Palladium−Cobalt-Mediated Double Annulation Process: A New Strategy to Chiral and Polysubstituted Bis-Cyclopentanoids on Carbohydrate Precursors

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The iodohydrins **2**, **4**, and **5** were prepared by the ring opening of benzyl 2-*O*-*p*-tosyl-3,4-anhydro-β-L-arabinopyranoside (**1**) or benzyl 2,3-anhydro-4-*O*-acetyl-α-D-ribopyranoside (**3**), respectively, using sodium acetate, sodium iodide, and acetic acid in acetone which on treatment with $POCl_3$ in pyridine yielded the unsaturated sugars **6** and **7**. After deacetylation of **7** with $MeOH/H_2O/Et_3N$ (3:2:1) and treatment of **8** with tosyl chloride/pyridine at 50 °C **9** was obtained. The reaction of benzyl 2-*O*-p-tosyl-3,4-dideoxy-α-D-*glycero*-pent-3-enopyranoside (**6**) and benzyl 2,3,4-trideoxy-4-chloro-β-L-*glycero*-pent-2-enopyranoside (**9**) with the sodium enolate of dimethyl propargylmalonate in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) afforded the branched-chain sugars **10** and **11**. The isomer **10** was obtained as a minor product from **6** with retention of configuration around C-2, and the major isomer **11** as a result of allylic rearrangement in a ratio of 1:9. On the other hand, compound **9** afforded **10** as a major product and its regioisomer **11** as a minor product in a ratio of 8:2; formation of the above mentioned isomeric mixture involves cis and trans diastereomeric intermediates during the reaction. Treatment of these precursors with $Co_2(CO)_8$ in benzene followed by oxidative decomplexation with DMSO yielded in a stereoselective manner the polysubstituted bis-cyclopentanoids **12** and **13**. The stereochemistry of **13** was assigned with the help of X-ray analysis. Attempts were made to prepare the tetracyclic systems **15** and **17** using **12** and **13** with 3-acetoxy-2-[(trimethylsilyl)methyl]-1-propene (**14**); however, the alkylation products **16** and **18** were obtained.

Introduction

Bis-cyclopentanoid rings of rich stereochemical functionality are key intermediates for the synthesis of pharmacologically interesting prostaglandin analogs[1] and are important substructural units of a wide variety of natural products, particularly polyquinanes[2] which were shown to possess significant biological activities ranging from simple antibiotic action to antitumor properties.[3] Much work has been invested for accessing these synthons.[4] Of special importance are the syntheses described by Fraser-Reid and co-workers,[4d−f] taking advantage of carbohydrate topology. In the last two decades, increased attention has been devoted to the organometallic-catalyzed functionalization and cyclization of enyne systems.[5] Of particular importance is the chemoselective alkylation of an allylic function by Pd-catalyzed cycloisomerization reactions[6] or the cobalt-mediated cyclization (Pauson−Khand reaction)[7] of 1,6-enynes. This heightened interest is based primarily upon the unusual selectivity and reactivity associated with such reactions which is not found in their classical organic reaction counterparts.

Carbohydrates constitute an abundant and relatively inexpensive source of chiral carbon compounds, and they are readily available with a variety of functional, stereochemical, and conformational features. Through chemical manipulation, these compounds can be transformed into versatile synthetic intermediates, that bear functional groups and chiral centers of a predetermined nature and are amenable to elaboration into the structural framework of many natural products. In this regard, studies in this laboratory have been engaged with the development of new methods for the efficient and economic synthesis of long-chain sugars,[8a] dihydro-[8b] and tetrahydrofurans,[8c,d] and γ-lactones,[8e] derived from car-

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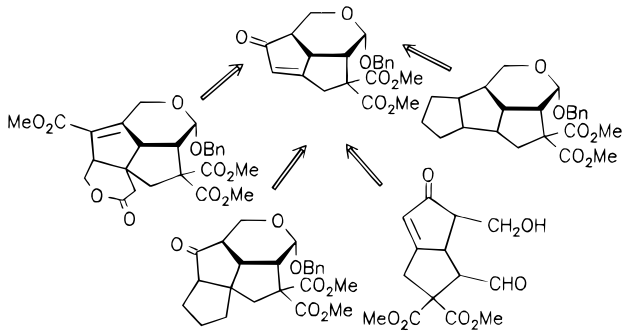
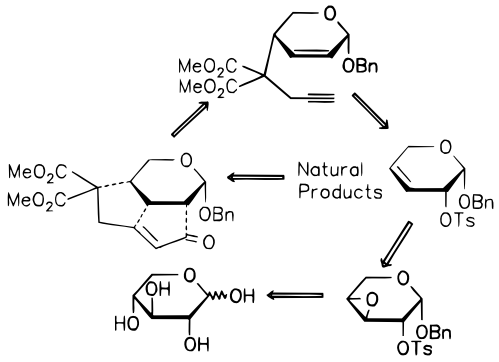


Figure 1. Polysubstituted bis-cyclopentanoids on carbohydrate precursors, synthons to differently configurated triquinane and prostacyclin skeletons.

Scheme 1

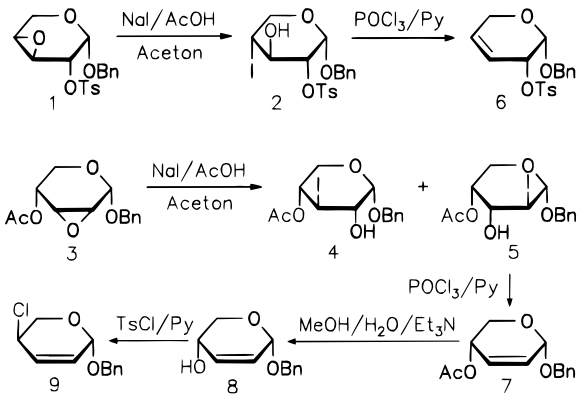


bohydrate templates. Recently, we have communicated preliminary results of a study[9] disclosing the potential applicability of palladium−cobalt organometallic annulation of carbohydrates. The present paper describes full details of our work that includes additional results elaborated on our chiral templates that can be further manipulated to different configured triquinanes and prostacyclin skeleta outlined in Figure 1. An advantage of our approach is that the stereochemical features of our synthons could be established unequivocally by subtle changes in the location and the stereochemistry of the allylic function in **6** and **9** and also by taking advantage of the conformational preference of the product as a result of the anomeric effect. The retrosynthetic analysis of our approach to the bis-cyclopentanoid systems shows the inherent simplicity of this strategy (Scheme 1).

Results and Discussion

Synthesis of Unsaturated Sugars. The starting sugars **6** and **9**, needed for the present study, were prepared from easily accessible benzyl 2-*O*-*p*-tosyl-3,4-anhydro-*β*-L-arabinopyranoside (**1**) and benzyl 2,3-anhydro-4-*O*-acetyl-α-D-ribopyranoside (**3**), respectively.[10,11] The first step proceeds via epoxide ring opening of **1** and **3**. When **1** was refluxed with sodium acetate, sodium iodide and acetic acid in acetone for 4−5 h,[11] the iodohydrin **2** was obtained as a single product adopting the $^4C_1$ conformation. The ^{1}H NMR spectrum shows two diaxial relationships between H-2/3 and H-3/4 with coupling constants $J_{2,3}$ = 9.4 Hz and $J_{3,4}$ = 10.5 Hz and one equatorial−axial relationship between H-1/2 with a small

Scheme 2



coupling of 3.6 Hz. In contrast, ring opening of **3** gave two products (**4** and **5**) in a ratio of 8:2 in 96% combined yield resulting from the nucleophilic attack at C-3 and C-2. The adoption of $^4C_1$ and $^1C_4$ conformations for the iodohydrins **4** and **5**, respectively, is concluded from the coupling constants between H-1 and H-2 in their ^{1}H NMR spectra. The iodohydrin **4** shows an equatorial−axial relationship between H-1 and H-2 with a coupling of 3.6 Hz and a diaxial relationship between H-2/3 and H-3/4 ($J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 10.8 Hz). On the other hand in iodohydrin **5**, a diaxial relationship between H-1/2 and H-2/3 with large couplings ($J_{1,2}$ = 7.7 Hz, $J_{2,3}$ = 9.7 Hz) and a small axial−equatorial coupling between H-3/4 ($J_{3,4}$ = 3.4 Hz) confirms adoption of the $^1C_4$ conformation. For formation of the olefinic sugars **6** and **7**, the MsCl/pyridine and TsCl/pyridine methods[12] were employed, but no satisfactory results were obtained. However, if the iodohydrin **2** and the mixture of **4** and **5** were treated with $POCl_3$ in pyridine at −40 °C,[11] the unsaturated sugars **6** and **7** were isolated in 70% and 55% yield, respectively. After deacetylation of **7** with a mixture of MeOH/H_2O/Et_3N (3:2:1),[13] the allyl alcohol **8** was obtained in quantitative yield. On treatment with tosyl chloride/pyridine at 50 °C this gave the 4-chloro compound **9** rather than the tosyl derivative, since the chloride ions formed during the reaction displace the highly reactive allylic sulfonate group in *situ*[13] (Scheme 2).

Design for the Synthesis of Long-Chain Sugars Using a Pd(0) Catalyst. In searching for a mild and chemoselective approach to C−C bond formation by the substitution of a vinylic C−H bond, we turned to the use of a palladation reaction for the activation step[14−17] and subsequent treatment with a nucleophile for the substitution step.[16a,17,18] Thus, alkylation of the olefinic sugars **6** and **9** involves the treatment of **6** with the sodium enolate of dimethyl propargylmalonate in refluxing THF in the presence of tetrakis(triphenylphosphine)palladium-

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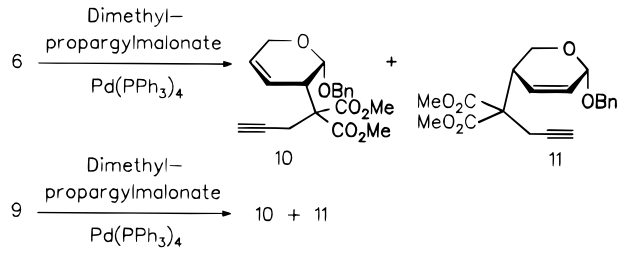
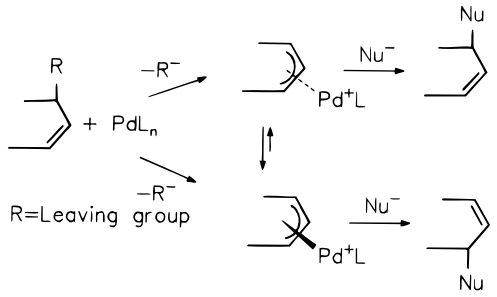
Scheme 3



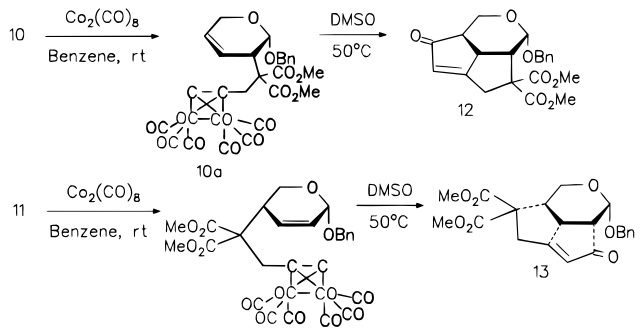
Scheme 4



(0) and triphenylphosphine,[19] leading to a mixture of the regioisomers **10** and **11** in a ratio of 1:9 in 92% combined yield (Scheme 3). When a similar palladium-catalyzed alkylation was performed with **7**, there was very little conversion; but interestingly, if **9** was treated with the sodium enolate of dimethyl propargylmalonate at 0 °C under these conditions the same mixture of the branched-chain sugars **10** and **11** was obtained in a ratio of 8:2 in 79% combined yield (Scheme 3). The regiochemical results observed for **10** and **11** can be understood by considering the mechanism of allylic alkylation[5a,20] according to Scheme 4, in which the cis and trans diastereomeric intermediates (palladium π-allyl complexes) are formed from the olefin in an activation step and then during the substitution step a new carbon−carbon bond can be formed at C(a) or C(b) either with retention of the olefin at its original position or with allyl rearrangement (overall inversion), resulting in the formation of the diastereomeric mixture (III and IV). The ratio of **10** and **11** from **6** or **9** indicates that, upon establishment of an equilibrium, the amount of the isomer IV exceeds that of the isomer III. Compounds **10** and **11** show characteristic chemical shifts and coupling constants for the olefinic proton that resonate in the δ 6.0−5.7 region having long vinylic couplings, $J_{3,4} = 10.2$ Hz and $J_{2,3} = 10.5$ Hz, respectively. The anomeric proton in **10** produced a triplet at δ 4.78 with a coupling constant of 2.6 Hz, while the ^{1}H NMR spectrum of **11** shows a doublet for the anomeric proton at δ 4.86 with a very weak allylic coupling of $J_{1,2} = 0.9$ Hz. Additional features of interest in **10** and **11** are small long-range couplings ($J = 2.7$ Hz) from the alkyne protons to the propargylic methylene protons.

Cobalt-Mediated Cyclopentannulation Process. The Pauson-Khand reaction[21] is a convenient synthetic route to bicyclic systems derived from 1,6-enynes, mediated by octacarbonyldicobalt. This increasingly popular organometallic process has been the subject of numerous studies and investigations by a number of groups.[22] Our own interests have focused on the observed stereoselectivity with respect to both, allylic and propargylic substituents. Here we report its application to the construction of bicyclic systems on sugar templates. On the basis of mechanistic hypothesis it can be reasonably predicted that the substrates **10** and **11** on treatment with octacarbonyldicobalt will form the hexacarbonyldicobalt complexes (**10a** and **11a**) by coordination of the acetylenic function followed by oxidative addition of the cyclic double bond which upon carbonylative insertion and oxidative decomplexation results in the bicyclopentanoid systems.[23] Therefore, the propargyl derivatives **10** and **11**, after reaction with $Co_2(CO)_8$ in benzene at rt, were converted quantitatively into the corresponding hexacarbonyldicobalt complexes **10a** and **11a** as red oils which upon heating to 50 °C with DMSO[24] afforded the tricyclic products **12** and **13** in 75% and 77% yield, respectively (Scheme 5). The ^{1}H NMR spectra show vinylic signals at δ 5.95 and 5.94 for **12** and **13**, respectively, and deshielded signals (δ 3.27 and 2.9) for the ring-fusion proton (H-4 in **12** and H-2 in **13**) adjacent to the keto function. The ^{1}H NMR spectra also give evidence that the carbonylative acetylenic insertion takes place from the same side as the propargylic moiety[25] (**12**: $J_{1,2} = 3.4$, $J_{2,3} = 7.1$, $J_{3,4} = 7.6$ Hz; **13**: $J_{1,2} = 7.9$, $J_{2,3} = 7.3$, $J_{3,4} = 6.6$ Hz). The absolute stereochemistry of the cis-fused cyclopentanoids was unambiguously assigned with the help of X-ray analysis for compound **13**. The X-ray structure analysis of compound **13** revealed no significant differences in the refinement between the model (R values $R1 = 0.0307$, $wR2 = 0.0797$, Flack parameter 0.05 with an esd of 0.77) and its inverse ($R1 = 0.0322$, $wR2 = 0.081$, Flack parameter 1.3 with an esd of 0.8). The first model above, however, is in agreement with the synthesis from known components. A graphic representation of the

Scheme 5



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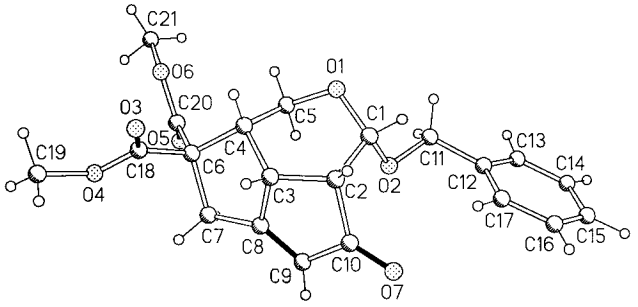
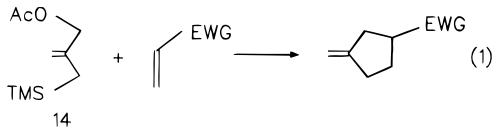


Figure 2. Perspective plot of compound **13** along with the atomic numbering scheme. Double bonds are shown in black with filled lines.

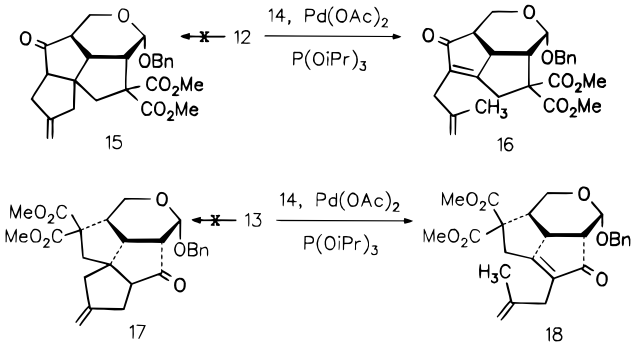
molecule is shown in Figure 2. The six-membered ring (O1, C1, C2, C3, C4, C5) with the calculated parameters of pucker $Q = 0.524$ A , $\Theta = 38.0°$ and $\Phi = 318.7°$ has a conformation midway between chair $^1C_4$ ($\Theta = 0$) and half-chair $^1H_6$ ($\Theta = 50-8$, $\Phi = 330°$). The endocyclic torsion angles in the sequence O1 to C5 are −55.4, 25.1, −16.1, 32.3, −57.4, and 73.6. There are no zero angles, but the small angle of −16.1 corresponds to that expected to be zero for the half-chair conformation $^1H_6$. The substituents O2, C10, C8, and C6 are in axial, bisectional, axial, and equatorial positions, respectively. The five-membered cyclopentenone ring (C2, C3, C8, C9, C10) exhibits an envelope conformation with the atom C2 being 36 pm outside the plane. The five-membered ring formed by the atoms C3, C4, C6, C7 and C8 is in a half-chair conformation confirmed by the calculated puckering parameter $\Phi = 201.5°$.

Implementation of the Pd-Catalyzed Cycloaddition Protocol. The following studies establish the feasibility of fusing a cyclopentane ring laterally to the bicyclic enone systems **12** and **13**.[26] During the past decade a large number of methods have been developed[27] for cyclopentane annulations. One of the more direct methods for this task is the palladium(II)-mediated [3 + 2] cycloaddition of 3-acetoxy-2-[(trimethyllsilyl)methyl]-1-propene (**14**)[28] to enone systems. B. M. Trost et al.[29−31] have explored the cycloaddition of **14** according to eq 1



as a general route for methylenecyclopentane formation. However, when **12** was treated with **14** in the presence of palladium(II) acetate and triisopropyl phosphite in refluxing THF,[32] unexpectedly the alkylation product **16**[28,33] was obtained instead of **15** in 30% yield with 60% recovery of the starting material (Scheme 6). Similar

Scheme 6



results were obtained with compound **13**. Variations in solvents (e.g. THF, toluene, dichloromethane),[33] catalysts (tetrakis(triphenylphosphine)palladium(0) and dibenzylideneacetone−palladium(0)−chloroform complex)[34] and ligands (triethyl phosphite, triphenyl phosphine)[34] and use of a catalytic amount of *n*-BuLi[35] gave almost the same results. Also, the reactions with 2-(chloromethyl)-3-(trimethylsilyl)propene[36] and $TiCl_4$ in CH_2Cl_2 did not lead to the expected tetracyclic systems **15** and **17**. Probably, alkylation products **16** and **18**, involving enolate formation, compete with the cycloaddition products **15** and **17**, or electron-transfer processes (e.g., oxidation of the Pd catalyst) in these cases disrupt the cycloaddition.[37,33,28]

Although the cyclopentation was not successful with the above mentioned reagents and conditions, there are a number of other reagents and methods reported in the literature[26−27,29a,38] which can be employed for cyclopentannulation on our bis-cyclopentanoid systems.

Summary

In summary, the palladium-catalyzed functionalization of the tosylate **6** and chloride **9** has proved to be a useful method for the preparation of the unsaturated branched-chain sugars **10** and **11**. These enyne precursors were successfully used for the regio- and stereoselective syntheses of bis-cyclopentanoids on sugar templates by the intramolecular Pauson−Khand cycloaddition reaction. The development of further useful conversions to natural products based upon these synthons is the object of ongoing studies in our laboratories.

Experimental Section

General Methods and Materials. All crystallographic investigations were performed on an automated four-circle single crystal diffractometer CAD4-T (ENRAF-NONIUS, Delft, NL) with graphite-monochromated Mo Kα radiation at low temperatures 211 K. The compound **13** crystallizes in the orthorhombic space group $P2_12_12_1$ with the lattice parameters $a = 879.5(1)$, $b = 1005.6(1)$, and $c = 2124.0(1)$ pm, $V = 1.8785(3)$ nm^3, and $Z = 4$. Calculations were performed with the programs CADSHEL,[39] SIR92,[40] SHEXL-93,[41] SHELXTL-PLUS,[42] and PLATON-95.[43] The authors have deposited all

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crystallographic data for compound **13** with the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen. These data can be obtained, on request, by quoting the names of authors, journal, and the deposit number CSD-401655. NMR spectra were obtained with the indicated solvents and chemical shifts are given in ppm on the δ scale from internal tetramethylsilane. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60 F-254, E. Merck, Darmstadt, Germany). Plates were visualized under UV light (where appropriate), sprayed with an orcinol/H_2SO_4 solution, and heated to develop. Preparative thin-layer chromatography was performed on 0.5 × 20 × 20 silica gel plates (60 F-254, E. Merck). Column chromatography was performed by using silica gel 60 (70−230 mesh ASTM, Merck). THF was distilled from sodium benzophenone and $POCl_3$ from calcium hydride under nitrogen. The reagent 3-acetoxy-2-[(trimethyllsilyl)-methyl]-1-propene was prepared according to the procedure given in reference 28. All other reagents were used as received.

Benzyl 2-*O*-p-tosyl-4-iodo-4-deoxy-α-D-xylopyranoside (2). Benzyl 2-*O*-*p*-tosyl-3,4-anhydro-β-L-arabinopyranoside (**1**) (3.24 g, 8.61 mmol) was dissolved in 130 mL of acetone and sodium iodide (5.16 g, 4 equiv, 34.4 mmol), sodium acetate (0.64 g, 0.9 equiv, 7.8 mmol), and 19.4 mL of acetic acid were added, and the reaction mixture was refluxed for 4−5 h. After cooling, the solvent was evaporated and acetic acid was removed by adding toluene. The syrup was dissolved in dichloromethane and washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$ solution, and finally water. The residue was dried (Na_2SO_4) and solvent removed by distillation under reduced pressure to give a solid product which was recrystallized from ethyl acetate and *n*-hexane to give 4.1 g (95%) of **2**: Mp 168−170 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.75 (br d, 2 H, J = 8.3 Hz), 7.32 (m, 5 H), 7.27 (br d, 2 H, J = 8.4 Hz), 5.40 (d, 1 H, J = 3.6 Hz), 4.70 (d, 1 H, J = 12.0 Hz), 4.43 (d, 1 H, J = 12.0 Hz), 4.30 (dd, 1 H, J = 9.2, 3.6 Hz), 4.13 (ddd, 1 H, J = 9.4, 3.2 Hz), 3.98 (dd, 1 H, J = 10.5, 5.2 Hz), 3.88 (dd, 1 H, J = 10.0, 4.7 Hz), 3.72 (t, 1 H, J = 10.0 Hz), 2.67 (d, 1 H, J = 3.4 Hz), 2.43 (s, 3 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 145.2, 137.1, 134.0, 129.9, 128.5−127.8, 96.4, 79.2, 71.6, 69.9, 64.0, 27.2, 21.7; $[\alpha]^{20}_D$ +34.1° (*c* 1.73, $CHCl_3$); MS (FD) m/z = 504.7 (M^+). Anal. Calcd for $C_{19}H_{21}IO_6S$ (504.34): C, 45.25; H, 4.20; I, 25.16; S, 6.36. Found: C, 44.77; H, 4.37; I, 24.61; S, 6.49.

Benzyl 3-Iodo-3-deoxy-4-*O*-acetyl-α-D-xylopyranoside (4) and Benzyl 2-iodo-2-deoxy-4-*O*-acetyl-α-D-arabinopyranoside (5). Using the procedure for **2**, compound **3** (4 g, 15.13 mmol) in 163 mL of acetone, sodium iodide (9.07 g, 4 equiv, 60.5 mmol), sodium acetate (1.1 g, 0.9 equiv, 13.6 mmol), and 13 mL of acetic acid afforded a mixture of the solid products **4** and **5**. A 3.8 g amount of **4** was recrystallized from ether and *n*-hexane, and the rest of the mixture of **4** and **5** was separated by column chromatography using petroleum ether to 5% ethyl acetate/petroleum ether to give 1 g (total in 81% yield) of **4** and 0.9 g (15%) of **5**. Compound **4**: Mp 87−89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.16 (m, 5 H), 4.92 (ddd, 1 H, J = 10.5, 5.5 Hz), 4.70 (d, 1 H, J = 3.6 Hz), 4.62 (d, 1 H, J = 11.7 Hz), 4.38 (d, 1 H, J = 11.6 Hz), 4.30 (t, 1 H, J = 10.8 Hz), 3.66 (ddd, 1 H, J = 10.4, 3.6 Hz), 3.54 (dd, 1 H, J = 10.7, 5.4 Hz), 3.39 (t, 1 H, J = 10.5 Hz), 2.24 (d, 1 H, J = 9.7 Hz), 1.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 136.5, 128.4−128.0, 96.4, 73.4, 71.7, 69.7, 60.1, 33.4, 20.8; $[\alpha]^{20}_D$ +100.2° (*c* 1.93, $CHCl_3$); MS (FD) m/z = 392.3 (M^+). Anal. Calcd for $C_{14}H_{17}IO_5$ (392.19): C, 42.87; H, 4.37; I, 32.36. Found: C, 43.13; H, 4.38; I, 32.30. Compound **5**: Mp 126−128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.24 (m, 5 H), 5.50 (dd, 1 H, J = 3.2, 2.0 Hz), 4.83 (d, 1 H, J = 11.7 Hz), 4.58 (d, 1 H, J = 11.4 Hz), 4.56 (d, 1 H, J = 7.7 Hz), 4.08 (dd, 1 H, J = 7.7, 9.7 Hz), 4.04 (dd, 1 H, J = 13.1, 3.6 Hz), 3.86 (dd, 1 H, J = 9.7, 3.4 Hz), 3.56 (dd, 1 H, J = 13.1, 1.8 Hz), 2.67 (br s, 1 H), 2.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 136.5, 128.4−128.0, 101.6, 73.1, 71.1, 69.3, 63.3, 33.1, 20.9; $[\alpha]^{20}_D$ +30.6° (*c* 1.0, $CHCl_3$); MS (FD) m/z = 392.3 (M^+). Anal. Calcd for $C_{14}H_{17}IO_5$ (392.19): C, 42.87; H, 4.37; I 32.36. Found: C, 42.29; H, 4.32; I, 32.34.

Benzyl 2-*O*-*p*-Tosyl-3,4-dideoxy-α-D-*glycero*-pent-3-enopyranoside (6). Compound **2** (2.3 g, 6.2 mmol) was dissolved in 20 mL of absolute pyridine and cooled at −40 °C. Freshly distilled $POCl_3$ (2 mL, 3.5 equiv, 21.6 mmol) was added dropwise with stirring, and the mixture was further stirred for 3−4 h at 0 °C. The reaction mixture was added to 300 mL of ice−water and stirred for 45 min. The hydrolyzed product was extracted with dichloromethane, and the organic phase was washed with saturated $Na_2S_2O_3$ solution and water. The residue was dried (Na_2SO_4) and filtered and solvent removed by distillation under reduced pressure to give a syrup which was purified by column chromatography using 60% petroleum ether/CH_2Cl_2 to CH_2Cl_2 to give 1.12 g (70%) product. Oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (br d, 2 H, J = 8.3 Hz), 7.30−7.21 (m, 5 H), 7.16 (br d, 1 H, J = 7.9 Hz), 5.84 (dq, 1 H, J = 10.5, 2.4 Hz), 5.54 (dm, 1 H, J = 10.5 Hz), 4.92 (br dd, 1 H, J = 3.8, 2.5 Hz), 4.78 (d, 1 H, J = 3.8 Hz), 4.65 (d, 1 H, J = 12.1 Hz), 4.40 (d, 1 H, J = 12.1 Hz), 4.12 (dq, 1 H, J = 14.6, 2.5 Hz), 3.93 (dq, 1 H, J = 14.3, 2.6 Hz), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 137.0, 130.2, 129.7−127.8, 121.1, 93.7, 72.1, 70.0, 60.3, 21.6, $[\alpha]^{20}_D$ +81.3° (*c* 4.0, $CHCl_3$); MS (FD) m/z = 361.1 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{20}O_5S$ (360.43): C, 63.32; H, 5.60; S, 8.90. Found: C, 63.0; H, 5.64; S, 8.43.

Benzyl 2,3-Dideoxy-4-*O*-acetyl-α-D-*glycero*-pent-2-enopyranoside (7). Using the procedure for **6**, the mixture of **4** and **5** (5 g, 12.8 mmol) in 40 mL of absolute pyridine and $POCl_3$ (4.1 mL, 3.5 equiv, 44.6 mmol) afforded a syrup which was purified by column chromatography using *n*-hexane to 5% CH_2Cl_2/*n*-hexane to give 1.74 g (55%) of **7**. Oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.30−7.20 (m, 5 H), 5.87 (dt, 1 H, J = 10.4, 1.1 Hz), 5.80 (dt, 1 H, J = 10.3, 2.0 Hz), 5.25 (m, 1 H), 4.95 (br s, 1 H), 4.75 (d, 1 H, J = 11.8 Hz), 4.50 (d, 1 H, J = 11.8 Hz), 3.84 (dd, 1 H, J = 11.3, 6.1 Hz), 3.75 (dd, 1 H, J = 11.0, 7.8 Hz), 2.0 (s, 3 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 129.1, 128.5, 128.0, 127.8, 93.3, 70.0, 65.1, 60.1, 21.0; $[\alpha]^{20}_D$ +100.7° (*c* 1.20, $CHCl_3$); MS (FD) m/z = 248.6 (M^+). Anal. Calcd for $C_{14}H_{16}O_4$ (248.28): C, 67.73; H, 6.50. Found: C, 67.19; H, 6.69.

Benzyl 2,3-Dideoxy-α-D-*glycero*-pent-2-enopyranoside (8). Compound **7** (1.5 g, 6.04 mmol) in 18 mL of methanol/water/triethylamine (3:2:1) was stirred at rt for 4 h. The solvent was carefully evaporated at rt. The residue was dissolved in dichloromethane, washed with water. The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated to give 1.24 g product in quantitative yield. Oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.30−7.20 (m, 5 H), 5.92 (dt, 1 H, J = 10.3, 1.2 Hz), 5.67 (dt, 1 H, J = 10.3, 2.2 Hz), 4.92 (br t, 1 H, J = 1.2 Hz), 4.74 (d, 1 H, J = 11.7 Hz), 4.50 (d, 1 H, J = 11.8 Hz), 4.15 (m, 1 H), 3.70 (dd, 1 H, J = 11.0, 5.5 Hz), 3.60 (dd, 1 H, J = 11.0, 8.3 Hz), 2.3 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 137.6, 133.3, 128.5, 128.1−127.4, 93.5, 70.0, 63.6, 63.1; $[\alpha]^{20}_D$ +74.6° (*c* 0.73, $CHCl_3$); MS (FD) m/z = 205.7 (M^+). Anal. Calcd for $C_{12}H_{14}O_3$ (206.24): C, 69.88; H, 6.84. Found: C, 69.69; H, 6.80.

Benzyl 2,3,4-Trideoxy-4-chloro-β-L-*glycero*-pent-2-enopyranoside (9). Compound **8** (1.1 g, 5.34 mmol) was dissolved in 10 mL of absolute pyridine, and *p*-toluenesulfonyl chloride (1.53 g, 1.5 equiv, 8.0 mmol) was added portionwise. The resulting mixture was stirred at 50 °C for 3−4 h and cooled to rt, and ice−water was added. The product was extracted with dichloromethane and washed with a 2 N HCl solution, a saturated $NaHCO_3$ solution, and finally water. The residue was dried (Na_2SO_4) and filtered and solvent removed by distilation under reduced pressure. The rest of the pyridine was evaporated by adding toluene which gave 1.12 g (94%) of a crystalline product. Mp 75−78 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.30−7.20 (m, 5 H), 6.50 (ddd, 1 H, J = 11.1, 1.2 Hz), 5.85 (dd, 1 H, J = 10.5, 3.1 Hz), 5.06 (dd, 1 H, J = 3.0, 0.9 Hz), 4.74 (d, 1 H, J = 11.7 Hz), 4.50 (d, 1 H, J = 11.7 Hz), 4.30

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(dd, 1 H, J = 12.5, 2.9 Hz), 4.23 (m, 1 H), 3.60 (dd, 1 H, J = 12.7, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 137.2, 128.5, 128.2, 128.1−127.9, 92.2, 69.9, 63.7, 49.9; $[\alpha]^{20}_D$ +207.8° (*c* 0.86 , $CHCl_3$); MS (FD) m/z = 224.2 (M^+). Anal. Calcd for $C_{12}H_{13}ClO_2$ (224.68): C, 64.15; H, 5.83; Cl, 15.78. Found: C, 63.96; H, 5.90; Cl, 14.37.

Propanedioic Acid, [2-(Benzyloxy)-2,3-dihydro-6*H*-pyran-3-yl]-2-propynyl-Dimethyl Ester (10). Benzyl 2,3,4-trideoxy-4-chloro-*β*-L-*glycero*-pent-2-enopyranoside (**9**) (1 g, 4.5 mmol), triphenylphosphine (29.3 mg, 2.5 mol %) and tetrakis-(triphenylphosphine)palladium (129 mg, 2.5 mol %) were dissolved in 10 mL of THF and stirred at 0 °C for 20 min under argon. In another flask, to a suspension of NaH (178.6 mg, 60% dispersion, 1 equiv, 4.5 mmol) in 10 mL of THF, dimethyl propargylmalonate (neat, 0.68 mL, 1 equiv, 4.5 mmol) was added dropwise under argon at 0 °C and the reaction mixture stirred for 20 min at the same temperature. The first solution was added to the second one via a double-ended needle, and the reaction mixture was stirred at 0 °C for 1 h. After completion of the reaction (TLC analysis), the solvent was evaporated, and the mixture of **10** and **11** was column chromatographed, eluting first with 5% CH_2Cl_2/petroleum ether followed by 40% CH_2Cl_2/petroleum ether to afford 1.07 g (67%) of **10** and 0.19 g (12%) of **11**. Compound **10**: Oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.25 (m, 5 H), 6.06 (br dd, 1 H, J = 10.2, 5.5 Hz), 5.85 (dq, 1 H, J = 10.2, 4.2 Hz), 4.78 (br d, 1 H, J = 2.6 Hz), 4.68 (d, 1 H, J = 11.8 Hz), 4.44 (d, 1 H, J = 11.8 Hz), 4.10 (dd, 1 H, J = 12.3, 4.2 Hz), 3.96 (d, 1 H, J = 12.2 Hz), 3.69 (s, 3 H), 3.64 (s, 3 H), 2.88 (br t, 1 H, J = 5.1 Hz), 2.84 (br d, 2 H, J = 2.6 Hz), 1.97 (t, 1 H, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.5, 137.9, 129.6, 128.8, 128.6−127.3, 119.9, 92.4, 78.5, 71.8, 69.3, 58.7, 52.9, 52.8, 35.7, 23.2; $[\alpha]^{20}_D$ −50.1° (*c* 1.8, $CHCl_3$); MS (FD) m/z = 358.1 (M^+). Anal. Calcd for $C_{20}H_{22}O_6$ (358.39): C, 67.03; H, 6.19. Found: C, 66.96; H, 6.34.

Propanedioic Acid, [6-(Benzyloxy)-3,6-dihydro-2*H*-pyran-3-yl]-2-propynyl-Dimethyl Ester (11). Using the procedure to prepare **10**, with benzyl 2-*O*-*p*-tosyl-3,4-dideoxy-α-D-*glycero*-pent-3-enopyranoside (**6**) (1 g, 1 equiv, 2.77 mmol), triphenylphosphine (29.14 mg, 4 mol %) and tetrakis(triphenylphosphine)palladium (128.4 mg, 4 mol %) in 10 mL of THF, NaH (277 mg, 60% dispersion, 2.5 equiv, 7.0 mmol), and dimethyl propargylmalonate (neat; 1.05 mL, 2.5 equiv, 7 mmol) in 10 mL of THF, after refluxing for 1 h, 0.1 g (10%) of **10** and 0.68 g (69%) of **11** were collected. Compound **11**: Oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.20 (m, 5 H), 6.0 (br dt, 1 H, J = 10.5, 0.9 Hz), 5.73 (dt, 1 H, J = 10.4, 2.7 Hz), 4.86 (br d, 1 H, J = 0.9 Hz), 4.65 (d, 1 H, J = 12.0 Hz), 4.43 (d, 1 H, J = 12.0 Hz), 3.84−3.80 (m, 2 H), 3.65 (s, 3 H), 3.62 (s, 3 H), 3.24 (m, 1 H), 2.82 (dd, 1 H, J = 17.5, 2.7 Hz), 2.76 (dd, 1 H, J = 17.5, 2.7 Hz), 2.0 (t, 1 H, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 169.0, 136.1, 129.7, 128.4, 127.9−127.6, 127.4, 93.2, 78.4, 72.1, 69.4, 58.9, 52.8, 36.8, 22.5; $[\alpha]^{20}_D$ +54.7° (*c* 1.93, $CHCl_3$); MS (FD) m/z = 357.9 (M^+). Anal. Calcd for $C_{20}H_{22}O_6$ (358.39): C, 67.03; H, 6.19. Found: C, 67.10; H, 6.19.

Benzyl 2,3,4-Trideoxyribopyranosido[4,3,2-*cd*]-10,10-bis(methoxycarbonyl)bicyclo[3.3.0]octan-7-en-6-one (12). Compound **10** (300 mg, 0.83 mmol) and $Co_2(CO)_8$ (315.2 mg, 1.1 equiv, 0.92 mmol) were dissolved in 5 mL of absolute benzene and stirred at rt for 2−3 h. Then, absolute DMSO (0.2 mL, 3 equiv, 2.5 mmol) was added, and the reaction mixture was stirred at 50 °C for 24 h. After completion of the reaction (TLC analysis), the solvent was evaporated and the residue column chromatographed using 60% to 90% CH_2Cl_2/*n*-hexane, affording 225 mg (75%) of an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.20 (m, 5 H), 5.60 (d, 1 H, J = 1.5 Hz), 4.70 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 3.4 Hz), 4.50 (d, 1 H, J = 11.9 Hz), 3.75 (dd, 1 H, J = 11.8, 7.6 Hz), 3.72 (s, 3 H), 3.68 (s, 3 H), 3.52 (d, 1 H, J = 19.4 Hz), 3.48 (m, 1 H), 3.28 (br dd, 1 H, J = 10.1, 7.6 Hz), 3.14 (br dd, 1 H, J = 19.4, 1.5 Hz), 3.02 (dd, 1 H, J = 11.7, 9.7 Hz), 2.78 (dd, 1 H, J = 7.1, 3.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.4, 183.7, 171.0, 168.9, 137.2, 128.4−127.7, 126.4, 97.0, 70.2, 65.7, 59.8, 53.3, 52.9, 51.3, 46.8, 37.6, 34.3; $[\alpha]^{29}_D$ −16.6° (*c* 1.46, CH_2Cl_2); MS (FD) m/z = 386.5 (M^+). Anal. Calcd for $C_{21}H_{22}O_7$ (386.40): C, 65.28; H, 5.74. Found: C, 65.33; H, 5.51.

Benzyl 2,3,4-Trideoxy-α-D-ribopyranosido[4,3,2-*cd*]-6,6-bis(methoxycarbonyl)bicyclo[3.3.0]octan-8-en-10-one (13). Using the procedure to prepare **12**, compound **11** (300 mg, 0.83 mmol) and $Co_2(CO)_8$ (315.17 mg, 1.1 equiv, 0.92 mmol) in 5 mL of absolute benzene and absolute DMSO (0.17 mL, 3 eq, 2.5 mmol) afforded 231 mg (77%) of the title compound. Mp 102−104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15−7.0 (m, 5 H), 5.79 (d, 1 H, J = 2.2 Hz), 4.90 (d, 1 H, J = 7.9 Hz), 4.34 (d, 1 H, J = 12.6 Hz), 4.15 (d, 1 H, J = 12.6 Hz), 3.59 (s, 3 H), 3.51 (s, 3 H), 3.38 (d, 1 H, J = 20.3 Hz), 3.20−3.13 (m, 2 H), 3.10 (t, 1 H, J = 12.0 Hz), 3.0 (t, 1 H, J = 6.6 Hz), 2.93 (d, 1 H, J = 20.2 Hz), 2.90 (t, 1 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.8, 180.6, 171.3, 168.8, 137.2, 128.2−127.1, 127.0, 94.3, 69.4, 63.1, 53.5, 53.2, 52.9, 49.8, 46.2, 38.9, 34.1; $[\alpha]^{29}_D$ +160.2° (*c* 0.68, CH_2Cl_2); MS (FD) m/z = 387 (M^+). Anal. Calcd for $C_{21}H_{22}O_7$ (386.40): C, 65.28; H, 5.74. Found: C, 64.94; H, 5.70.

Benzyl 2,3,4-Trideoxyribopyranosido[4,3,2-*cd*]-10,10-bis(methoxycarbonyl)-7-(2-methyl-2-propenyl)bicyclo-[3.3.0]octan-7-en-6-one (16). To a mixture of triisopropyl phosphite (0.04 mL, 7 eq, 0.18 mmol) and $Pd(OAc)_2$ (5.8 mg, 10 mol %) in 5 mL of THF were added **12** (100 mg, 0.26 mmol) in 3 mL of THF and 3-acetoxy-2-[(trimethyllsilyl)methyl]-1-propene (**14**; 142.72 mg, 3.4 equiv, 0.88 mmol), and the reaction mixture was refluxed for 48 h. As soon as there was no further conversion, the reaction was stopped by adding 5 mL of *n*-hexane/ethyl acetate (8:2) and the mixture filtered through Celite. The starting material and product were separated on TLC plates using 10% ethyl acetate/dichloromethane to give **16** (30%) and recovered starting material (60%). Oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.30−7.25 (m, 5 H), 4.70 (br s, 1 H), 4.67 (d, 1 H, J = 11.8 Hz), 4.61 (br s, 1 H) 4.60 (br s, 1 H), 4.50 (d, 1 H, J = 11.8 Hz), 3.75 (br t, 1 H, J = 11.7 Hz), 3.72 (s, 3 H), 3.67 (s, 3 H), 3.45 (d, 1 H, J = 19.4 Hz), 3.40 (m, 1 H), 3.28 (br dd, 1 H, J = 9.6, 7.6 Hz), 3.0 (d, 1 H, J = 20.2 Hz), 2.97 (dd, 1 H, J = 11.4, 9.6 Hz), 2.80 (br s, 2 H), 2.78 (dd, 1 H, J = 6.8, 3.0 Hz), 1.58 (s, 3 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 206.7, 170.7, 171.1, 169.1, 141.6, 137.2, 135.8, 128.5−127.8, 111.9, 96.9, 70.3, 63.3, 59.8, 53.4, 53.0, 50.5, 44.7, 37.6, 33.3, 31.8, 22.5; $[\alpha]^{20}_D$ +22.6° (*c* 1.13, $CHCl_3$); MS (FD) m/z = 440.3 (M^+). $C_{25}H_{28}O_7$ (440.49).

Benzyl 2,3,4-Trideoxy-α-D-ribopyranosido[4,3,2-*cd*]-6,6-bis(methoxycarbonyl)-9-(2-methyl-2-propenyl)bicyclo-[3.3.0]octan-8-en-10-one (18). Using the procedure for **16**, triisopropyl phosphite (0.04 mL, 7 equiv, 0.18 mmol), $Pd(OAc)_2$ (5.8 mg, 10 mol %) in 5 mL of THF, **13** (100 mg, 0.26 mmol) in 3 mL of THF, and **14** (142.72 mg, 3.4 equiv, 0.88 mmol) gave **18** (30%) and recovered starting material (60%). Oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.10 (m, 5 H), 5.10 (d, 1 H, J = 7.8 Hz), 4.68 (br s, 1 H), 4.63 (br s, 1 H), 4.45 (d, 1 H, J = 12.3 Hz), 4.30 (d, 1 H, J = 12.3 Hz), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.46 (d, 1 H, J = 20.4 Hz), 3.32 (ddd, 1 H, J = 9.6, 6.6, 1.5 Hz), 3.22 (m, 2 H), 3.13 (t, 1 H, J = 6.6 Hz), 3.09 (t, 1 H, J = 7.6 Hz), 2.92 (d, 1 H, J = 20.4 Hz), 2.80 (br t, 2 H, J = 15.7 Hz), 1.50 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.3, 173.9, 171.4, 169.1, 141.5, 137.1, 136.1, 128.2−127.4, 112.2, 94.5, 69.5, 63.0, 53.6, 53.2, 52.8, 49.0, 44.4, 39.0, 33.3, 32.2, 22.2; $[\alpha]^{20}_D$ +101.6° (*c* 1.06, $CHCl_3$); MS (FD) m/z = 440.3 (M^+). $C_{25}H_{28}O_7$ (440.49).

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