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Synthesis of Enantiomerically Pure Highly Functionalized Furanoid Glycal and 2,5-Dihydrofuran Building Blocks[‡]

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Dedicated to Professor Dr. Ralf Miethchen[‡‡]

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Differently protected enantiomerically pure furanoid glycals (**5a**–**d**) and highly functionalized 2,5-dihydrofurans (**6a**–**b**) were synthesized from their respective 2,3,4-trisubstituted tetrahydrofurans. These furanoid glycals were identified as 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-arabino-hex-1-enitol, 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-ribo-hex-1-enitol, 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-ribo-hex-1-enitol and 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-arabino-hex-1-enitol, respectively.

Introduction

A great deal of interest has been devoted in recent years towards the synthesis of furanoid glycals, owing to the fact that they have been used as key intermediates in the preparation of structurally diverse compounds with various biological activities such as polyether antibiotics,[1a] 6-*epi*-leukotrienes C & D,[1b] palladium-mediated coupling reaction leading to C-nucleosides,[1c] antiviral and antitumour C-nucleosides,[1d] α-arabino nucleosides,[1e] 2′,3′-dideoxynucleosides[1f] and more recently 2′-deoxynuleosides.[1g] The first known glycal derivative with a furanose structure, namely, 1,4-anhydro-3,5-di-*O*-benzoyl-2-deoxy-D-*erythro*-pent-1-enitol, was synthesized by Ness and Fletcher in 1963, but several protection and deprotection steps were necessary for the synthesis of the appropriate precursor 3,5-di-*O*-benzoyl-2-*O*-*p*-nitrophenylsulfonyl-β-D-ribosyl bromide.[2] Over the years, different methodologies for the synthesis of furanoid glycals have been reported: (i) Reduction of protected glycosyl halides with reducing agents like lithium in liquid ammonia (Ireland's method) and Na-naphthalene.[3] (ii) Reaction of glycosyl phenyl sulfones with samarium(II) iodide in THF.[4] (iii) Molybdenum-catalyzed alkynol cyclization.[5] (iv) Elimination from 2-deoxypentofuranose derivatives such as 1-*O*-mesylates,[6] nucleosides[7] and 1,2-diols.[8] (v) Oxidative elimination of 1-phenylselenenylfuranosides and 2-phenylselenenyl-1,4-anhydroalditols,[9] and very recently, reaction of furanosyl sulfoxides with *n*BuLi in THF at –78 °C.[10] Similarly, the stereoselective synthesis of functionalized 2,5-dihydrofurans has also been reported due to their importance as structural motifs and presence in a wide variety of natural products exhibiting various biological activities.[11–13] As mentioned above, several methods are available for synthesis of furanoid glycals or 4,5-dihydrofurans but difficulties are generally encountered with the formation of unstable glycal,[2] usage of expensive starting materials[7] and, in some cases, low yields of the desired products; that is why improvements in the existing methods are still desirable. To overcome all these limitations, herein we wish to describe a simple protocol for the synthesis of stereochemically different furanoid glycals **5a** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-arabino-hex-1-enitol), **5b** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-ribo-hex-1-enitol), **5c** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-ribo-hex-1-enitol),[14a] **5d** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-arabino-hex-1-enitol)[3c,14] and also highly functionalized 2,5-dihydrofurans **6a**,**b** (Figure 1) from easily accessible enantiomerically pure 2,3,4-trisubstituted THF scaffolds (**2a**–**d**). The synthesis of these THF building blocks was recently reported from our laboratory.[15] Subsequently, their utility was exemplified by achieving the syntheses of jaspine B,[16a] enantiomerically pure γ-azidotetrahydrofuran carboxylic acids[16b] and oxybiotin, an oxygen analogue of biotin.[16c] Further utilization of versatile THF scaffolds **2** to obtain

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title compounds **5a**–**d** and **6a**,**b** of different configurations at all the chiral centres with ethylene glycol chain is reported herein. To the best of our knowledge, no examples of the synthesis of enantiomerically pure furanoid glycals **5a**,**b** and functionalized 2,5-dihydrofurans **6a**,**b** have been reported so far.

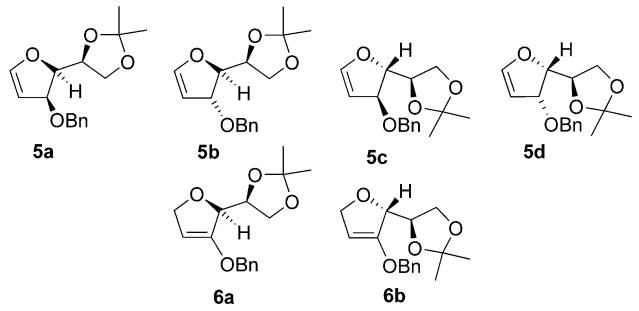
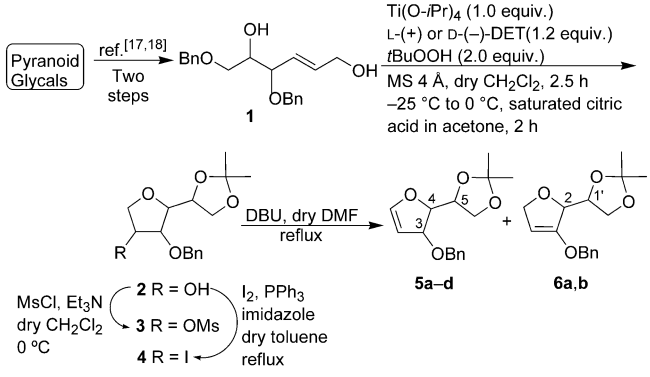


Figure 1. Structures of furanoid glycals and highly functionalized 2,5-dihydrofurans.

Results and Discussion

Our approach to obtain a family of furanoid glycals (**5a**–**d**) of different configurations at the 3-, 4- and 5-positions and functionalized 2,5-dihydrofurans (**6a**,**b**) of different configurations at the 2- and 1′-positions from enantiopure THF scaffolds (**2a**–**d**) is outlined in Scheme 1.



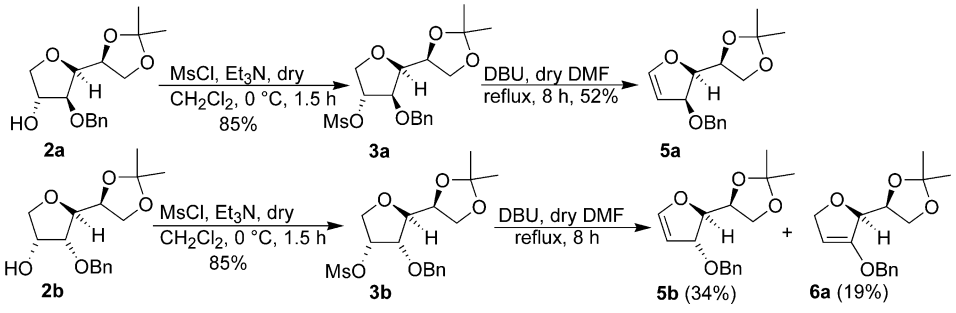
Scheme 1. General strategy for the synthesis of furanoid glycals **5a**–**d** and functionalized 2,5-dihydrofurans **6a**,**b**.

The free hydroxy group in **2a** was protected with methanesulfonyl chloride[16a,16b] in the presence of triethylamine to afford corresponding mesyl derivative **3a**. OMs-protected THF **3a** in dry DMF was subjected to a thermal elimination reaction for 8 h in the presence of DBU[19] to furnish furanoid glycal **5a** (52%) as a single product. The regioselective elimination of MsOH in this case presumably resulted from the antiperiplanar arrangement of the OMs leaving group at C4 and one of the hydrogen atoms at C5 (Scheme 2). However, a similar experiment with DBU in refluxing dry toluene or dry DCM did not afford the elimination product.

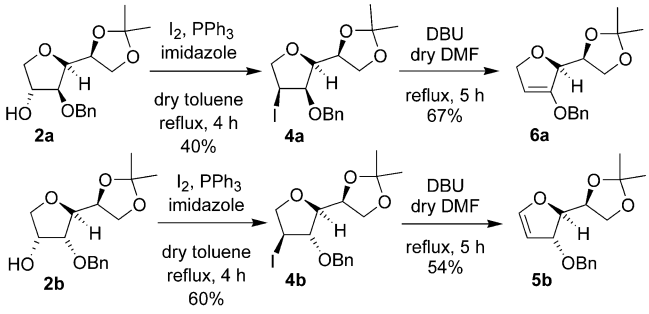
Having this result in hand, we extended our study of the elimination reaction to other mesylated THFs (**3b**–**d**) prepared from their respective THF scaffolds (**2b**–**d**) to obtain furanoid glycals (**5b**–**d**). When mesylated THF **3b** was heated at reflux with DBU in dry DMF for 8 h, a mixture of two compounds was formed. Column chromatographic purification of the mixture led to the isolation of **5b** and **6a** in 34 and 19% yield, respectively. Whereas C3 had opposite stereochemistry in **3a** and **3b**, the stereochemistry of C4 in **3b** was the same as that in **3a**, and therefore, the formation of glycal **5b** was quite obvious. The formation of more substituted olefin **6a** was also possible in this case as the leaving groups to be eliminated were in the antiperiplanar arrangement.

Here, we thought that the formation of olefin **6a** could be also possible from **2a** via an intermediate where H3 and the leaving group should be antiperiplanar. The formation of this pivotal intermediate required S_N2 displacement of the secondary hydroxy group at C4 in **2a** by an appropriate leaving group followed by its elimination along with H3 in an E2 fashion. Thus, when stereochemically inverted iodide **4a** prepared by Garegg–Samuelsson reaction[20] from **2a** was heated at reflux with DBU in dry DMF for 5 h, trisubstituted olefin **6a** was obtained as a single product in 67% yield. However, the regioselective elimination of HI from **4b** prepared from **2b**, following the above reaction conditions, gave glycal **5b** as a single product in 54% yield (Scheme 3).

Our study on the elimination reaction was further extended to other mesylated THF scaffolds. Thus, when mesylate **3c**, prepared from **2c**, in dry DMF was heated at reflux with DBU furanoid glycal **5c** was obtained as a single product in 52% yield. In contrast, thermal elimination of MsOH in **3d** obtained from THF scaffold **2d** furnished a mixture



Scheme 2. Synthesis of furanoid glycals **5a**,**b** and functionalized 2,5-dihydrofuran **6a**.



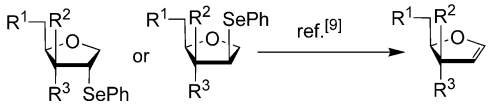
Scheme 3. Synthesis of furanoid glycal **5b** and functionalized 2,5-dihydrofuran **6a**.

of products, whose chromatographic purification led to the isolation of functionalized 2,5-dihydrofuran **6b** as the major product in 61% yield and an inseparable mixture of furanoid glycals **5d** and **5c** as minor products in a combined 5% yield. ^{1}H NMR spectroscopic analysis of the glycal mixture demonstrated that it contained **5d** and **5c** in a 1:0.2 ratio (Scheme 4).

Whereas iodo derivative **4c**, derived from **2c**, afforded functionalized 2,5-dihydrofuran **6b** as the major product in 64% yield and furanoid glycal **5c** in 29% yield upon thermal elimination, stereoisomer **4d**, obtained from **2d**, under the identical reaction conditions furnished a product (single spot on TLC) that was purified by column chromatography in 67% yield. Its ^{1}H NMR spectrum identified it as an inseparable mixture of glycals **5d** and **5c** in a 1:0.2 ratio (Scheme 5).

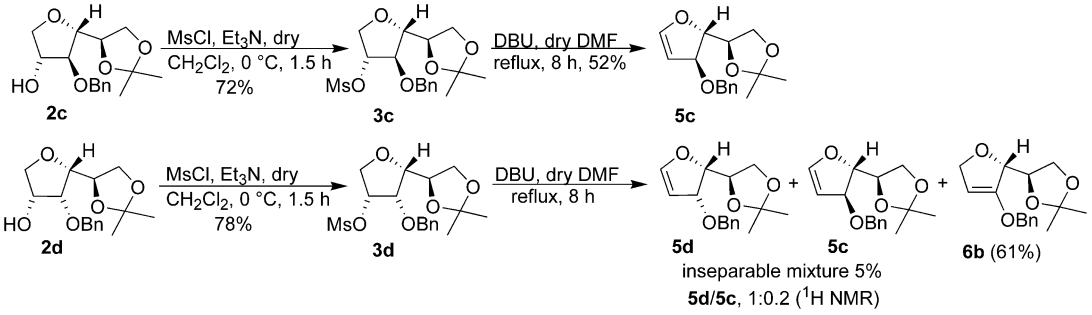
Noteworthy is that when **3d** or **4d** was heated at reflux with DBU in dry DMF C3 was epimerized in either case, resulting in the formation of an inseparable isomeric mixture of furanoid glycals containing **5c** and **5d**. Unfortunately, we do not have a suitable explanation for this.

Castillón and Kassou[9] reported the synthesis of differently protected *erythro*- and *threo*-configured furanoid glycals by oxidative elimination of their respective diastereomeric 2-deoxy-2-phenylselenenyl-1,4-anhydroalditols in the presence of *t*BuOOH, Ti(O-*i*Pr)$_4$ and Et*i*Pr$_2$N in refluxing CH_2Cl_2 or $C_2H_4Cl_2$ for 36–48 h (Scheme 6). In their study, the stereochemical requirement to obtain furanoid glycal exclusively was 1,2-*syn* elimination of PhSeOH. Here, both epimers at C2 showed identical regioselective outcome, as no 2,3-*syn* elimination of PhSeOH was observed to produce 2,5-dihydrofuran. On the contrary, in our above-described study, the stereochemical requirement was *anti* elimination of MsOH or HI to furnish either furanoid glycals or 2,5-dihydrofurans.

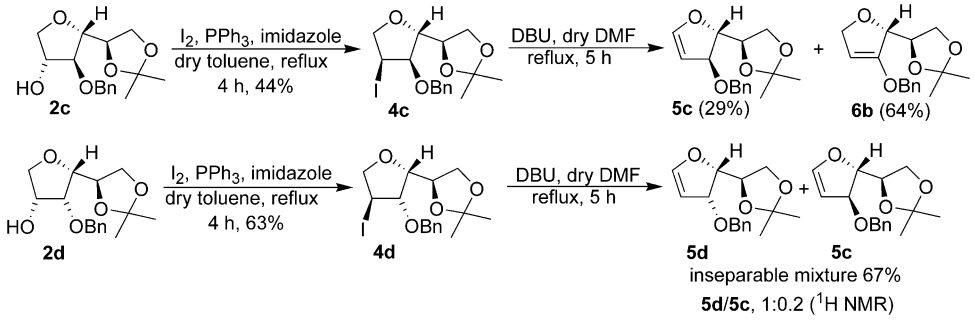


Scheme 6. Synthesis of differently protected *erythro* and *threo* furanoid glycals from diastereomeric 2-deoxy-2-phenylselenenyl-1,4-anhydroalditols.

From the above study, it can be concluded that the product distribution in each case was governed essentially by the relative disposition of the groups (mesyl or iodine at C4 and



Scheme 4. Synthesis of furanoid glycals **5c**,**d** and functionalized 2,5-dihydrofuran **6b**.



Scheme 5. Synthesis of furanoid glycals **5c**,**d** and functionalized 2,5-dihydrofuran **6b**.

neighbouring H atoms) to be eliminated. In the formation of either glycal or olefin, the E2 elimination took place most readily when the hydrogen atom and the leaving group were in an antiperiplanar arrangement. Further, it can be argued that E2 elimination of MsOH from **3b** leading to the formation of two products in which furanoid glycal **5b** (Hofmann product) was formed predominantly over Saytzeff product **6a** (more substituted olefin) may be attributed to the involvement of a conformation in which the leaving group, 4-OMs, and one of the hydrogen atoms at C5 adopted a relatively higher degree of antiperiplanar arrangement relative to the antiperiplanar arrangement of 4-OMs and H3. In contrast, the formation of Saytzeff product **6b** as the major product and a mixture of glycals **5c**,**d** as the minor product, both from **3d**, could be attributed to the comparable torsion angles subtended by the OMs group and the H atom across the C4–C3 and C4–C5 bond, respectively. Similarly, E2 elimination of HI from **4c** gave expected Saytzeff product **6b** as the major product over furanoid glycal **5c** as a result of the same reason described in the case of E2 elimination of MsOH from **3d**.

Conclusions

In summary, we have discussed the synthesis of highly functionalized furanoid glycals (4,5-dihydrofurans) **5a**–**d** and 2,5-dihydrofurans **6a**,**b**, which all have an ethylene glycol chain. The construction of the double bonds, which is the main topic of the present work, was accomplished by carrying out a base-induced E2 elimination of enantiomerically pure C4 mesylate or iodo THF scaffolds (**3** or **4**) by utilizing inexpensive reagents with a simple experimental and workup procedure. The reaction conditions (DBU, dry DMF, reflux) employed to obtain the title chiral building blocks were optimized depending on the stereochemistry of the starting materials. We also showed that furanoid glycals **5a** and **5c** or functionalized 2,5-dihydrofurans **6a** and **6b** can be synthesized exclusively or in major quantity from the same 2,3,4-trisubstituted THF scaffolds **2a** and **2c**, respectively, by changing the leaving group at C4. Furthermore, it can be emphasized that our present study provides two pairs of enantiomeric furanoid glycals (4,5-dihydrofurans) **5a**, **5d** and **5b**, **5c** and one pair of enantiomeric 2,5-dihydrofurans **6a**, **6b** (Figure 1). These furanoid glycals and functionalized 2,5-dihydrofurans have various sites of diversification (Figure 2) and, therefore, they may find wide synthetic applications as important chiral building blocks for the generation of structurally diverse compounds. They could also be utilized for the synthesis of naturally occurring compounds or molecules of various biological interest. Work in this direction is currently ongoing in our laboratory.

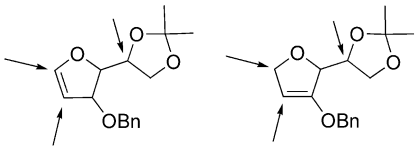


Figure 2. Sites of diversification.

Experimental Section

General Methods: Organic solvents were dried by standard methods. All products were characterized by ^1H, ^{13}C, 2D homonuclear COSY (correlation spectroscopy) for compound **5b**, heteronuclear single quantum coherence (HSQC), IR, MS (ESI) and HRMS (EI; C, H, O). Analytical TLC was performed by using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was accomplished with $CeSO_4$ (1% in 2.0 N H_2SO_4) and subsequent charring over a hot plate. Column chromatography was performed by using silica gel (60–120 mesh). NMR spectra were recorded with a Bruker Avance 300 (300 MHz for ^1H and 75 MHz for ^{13}C). Experiments were recorded in $CDCl_3$ or $CDCl_3$ + CCl_4 (1:1) at 25 °C. Chemical shifts are given on the δ scale and are referenced to TMS at δ = 0.00 ppm for proton and 0.00 ppm for carbon. For ^{13}C NMR, reference $CDCl_3$ appeared at δ = 77.00 ppm. For ^{13}C NMR in $CDCl_3$ + CCl_4, CCl_4 appeared at δ = 96.2 ppm. IR spectra were recorded with Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded with a JEOL JMS-600H high-resolution spectrometer by using EI mode at 70 eV. Optical rotations were determined with an Autopol III polarimeter by using a 1 dm cell at 25–29 °C in chloroform as the solvent; concentrations mentioned are in g/100 mL.

General Procedure for the Preparation of 4-Iodo THF Scaffolds: A stirred solution of **2a** (110 mg, 0.37 mmol) in dry toluene (10 mL) was treated with PPh_3 (196 mg, 0.748 mmol), imidazole (108 mg, 1.49 mmol) and iodine (190 mg, 0.748 mmol). The reaction mixture was heated at reflux at 110 °C for 4 h until completion of the reaction (TLC control) and then cooled to room temperature. Afterwards, the reaction mixture was diluted with EtOAc (5 mL), and the solvent was removed under reduced pressure. The excess amount of iodine in the residue obtained was quenched with a saturated aqueous $Na_2S_2O_7$ solution (5 mL), and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated to afford the crude product that was purified by column chromatography (60–120 mesh silica gel) to furnish pure **4a** (61 mg, 40%). Similar reaction protocol was adopted for the synthesis of **4b**, **4c** and **4d**.

General Procedure for the Preparation of Furanoid Glycals from Mesylated THF Scaffolds: To a stirred solution of mesylate **3a** (100 mg, 0.268 mmol) in dry DMF (5 mL) was added DBU (0.1 mL, 0.672 mmol), and the mixture was stirred under reflux for 8 h until completion of the reaction (TLC control). The resulting reaction mixture was cooled to room temperature and water (5 mL) was added. Afterwards, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (60–120 mesh silica gel) to furnish pure furanoid glycal **5a** (39 mg, 52%). Similar reaction protocol was adopted for the synthesis of compounds **5b**, **5c** and **5d**.

General Procedure for the Preparation of Furanoid Glycals from 4-Iodo THF Scaffolds: To a solution of compound **4b** (46 mg, 0.114 mmol) in dry DMF (5 mL) was added DBU (0.04 mL, 0.284 mmol), and the mixture was stirred under reflux for 5 h until completion of the reaction (TLC control). The resulting reaction

mixture was cooled to room temperature and diluted with water (5 mL). Afterwards, the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography (60–120 mesh silica gel) furnished pure furanoid glycal **5b** (17 mg, 54%).

General Procedure for the Preparation of Functionalized 2,5-Dihydrofurans (6a,b) either from Mesylated or 4-Iodo THF Scaffolds: General procedure to obtain functionalized 2,5-dihydrofurans was similar to the general procedure followed for the preparation of furanoid glycals.

Compound 4a: Light yellow oil; yield: 61 mg (40%). Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = +3.28 (*c* = 0.19, $CHCl_3$). R_f = 0.59 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 697, 1061, 1250, 1637, 2922 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.35 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 3.91–4.13 (m, 6 H, 2′-H, 2-H, 3-H, 5-H), 4.19–4.34 (m, 2 H, 1′-H, 4-H), 4.72 (d, *J* = 10.5 Hz, 1 H, CH_2Ph), 4.87 (d, *J* = 10.5 Hz, 1 H, CH_2Ph), 7.30–7.45 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.8 (CH), 25.4 (CH_3), 26.8 (CH_3), 67.2 (CH_2), 73.7 (CH), 74.5 (CH_2Ph), 74.6 (CH_2), 79.4 (CH), 81.4 (CH), 109.0 (C_q), 127.9 (ArC), 128.3 (ArC), 128.4 (ArC), 137.6 (ArC_q) ppm. MS (ESI): *m*/*z* = 405 $[M + H]^+$. HRMS (EI): calcd. for $C_{15}H_{18}IO_4$ $[M - CH_3]^+$ 389.0250; found 389.0255.

Compound 4b: Light yellow oil; yield: 91 mg (60%). Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = +6.47 (*c* = 0.17, $CHCl_3$). R_f = 0.65 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 752, 1072, 1265, 1517, 1650, 2919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.37 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.78 (dd, *J* = 3.1, 7.8 Hz, 1 H, 3-H), 3.93 (dd, *J* = 4.9, 8.6 Hz, 1 H, 2a′-H), 4.06–4.19 (m, 3 H, 2b′-H, 5-H), 4.23–4.26 (m, 1 H, 4-H), 4.29–4.35 (m, 1 H, 1′-H), 4.48–4.49 (m, 1 H, 2-H), 4.62 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.67 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 7.31–7.39 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.9 (CH), 25.2 (CH_3), 26.8 (CH_3), 67.4 (CH_2), 72.2 (CH_2Ph), 76.3 (CH_2), 76.6 (CH), 86.3 (CH), 89.1 (CH), 109.7 (C_q), 127.9 (ArC), 128.0 (ArC), 128.5 (ArC), 137.5 (ArC_q) ppm. MS (ESI):*m*/*z* = 405 $[M + H]^+$. HRMS (EI): calcd. for $C_{15}H_{18}IO_4$ $[M - CH_3]^+$ 389.0250; found 389.0242.

Compound 4c: Light yellow oil; yield: 66 mg (44%). Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = +26.9 (*c* = 0.19, $CHCl_3$). R_f = 0.58 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 631, 1098, 1237, 1517, 2919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.32 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.70–3.83 (m, 2 H, 2a′-H, 3-H), 3.89–4.05 (m, 4 H, 1′-H, 2b′-H, 2-H, 5a-H), 4.15–4.22 (m, 2 H, 4-H, 5b-H), 4.57 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.68 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 7.27–7.41 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.9 (CH), 25.5 (CH_3), 26.5 (CH_3), 66.2 (CH_2), 72.2 (CH_2Ph), 74.9 (CH_2), 75.7 (CH), 78.9 (CH), 82.8 (CH), 109.7 (C_q), 127.9 (ArC), 128.2 (ArC), 128.4 (ArC), 137.2 (ArC_q) ppm. MS (ESI): *m*/*z* = 405 $[M + H]^+$. HRMS (EI): calcd. for $C_{15}H_{18}IO_4$ $[M - CH_3]^+$ 389.0250; found 389.0260.

Compound 4d: Light yellow oil; yield: 95 mg (63%). Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = +2.41 (*c* = 0.27, $CHCl_3$). R_f = 0.68 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 754, 1071, 1215, 1376, 1634, 2375, 2922 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.35 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 3.89–3.97 (m, 1 H, 2a′-H), 4.01–4.16 (m, 2 H, 2b′-H, 5a-H), 4.19–4.25 (m, 1 H, 4-H), 4.28–4.36 (m, 3 H, 1′-H, 2-H, 3-H), 4.50 (dd, *J* = 5.1, 10.5 Hz, 1 H, 5b-H), 4.60 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.66 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 7.31 (br. s, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4, 25 °C): δ = 23.6 (CH), 25.6 (CH_3), 27.0 (CH_3), 67.2 (CH_2), 72.7 (CH_2Ph), 73.4 (CH), 76.4 (CH_2), 80.7 (CH), 86.9 (CH), 108.9 (C_q), 127.8 (ArC), 128.1 (ArC), 128.5 (ArC), 137.5 (ArC_q) ppm. MS (ESI): *m*/*z* = 405 $[M + H]^+$. HRMS (EI): calcd. for $C_{15}H_{18}IO_4$ $[M - CH_3]^+$ 389.0250; found 389.0249.

Compound 5a: Colourless oil; yield: 39 mg (52%) from **3a**. Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = +95.29 (*c* = 0.58, $CHCl_3$). R_f = 0.68 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 732, 1065, 1260, 1352, 1461, 1595, 2856, 2926 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.39 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.99 (dd, *J* = 6.4, 8.7 Hz, 1 H, 6a-H), 4.11 (dd, *J* = 6.7, 8.6 Hz, 1 H, 6b-H), 4.44 (dd, *J* = 5.1, 7.0 Hz, 1 H, 4-H), 4.49–4.62 (m, 3 H, 5-H, CH_2Ph), 4.63–4.67 (m, 1 H, 3-H), 5.29 (t, *J* = 2.6 Hz, 1 H, 2-H), 6.63 (d, *J* = 2.7 Hz, 1 H, 1-H), 7.30–7.37 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.2 (CH_3), 26.5 (CH_3), 65.9 (CH_2), 71.0 (CH_2Ph), 73.1 (CH), 79.2 (CH), 84.1 (CH), 101.9 (CH), 108.7 (C_q), 127.5 (ArC), 127.6 (ArC), 128.4 (ArC), 138.4 (ArC_q), 150.6 (CH) ppm. MS (ESI): *m*/*z* = 299 $[M + Na]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362; found 276.1361.

Compound 5b: Colourless oil; yield: 25 mg (34%) from **3b**, 17 mg (54%) from **4b**. Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = –40.0 (*c* = 0.09, $CHCl_3$). R_f = 0.7 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 738, 1069, 1213, 1372, 1457, 1615, 2341, 2370, 2855, 2923 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.36 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.84–3.90 (m, 1 H, 5-H), 3.96 (dd, *J* = 4.8, 8.6 Hz, 1 H, 6a-H), 4.09 (dd, *J* = 6.3, 8.7 Hz, 1 H, 6b-H), 4.38 (dd, *J* = 2.4, 8.2 Hz, 1 H, 4-H), 4.51 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.59 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.73–4.76 (m, 1 H, 3-H), 5.18 (t, *J* = 2.6 Hz, 1 H, 2-H), 6.55 (dd, *J* = 0.7, 2.6 Hz, 1 H, 1-H), 7.29–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4, 25 °C): δ = 25.4 (CH_3), 27.0 (CH_3), 67.3 (CH_2), 69.6 (CH_2Ph), 74.2 (CH), 82.5 (CH), 86.7 (CH), 101.0 (CH), 109.7 (C_q), 127.6 (ArC), 127.8 (ArC), 128.4 (ArC), 138.4 (ArC_q), 149.9 (CH) ppm. MS (ESI): *m*/*z* = 277 $[M + H]^+$, 299 $[M + Na]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362; found 276.1359.

Compound 5c: Colourless oil; yield: 39 mg (52%) from **3c**, 9 mg (29%) from **4c**. Eluent for column chromatography: EtOAc/hexane (1:49). $[\alpha]_D^{25}$ = +98.6 (*c* = 0.60, $CHCl_3$). R_f = 0.71 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 738, 1068, 1216, 1376, 1457, 1613, 2366, 2927 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4, 25 °C): δ = 1.34 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.77–3.84 (m, 1 H, 5-H), 3.93 (dd, *J* = 4.8, 8.6 Hz, 1 H, 6a-H), 4.06 (dd, *J* = 6.4, 8.5 Hz, 1 H, 6b-H), 4.32 (dd, *J* = 2.3, 8.5 Hz, 1 H, 4-H), 4.48 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.58 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.71 (br. s, 1 H, 3-H), 5.13 (t, *J* = 2.5 Hz, 1 H, 2-H), 6.50 (d, *J* = 2.5 Hz, 1 H, 1-H), 7.25–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.2 (CH_3), 26.8 (CH_3), 67.1 (CH_2), 69.6 (CH_2Ph), 74.2 (CH), 82.4 (CH), 86.5 (CH), 101.0 (CH) 109.7 (C_q), 127.6 (ArC), 127.8 (ArC), 128.4 (ArC), 138.3 (ArC_q), 150.0 (CH) ppm. MS (ESI): *m*/*z* = 277 $[M + H]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362; found 276.1363.

Compounds 5d+5c: Inseparable diastereomeric mixture (**5d/5c**, 1:0.2); colourless oil; yield: 4 mg (5%) from **3d**, 21 mg (67%) from **4d**. Eluent for column chromatography: EtOAc/hexane (1:49). R_f = 0.71 (EtOAc/hexane, 1:4). ^1H NMR (300 MHz, $CDCl_3$ + CCl_4, 25 °C): δ = 1.34 (s, 0.7 H, CH_{3D}), 1.37 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.46 (s, 0.7 H, CH_{3D}), 3.79–3.84 (m, 0.2 H, 5-H_D), 3.95 (dd, *J* = 6.3, 8.6 Hz, 1 H, 6a-H), 4.07 (dd, *J* = 6.5, 8.6 Hz, 1 H, 6b-H), 4.31 (d, *J* = 2.5 Hz, 0.1 H, 4-H_D), 4.35 (t, *J* = 6.3 Hz, 1 H, 4-H), 4.47–4.57 (m, 4 H, 5-H, CH_2Ph, CH_2Ph_D), 4.61 (dd, *J* = 2.3, 7.1 Hz, 1 H, 3-H), 4.71–4.72 (m, 0.2 H, 3-H_D), 5.13 (t, *J* = 2.7 Hz, 0.2 H, 2-H_D), 5.24 (t, *J* = 2.5 Hz, 1 H, 2-H), 6.49 (d, *J* = 2.5 Hz, 0.2 H, 1-H_D), 6.58 (d, *J* = 2.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$ + CCl_4, 25 °C): δ = 25.4 (CH_{3D}), 25.5 (CH_3), 26.7 (CH_3), 27.0 (CH_{3D}), 66.2 (CH_2), 67.2 (CH_{2D}), 69.6 (CH_2Ph_D), 71.0 (CH_2Ph), 73.0 (CH), 74.2 (CH_D), 79.3 (CH), 82.5 (CH_D), 84.3 (CH), 86.7 (CH_D), 101.0 (CH_D), 102.0 (CH), 108.8 (C_q), 127.5, 127.6, 127.8, 128.4 (ArC, ArC_D), 138.5 (ArC_q), 149.9 (CH_D), 150.5 (CH) ppm. MS (ESI): *m*/*z* = 299 $[M + Na]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362; found 276.1357.

Compound 6a: Colourless oil; yield: 14 mg (19%) from **3b**, 21 mg, (67%) from **4a**. Eluent for column chromatography: EtOAc/hexane (1:24). $[\alpha]_D^{25}$ = –14.2 (*c* = 0.12, $CHCl_3$). R_f = 0.48 (EtOAc/hexane, 1:4). IR (neat): $\tilde{\nu}$ = 765, 1072, 1222, 1375, 1654, 2363, 2858, 2926 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.37 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.89–3.97 (m, 2 H, 2′-H), 4.35 (td, *J* = 2.9, 6.9 Hz, 1 H, 1′-H), 4.65–4.67 (m, 2 H, 5-H), 4.78 (d, *J* = 1.6 Hz, 1 H, 4-H), 4.80–4.85 (m, 1 H, 2-H), 4.87 (br. s, 2 H, CH_2Ph), 7.32–7.40 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.4 (CH_3), 26.3 (CH_3), 64.3 (CH_2), 72.3 (CH_2Ph), 73.7 (CH_2), 77.3 (CH), 80.7 (CH), 93.0 (CH), 109.5 (C_q), 127.3 (ArC), 128.2 (ArC), 128.6 (ArC), 136.1 (ArC_q), 154.3 (C_q) ppm. MS (ESI): *m*/*z* = 299 $[M + Na]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362; found 276.1370.

Compound 6b: Colourless oil; yield: 45 mg (61%) from **3d**, 20 mg (64%) from **4c**. Eluent for column chromatography: EtOAc/hexane (1:24). $[\alpha]_D^{25}$ = +18.2 (*c* = 0.17, $CHCl_3$). R_f = 0.41 (EtOAc/hexane, 1:4): IR (neat): $\tilde{\nu}$ = 767, 1071, 1218, 1662, 2854, 2923 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.89–3.97 (m, 2 H, 2′-H), 4.35 (td, *J* = 2.9, 6.9 Hz, 1 H, 1′-H), 4.66–4.68 (m, 2 H, 5-H), 4.78 (d, *J* = 1.5 Hz, 1 H, 4-H), 4.81–4.84 (m, 1 H, 2-H), 4.87 (br. s, 2 H, CH_2Ph), 7.31–7.41 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.4 (CH_3), 26.3 (CH_3), 64.2 (CH_2), 72.3 (CH_2Ph), 73.7 (CH_2), 77.3 (CH), 80.7 (CH), 93.0 (CH), 109.4 (C_q), 127.3 (ArC), 128.2 (ArC), 128.6 (ArC), 136.1 (ArC_q), 154.2 (C_q) ppm. MS (ESI): *m*/*z* = 299 $[M + Na]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.1362; found 276.1352.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds.

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