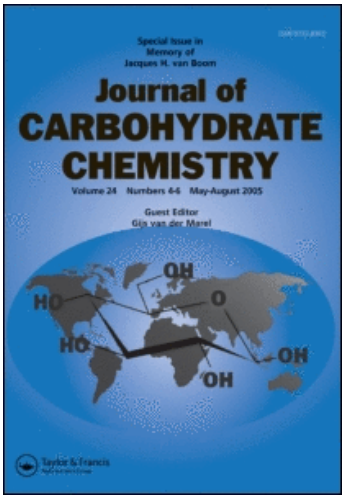

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The Chiron Approach to Pironetins: Synthesis of the δ-Lactonic Fragment and Modified Building Blocks from D-Glucal

Francisco Sarabia[a]; Miguel García-Castro[a]; Samy Chammaa[a]; Antonio Sánchez-Ruiz[a]
[a] Department of Biochemistry, Molecular Biology and Organic Chemistry, Faculty of Sciences, University of Malaga, Malaga, Spain

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The Chiron Approach to Pironetins: Synthesis of the δ-Lactonic Fragment and Modified Building Blocks from D-Glucal

Francisco Sarabia, Miguel García-Castro, Samy Chammaa, and Antonio Sánchez-Ruiz

Department of Biochemistry, Molecular Biology and Organic Chemistry, Faculty of Sciences, University of Malaga, Malaga, Spain

The synthesis of the δ-lactonic fragment of pironetin (**1**), a natural product with outstanding antimitotic properties, is reported. The synthesis was achieved from commercially available tri-O-acetyl-D-glucal (**6**) that was employed as starting material for the preparation of ethyl ketone **4**, through a synthetic sequence that included a Ferrier rearrangement of **6** and suitable functional group manipulations of the resulting O-glycoside **7** to obtain the 4-ethyl glycoside **11**, together with a series of 4-C-alkyl modified derivatives. The completion of the synthesis of **4** was performed via chain elongation at C-6 by the introduction of a nitrile group and subsequent reduction, nucleophilic attack with ethyl magnesium bromide, and, finally, oxidation of the resulting alcohol **20**.

Keywords Pironetin, Ferrier rearrangement, Antimitotic agents, Chiron approach

INTRODUCTION

Isolated by two independent research groups from culture broths of *Streptomyces sp.* NK10958[1] and *Streptomyces prunicolor* PA-48153,[2] pironetin (**1**, PA-48153C) belongs to the privileged class of natural products with

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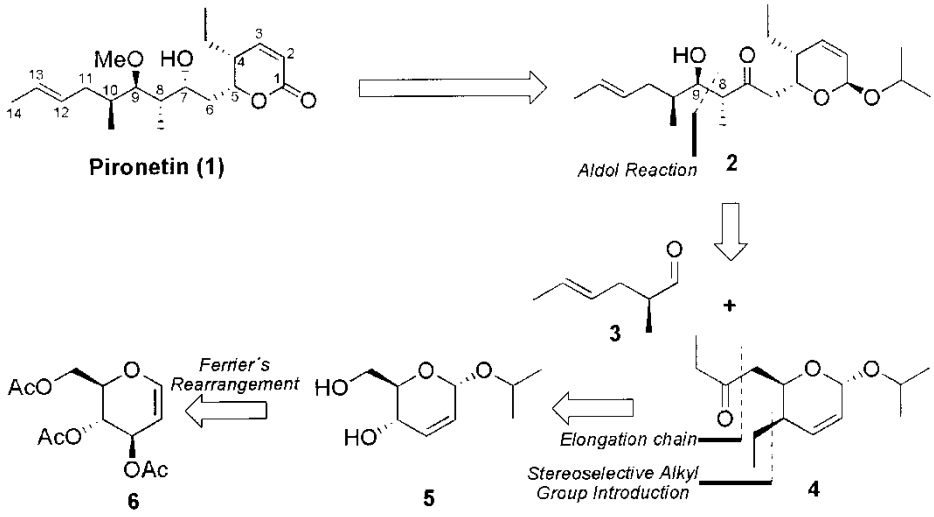
Address correspondence to Francisco Sarabia, Department of Biochemistry, Molecular Biology and Organic Chemistry, Faculty of Sciences, University of Malaga, 29071, Malaga, Spain. E-mail: frsarabia@uma.es

antimitotic properties in virtue of its capacity of interacting with tubulines, producing inhibition of their assembly to microtubules.[3] Initially, pironetin was identified as a plant growth regulator, inducing shortening of the plant height of rice,[4] and later, as a potent immunosuppressant,[5] with a potency similar to the well-known immunosuppressive agents cyclosporine A and FK-506.[6] Particularly intriguing and stimulating was, however, the disclosure of its antitumoral properties, by induction of microtubule disassembly in cells type 3Y1 and inhibition glutamate-induced tubulin assembly in a 10-μM range concentration, which elicited a great deal of interest in the scientific community.[7] The result of this biological action was the arrest of cellular growth at the M-phase and, like other microtubule inhibitors, pironetin seems to induce the phosphorylation of Bcl-2, which triggers apoptosis.[8] The binding mode of pironetin to tubuline was initially surmised in a vinblastine-like mode due to its capacity of inhibiting tubulin binding of vinblastine. In fact, although effective doses of pironetin were slightly superior than those of vinblastine, against HL-60 cells, its K_d value was 10-fold lower, as an indicator of a greater affinity for tubulin than that of vinblastine. In contrast to these exciting findings, recent biological assays[9] have revealed that the binding site is located on the surface of α-tubulin, the Lys352 residue being responsible for a covalent binding with pironetin through a Michael addition of the terminal amino group of this amino acid to the α,β-unsaturated δ-lactone moeity.[10] In fact, structure-activity relationship studies of pironetin analog have reflected the importance of the 2-pyranone ring system as well as the hydroxyl group at C-7 in its antitumor properties.[11] All these outstanding biological properties exhibited by pironetin renders it as an enticing synthetic endeavor. Thus, several total syntheses of pironetin (**1**) have been reported, including linear asymmetric[12] and chiron approaches[13] to total syntheses. Despite its relatively small size, pironetin offers both a challenge and an opportunity for the development of a new class of novel anticancer agents, which captured our attention and encouraged us to initiate a program directed toward its total synthesis, according to a synthetic strategy capable of generating analogs by a convergent and flexible route. To this end, we devised, in retrosynthetic terms, a dissection at the C-8/C-9 bond of compound **2**, obtained after the appropriate functional group transformations of **1**, via a retro-aldol reaction, to produce aldehyde **3** and ketone **4** as advanced precursors of **1**. The synthesis of the δ-lactonic fragment, contained in **4**, was planned according to an appropiate chain elongation method at C-6 and the incorporation of an ethyl group at C-4, leading to glycoside **5** as a potential and valuable precursor, whose synthesis could be achieved via a Ferrier rearrangement from the commercially available tri-O-acetyl-D-glucal (**6**). Herein we wish to report the synthesis of the δ-lactonic derivative **4** together with 4-C-alkyl modified analog according to the delineated retrosynthetic analysis depicted in Scheme 1.



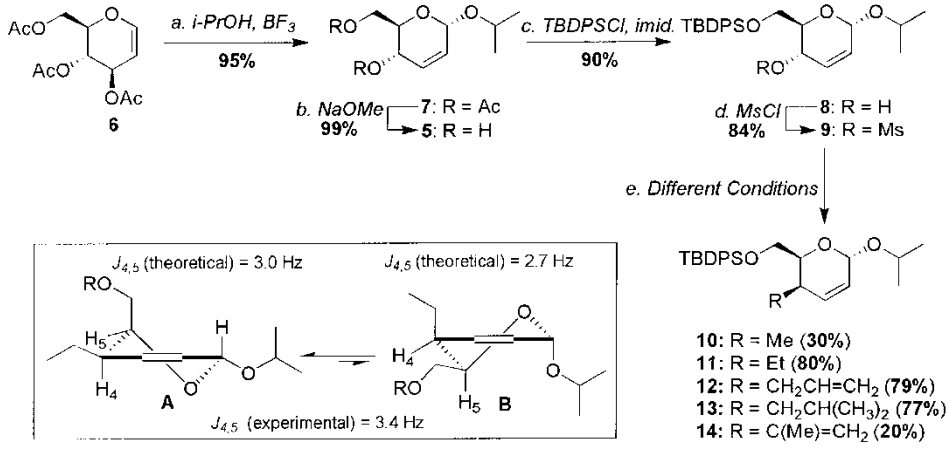
Scheme 1: Structure of pironetin (**1**) and retrosynthetic analysis.

RESULTS AND DISCUSSION

The synthesis of the subtarget molecule **4** commenced with the Ferrier rearrangement[14] of commercially available tri-O-acetyl-D-glucal (**6**) (Tri-O-acetyl-D-Glucal (**6**) was purchased from Aldrich.) by reaction with isopropyl alcohol in the presence of boron trifluoride to afford O-glycoside **7** in 95% yield as a 9:1 mixture of α:β anomers. Methanolysis of **7** by reaction with sodium methoxide, followed by selective silylation of the resulting diol **5**, provided silyl ether **8**, which was treated with methanesulphonyl chloride in the presence of triethyl amine to obtain the mesylate **9**, a product that was considered very suitable to attempt the introduction of the ethyl group contained at C-4 of the δ-lactonic fragment. In a first attempt, **9** was reacted with Et_2CuLi,[15] a reagent that was generated in situ by treatment of two equivalents of ethyllithium (Ethyllithium was purchased from Aldrich as a 0.5-M solution in benzene/cyclohexane 90/10.) with CuI. However, the result was not satisfactory because of the recovery of starting material. In a similar reaction, however, **9** reacted smoothly with Me_2CuLi to obtain the 4-methyl derivative **10**, albeit in a low 30% yield. Gratifyingly, the treatment of **9** with either EtMgBr/CuCN[16] or Et_2Zn/CuCN[17] furnished the desired 4-ethyl derivative **11** in an 80% yield for both cases. Combining NMR spectroscopic methods with theoretical calculations (Theoretical calculations of both conformers **A** and **B**, corresponding to the α-anomer, were performed with HyperChem 5.0, preoptimizing with MM+ as the force field with a gradient limit of 0.001 kcal/(Å.mol), followed by full optimization with AM1, obtaining energy values of −115927,88 and −115925,83 kcal/mol for conformers **A** and

B respectively. Coupling constants were determined by the Karplus equation $J = 4.22 - 0.5.\cos\,\alpha + 4.5.\cos\,2\alpha$. Similar conformational studies were undertaken for the β-anomer of **11** and for the α/β anomers of the 4-(S) diastereoisomer, but in any case the resulting calculated J were in accordance with the experimental value of $J_{4,5}$ for compound **11**.[18]) let us to confirm the 4-(R) configuration of product **11** as a result of a S_{N2} process (Sch. 2). This successful result prompted us to prepare a family of 4-C-alkyl analog, which could be of interest for future biological evaluations, taking into account the apparent key importance of the 2-pyranone system in their binding to tubulines. In addition, this synthesis represents useful convergent approaches, particularly to related natural products that contain the same 4-C-alkyl-α,β-unsaturated δ-lactonic fragment.[19] Then, exposure of **9** to the action of different alkyl magnesium bromides in the presence of CuCN afforded the corresponding 4-C-alkyl derivatives **10**–**14** in a wide range of yields (20–80%) (Sch. 2).

For the completion of the synthesis of the coveted ethyl ketone **4**, compound **11** was desilylated by treatment with TBAF, and the resulting alcohol **15** was activated as its O-mesyl derivative **16**, which was subjected to the action of NaCN in refluxing DMF[20] to afford, after 24 h, the nitrile derivative **17** in a 95% yield. Our strategy toward **4** was set forth on the notion that nitrile **17** might be amenable to a nucleophilic attack of ethyl magnesium bromide to provide **4** directly. However, our unrelenting efforts to effect this direct transformation were thwarted by the fragile nature of the glycosidic bond, which was highlighted during the acidic work-up of the imine intermediate **18**, occurring the cleavage of such glycosidic bond. Different attempts to unmask the ketone group from imine **18** under a wide variety of milder acidic conditions[21] were similarly unsuccessful. These results forced us to overcome the lability of the glycosidic bond by a sequence entailing reduction of nitrile **17**, nucleophilic



Scheme 2: Synthesis of 4-C-alkyl glycoside derivatives **10**–**14**.

attack of the resulting aldehyde, and subsequent oxidation. Thus, reduction to aldehyde **19** of nitrile **17** was accomplished by treatment with DIBAL-H in 60% yield. The resulting aldehyde **19** was then reacted with ethyl magnesium bromide to provide alcohol **20** in an 85% yield as a 1:1 mixture of diastereoisomers, which was finally transformed into the ketone **4** by reaction with TPAP[22] in 88% yield (Sch. 3).

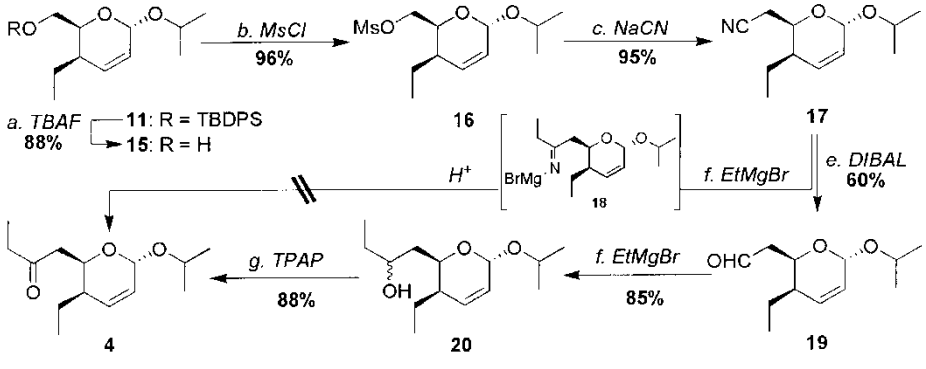
Having successfully synthesized the subtarget compound **4** in an efficient manner, our next objective will be to achieve the total synthesis of pironetin **1**, according to the retrosynthetic blueprint showed in Scheme 1, which might offer us, in addition, the possibility of providing analog by modification at C-4 and at C-7 positions for future biological evaluations as antimitotic agents. These synthetic efforts are currently in progress and will be reported in due course.

EXPERIMENTAL

General Techniques

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone and methylene chloride and methanol from calcium hydride. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All solutions used in work-up procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and



Scheme 3: Synthesis of ketone **4**.

heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on a Bruker Avance-400 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. ^{1}H NMR assignments were undertaken based on two-dimensional COSY experiments (cosygp experiment). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a Kratos MS 80 RFA mass spectrometer under fast atom bombardment (FAB) conditions.

Isopropyl 4,6-Di-O-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (7). To a solution of tri-O-acetyl D-glucal (**6**) (10 g, 36.76 mmol, 1.0 equiv) in CH_2Cl_2 (70 mL) was added ^{i}PrOH (14.1 mL, 183.8 mmol, 5.0 equiv) and $BF_3 \cdot OEt_2$ (9.21 mL of a 48% solution, 47.79 mmol, 1.3 equiv) at 0°C. After stirring for 3 h, the reaction mixture was warmed to rt, treated with a saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2 (30 mL). After separation of both layers, the aqueous phase was extracted with CH_2Cl_2 and the combined organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was subjected to purification by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain O-glycoside **7** as an unseparable 9:1 mixture of α:β anomers (9.51 g, 95%): Yellow oil; $R_f = 0.55$ (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.12 (d, $J = 5.9$ Hz, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 3.93 (ddd, $J = 5.4$, 5.9, 6.4 Hz, 1H), 4.06-4.12 (m, 1H), 4.12–4.22 (m, 2H), 5.07 (bs, 1H), 5.24 (dd, $J = 1.6$, 9.7 Hz, 1H), 5.75 (dt, $J = 2.1$, 10.2 Hz, 1H), 5.81 (bd, $J = 10.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.7, 21.1, 23.6, 62.8, 64.3, 70.4, 71.2, 92.5, 127.0, 133.2, 170.3.

Isopropyl 2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranoside (5). A solution of O-glycoside **7**(9.51 g, 34.92 mmol, 1.0 equiv) in MeOH (60 mL) was treated with NaOMe (377 mg, 6.98 mmol, 0.2 equiv) at 25°C. After stirring for 1 h, the crude mixture was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (silica gel, 90% EtOAc in hexanes → EtOAc) to obtain diol **5** (6.51 g, 99%) as a white solid: $R_f = 0.13$ (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.12 (d, $J = 5.9$ Hz, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 3.68 (dt, $J = 4.5$, 9.0 Hz, 1H), 3.75–3.86 (m, 2H), 3.89 (sep, 1H), 4.15 (bd, $J = 4.5$ Hz, 1H), 5.04 (bs, 1H), 5.68 (dt, $J = 2.1$, 10.2 Hz, 1H), 5.88 (bd, $J = 10.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.8, 23.6, 62.8, 64.3, 70.4, 71.2, 92.5, 127.0, 133.2.

Isopropyl 6-O-*tert*Butyldiphenylsilyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (8). To a solution of diol **5**(6.51 g, 34.57 mmol, 1.0 equiv) in DMF (40 mL) was added TBDPSCl (10.62 mL, 41.48 mmol, 1.2 equiv) and imidazole (3.06 g, 44.94 mmol, 1.3 equiv) at 0°C. After stirring for 2 h at this temperature, the reaction mixture was quenched by addition of MeOH, diluted with Et_2O (50 mL), and followed by addition of a saturated aqueous NH_4Cl solution. After separation of both layers, the aqueous phase was extracted with ether and the combined organic solution was washed with water and brine. The organic solution was then dried ($MgSO_4$) and filtered, and, after concentration under reduced pressure, the resulting crude product was subjected to purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain silyl ether **8** (13.26 g, 90%) as a colorless oil: $R_f = 0.31$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.07 (s, 9H), 1.15 (d, $J = 5.9$ Hz, 3H), 1.16 (d, $J = 6.4$ Hz, 3H), 3.82-4.06 (m, 4H), 4.22 (dd, $J = 1.6$, 8.1 Hz, 1H), 5.04 (bs, 1H), 5.72 (dt, $J = 2.1$, 10.2 Hz, 1H), 5.94 (bd, $J = 10.2$ Hz, 1H), 7.34–7.48 (m, 6H), 7.61-7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.1, 25.2, 26.7, 66.2, 68.2, 107.0, 110.1, 127.7, 129.7, 132.8, 135.4, 141.9.

Isopropyl 6-O-*tert*Butyldiphenylsilyl-2,3-dideoxy-4-O-methylsulphonyl-α-D-*erythro*-hex-2-enopyranoside (9). To a solution of silyl ether **8** (7.2 g, 16.89 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added TEA (4.69 mL, 33.78 mmol, 2.0 equiv), followed by a dropwise addition of methanesulphonyl chloride (1.94 mL, 25.34 mmol, 1.5 equiv) at 0°C. After stirring for 1.5 h, the reaction mixture was warmed at rt, and a saturated aqueous NH_4Cl solution and ether (50 mL) were added. After decantation of both layers, the aqueous phase was extracted with ether and the combined organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain compound **9** (7.2 g, 84%) as a colorless oil: $R_f = 0.35$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.07 (s, 9H), 1.16 (d, $J = 5.9$ Hz, 3H), 1.17 (d, $J = 6.4$ Hz, 3H), 2.92 (s, 3H), 3.87 (d, $J = 3.2$ Hz, 2H), 3.92–4.02 (m, 2H), 5.14 (bs, 1H), 5.29 (dd, $J = 1.6$, 9.7 Hz, 1H), 5.86 (dt, $J = 2.1$, 10.2 Hz, 1H), 6.08 (bd, $J = 10.2$ Hz, 1H), 7.34–7.46 (m, 6H), 7.65–7.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.1, 23.5, 25.2, 26.6, 39.0, 62.3, 70.3, 112.7, 127.5, 129.6, 135.5, 135.8, 140.6. FAB HRMS (NBA) m/e 527.1893, $M + Na^+$ calcd for $C_{26}H_{36}O_6SSi$ 527.1899.

Isopropyl 4-C-Alkyl-6-O-*tert*butyldiphenylsilyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranosides 10-14. Procedure A: To a suspension of CuCN (89 mg, 0.993 mmol, 2.5 equiv) in THF (7 mL) was added the Grignard reagent (2.00 mmol, 5.0 equiv) at −40°C and stirred for 5 min, prior to the addition of a solution of mesylate **9** (200 mg, 0.397 mmol, 1.0 equiv) in THF (4 mL) at −40°C. The reaction mixture was left to reach −18°C, and stirred

until depletion of starting material (ca 20 min). Then the reaction mixture was treated with MeOH and diluted with ether (15 mL) and a saturated aqueous NH_4Cl solution added. After decantation of both layers, the aqueous phase was separated and extracted with ether and the combined organic extracts were sequentially washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The obtained crude product was subjected to purification by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain the corresponding 4-C-alkyl glycoside. **Procedure B:** To a suspension of CuCN (1.775 g, 19.83 mmol, 2.0 equiv) in THF (25 mL) was added Et_2Zn (19.8 mL of a 1.0 M solution, 19.83 mmol, 2.0 equiv) at 0°C. After stirring for 10 min, a solution of mesylate **9** (5.0 g, 9.91 mmol, 1.0 equiv) in THF (35 mL) was dropwise added. The reaction mixture was stirred for 20 min at 0°C, and then it was quenched with MeOH. Dilution with ether (30 mL) was followed by addition of a saturated aqueous NH_4Cl solution, the phases were separated, and the aqueous layer was extracted with ether. The combined organic solutions were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% EtOAc in hexanes) furnished compound **11** (3.48 g, 80%) as a colorless oil.

Isopropyl 4-C-Methyl-6-O-*tert*butyldiphenylsilyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (10). (Colorless oil, 30%): $R_f = 0.79$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (d, $J = 7$ Hz, 3H), 1.07 (s, 9H), 1.15 (d, $J = 6.4$ Hz, 3H), 1.24 (d, $J = 6.4$ Hz, 3H), 1.90–1.97 (m, 1H), 3.71(dd, $J = 5.9$, 10.2 Hz, 1H), 3.79 (dd, $J = 5.9$, 10.2 Hz, 1H), 3.98 (dt, $J = 12.4$, 5.9 Hz, 1H), 4.23–4.31 (m, 1H) 4.22–4.32 (m, 1H), 4.88 (bs, 1H), 5.70–5.79 (m, 1H), 5.86 (bd, $J = 10.2$ Hz, 1H), 7.34–7.46 (m, 6H), 7.67–7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.2, 20.5, 23.6, 26.8, 30.6, 45.6, 66.5, 68.7, 96.7, 99.1, 127.7, 129.6, 133.6, 135.7.

Isopropyl 4-C-Ethyl-6-O-*tert*butyldiphenylsilyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (11). (Colorless oil, 80%): $R_f = 0.75$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 0.96 (t, $J = 7.5$ Hz, 3H), 1.09 (s, 9H), 1.17 (d, $J = 6.4$ Hz, 3H), 1.24 (d, $J = 6.4$ Hz, 3H), 1.38–1.58 (m, 2H), 1.90–1.97 (m, 1H), 3.71 (dd, $J = 5.9$, 10.2 Hz, 1H), 3.79 (dd, $J = 5.9$, 10.2 Hz, 1H), 3.98 (dt, $J = 12.4$, 5.9 Hz, 1H), 4.23–4.31 (m, 1H), 4.83 (bs, 1H), 5.78 (d, $J = 10.2$ Hz, 1H), 5.83 (dd, $J = 10.2$, 3.4 Hz, 1H), 7.36–7.46 (m, 6H), 7.69–7.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.3, 19.2, 21.5, 23.5, 26.4, 26.8, 41.0, 66.5, 68.7, 69.3, 97.6, 125.7, 127.4, 127.6, 129.6, 133.5, 135.6.

Isopropyl 4-C-Allyl-6-O-*tert*butyldiphenylsilyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (12). (Colorless oil, 79%): $R_f = 0.87$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (s, 9H),

1.15 (d, $J = 6.4$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 2.08–2.26 (m, 3H), 3.71 (dd, $J = 5.9$, 10.2 Hz, 1H), 3.78 (dd, $J = 5.9$, 10.2 Hz, 1H), 3.96 (dt, $J = 12.4$, 5.9 Hz, 1H), 4.25–4.30 (m, 1H), 4.82 (bs, 1H), 5.04 (d, $J = 10.2$ Hz, 1H), 5.07 (d, $J = 10.2$ Hz, 1H), 5.75–5.85 (m, 3H), 7.35–7.46 (m, 6H), 7.67–7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.2, 21.6, 23.5, 26.8, 37.7, 39.1, 66.4, 68.9, 69.4, 97.1, 116.4, 126.1, 127.1, 127.6, 129.6, 133.5, 135.6, 135.7, 136.1.

Isopropyl 4-C-Isobutyl-6-O-*tert*butyldiphenylsilyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (13). (Colorless oil, 77%): $R_f = 0.79$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (d, $J = 6.4$ Hz, 6H), 1.07 (s, 9H), 1.08–1.11 (m, 5H), 1.18–1.23 (m, 4H), 2.10 (d, $J = 7.0$ Hz, 1H), 3.64–3.79 (m, 2H), 3.82–3.97 (m, 1H), 4.03 (dt, $J = 5.9$, 12.4 Hz, 1H), 4.76 (bs, 1H), 5.75 (d, $J = 10.2$ Hz, 1H), 6.03-6.11 (m, 1H), 7.32-7.47 (m, 6H), 7.63 – 7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.2, 23.5, 26.4, 26.4, 26.8, 39.6, 66.5, 68.7, 69.3, 97.6, 125.7, 127.4, 127.6, 129.6, 133.5, 135.6.

Isopropyl 4-C-Isopropenyl-6-O-*tert*butyldiphenylsilyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (14). (Colorless oil, 20%): $R_f = 0.81$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04 (s, 3H), 1.06 (s, 9H), 1.15 (d, $J = 5.9$ Hz, 3H), 1.22 (d, $J = 6.4$ Hz, 3H), 2.67 (bs, 1H), 3.62–3.70 (m, 1H), 3.78 (dd, $J = 5.9$, 10.2 Hz, 1H), 3.94 (dt, $J = 12.4$, 6.4 Hz, 1H), 4.23–4.30 (m, 1H), 4.79 (bs, 1H), 4.84 (bs, 2H), 5.63–5.70 (m, 1H), 5.91 (d, $J = 10.2$ Hz, 1H), 7.33 – 7.45 (m, 6H), 7.65–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.2, 21.4, 23.5, 26.8, 47.7, 66.4, 68.5, 68.8, 96.9, 113.2, 125.5, 126.5, 127.6, 129.6, 133.5, 135.6, 144.7.

Isopropyl 4-C-Ethyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (15). A solution of compound **11** (3.48 g, 7.94 mmol, 1.0 equiv) in THF (40 mL) was treated with TBAF (11.9 mL of a 1.0 M solution in THF, 11.91 mmol, 1.5 equiv) at 25°C. After stirring for 20 min, a saturated aqueous NH_4Cl solution and ether (30 mL) were added. After decantation of both layers, the aqueous phase was extracted with ether and the combined organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude alcohol was subjected to purification by flash column chromatography (silica gel, 30% EtOAc in hexanes), providing pure alcohol **15** (2.32 g, 88%) as a colorless oil: $R_f = 0.25$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.96 (t, $J = 7.5$ Hz, 3H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.24 (d, $J = 6.4$ Hz, 3H), 1.39–.56 (m, 2H), 1.90–1.98 (m, 1H), 3.60 (dd, $J = 6.4$, 11.3 Hz, 1H), 3.72 (dd, $J = 3.2$, 11.3 Hz, 1H), 3.98 (dt, $J = 5.9$, 12.4 Hz, 1H), 4.26–4.32 (m, 1H), 4.85 (bs, 1H), 5.63 (d, $J = 10.2$ Hz, 1H), 5.84–5.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.4, 21.5, 23.5, 26.8, 41.0, 65.2, 68.6, 68.9, 97.5, 124.5, 128.7.

Isopropyl 4-C-Ethyl-6-O-methylsulphonyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (16). To a solution of alcohol **15** (1.0 g, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added TEA (0.68 mL, 10 mmol, 2.0 equiv) and methanesulphonyl chloride (0.58 mL, 7.5 mmol, 1.5 equiv) at 0°C. After stirring for 45 min at this temperature, the reaction mixture was diluted with ether (35 mL), and a saturated aqueous NH_4Cl solution was added. Separation of both layers was followed by extractions of the aqueous phase with ether. The combined organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (silica gel, 40% EtOAc in hexanes) provided mesylate **16** (1.34 g, 96%) as a colorless oil: $R_f = 0.34$ (silica gel, 40% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.96 (t, $J = 7.5$ Hz, 3H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.37–1.56 (m, 2H), 1.91–1.98 (m, 1H), 3.05 (s, 3H), 3.97 (dt, $J = 6.4$, 12.4 Hz, 1H), 4.24 (dd, $J = 6.4$, 10.7 Hz, 1H), 4.29 (dd, $J = 3.8$, 10.7 Hz, 1H), 4.44–4.49 (m, 1H), 4.83 (bs, 1H), 5.62 (d, $J = 10.7$ Hz, 1H), 5.89–5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.3, 21.5, 23.5, 26.4, 37.7, 40.9, 66.7, 69.0, 71.2, 97.5, 122.6, 129.9. FAB HRMS (NBA) m/e 301.1089, $M + Na^+$ calcd for $C_{12}H_{22}O_5S$ 301.1086.

2-((2*S*,3*R*,6*S*)-3-Ethyl-3,6-dihydro-6-isopropoxy-2*H*-pyran-2-yl)-acetonitrile (17). To a solution of mesylate **16** (1.34 g, 4.80 mmol, 1.0 equiv) in DMF (50 mL) was added sodium cyanide (1.40 g, 28.8 mmol, 6.0 equiv) and the resulting suspension was heated at 65°C. After stirring for 24 h, the reaction mixture was warmed at rt, diluted with ether (50 mL), and washed with water. Both layers were separated, the aqueous phase was extracted with ether, and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford nitrile **17** (957 mg, 95%) as a colorless oil: $R_f = 0.50$ (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.96 (t, $J = 7.5$ Hz, 3H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.41–1.59 (m, 2H), 1.89–1.96 (m, 1H), 2.58 (dd, $J = 6.4$, 10.7 Hz, 2H), 3.97 (dt, $J = 6.4$, 12.4 Hz, 1H), 4.40–4.46 (m, 1H), 4.83 (bs, 1H), 5.65 (d, $J = 10.7$ Hz, 1H), 5.92 (dd, $J = 4.3$, 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.4, 21.5, 23.4, 26.5, 40.8, 64.0, 69.1, 97.7, 117.1, 124.6, 129.6.

2-((2*S*,3*R*,6*S*)-3-Ethyl-3,6-dihydro-6-isopropoxy-2*H*-pyran-2-yl)-acetaldehyde (19). A solution of nitrile **17** (606 mg, 3.11 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) was treated with DIBAL-H (4.4 mL of a 1.0 M solution in toluene, 4.4 mmol, 1.4 equiv) at −78°C. After stirring for 4 h, the reaction mixture was quenched with ethyl acetate at −78°C, warmed to rt, and treated with a saturated aqueous sodium-potassium tartrate solution for 30 min. After decantation of both layers, the aqueous phase was extracted

with EtOAc, and the combined organic solutions were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was subjected to purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain aldehyde **19** (396 mg, 60%) as a colorless oil: $R_f = 0.70$ (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (t, $J = 7.5$ Hz, 3H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.24 (d, $J = 6.4$ Hz, 3H), 1.36–1.53 (m, 2H), 1.88–1.95 (m, 1H), 2.56–2.60 (m, 2H), 3.97 (dt, $J = 6.4$, 12.4 Hz, 1H), 4.68–4.74 (m, 1H), 4.78 (bs, 1H), 5.67 (d, $J = 10.7$ Hz, 1H), 5.82 (dd, $J = 4.3$, 10.2 Hz, 1H), 9.81 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 11.4, 21.5, 23.4, 26.5, 40.8, 64.0, 69.1, 97.7, 124.6, 129.6, 202.3.

(2*S*,3*R*,6*S*)-3-Ethyl-3,6-dihydro-2-((2*R*,*S*)-2′-hydroxybutyl)-6-isopropoxy-2*H*-pyran (20). To a solution of aldehyde **19** (396 mg, 1.87 mmol, 1.0 equiv) in THF (20 mL) was added EtMgBr (3.4 mL of a 1.0 M solution in THF, 3.36 mmol, 1.8 equiv) at 0°C. After stirring for 1 h, the reaction mixture was quenched with MeOH at 0°C and was warmed to rt. Then, a saturated aqueous NH_4Cl solution was added and extracted with ether (20 mL). After decantation of both layers, the aqueous phase was extracted with ether, and the combined organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% EtOAc in hexanes) afforded alcohol **20** (385 mg, 85%) as a 1:1 diastereomeric mixture: Colorless oil; $Rf_1 = 0.20$ and $Rf_2 = 0.27$ (silica gel, 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91–0.99 (m, 6H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.25 (d, $J = 6.4$ Hz, 3H), 1.38–1.61 (m, 4H), 1.67–1.73 (m, 2H), 1.86–1.94 (m, 1H), 3.75–3.82 (m, 1H), 3.97 (dt, $J = 5.9$, 12.4 Hz, 1H), 4.37–4.44 (m, 1H), 4.50–4.55 (m, 1H), 4.81 (bs, 1H), 5.61 (dd, $J = 10.2$ Hz, 1H), 5.70–5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 9.8, 11.4, 21.5, 23.5, 26.6, 26.9, 30.1, 40.2, 40.8, 66.3, 68.7, 70.1, 73.2, 97.7, 126.3, 127.2. FAB HRMS (NBA) m/e 265.1782, $M + Na^+$ calcd for $C_{14}H_{26}O_3$ 265.1779.

1-((2*S*,3*R*,6*S*)-3-Ethyl-3,6-dihydro-6-isopropoxy-2*H*-pyran-2-yl)-2-butanone (4). To a solution containing alcohol **20** (385 mg, 1.59 mmol, 1.0 equiv), 4 Å molecular sieves (1.6 g), and NMO (278 mg, 2.38 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) was added TPAP (56 mg, 0.16 mmol, 0.1 equiv) at 0°C. After stirring for 10 min at this temperature, the reaction mixture was stirred for an additional hour at rt. Then, the reaction mixture was diluted with ether (20 mL) and a saturated aqueous NH_4Cl solution was added. The aqueous phase was separated and extracted with ether and the combined organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes), to obtain ketone **4** (336 mg, 88%) as a colorless oil: $R_f = 0.47$ (silica gel, 25%

EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94 (t, $J = 7.5$ Hz, 3H), 1.06 (t, $J = 7.5$ Hz, 3H), 1.14 (d, $J = 5.9$ Hz, 3H), 1.25 (d, $J = 6.4$ Hz, 3H), 1.36–1.53 (m, 2H), 1.84–1.92 (m, 1H), 2.49 (q, $J = 7.5$ Hz, 2H), 2.51 (dd, $J = 4.8$, 15.6 Hz, 1H), 2.67 (dd, $J = 8.6$, 15.6 Hz, 1H), 3.96 (dt, $J = 5.9$, 12.4 Hz, 1H), 4.63–4.70 (m, 1H), 4.74 (bs, 1H), 5.63 (bd, $J = 10.2$ Hz, 1H), 5.75 (dd, $J = 5.9$, 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 7.5, 11.4, 21.4, 23.4, 26.6, 29.7, 30.3, 36.8, 40.8, 47.5, 64.6, 68.4, 97.3, 127.0, 127.5, 209.2. FAB HRMS (NBA) m/e 263.1625, $M + Na^+$ calcd for $C_{14}H_{24}O_3$ 263.1623.

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