procedure for Reaction of 2 with Aldehydes. To a solution of 4-bromo-2-enopyranoside **2** in H_2O (system A) or THF/H_2O (1/1) (system B) were added indium powder (2 equiv) and the corresponding aldehyde (2 equiv). The suspension was stirred at room temperature until the reaction was complete, as judged by consumption of the 4-bromo-2-enopyranoside **2** (see Table 1). The reaction was then quenched with a saturated aqueous $NaHCO_3$ solution, filtered, and concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate: 4/1 to 1/3) gave the corresponding 2-*C*-branched sugars.

Ethyl 2-*C*-[(*S*)-1-Phenyl-1-hydroxymethyl]-3,4-dideoxy-α-D-threo-hex-3-enopyranoside (3). White crystals (95%), mp 139−140 °C (CH_2Cl_2). $[\alpha]_D^{27}$: +101.8° (c 1.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 2.47−2.51 (m, 1H), 3.46−3.59 (m, 1H), 3.65 (dd, J = 5.4, 11.2 Hz, 1H), 3.74−3.87 (m, 2H), 4.28 (m, 1H), 4.64 (d, J = 7.3 Hz, 1H), 5.13 (s, 1H), 5.43−5.51 (m, 1H), 5.73 (dd, J = 1.2, 10.5 Hz, 1H), 7.25−7.31 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1, 46.1, 63.4, 64.8, 68.8, 75.1, 96.7, 125.3, 126.4, 127.4, 127.8, 128.5, 142.1. MS (EI) m/z: 287.1 $(M + Na)^+$. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.06; H, 7.73; O, 24.04.

1,7-*O*-Benzylidene-2-*C*-[(*S*)-1-phenyl-1-hydroxymethyl]-3,4-dideoxy-β-D-threo-hex-3-enopyranoside (4) and 1,6-Anhydro-2-*C*-[(*S*)-1-phenyl-1-hydroxymethyl]-3,4-dideoxy-β-D-threo-hex-3-enopyranoside (5). To a solution of **3** (190 mg, 0.719 mmol) in CH_2Cl_2 (5 mL) under argon were added zinc chloride (117 mg, 0.863 mmol) and benzaldehyde (365μL, 3.59 mmol). The suspension was stirred at room-temperature overnight, then quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed several times with a saturated aqueous $NH_4^+Cl^-$ solution, dried ($MgSO_4$), and then concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate: 10/1 to 1/1) gave first **5** (108 mg, 69%) then **4** (47 mg, 20%).

4. White solid. $[\alpha]_D^{28}$: +24.7° (c 1.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.63−2.70 (m, 1H), 3.79 (dd, J = 6.3, 11.5 Hz, 1H), 3.90 (dd, J = 3.4 Hz, 1H), 4.59 (m, 1H), 4.91 (d, J = 10.7 Hz, 1H), 5.39 (d, J = 2.9 Hz, 1H), 5.44 (dddd, J = 2.9, 6.8, 10.3 Hz, 1H), 5.73 (d, J = 10.3 Hz, 1H), 6.33 (s, 1H), 7.35−7.62 (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 41.0, 65.0, 76.7, 81.0, 94.9, 95.3, 125.7, 126.3, 127.0, 128.1, 128.2, 128.3, 128.9, 137.6, 138.7. MS (EI) m/z: 347.1 $(M + Na)^+$. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21; O, 19.73. Found: C, 73.86; H, 6.27; O, 19.89.

5. Colorless oil. $[\alpha]_D^{26}$: +8.3° (c 1.3, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.94−2.98 (m, 1H), 3.35 (d, J = 6.8 Hz, 1H), 3.77 (m, 1H), 4.02 (d, J = 6.3 Hz, 1H), 4.68 (t, J = 4.4 Hz, 1H), 4.80 (t, J = 6.8 Hz, 1H), 5.45 (td, J = 2.0, 9.8 Hz, 1H), 5.63 (t, J = 2.0 Hz, 1H), 6.10 (dddd, J = 2.0, 4.4, 9.8 Hz, 1H), 7.29−7.40 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 49.3, 71.1, 72.6, 74.4, 101.7, 126.1, 126.7, 127.7, 128.5, 129.7, 133.5. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; O, 21.99. Found: C, 71.74; H, 6.52; O, 22.16.

Ethyl 2-*C*-[Hydroxymethyl]-3,4-dideoxy-α-D-threo-hex-3-enopyranoside (6). Colorless oil (97%). $[\alpha]_D^{27}$: +24.6° (c 1.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 2.26−2.29 (m, 1H), 2.76 (m, 2H), 3.49−3.84 (m, 6H), 4.23 (m, 1H), 4.96 (s, 1H), 5.75 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1, 41.6, 63.3, 63.4, 64.6, 68.9, 98.2, 124.5, 127.8. MS m/z: 211.1 $(M + Na)^+$.

Ethyl 2-*C*-[Hydroxymethyl]- 6,7-di-O-acetyl-3,4-dideoxy-α-D-threo-hex-3-eno-pyranoside (7). Colorless oil (93%). $[\alpha]_D^{29}$: +69.6° (c 1.3, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.34−2.41 (m, 1H), 3.54 (qd, J = 7.0, 9.7 Hz, 1H), 3.75−3.92 (m, 2H), 4.05−4.14 (m, 3H), 4.32−4.36 (m, 1H), 4.88 (s, 1H), 5.73 (s, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 15.1, 20.8, 38.9, 63.6, 64.5, 65.5, 66.7, 96.7, 123.9, 127.2, 170.7, 170.8. MS (EI) m/z: 295.1 $(M + Na)^+$. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40; O, 35.25. Found: C, 57.22; H, 7.48; O, 35.19.

Ethyl 2-*C*-[(*R,S*)-1-Hydroxybutyl]-3,4-dideoxy-α-D-threo-3-enopyranoside (8a,b). Colorless oil (71%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, J = 6.3 Hz, 6H), 1.22 (t, J = 7.0 Hz, 6H), 1.32−1.53 (m, 4H), 1.80−1.87 (m, 4H), 2.09−2.16 (m, 1H), 2.24−2.27 (m, 1H), 2.80 (brs, 1H), 3.50−3.89 (m, 10H), 4.26 (m, 2H), 4.93 (s, 1H), 5.11 (s, 1H), 5.78−5.87 (m, 4H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.0, 15.1, 18.8, 19.2, 36.9, 37.1, 43.6, 44.8, 63.2, 63.3, 64.5, 64.8, 68.7, 69.1, 72.4, 72.6, 96.7, 100.1, 123.0, 125.5, 127.3, 128.5. MS (EI) m/z: 253.1 $(M + Na)^+$.

Ethyl 6,7-Di-*O*-acetyl-2-C-[(R,S)-1-hydroxybutyl]-3,4-dideoxy-α-D-threo-3-enopyranoside (9a,b). Colorless oil (91%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 6H), 1.19 (t, J = 7 Hz, 6H), 1.20−1.65 (m, 8H), 2.03 (s, 6H), 2.06 (s, 6H), 2.28−2.36 (m, 2H), 3.51 (qd, J = 7.3, 9.7 Hz, 2H), 3.70−3.84 (m, 2H), 4.06−4.22 (m, 4H), 4.30−4.34 (m, 2H), 4.78 (s, 1H), 4.90 (s, 1H), 4.90−5.03 (m, 2H), 5.76 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.7, 13.9, 15.0, 18.1, 19.0, 20.7, 20.8, 21.0, 21.1, 32.9, 33.2, 42.5, 42.8, 63.1, 63.3, 65.5, 65.6, 66.0, 66.3, 73.5, 74.3, 96.7, 96.8, 123.9, 124.1, 126.9, 170.3, 170.5, 170.8. MS (EI) m/z: 337.2 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34; O, 30.53. Found: C, 60.91; H, 8.43; O, 30.81.

Ethyl 2-*C*-[(*R,S*)-5-Hydroxypenta-1(*cis*),3(*trans*)-dienyl]-3,4-dideoxy-α-D-threo-hex-3-eno-pyranoside (10a,b). To a stirred solution of 4-bromo-2-enopyranoside **2** (100 mg, 0.421 mmol) in H_2O (3 mL) was added indium powder (145 mg, 1.26 mmol). After 3 h at room temperature, the reaction was

quenched with a saturated aqueous $NaHCO_3$ solution, filtered, and concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate: 3/1 to 0/1) gave a 85/15 mixture of **10a,b** (51 mg, 45%).

Colorless oil. ^{1}H NMR for **10a** (C-7 (S); major diastereoisomer). (200 MHz, CD_3OD) δ 1.21 (t, J = 7.0 Hz, 3H), 2.04−2.11 (m, 1H), 3.48−3.65 (m, 3H), 3.76−3.93 (m, 1H), 4.08−4.15 (m, 3H), 4.48 (t, J = 9.5 Hz, 1H), 5.14 (s, 1H), 5.37 (t, J = 10.3 Hz, 1H), 5.54−5.62 (m, 1H), 5.70−5.89 (m, 2H), 6.12 (t, J = 11.2 Hz, 1H), 6.55 (dd, J = 11.2, 14.9 Hz, 1H).^{13}C NMR for **10a** (50.3 MHz, CD_3OD) δ 15.5, 46.8, 63.2, 64.3, 65.5, 69.5, 70.6, 98.1, 125.2, 127.0, 128.3, 131.0, 132.4, 135.6. MS (EI high resolution) for **10a,b** *m/z*: Calcd for $C_{14}H_{22}O_5$ Na: 293.13715. Found: 293.13649.

Ethyl 6,7-Di-*O*-acetyl-2-C-[(R,S)-5-hydroxypenta-1(*cis*), 3(*trans*)-dienyl]-3,4-dideoxy-α-D-threo-hex-3-enopyranoside (11a,b). Colorless oil (91%). ^{1}H NMR for **11a** (C-7 (S), major stereoisomer) (200 MHz, $CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 3H), 2.00−2.08 (3s, 9H), 2.38 (m, 1H), 3.46−3.59 (m, 1H), 3.74−3.84 (m, 1H), 4.05−4.25 (m, 2H), 4.35 (m, 1H), 4.55−4.62 (m, 2H), 4.83 (s, 1H), 5.31 (m, 1H), 5.56 (t, J = 8.9 Hz, 1H), 5.65−5.85 (m, 3H), 6.14 (t, J = 11.2 Hz, 1H), 6.65 (m, 1H). ^{13}C NMR for **11a** (50.3 MHz, $CDCl_3$) δ 15.1, 20.8, 21.1, 42.8, 63.7, 64.3, 65.6, 66.8, 70.4, 96.3, 123.9, 127.2, 128.5, 130.1, 132.0, 169.8, 170.7, 170.8. Anal. Calcd for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12. Found: C, 61.13; H, 7.25.

Condensation with Aldehyde 12. Compound 13. Colorless oil (94%). $[\alpha]^{27}_D$: +5.5° (c 1.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, J = 7 Hz, 3H), 1.31 (s, 3H), 1.47 (s, 3H), 2.66 (m, 1H), 3.43−3.88 (m, 4H), 4.04−4.11 (m, 2H), 4.19 (dd, J = 1.9, 9.3 Hz, 1H), 4.29 (m, 1H), 4.59 (d, J = 3.9 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 4.71 (d, 1H), 5.00 (s, 1H), 5.90 (d, 1H), 5.89−5.93 (m, 2H), 7.20−7.40 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1, 26.3, 26.9, 40.4, 63.2, 64.2, 69.0, 69.3, 72.4, 80.0, 81.5, 82.4, 100.2, 105.0, 111.7, 122.6, 127.7, 127.9, 128.5, 129.2, 137.5. MS (EI) *m/z*: 459.2 (M + Na)$^+$. Anal. Calcd for $C_{23}H_{32}O_8$: C, 63.29; H, 7.39; O, 29.32. Found: C, 62.95; H, 7.56; O, 29.95.

Benzylidene Derivative (14). The primary hydroxyl group in compound **13** (87 mg, 0.2 mmol) was first regioselectively acetylated with Ac_2O (21μL, 0.22 mmol) in pyridine (300μL) for 12 h at 0 °C. After coevaporation with toluene, flash chromatography gave the monoacetylated compound (92 mg, 97%) Then, following the same experimental protocol described for the preparation of compound **4**, except that the reaction was quenched after 2 h at room temperature, compound **14** was obtained as a colorless oil (26 mg, 24%). $[\alpha]^{27}_D$: −21° (c 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.41 (s, 3H), 2.00 (s, 3H), 2.60 (m, 1H), 4.03 (s, 1H), 4.21 (m, 2H), 4.32 (d, J = 11.0 Hz, 1H), 4.35 (d, 1H), 4.45 (m, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 3.7 Hz, 1H), 4.64 (d, 1H), 5.37 (s, 1H), 5.50 (s, 1H), 5.84 (d, 1H), 5.83−5.95 (m, 2H), 7.18−7.52 (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.0, 26.3, 26.9, 34.1, 67.3, 70.9, 72.4, 73.2, 76.9, 80.9, 82.3, 95.6, 99.5, 105.0, 112.0, 122.2, 126.1, 127.6, 128.2, 128.5, 128.6, 128.9, 130.2, 133.6, 137.3, 137.4, 170.9. MS (EI) *m/z*: 561.2 (M + Na)$^+$. Anal. Calcd for $C_{30}H_{34}O_9$: C, 66.90; H, 6.36; O, 26.74. Found: C, 66.76; H, 6.61; O, 27.04.

Condensation with Aldehyde 15. Following the general procedure, a 1:1 mixture of compounds **16a,b** was obtained as a colorless oil (55%) which was directly peracetylated and partially separated by flash chromatography (petroleum ether−AcOEt, 2/8) to give first the pure C-7 (S) stereoisomer **17a** followed by the C-7 (R) stereoisomer **17b** (96%).

17a. Colorless oil. $[\alpha]^{27}_D$: +24.9° (c 1.1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (t, J = 7 Hz, 3H), 2.05 (s, 3H), 2.12 (s, 3H), 2.57 (m, 1H), 3.37−3.56 (m, 4H), 3.62−3.82 (m, 5H), 4.08 (dd, J = 3.9, 11.2 Hz, 1H), 4.22 (dd, J = 6.3 Hz, 1H), 4.34 (m, 1H), 4.48−4.67 (m, 4H), 4.81−4.92 (m, 4H), 5.03 (s, 1H), 5.46 (dd, J = 1.0, 5.4 Hz, 1H), 5.75 (m, 1H), 5.91 (m, 1H), 7.15−7.45 (m, 20H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1, 20.9, 21.1, 42.0, 63.5, 65.6, 66.7, 68.8, 70.1, 73.3, 74.9, 75.0, 75.6, 77.7, 78.1, 78.3, 79.4, 87.7, 97.0, 125.0, 126.5, 127.5−128.4, 137.1−138.4, 170.0, 170.1. Anal. Calcd for $C_{47}H_{54}O_{11}$: C, 71.01; H, 6.85; O, 22.14. Found: C, 70.83; H, 6.92; O, 22.28.

17b. Colorless oil. $[\alpha]^{27}_D$: +16.8° (c 1.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (t, J = 7 Hz, 3H), 2.03 (s, 6H), 2.63 (m, 1H), 3.36−3.81 (m, 9H), 4.03 (dd, J = 6.3, 11.2 Hz, 1H), 4.19 (dd, J = 3.9 Hz, 1H), 4.32 (m, 1H), 4.47−4.95 (m, 8H), 4.90 (s, 1H), 5.38 (dd, J = 1.0, 7.8 Hz, 1H), 5.79−5.82 (m, 2H), 7.17−7.34 (m, 20H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.1, 20.8, 21.0, 40.2, 63.5, 65.7, 66.7, 68.8, 73.3, 75.0, 75.7, 78.0, 78.7, 79.0, 79.5, 87.4, 96.9, 125.3, 127.1, 127.1−128.4, 137.7−138.3, 169.8, 170.9. Anal. Calcd for $C_{47}H_{54}O_{11}$: C, 71.01; H, 6.85. Found: C, 71.41; H, 7.34.

Ethyl 2-C-[(S)-1-Phenyl-1-hydroxymethyl]-α-D-altropyranoside (18). To a solution of **3** (200 mg, 0.757 mmol) in acetone/water (8/1, 5 mL) were added 4-methylmorpholine-*N*-oxide monohydrate (204 mg, 1.51 mmol) and osmium tetroxide (0.2M/THF, 190 μL, 0.05 eq). The reaction mixture was stirred overnight at room temperature then diluted with AcOEt and washed several times with a saturated aqueous Na_2SO_3 solution. The organic phase was dried ($MgSO_4$) then concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate: 1/1 to 0/1) gave the triol **18** (198 mg, 88%). White crystals, mp 122−124 °C (CH_3OH/CH_2Cl_2). $[\alpha]_D^{25}$: +25.5° (c 1.2, CH_3OH). ^{1}H NMR (250 MHz, CD_3OD) δ 1.22 (t, J = 7.1 Hz, 3H), 2.36 (ddd, 1H), 3.24 (t, J = 2.9 Hz, 1H), 3.50 (ddd, J = 7.3, 9.8, 9.8 Hz, 1H), 3.60 (dd, J = 3.4 Hz, 1H), 3.75−3.90 (m, 4H), 4.63 (d, J = 9.7 Hz, 1H), 5.27 (s, 1H), 7.30−7.39 (m, 5H). ^{13}C NMR (62.9 MHz, CD_3OD) δ 15.3, 53.2, 63.0, 64.6, 65.7, 70.1, 70.4, 72.8, 99.3, 127.8, 129.0, 129.7, 144.0. MS (EI) *m/z*: 321.1 (M + Na)$^+$. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43; O, 32.18. Found: C, 59.77; H, 7.46; O, 32.14.

1,3,4,6,7-Penta-*O*-acetyl-2-*C*-[(*S*)-1-phenyl-1-acetoxymethyl]-α-D-mannopyranose (20). To a cooled (0 °C) solution of **5** (80 mg, 0.366 mmol) in CH_2Cl_2 (5 mL) was added 3-chloroperoxy-benzoic acid (126 mg, 0.734 mmol). After stirring overnight at 40 °C, the reaction mixture was diluted with CH_2Cl_2 and then washed with a saturated aqueous $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and then concentrated to give a crude mixture of epoxide **19** (1/15). Acetic acid (2 mL) and acetic anhydride (0.5 mL) were then added, followed by a catalytic amount of $BF_3.OEt_2$. After heating at 55 °C overnight, the reaction mixture diluted with ether was washed several times successively with a saturated aqueous $NaHCO_3$ solution and a saturated aqueous $NH_4^+Cl^-$ solution. The organic phase was dried ($MgSO_4$) and then concentrated. Flash chromatography (petroleum ether/ethyl acetate: 5/1 to 1/1) of the residue gave **20** (102 mg, 58%). Colorless oil. $[\alpha]^{27}_D$: −4.9° (c 1.1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.03 (s, 3H), 2.12 (s, 3H), 2.14 (s, 6H), 2.91−2.97 (m, 1H), 4.00−4.08 (m, 1H), 4.19 (m, 2H), 5.30 (dd, J = 5.6, 9.5 Hz, 1H), 5.50 (t, J = 9.5 Hz, 1H), 6.03 (d, J = 8.3 Hz, 1H), 6.29 (s, 1H), 7.27−7.33 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.2, 20.6, 20.7, 20.9, 21.1, 45.5, 62.5, 65.8, 69.7, 70.4, 72.0, 91.3, 126.8, 128.3, 128.7, 138.3, 168.6, 169.2, 169.5, 170.1, 170.7. MS (EI) *m/z*: 503.0 (M + Na)$^+$. Anal. Calcd for $C_{23}H_{28}O_{11}$: C, 57.50; H, 5.87. Found: C, 57.55; H, 6.02.

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