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TETRAHEDRON: *ASYMMETRY*

A convenient route to enantiomerically pure bicyclo[4.3.0]nonanes from sugar allyltin derivatives

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Abstract

Tandem Wittig-type Diels–Alder reactions between sugar derived phosphonates and dienoaldehydes obtained from sugar allyltins lead, with high stereoselectivity, to complex oxygenated perhydroindene derivatives with the *trans* junction between the five- and six-membered rings. The configuration at the newly created stereogenic centers in such bicyclo[4.3.0] systems may be monitored by the geometry of chiral phosphonates.

1. Introduction

Stereoselective synthesis of carbocyclic derivatives via Diels–Alder reactions is one of the most important processes in the creation of the carbon–carbon bonds.[1] Intramolecular versions of this reaction open a convenient route to bicyclic products;[2] application of chiral precursors allows enantiomerically pure bicyclic adducts to be obtained.

Recently we elaborated a convenient method for the preparation of chiral dienoaldehydes **1** — with the *trans* geometry of the internal double bond — from sugar allyltins[3] **2**. Compounds **1**, by reaction with $Ph_3P{=}CHCO_2Me$, are easily converted into trienes **3** with the *trans* geometry of the newly created double bond. Although the trienes are stable under normal conditions, they undergo intramolecular [4+2] cycloaddition to bicyclic products **4** either in the presence of Lewis acids or under high pressure (> 10 kbar).[4]

Since trienes **3** are prepared from chiral aldehyde **1** and an achiral C_2-unit (from $Ph_3P{=}CHCO_2R$), the configuration at the newly created stereogenic centers at C1, C5 and C6 resulting from cyclization of **3** is dependent on the configuration of the starting aldehyde and consequently the allyltin derivative used as substrate. We observed that the stereoselectivity of the process was also dependent on the conditions of the cyclization.

Under high pressure, only one stereoisomer was formed (**4a** from D-*xylo*-, **4b** from D-*lyxo*- and **4c** from L-*arabino*-triene). However, the Lewis acid catalyzed reaction of **3a** and **3b** was less selective

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and provided the corresponding bicyclic products as a ca. 3:1 mixture of isomers. Only cyclization of **3c** gave bicyclo[4.3.0]non-2-ene **4c** as a single isomer (Fig. 1).[4]

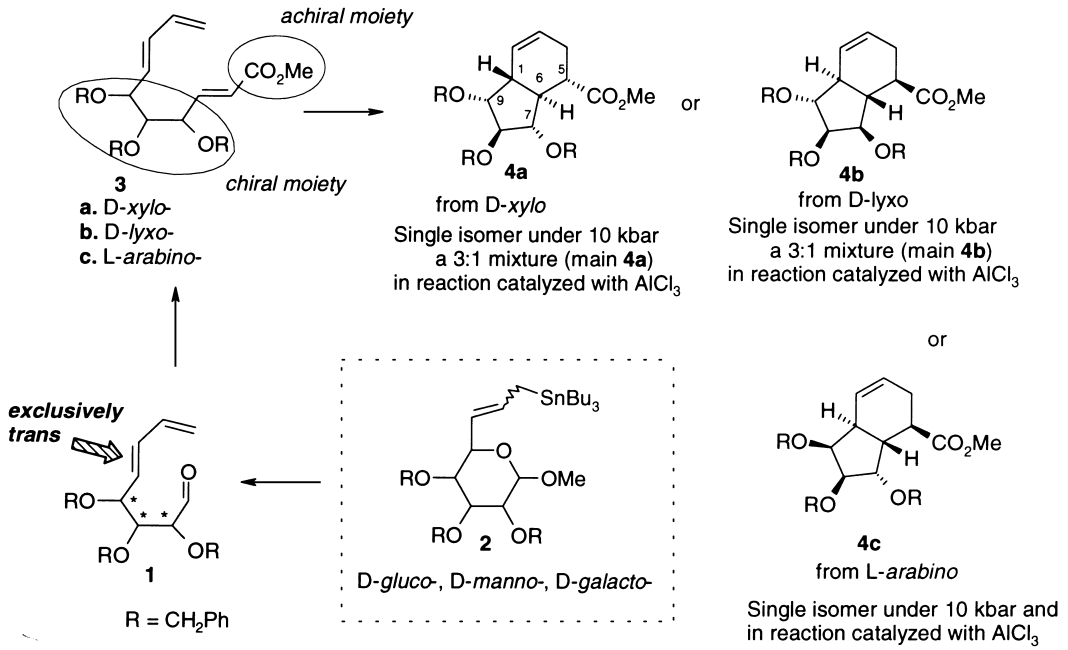


Figure 1. Stereoselective synthesis of highly oxygenated perhydroindenes from sugar allyltins

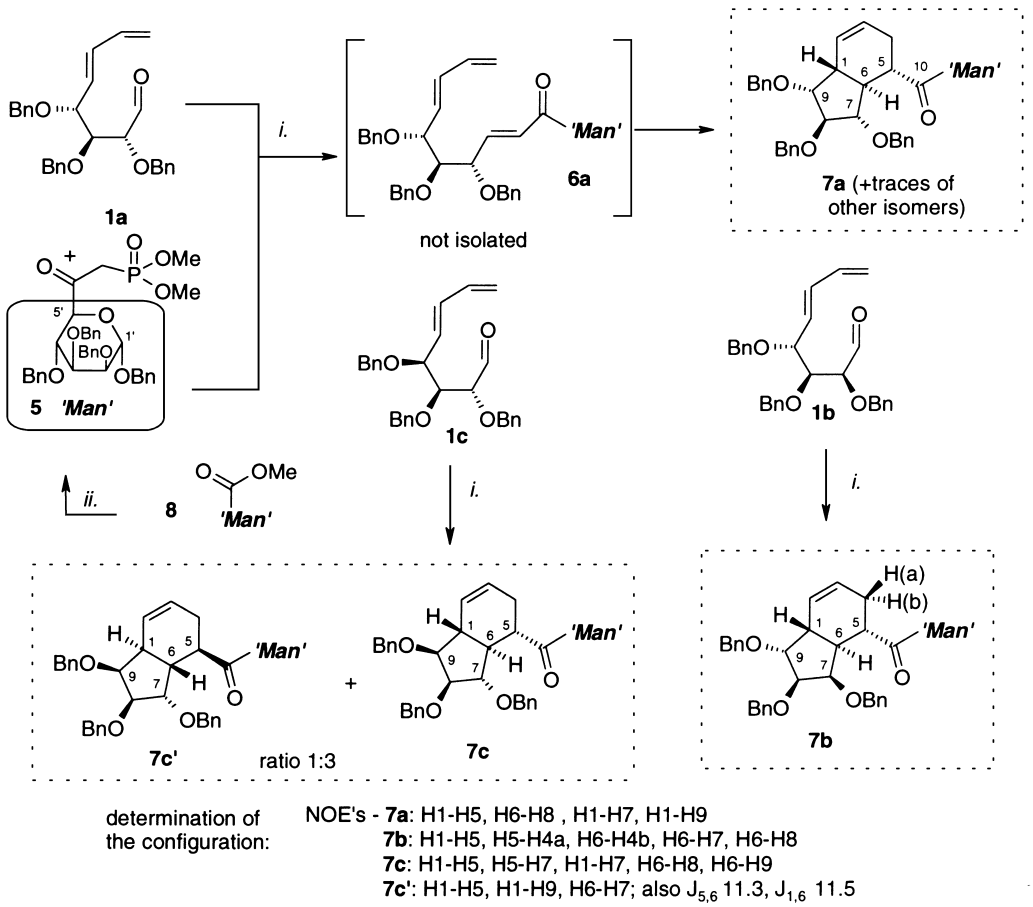
The influence of the aldehyde's pre-existing stereogenic centers might be, eventually, overcome if — instead of the CO_2Me group — the chiral unit would be introduced at the double bond of the dienophile in triene **3**.

2. Results and discussion

Dienoaldehydes **1** could be readily converted into appropriate trienes in which the dienophile part is substituted at both ends with chiral moieties. This might be achieved using the Wittig–Horner methodology applied recently by us for the preparation of long chain monosaccharides.[5] Aldehydes **1** reacted with phosphonate **5** (prepared according to Ref. 5 and Scheme 1; for details see Experimental) under phase transfer conditions (K_2CO_3, 18-crown-6 in toluene at room temperature) to afford the corresponding trienes (i.e. **6a**) which, contrary to **3**, could not be isolated, but underwent spontaneous cyclization to **7** (Scheme 1). This fact — spontaneous cyclization — was not very surprising, because activation of the dienophile by a ketone group in **6** is much more pronounced than that exerted by an ester function in **3** and thus the cyclization reaction should proceed more readily.

Reaction of the D-*xylo*-aldehyde **1a** with phosphonate **5** gave a single stereoisomer[†] **7a** (Scheme 1) with the same configuration at the three newly created stereogenic centers as in adduct **4a** (cf. Fig. 1).

[†] The configurations at the C1, C5 and C6 centers in **7** were determined from the NMR experiments: COSY and NOESY; see Schemes 1 and 2 and Experimental.



Scheme 1. (i) Compound **5**, K_2CO_3, 18-crown-6, toluene, rt, overnight; (ii) BuLi, $MeP(O)(OMe)_2$, THF, –78°C

Interestingly, the stereoselectivity of this process was much better than that observed for the Lewis acid catalyzed cyclization of the ester analog (**3a**→**4a**+isomer in ca. 3:1 ratio; cf. Fig. 1). Analogous reaction of the D-*lyxo*-aldehyde **1b** was also highly selective and afforded bicyclo[4.3.0]-non-2-ene **7b** as a single isomer with the opposite configuration at C1, C5 and C6 as compared to compound **4b**.

Less selective was the reaction of the L-*arabino*-analog **1c** (ratio of **7c**:**7c**′ = 3:1); however, even in this case the opposite isomer **7c** was also formed as the main product in this process, while isomer **7c**′ (with the same configuration at C1, C5 and C6 as in **4c**) was the minor one. In all these processes only the products with the *trans* junction of the five- and six-membered rings (C1–C6) were formed, which might be explained by a preferred *endo*-type [4+2] intramolecular cyclization (Ref. 4, cf. Fig. 2).

The results obtained here indicated also that the 'external' chirality, i.e. that of a dienophile part of the molecule arising from **5** [dimethyl (benzyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hepto-pyranos-6-ulos-7-yl)phosphonate[6]], is much more important than the geometry of dienoaldehydes **1a**–**c**. The explanation of such phenomenon is shown in Fig. 2.

Although the three stereogenic centers (arising from aldehyde **1**) have an influence on the steric course of the cyclization (cf. Fig. 1), the influence of the chirality of the sugar ring (from phosphonate)

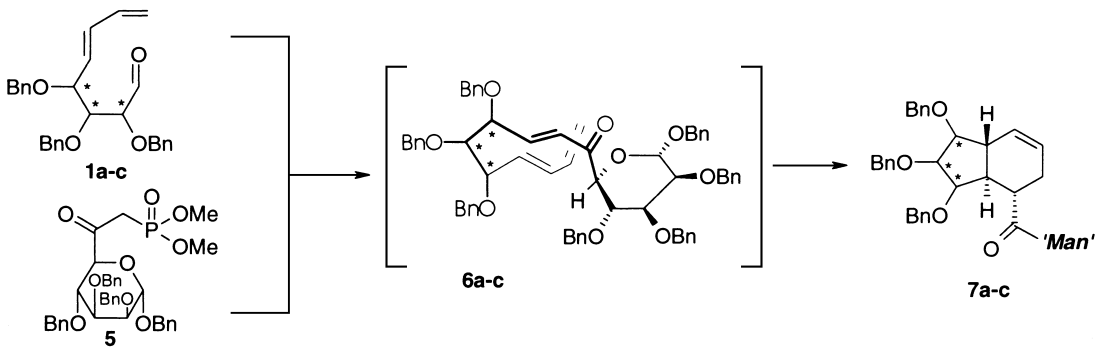
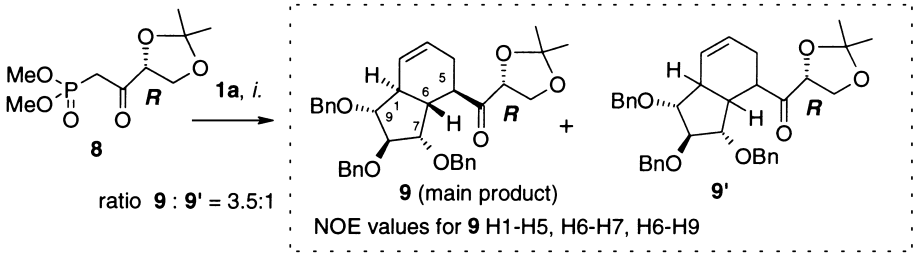


Figure 2. Transition state for the cyclization of trienes **6a–c**

is much more pronounced. The *endo* transition state shown in Fig. 2 allows for better overlapping of not only the diene and enone parts, but also of the orbitals of the ring oxygen atom.

If this assumption is correct, reaction of aldehydes **1** with the phosphonate partner, having the opposite configuration at the C-α to the carbonyl group, should lead to the [4.3.0]bicyclic system with the opposite geometry at the three newly created stereogenic centers at C1, C5 and C6.

Indeed, reaction of phosphonate **8** (prepared[7] from 2,3-*O*-isopropylidene-D-glyceraldehyde) with aldehyde **1a** (D-*xylo*) proved this hypothesis, and the corresponding stereoisomeric compound **9** with the opposite configuration at the C1, C5 and C6 centers (as compared to **7a–c**) was formed as the main product in this process (Scheme 2).



Scheme 2. (i) Toluene, K_2CO_3, 18-crown-6, rt

The configuration of the main product **9** was established by detailed ^{1}H NMR experiments (performed on an inseparable ca. 3.5:1 mixture of **9** and **9′**). Strong NOE correlations (2D NOESY spectrum) were observed between H1–H5, H6–H7 and H6–H9, whilst no correlation was seen between H1–H6 signals.

We were not able, however, to assign the configuration of the minor isomer **9′**, since the diagnostic signals of **9′** could not be seen in the ^{1}H NMR spectrum of the mixture **9**/**9′**.

However, the most important feature coming from the last reaction was the possibility to change the configuration at all three newly created stereogenic centers simply by changing the configuration of the phosphonate.

The results obtained in this last reaction (leading to **9** and **9′**) completed the enantioselective synthesis of all possible (*trans*) stereoisomers of the bicyclo[4.3.0]non-2-ene system with the three alkoxy groups located in the five-membered ring (Fig. 3).

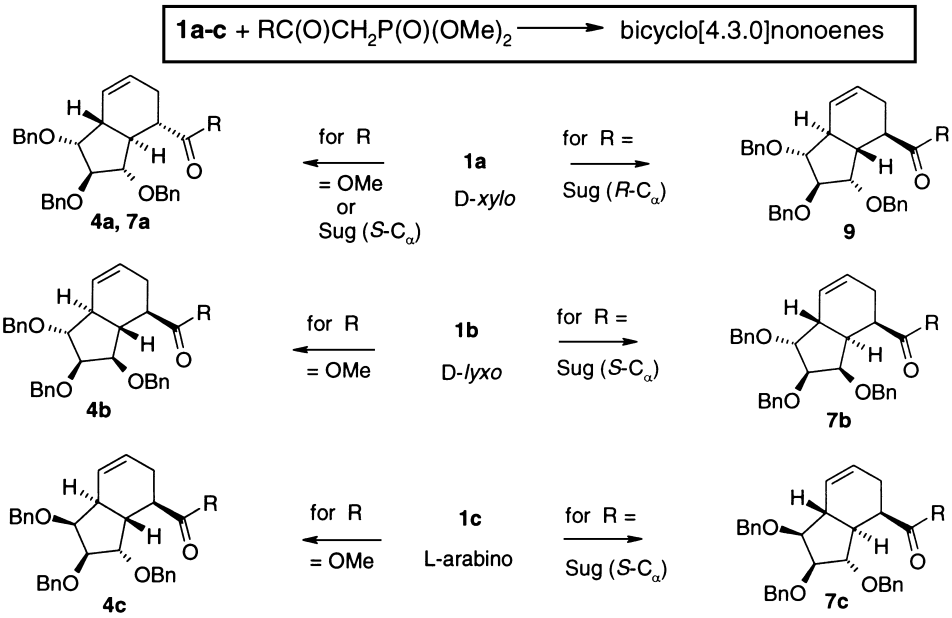


Figure 3. Preparation of stereoisomeric bicyclo[4.3.0]nonenes

3. Conclusion

The efficient method for the preparation of enantiomerically pure, highly oxygenated bicyclo[4.3.0]-nonene derivatives with the *trans* junction between the five- and six-membered rings has been elaborated. The key-step consists of the intramolecular [4+2] cyclization of sugar derived nonatrienes, which are prepared easily from the corresponding dienoaldehydes **1** (obtained by controlled decomposition of sugar allyltins[3b]) and the Wittig-type reagents.

Such trienes with the ester group on the dienophile part are stable and the cyclization must be induced by Lewis acid catalysis.[4] Those with the ketone group (prepared by reaction of **1** with sugar phosphonates) are very reactive and undergo spontaneous cyclization under the conditions of the Wittig–Horner reaction.

The absolute configuration at the three newly created stereogenic centers in the bicyclic products (C1, C5 and C6) can be directed either by the chirality of the 'diene part' (i.e. dienoaldehyde **1**) or the 'external' chirality of the sugar phosphonate used. This 'external' chirality surpasses the chirality of the dienoaldehyde, and manipulation of the configuration of phosphonates allows the *trans* bicyclo[4.3.0]nonene derivatives with the desired stereochemistry at the newly created stereogenic centers to be obtained.

4. Experimental

4.1. General

NMR spectra were recorded with a Bruker AM 500 spectrometer for solutions in $CDCl_3$ (internal Me_4Si, COSY and/or HETCOR and DEPT correlations assigned most of the resonances). The

relative configurations of the protons were determined by NOESY experiments. 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 for 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 sulfate.

4.2. *Reaction of chiral phosphonates with unsaturated aldehydes*

To a solution of aldehyde **1** (1 mmol) in anhydrous toluene (15 mL), appropriate phosphonate (**5** or **8**; 1 mmol) was added followed by potassium carbonate (0.5 g) and 18-crown-6 (ca. 30 mg). The mixture was stirred overnight at room temperature, diluted with ethyl acetate (30 mL), washed with water, dried and concentrated, and the products were isolated by column chromatography (hexane:ethyl acetate, 8:1).

- Reaction of **1a** with **5** afforded **7a** as a single stereoisomer in 80% yield.
- Reaction of **1b** with **5** afforded **7b** as a single stereoisomer in 74% yield.
- Reaction of **1c** with **5** afforded **7c′** (18%) and **7c** (64%) in the ratio 1:3 (NMR).
- Reaction of **1a** with **8** afforded 76% of an inseparable mixture of **9** and **9′** in the ratio 3.5:1 (NMR).

4.2.1. *1(*R*),5(*S*),6(*S*),7(*S*),8(*S*),9(*R*)-7,8,9-Tri-benzyloxy-5-(benzyl 2,3,4-tri-*O*-benzyl-6-ulos-α-D-*manno-*hexo-pyranos-6-yl)bicyclo[4.3.0]non-2-ene* **7a**

$[\alpha]_D$ +12.0; ^{1}H NMR δ: 5.83 (dd, $J_{2,3}$ 10.0, $J_{1,2}$ 1.5, H-2), 5.65 (m, H-3), 4.98 (d, $J_{1',2'}$ 2.1, H-1′), 4.24 (d, $J_{4',5'}$ 8.7, H-5′), 4.15 (dd, $J_{3',4'}$ 8.5, H-4′), 3.93 (dd, $J_{2',3'}$ 2.2, H-3′), 3.88 (d, $J_{8,9}$ 0, $J_{7,8}$ 3.3, H-8), 3.79 (d, $J_{1,9}$ 4.5, H-9), 3.75 (dd, $J_{6,7}$ 9.5, H-7), 3.72 (dd, H-2′), 2.95 (m, H-5), 2.69 (m, H-6), 2.40 (m, H-4a), 2.27 (m, H-1), 2.08 (m, H-4b); ^{13}C NMR δ: 207.0 (C-10), 127.0 and 125.5 (C-2,3), 97.8 (C-1′), 88.8 (double intensity), 80.6, 79.3, 76.2, 75.2 and 74.7 (C-7,8,9,2′,3′,4′,5′), 74.6, 72.6, 72.4, 71.7, 71.2, 70.6 and 69.8 (7×O*C*H$_2$Ph), 49.1, 43.9 and 43.6 (C-1,5,6), 29.6 (C-4); NOEs: H1–H5, H6–H8, H1–H7, H1–H9. MS *m/z*: 999 (M+Na$^+$; 40%). Anal. calcd for $C_{64}H_{64}O_9 \cdot H_2O$ (995.2): C, 77.24; H, 6.69. Found: C, 77.64; H, 6.57.

4.2.2. *1(*R*),5(*S*),6(*S*),7(*R*),8(*S*),9(*R*)-7,8,9-Tri-benzyloxy-5-(benzyl 2,3,4-tri-*O*-benzyl-6-ulos-α-D-*manno-*hexo-pyranos-6-yl)bicyclo[4.3.0]non-2-ene* **7b**

$[\alpha]_D$ +27.4; ^{1}H NMR δ: 5.94 (dd, $J_{2,3}$ 9.8, $J_{1,2}$ 1.3, H-2), 5.56 (m, H-3), 4.82 (d, $J_{1',2'}$ 2.1, H-1′), 4.34 (H-7), 4.01 (H-9), 3.98 (H-8), 3.91 (dd, $J_{2',3'}$ 3.0, $J_{3',4'}$ 9.0, H-3′), 3.73 (dd, H-2′), 3.27 (m, H-5), 2.90 (m, H-1), 2.31 (m, H-4a), 2.22 (m, H-6), 1.98 (m, H-4b); ^{13}C NMR δ: 207.0 (C-10), ∼127.0 and 125.5 (C-2,3), 98.6 (C-1′), 88.9, 82.3, 79.5, 76.4, 74.6, 74.2 and 72.5 (C-7,8,9,′2,3′,4′,5′), 75.0, 73.4, 72.6, 72.3, 71.9, 71.0 and 70.2 (7×O*C*H$_2$Ph), 44.2, 42.4 and 41.8 (C-1,5,6), 29.1 (C-4); NOEs: H1–H5, H5–H4a, H6–H4b, H6–H7, H6–H8, no correlation H1–H6. MS *m/z*: 999 (M+Na$^+$; 26%). Anal. calcd for $C_{64}H_{64}O_9$ (977.2): C, 78.66; H, 6.60. Found: C, 78.88; H, 6.46.

4.2.3. *1(*R*),5(*S*),6(*S*),7(*S*),8(*S*),9(*S*)-7,8,9-Tri-benzyloxy-5-(benzyl 2,3,4-tri-*O*-benzyl-6-ulos-α-D-*manno-*hexo-pyranos-6-yl)bicyclo[4.3.0]non-2-ene* **7c**

$[\alpha]_D$ −18.4; ^{1}H NMR δ: 5.91 (dd, $J_{2,3}$ 9.8, $J_{1,2}$ 1.6, H-2), 5.58 (m, H-3), 4.97 (d, $J_{1',2'}$ 2.4, H-1′), 3.90 (dd, $J_{7,8}$ 2.3, $J_{8,9}$ 6.2, H-8), 3.82 (dd, $J_{6,7}$ 9.3, H-7), 3.73 (dd, $J_{2',3'}$ 2.6, H-2′), 3.57 (dd, $J_{1,9}$

11.2, H-9), 2.95 (m, H-5), 2.55 (m, H-1), 2.29 (m, H-4a), 2.08 (m, H-4b), 1.88 (m, H-6); ^{13}C NMR δ: 207.0 (C-10), ~127.0 (C-2,3), 98.3 (C-1′), 87.3 (C-7), 81.4 (C-8), 81.0 (C-9), 79.4, 76.0, 74.9 (C-2′) and 74.7, 75.7, 72.7, 72.6, 72.4, 72.1, 71.8 and 70.1 (7×O*C*H$_2$Ph), 48.0 (C-5), 44.0 (C-6), 43.6 (C-1), 30.3 (C-4); H1–H5, H5–H7, H1–H7, H6–H8, H6–H9. MS *m*/*z*: 999 (M+Na$^+$). Anal. calcd for $C_{64}H_{64}O_9$ (977.2): C, 78.66; H, 6.60. Found: C, 78.50; H, 6.60.

*4.2.4. 1(*R*),5(*S*),6(*R*),7(*S*),8(*S*),9(*R*)-7,8,9-Tri-benzyloxy-5-(benzyl 2,3,4-tri-*O*-benzyl-6-ulos-α-D-*manno-*hexo-pyranos-6-yl)bicyclo[4.3.0]non-2-ene* ***7c′***

[α]$_D$ +24.6; ^{1}H NMR δ: 5.89 (dd, $J_{2,3}$ 9.9, $J_{1,2}$ 2.0, H-2), 5.64 (m, H-3), 4.85 (d, $J_{1',2'}$ 2.2, H-1′), 4.13 (dd, $J_{1,9}$ 1.5, $J_{8,9}$ 5.0, H-9), 3.98 (dd, $J_{7,8}$ 2.0, $J_{6,7}$ 6.7, H-7), 3.84 (dd, H-8), 3.69 (dd, $J_{2',3'}$ 2.5, H-2′), 3.21 (m, $J_{4,5}$ 5.6 and 11.1, $J_{5,6}$ 11.3, H-5), 2.75 (m, $J_{1,6}$ ~11.5, H-6), 2.46 (m, H-4a), 2.42 (m, H-1), 2.15 (m, H-4b); ^{13}C NMR δ: 208.3 (C-10), ~128 (C-3), 126.5 (C-2), 97.5 (C-1′), 88.7 (C-3′), 82.6 (C-7), 79.5 (C-8), 78.0 (C-9), 74.9 (C-4′), 74.8 (C-2′), 73.2 (C-5′), 75.7, 74.7, 72.6, 72.2, 71.6, 71.2 and 69.2 (7×O*C*H$_2$Ph), 44.9 (C-5), 44.1 (C-1), 43.6 (C-6), 30.2 (C-4); NOEs: H1–H5, H1–H9, H6–H7. MS *m*/*z*: 999 (M+Na$^+$). Anal. calcd for $C_{64}H_{64}O_9$ (977.2): C, 78.66; H, 6.60. Found: C, 78.33; H, 6.51.

*4.2.5. 1(*R*),5(*S*),6(*R*),7(*S*),8(*S*),9(*R*)-7,8,9-Tri-benzyloxy-5-(1,2-*O*-isopropylidene-D-*glycero-*3-ulos-3-yl)bicyclo[4.3.0]non-2-ene* ***9*** *(and its stereoisomer* ***9′****)*

MS *m*/*z* (for the mixture): 591.2714 [$C_{36}H_{40}O_6Na$ (M+Na$^+$) requires: 591.2723]. Main isomer **9**: ^{1}H NMR δ: 5.96 (dd, $J_{2,3}$ 9.8, $J_{1,2}$ 1.5, H-2), 5.61 (m, H-3), 4.47 (dd, $J_{11,12}$ 6.5, $J_{11,12'}$ 7.6, H-11), 4.07 (dd, $J_{12,12'}$ 8.5, H-12), 3.97 (m, H-7,8), 3.84 (dd, H-12′), 3.65 (dd, $J_{1,9}$ 10.5, $J_{8,9}$ 3.8, H-9), 3.40 (m, H-5), 2.75 (m, H-1), 2.60 (m, H-4a), 2.06 (m, H-6), 2.00 (m, H-4b), 1.33 and 1.30 (CMe$_2$); ^{13}C NMR δ: 212.1 (C-10), 128.1 (C-2), 126.2 (C-3), 111.0 (*C*Me$_2$), 89.6 (C-7), 88.6 (C-9), 81.0 (C-8), 79.9 (C-11), 72.3, 71.7 and 70.7 (3×O*C*H$_2$Ph), 66.0 (C-12), 43.7 (C-1), 42.7 (C-6), 42.6 (C-5), 29.5 (C-4), 25.8 and 25.3 (C*Me*$_2$).

Minor isomer **9′**: ^{1}H NMR δ: 5.85 (d, $J_{2,3}$ 10.1, $J_{1,2}$ ~0, H-2), 5.77 (m, H-3), 4.32 (dd, $J_{11,12}$ 7.5, $J_{11,12'}$ 5.8, H-11), 3.95 (H-12,12′), 3.91 (m, H-7,9), 3.84 (H-9), 3.40 (m, H-5), 2.54 (m, H-4a), 2.41 (m, H-1,6), 2.04 (m, H-4b), 1.39 and 1.32 (CMe$_2$); ^{13}C NMR δ: 212.0 (C-10), 128.1 (C-3), 125.2 (C-2), 110.5 (*C*Me$_2$), 89.3 (C-7), 88.2 (C-9), 80.8 (C-8), 80.5 (C-11), 71.9, 71.1 and 70.9 (3×O*C*H$_2$Ph), 65.9 (C-12), 45.5 and 43.7 (C-1,6), 44.8 (C-5), 28.3 (C-4), 26.1 and 25.2 (C*Me*$_2$).

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