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Carbohydrate Research 340 (2005) 1301–1309
Carbohydrate RESEARCH

Highly functionalised cyclobutanols via samarium(II) iodide-induced pinacol cyclisations of carbohydrate-derived 1,4-diketones

D. Bradley G. Williams,* Judy Caddy and Kevin Blann

Department of Chemistry, University of Johannesburg, PO Box 524, Auckland Park, 2006, South Africa

Received 31 May 2004; received in revised form 11 February 2005; accepted 11 February 2005
Available online 23 March 2005

Abstract—D-Ribofuranose and D-arabinofuranose derivatives were converted in a few steps into their 1,4-diketone derivatives, which were pinacol cyclised under the action of SmI_2 to form the corresponding chiral cyclobutanediol products. These products can potentially be applied to the synthesis of anti-viral agents, some of whose structures incorporate chiral cyclobutanediol moieties.

Keywords: Carbocycles; Carbohydrates; Radical reactions; Samarium

1. Introduction

The pinacol coupling reaction is a well-known process,[1] which continues to be employed in the synthesis of complex organic molecules.[2] Its intramolecular version provides a direct route to cyclic 1,2-diols, which can be further elaborated into a range of functional groups. A number of metal reducing agents promote pinacol coupling reactions,[3] but of these samarium(II) iodide is frequently superior in terms of chemical yield, and chemo- and stereoselectivity.[4] The SmI_2-induced conversion of carbohydrates into carbocycles has become well documented in the past few years,[5] and some chiral cyclopentane-[4b,5h] and cyclohexanediols[2b,c,5h] have been prepared using the Sm^{2+}-mediated pinacol coupling reaction. The same reaction to prepare cyclobutanediols from carbohydrates has, to our knowledge, not been reported. Chiral, non-racemic cyclobutanols are highly desirable from a pharmaceutical/medicinal perspective, since such materials form integral parts of various anti-viral agents[6] and sedatives.[7] Our work on Sm(II)-induced 4-*exo*-*trig* cyclisations[8] of carbohydrate derivatives into chiral cyclobutane derivatives suggested that a pinacol reaction might also be employed to form small rings, especially chiral 1,2-diols. We herein describe the conversion of some carbohydrate derivatives (of D-ribose and D-arabinose) into chiral cyclobutane-1,2-diol products.

2. Results and discussion

Hoffmann and co-workers[9] have previously described a 1,4-pinacolisation methodology employing SmI_2 that is useful for the production of strained unfunctionalised systems containing a 1,2-cyclobutanediol moiety. We believed that a SmI_2-mediated pinacolisation would be an appropriate technology for preparing functionalised chiral cyclobutane derivatives, and, in keeping with our continued interest in SmI_2-promoted transformations,[5a,b,8,10] we turned our attention to carbohydrate-derived 1,4-diketones. These diketone substrates were readily accessible by treatment of the appropriate lactol precursors with Grignard- or lithium reagents, and the diols so obtained were smoothly oxidised directly to the diketones using Swern methodology (see Experimental section).

The investigation was initiated with the synthesis of the diketone **2** from the isopropylidene-protected 5-deoxy-D-ribose derivative **1** (prepared from D-ribose, see Ref. 11) using straightforward transformations.

* Corresponding author. Tel.: +27 11 489 3431; fax: +27 11 489 2819; e-mail: dbgw@rau.ac.za

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doi:10.1016/j.carres.2005.02.006

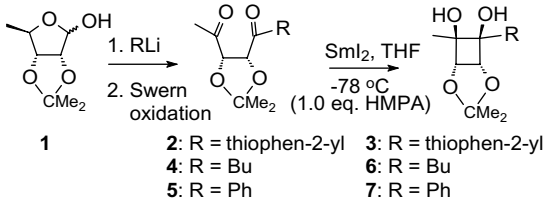
The substrate **2** was treated with SmI_2 using a variety of conditions, including those discussed by Hoffmann,[9] which involved addition of the substrate in THF to a soln of SmI_2 in THF at reflux. After some experimentation, a best yield of 55% of the desired cyclobutanol derivative **3** was obtained when treating the substrate diketone **2** with SmI_2 in THF at −78 °C (Scheme 1).

The assigned stereochemistry of cyclobutanediol **3** was based on extensive NOE NMR studies. The assignment took into account the fact that the cis relative stereochemistry of the diol moiety is certain since the Sm-mediated pinacol reaction is a stereospecific reaction,[2c,5g,h,9a] together with the known absolute (and *cis* relative) stereochemistry at the isopropylidene ring system (Chart 1).

The 'direction' of cyclisation (i.e., whether the diol moieties are 'up' or 'down' on the product as drawn) is primarily determined by the relative size/steric bulk of the chelated samarium ion versus that of the terminal functional groups adjacent to the carbonyl functionality in the starting material, together with the presence/absence of a ring system or other bulky group on the ring which would enhance the directing effect. For example, the isopropylidene-tethered ribose derivatives typically provide products in which the diol is 'up' on the product, since the sterically demanding chelated Sm(III) ion and its attendant ligands (lanthanide complexes demonstrate high co-ordination numbers[12]) prefer an orientation trans with respect to the bulky isopropylidene group in the transition state, as shown in Chart 2. We have previously observed this effect in the preparation of cyclobutanes via a ketyl-olefin radical cyclisation, in which the products of cyclisation were also predominantly those in which the cyclisation was effected with the samarium ion trans with respect to the isopropylidene group.[8]

The pinacol cyclisation step was not as successful for other diketone substrates, including those structurally similar to **3** and others that were more highly functionalised. For example, diketones **4** and **5** (Scheme 1) were subjected to SmI_2-mediated pinacol cyclisation under conditions described above, without success. However, the addition of HMPA as co-solvent (1 equiv) allowed successful reactions, affording diols **6** (12%) and **7** (10%), respectively. This co-solvent activates SmI_2[13] but also inhibits pinacol reactions,[12] as chelation of the samarium by the diketone[14] is prevented due to the presence of a stable Sm-HMPA complex. Nonetheless, studies in our laboratories have shown that 1 equiv of HMPA activates SmI_2 while still allowing pinacolisation reactions.[15]

Other D-ribose derivatives investigated included diketones **11** and **12** (Scheme 2). Diketone **11** failed altogether to demonstrate the cyclisation reaction under a wide range of reaction conditions, providing instead products indicative of α-elimination (see Scheme 3 for representative structures), indicated primarily by signals corresponding to aliphatic CH_3 and CH_2 moieties in the respective NMR spectra. (For a complete discussion on Sm(II)-mediated elimination reactions, see Ref. 16.) However, the more reactive aromatic-conjugated ketone[10a] **12**, when subjected to SmI_2-mediated cyclisation



Scheme 1.

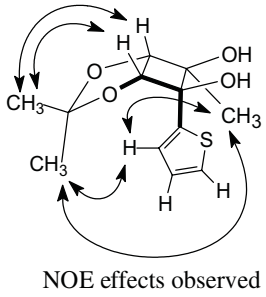


Chart 1.

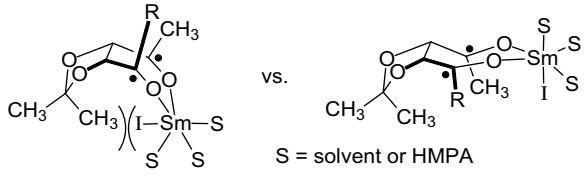
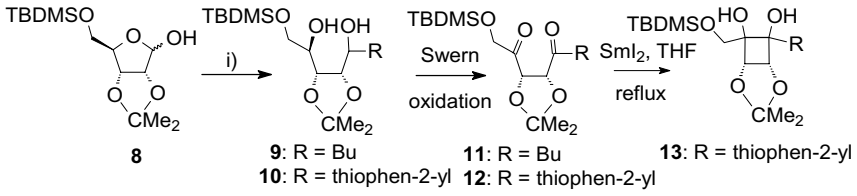
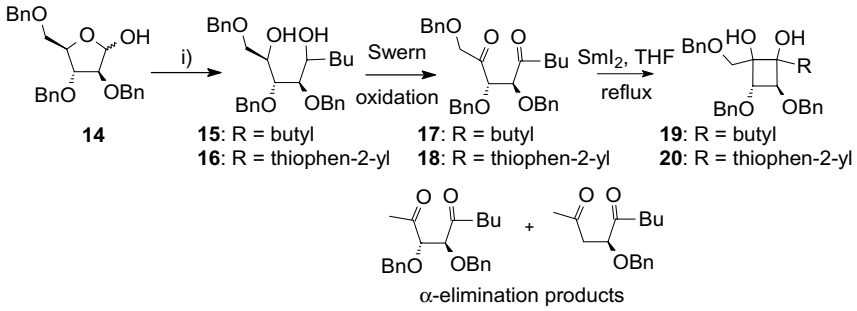


Chart 2.



Scheme 2. (i) BuMgBr, Et_2O or thiophen-2-yllithium, THF.



Scheme 3. (i) BuMgBr, Et_2O or thiophen-2-yllithium, THF.

allowed isolation of product **13** (Scheme 2) in a yield of 8%, again affording multiple products of α-elimination.

Diketone substrates for the pinacol cyclisation step bearing different stereochemistry to those described above, namely **17** and **18**, were readily prepared from tri-*O*-benzyl D-arabinose (Scheme 3). These diketones were subjected to reaction with SmI_2 in THF under reflux, affording cyclic products **19** and **20** in yields of 15% and 20%, respectively. These reactions clearly demonstrated that the rotational restriction imposed by the isopropylidene ring of the corresponding ribose derivatives was not a prerequisite for pinacol coupling reactions, in contradistinction to the 4-*exo-trig* reactions that generate chiral cyclobutanes but which specifically require a rotationally restrictive molecular make-up.[8] This outcome rests with the fact that the pinacolisation requires both ketone oxygens of the molecule to be simultaneously complexed to the Sm-ion (see Chart 2), which, in the event, imposes a specific conformation on the ketyl-radical intermediates.

Pinacol coupling designed to prepare small rings is, this research demonstrates, not as general as one might expect after reviewing Hoffmann's work since in no case in that work did a substrate possess leaving groups α to the carbonyls. What the present work has established is that, in the presence of a leaving group, elimination of that group is frequently preferred over a pinacol reaction that will generate a strained ring system. It is therefore important to bear this in mind when planning a synthesis involving this methodology.

In conclusion, we have developed a procedure for the conversion of D-ribose and D-arabinose derivatives into highly functionalised, chiral, non-racemic cyclobutanes, and have exposed some limitations of this reaction as applied to multifunctional substrates. The success of the cyclisation reaction is rather dependent upon the nature of the functionality α to the carbonyl groups (i.e., aromatic vs aliphatic ketones) and to a larger extent on the presence or absence of a leaving group α to the carbonyl. Additionally, it has been found that small amounts of HMPA additive were beneficial to especially difficult reactions.

3. Experimental

3.1. General

Thin layer chromatography (TLC) was conducted quantitatively on Merck GF_{254} pre-coated silica gel glass plates (0.25 layer). Visualisation was achieved under UV light (254 nm) and/or after spraying the TLC plate with a chromic acid soln followed by heating. 'Flash column chromatography' refers to column chromatography under nitrogen pressure (ca. 50 kPa). The columns were loaded with E. Merck Kieselgel 60 (230–400 mesh) and eluted with appropriate solvent mixtures in a vol/vol ratio. Acetone was dried over anhyd K_2CO_3 for 24 h. The salt was filtered off and the solvent subsequently distilled from 3 Å molecular sieves and stored under N_2. THF was pre-dried over freshly ground KOH, which was then filtered off and the solvent was dried using sodium-benzophenone under N_2. The solvent was distilled under N_2 immediately prior to use. Dichloromethane was heated over CaH_2 under N_2 with subsequent distillation. MeOH was distilled from Mg/I_2 and stored over 3 Å molecular sieves. Ethyl acetate was distilled from K_2CO_3 using a Vigreux distillation column. Hexanes were simply distilled prior to use. HMPA was heated over CaH_2 under an argon atmosphere for one week prior to its use. The solvent was only used if freshly distilled. Pyridine was pre-dried over anhyd $CaCl_2$ and then distilled from 3 Å molecular sieves. NMR spectra were recorded using a Varian Gemini 2000, 300 MHz spectrometer. The samples were usually made up in $CDCl_3$. The ^1H NMR data are referenced to the residual solvent peak of $CDCl_3$ [δ = 7.24 ppm]. The relative stereochemistry was determined after studying nuclear Overhauser effect spectra. ^{13}C NMR data are referenced to the solvent peak of $CDCl_3$ (δ = 77.0 ppm). The compilation of fragmentation determinations were recorded on a Finnigan Matt 8200 spectrometer at an electron impact of 70 eV, while FAB-HRMS spectra were recorded on a Varian E7070 using glycerol or nitrobenzylalcohol as the matrix. A Perkin–Elmer 881 spectrometer was used to record IR spectra using dry chloroform as the solvent.

A Jasco model DIP-730 spectropolarimeter having a cell with a 10 mm path length was used to determine optical rotations. The concentration *c* indicates the concentration of the sample in grams per 100 mL of soln. Melting points were determined using a Reichert Thermopan microscope together with a Koffler hot-stage and are uncorrected. All reactions were performed in flamed out glass apparatus using dry solvents unless otherwise stated. All samarium diiodide reactions were carried out under argon using degassed solvents while standard chemistry was done under an atmosphere of nitrogen. Room temperature refers to a temperature ranging from 20 to 25 °C. The standard work-up procedure involved adding water to the reaction mixture and extracting it repeatedly with EtOAc. The organic layer was then separated and rinsed with brine and finally with water. After separation and drying of the organic phase with anhyd $MgSO_4$, the solvent was removed under diminished pressure at a temperature of ca. 40 °C. The crude product was then purified by flash column chromatography.

3.2. (2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(thiophen-2-yl)-1,4-pentanedione (2)

To a soln of thiophene (505 mg, 6.00 mmol) in THF (20 mL) was added *n*-butyllithium (1.0 equiv, 1.6 M hexane soln) dropwise at 0 °C. The soln was allowed to warm to room temperature and stirred for a further hour. This soln was added dropwise to a soln of **1** (348 mg, 2.00 mmol) in THF (9 mL) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was quenched with H_2O, the solvent was removed under diminished pressure and a CH_2Cl_2/water extraction was carried out.

The crude product diol was partially purified on a silica column (this material was found to be somewhat unstable) and directly subjected to Swern oxidation as follows:

A soln of trifluoroacetic anhydride (TFAA, 1.41 mL, 10.00 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise to a soln of Me_2SO (0.71 mL, 10.00 mmol) in CH_2Cl_2 (9.0 mL) at −78 °C and stirred for 1 h at the same temperature. To the stirring mixture was added dropwise a soln of the crude product from the directly preceding reaction in CH_2Cl_2 (6.0 mL) at −78 °C, and thereafter the reaction mixture was stirred for an additional 2 h at the same temperature. A soln of Et_3N (2.23 mL, 16.00 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise, and the stirring continued for 0.5 h at −78 °C. The reaction mixture was removed from cooling bath and allowed to reach room temperature with stirring. The reaction mixture was partitioned between CH_2Cl_2 and ice water, and the product was purified by column chromatography (5:1 hexanes–EtOAc), and isolated as a light yellow oil (150 mg, 0.591 mmol, 30% over two steps).

TLC: R_f 0.58 (2:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3620, 3440, 3040, 1710, 1422 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 7.88 (dd, 1H, *J* 3.9 and 1.2 Hz, H2′), 7.68 (dd, 1H, *J* 5.1 and 1.2 Hz, H4′), 7.12 (dd, 1H, *J* 5.1 and 3.9 Hz, H3′), 5.42 (d, 1H, *J* 6.8 Hz, H2), 4.70 (d, 1H, *J* 6.8 Hz, H3), 2.28 (s, 3H, H5a, b and c), 1.54 (s, 3H, C*H*$_3$-isopropylidene), 1.45 (s, 3H, C*H*$_3$-isopropylidene); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 206.2 (C4), 188.0 (C1), 141.3 (C1′), 135.1 (C3′), 134.3 (C2′), 128.2 (C4′), 112.5 (acetal-C), 82.2 (C3), 80.8 (C2), 27.7 (C5), 26.9 (*C*H$_3$-isopropylidene), 25.7 (*C*H$_3$-isopropylidene); HRMS: Found 254.3140. Calculated for $C_{12}H_{14}SO_4$ 254.3146; EIMS: *m*/*z* 254 (M^+, 28%), 136 (100%).

3.3. (1*R*,2*S*,3*R*,4*S*)-2-Methyl-3,4-*O*-isopropylidene-1-(thiophen-2-yl)-cyclobutane-1,2,3,4-tetraol (3)

The diketone **2** (100 mg, 0.394 mmol) in THF (8 mL) was added dropwise to a soln of SmI_2 (1.18 mmol, 3.0 equiv) in THF (12 mL) at −78 °C under argon. The reaction mixture was allowed to warm to room temperature over 24 h and then quenched by exposure to the atmosphere. The mixture was filtered through a thin pad of silica and chromatographed, affording the desired product as an oil (55 mg, 0.215 mmol, 55%).

$[\alpha]_D$: −16.4 (*c* 1, EtOAc); TLC: R_f 0.57 (2:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3600, 3440, 3040, 1660 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 7.26–7.23 (m, 2H, H3′, H4′), 6.98 (dd, 1H, *J* 4.8 and 3.9 Hz, H2′), 4.61 (d, 1H, *J* 5.9 Hz, H2), 4.52 (d, 1H, *J* 5.9 Hz, H3), 3.86 (br s, 1H, OH), 3.05 (br s, 1H, OH), 1.58 (s, 3H, C*H*$_3$-isopropylidene), 1.31 (s, 3H, C*H*$_3$-isopropylidene), 1.16 (s, 3H, CH_3); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 142.0 (C1′), 126.6 (C4′), 125.7 (C3′), 125.0 (C2′), 115.2 (acetal-C), 82.0 (C2), 80.4 (C1), 79.7 (C4), 74.2 (C3), 25.7 (*C*H$_3$-isopropylidene), 25.4 (*C*H$_3$-isopropylidene), 20.1 (CH_3); HRMS: Found 256.0768. Calculated for $C_{12}H_{16}SO_4$ 256.0769; EIMS: *m*/*z* 256 (M^+, 7%), 136 (100%).

3.4. (3*S*,4*R*)-3,4-Dihydroxy-3,4-*O*-isopropylidene-2,5-nonanedione (4)

Magnesium (103 mg, 4.25 mmol) was added to a flamed out two-neck flask fitted with a reflux condenser and a dropping funnel. A soln of butyl bromide (0.46 mL, 4.28 mmol) in THF (4 mL) was added dropwise to the magnesium with constant stirring. A small iodine crystal was added to initiate the reaction. An ice bath was used to cool the reaction mixture to prevent excessive boiling. After addition of the butyl bromide soln, the reaction mixture was heated to 50 °C for 15 min.

Both Grignard reagent (see above) and ribose derivative **1** (74 mg, 0.425 mmol) in THF (2 mL) were cooled to 0 °C, and the Grignard reagent was added dropwise to the substrate soln with constant stirring. The reaction mixture was allowed to warm to room temperature, the

solvent was removed under diminished pressure and the residue washed with $NaHCO_3$ and extracted with EtOAc. The general Swern oxidation procedure (see **2**) was carried out to oxidise the diol precursor, affording the requisite diketone after purification by column chromatography (10:1 hexanes–EtOAc) (35 mg, 0.154 mmol, 36% over two steps).

TLC: R_f 0.42 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 1766, 1759, 1745, 1727, 1658, 1640, 1241, 1081, 869 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 4.71 (d, 1H, *J* 7.5 Hz, H4), 4.66 (d, 1H, *J* 7.5 Hz, H3), 2.53 (td, 2H, *J* 7.5 and 4.2 Hz, H6a and b), 2.19 (s, 3H, H1a, b and c), 1.54 (s, 3H, C*H*$_3$-isopropylidene), 1.53–1.01 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.37 (s, 3H, C*H*$_3$-isopropylidene), 0.86 (t, 3H, *J* 7.5 Hz, $(CH_2)_3CH_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 207.6 (C2), 205.8 (C5), 111.8 (acetal-C), 82.0 (C4), 81.8 (C3), 39.9 (C6), 27.7 (C1), 26.7 (C7), 25.3 (*C*H$_3$-isopropylidene), 24.9 (*C*H$_3$-isopropylidene), 22.1 (C8), 13.8 (C9); HRMS: Found 228.1359. Calculated for $C_{12}H_{20}O_4$ 228.1362; CIMS: 229 (MH^+, 100%), 211 (M^+-OH, 8%), 199 ($M^+-CH_2CH_3$, 6%), 185, ($M^+-CH_2CH_2CH_3$, 22%), 171 (M^+−butyl, 5%).

3.5. (2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-phenyl-1,4-pentanedione (5)

Dione **5** was prepared from **1** (48 mg, 0.76 mmol) by reaction with phenylmagnesium bromide (7.60 mmol) according to the Grignard method as described above for **4**, followed by Swern oxidation according to the general method described for **2**. The product was purified by column chromatography (4:1 hexanes–EtOAc) providing the diketone as a clear oil (43 mg, 0.172 mmol, 62% over two steps).

TLC: R_f 0.39 (4:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 2671, 1735, 1706, 1700, 1602, 1520, 1498, 1453, 1099, 1027, 864 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 7.97 (d, 2H, *J* 7.5 Hz, *ortho* aromatics), 7.58 (t, 1H, *J* 7.2 Hz, *para* aromatics), 7.46 (dd, 2H, *J* 7.5 and 7.25 Hz, *meta* aromatics), 5.65 (d, 1H, *J* 6.6 Hz, H2), 4.73 (d, 1H, *J* = 6.6 Hz, H3), 2.36 (s, 3H, H5a, b and c), 1.49 (s, 3H, C*H*$_3$-isopropylidene), 1.48 (s, 3H, C*H*$_3$-isopropylidene); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 206.8 (C4), 194.4 (C1), 134.9 (*ipso*), 133.7 (*para*), 129.1 (*ortho*), 128.6 (*meta*), 112.3 (acetal-C), 82.0 (C2), 80.1 (C3), 27.7 (C5), 27.0 (*C*H$_3$-isopropylidene), 25.8 (*C*H$_3$-isopropylidene); HRMS: Found 248.1048. Calculated for $C_{14}H_{16}O_4$ 248.1049; EIMS: *m*/*z* 249 (MH^+, 0.02%), 122 ($M^+-C_7H_9O_2$, 33%), 105 ($M^+-C_7H_5O$, 100%).

3.6. (3*R*,4*S*)-1-(1-Butyl)-2-methyl-3,4-*O*-isopropylidene-cyclobutane-1,2,3,4-tetraol (6)

The diketone (70 mg, 0.302 mmol) in THF (4 mL) was added dropwise to a soln of SmI_2 (0.906 mmol, 3.0 equiv) and HMPA (1 equiv/Sm) in THF (12 mL) at −78 °C under argon. The mixture was allowed to warm to room temperature over 24 h and the reaction mixture was quenched by exposure to the atmosphere. The mixture was filtered through a thin pad of silica and chromatographed. The desired product was obtained as an oil (8 mg, 0.035 mmol, 12%).

$[\alpha]_D$: −14.7 (*c* 1.0, $CHCl_3$); TLC: R_f 0.42 (2:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3601, 3455, 3040, 3033, 1701, 1664 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 4.32 (d, 1H, *J* 5.5 Hz, H3), 4.18 (d, 1H, *J* = 5.5 Hz, H4), 2.81 (s, 1H, OH), 1.54 (s, 3H, C*H*$_3$), 1.35–1.23 (m, 6H, $(CH_2)_3CH_3$), 1.29 (s, 1H, 3H, C*H*$_3$-isopropylidene), 1.24 (s, 3H, C*H*$_3$-isopropylidene), 0.90 (t, 3H, *J* 6.6 Hz, $(CH_2)_3CH_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 114.2 (acetal-C), 81.7 (C1), 79.6 (C4), 77.7 (C3), 72.2 (C2), 31.1 ($CH_2CH_2CH_2CH_3$), 29.6 ($CH_2CH_2CH_2CH_3$), 25.4 (*C*H$_3$-isopropylidene), 24.9 (*C*H$_3$-isopropylidene), 23.2 ($CH_2CH_2CH_2CH_3$), 20.5 (*C*H$_3$), 14.0 ($CH_2CH_2CH_2CH_3$); HRMS: Found 230.1511. Calculated for $C_{12}H_{22}O_4$ 230.1518; CIMS: 231 (MH^+, 11%), 230 (M^+, 3%), 215 (M^+-CH_3, 24%), 201 ($M^+-CH_2CH_3$, 16%), 173 (M^+−Bu, 3%), 155 (M^+−Bu−H_2O, 18%).

3.7. (3*R*,4*S*)-2-Methyl-1-phenyl-3,4-*O*-isopropylidene-cyclobutane-1,2,3,4-tetraol (7)

The diketone (60 mg, 0.242 mmol) was subjected to the same cyclisation reaction conditions as the butyl analogue (**6**) to form the desired cyclobutane product as an oil (6 mg, 0.024 mmol, 10%).

$[\alpha]_D$: −3.1 (*c* 1.0, $CHCl_3$); TLC: R_f 0.41 (3:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3610, 3454, 3450, 3030, 3032, 1700, 1660 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 7.52 (dd, 2H, *J* 8.4 and 1.6 Hz, aromatics), 7.37–7.29 (m, 3H, aromatics), 4.73 (d, 1H, *J* 5.1 Hz, H4), 4.54 (d, 1H, *J* 5.1 Hz, H3), 2.73 (br s, 1H, OH), 1.91 (br s, 1H, OH), 1.51 (s, 3H, C*H*$_3$), 1.43 (s, 1H, 3H, C*H*$_3$-isopropylidene), 1.35 (s, 3H, C*H*$_3$-isopropylidene); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 136.7 (*ipso*) 128.6 (*ortho*), 128,2 (*meta*), 128.0 (*para*), 109.7 (acetal-C), 81.5 (C2), 77.5 (C4), 76.2 (C3), 66.6 (C1), 25.5 (*C*H$_3$-isopropylidene), 25.4 (*C*H$_3$-isopropylidene), 21.4 (*C*H$_3$); HRMS: Found 250.1207. Calculated for $C_{14}H_{18}O_4$ 250.1205; CIMS: 251 (MH^+, 24%), 250 (M^+, 4%), 233 (M^+-OH, 2%).

3.8. 5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribose (8)

A soln of 2,3-*O*-isopropylidene-D-ribose[16] (75 mg, 0.40 mmol) and imidazole (10% m/m) in pyridine (1 mL) was cooled to 0 °C. To this soln was added *tert*-butyldimethylsilylchloride (67 mg, 0.43 mmol), after which the soln was allowed to warm to room temperature and stirred at this temperature for 6 h. The solvent was removed under diminished pressure, and the residue

purified by flash chromatography to afford the silyl ether as an oil (85 mg, 0.28 mmol, 70%).

TLC: R_f 0.80 (3:1 hexanes–EtOAc); ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 5.26 (d, 1H, *J* 12.0 Hz, H1), 4.72 (d, 1H, *J* 12.0 Hz, OH), 4.67 (d, 1H, *J* 5.7 Hz, H2), 4.48 (d, 1H, *J* 5.7 Hz, H3), 4.34 (br s, 1H, H4), 3.73–3.75 (m, 2H, H5), 1.47 (s, 3H, CH_3-isopropylidene), 1.30 (s, 3H, CH_3-isopropylidene), 0.91 (s, 9H, C(CH_3)$_3$), 0.12 (s, 6H, SiC$H_3 \times 2$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 112.0 (acetal C), 103.4 (C1), 87.6 and 87.0 (C3, C2), 81.7 (C4), 64.8 (C5), 26.5 (*C*H_3-isopropylidene), 25.8 (C(*C*H_3)$_3$), 25.0 (*C*H_3-isopropylidene), 18.3 (*C*(CH$_3$)$_3$), −5.6 (Si*C*$H_3 \times 2$); HRMS: Found 304.1711. Calculated for $C_{14}H_{28}O_5Si$ 304.1706; EIMS: *m*/*z* 289 (M^+-CH_3, 15%), 247 (M^+-t-Bu, 65%), 189 (M^+-TBDMS, 65%), 75 (100%).

3.9. 1-(1-Butyl)-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribitol (9)

A Grignard reaction (see compound **4**) of **8** (500 mg, 1.645 mmol) using butylmagnesium bromide (16.45 mmol) afforded the desired diol as a colourless oil after chromatography (8:1 hexanes–EtOAc) (420 mg, 1.159 mmol, 70%).

TLC: R_f 0.39 (8:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3600, 3340, 3040, 2960, 1710, 1680 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 4.09 (br s, 1H, OH), 4.02–3.95 (m, 2H, H2 and H4), 3.87–3.75 (m, 2H, H1 and H3), 3.85 (dd, 1H, *J* 9.9 and 3.3 Hz, H5a), 3.60 (dd, 1H, *J* 9.9 and 7.2 Hz, H5b), 3.29 (br s, 1H, OH), 1.80–1.30 (m, 6H, (CH_2)$_3$CH$_3$), 1.34 (s, 3H, CH_3-isopropylidene), 1.30 (s, 3H, CH_3-isopropylidene), 0.89 (s, 12H, C(CH_3)$_3$, (CH$_2$)$_3$CH_3), 0.07 (s, 6H, SiC$H_3 \times 2$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 108.4 (acetal-C), 81.1 (C2), 77.4 (C3), 69.3 (C4), 68.9 (C1), 64.4 (C5), 33.8 (C1′), 28.1 (*C*H_3-isopropylidene), 27.5 (*C*H_3-isopropylidene), 25.9 (C(*C*H_3)$_3$), 25.5 (C2′), 22.9 (C3′) 18.4 (*C*(CH$_3$)$_3$), 14.2 (C4′), −5.29 (Si*C*H_3), −5.34 (Si*C*H_3); HRMS: Found 362.2491 Calculated for $C_{18}H_{38}O_5Si$ 362.2489; EIMS: *m*/*z* 362 (M^+, 20%), 331 ($M^+-C_2H_7$, 100%).

3.10. 5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-1-(thiophen-2-yl)-D-ribitol (10)[17]

The general procedure to introduce a thiophene group using thiophene (505 mg, 6.00 mmol) and *n*-BuLi (see compound **2**) was carried out with the protected ribose derivative **8** (608 mg, 2.000 mmol). The crude product was then purified on a silica column. Two diastereomers could be isolated as light yellow oils (total yield 460 mg, 1.186 mmol, 59%), which were combined and used as a mixture in the following step.

3.10.1. Diastereomer 1. TLC: R_f 0.40 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3452, 2902, 1251, 1073 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.27–7.23 (m, 1H, aromatic), 7.12–7.09 (m, 1H, aromatic), 6.99–6.94 (m, 1H, aromatic), 5.13 (dd, 1H, *J* 9.3 and 2.4 Hz, H1), 4.78 (d, 1H, *J* 3.0 Hz, OH), 4.34 (dd, 1H, *J* 9.6 and 5.4 Hz, H3), 4.14 (dd, 1H, *J* 9.3 and 5.4 Hz, H2), 3.96–3.65 (m, 3H, H4, H5a and b), 3.42 (d, 1H, *J* 3.3 Hz, OH), 1.38 (s, 3H, CH_3-isopropylidene), 1.29 (s, 3H, CH_3-isopropylidene), 0.91 (s, 9H, C(CH_3)$_3$), 0.10 (s, 6H, SiC$H_3 \times 2$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 144.9 (C1′), 126.4 (C3′), 124.9 (C2′), 124.6 (C4′), 109.0 (acetal-C), 81.5 (C3), 77.2 (C2), 69.3 (C5), 68.0 (C1), 64.2 (C4), 28.1 (*C*H_3-isopropylidene), 25.9 (C(*C*H_3)$_3$), 25.4 (*C*H_3-isopropylidene), 18.4 (*C*(CH$_3$)$_3$), −5.27 (Si*C*H_3), −5.33 (Si*C*H_3); HRMS: Found 388.1751. Calculated for $C_{18}H_{32}O_5SSi$ 388.1740; EIMS: *m*/*z* 388 (M^+, 2%), 275 (M^+-thiophenyl$-C_2H_6$, 13%), 73 (100%).

3.10.2. Diastereomer 2. TLC: R_f 0.34 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3451, 2902, 1252, 1073 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.27–7.22 (m, 1H, aromatic), 7.07–7.05 (m, 1H, aromatic), 7.98–6.94 (m, 1H, aromatic), 5.39 (dd, 1H, *J* 7.8 and 1.7 Hz, H1), 4.70 (dd, 1H, *J* 6.3 and 2.4 Hz, H3), 4.13 (dd, 1H, *J* 9.3 and 6.3 Hz, H2), 4.15–4.01 (m, 1H, H4), 3.82 (dd, 1H, *J* = 10.2 and 3.3 Hz, H5a), 3.69 (dd, 1H, *J* 10.2 and 5.1 Hz, H5b), 3.11 (d, 1H, *J* 7.8 Hz, OH), 2.75 (d, 1H, *J* 5.7 Hz, OH), 1.53 (s, 3H, CH_3-isopropylidene), 1.36 (s, 3H, CH_3-isopropylidene), 0.89 (s, 9H, C(CH_3)$_3$), 0.08 (s, 6H, SiC$H_3 \times 2$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 145.9 (C1′), 126.4 (C3′), 125.0 (C2′), 124.4 (C4′), 108.7 (acetal-C), 80.0 (C3), 76.3 (C2), 69.3 (C5), 67.5 (C1), 64.3 (C4), 26.9 (*C*H_3-isopropylidene), 25.9 (C(*C*H_3)$_3$), 24.7 (*C*H_3-isopropylidene), 18.4 (*C*(CH$_3$)$_3$), −5.27 (Si*C*H_3), −5.38 (Si*C*H_3); HRMS: Found 388.1748. Calculated for $C_{18}H_{32}O_5SSi$ 388.1740; EIMS: *m*/*z* 275 (M^+-thiophenyl$-C_2H_6$, 13%), 43 (100%).

3.11. (3*S*,4*R*)-1-*O*-*tert*-Butyldimethylsilyl-1,3,4-trihydroxy-3,4-*O*-isopropylidene-2,5-nonanedione (11)

The general Swern oxidation method (see compound **2**) was used to oxidise **9** (362 mg, 1.000 mmol). The product was purified by column chromatography (5:1 hexanes–EtOAc) to afford the dione as an oil (257 mg, 0.718 mmol, 72%).

TLC: R_f 0.42 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3600, 3440, 3040, 2960, 1720 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 4.91 (d, 1H, *J* 6.9 Hz, H3), 4.83 (d, 1H, *J* 6.9 Hz, H4), 4.43 (d, 1H, *J* 17.7 Hz, H1a), 4.29 (d, 1H, *J* 17.7 Hz, H1b), 2.66–2.47 (m, 2H, CH_2(CH$_2$)$_2$CH$_3$), 1.57–1.23 (m, 4H, CH$_2$(CH_2)$_2$CH$_3$), 1.51 (s, 3H, CH_3-isopropylidene), 1.40 (s, 3H, CH_3-isopropylidene), 0.89–0.87 (m, 12H, (CH$_2$)$_3$CH_3, C(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 208.2 (C5), 204.7 (C2), 111.1

(acetal-C), 82.0 (C4), 79.8 (C3), 68.3 (C1), 39.3 (C6), 26.9 (*C*H$_3$-isopropylidene), 25.8 (C(*C*H$_3$)$_3$), 25.4 (*C*H$_3$-isopropylidene), 25.0 (C7) 22.2 (C8), 18.4 (*C*(CH$_3$)$_3$), 13.9 (C9), −5.4 (SiCH$_3$), −5.6 (SiCH$_3$); HRMS: Found 358.2167. Calculated for $C_{18}H_{34}O_5Si$ 358.2176; EIMS: *m*/*z* 343 (M^+-CH_3, 2%), 301 (M^+-Bu, 6%), 243 (M^+-TBDMS, 15%), 85 (100%).

3.12. (3*S*,4*R*)-1-*O*-*tert*-Butyldimethylsilyl-1,3,4-trihydroxy-3,4-*O*-isopropylidene-1-(thiophen-2-yl)-2,5-pentanedione (12)[17]

The general procedure to perform a Swern oxidation (see compound **2**) was carried out to oxidise **10** (393 mg, 1.013 mmol), and the product was purified by column chromatography (5:1 hexanes–EtOAc) to yield a yellow oil (203 mg, 0.529 mmol, 52%).

TLC: R_f 0.28 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 2903, 1721, 1651, 1402, 1240 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.94 (dd, 1H, *J* 3.9 and 1.2 Hz, H2′), 7.67 (dd, 1H, *J* 5.0 and 1.2 Hz, H4′), 7.12 (dd, 1H, *J* = 4.8 and 3.9 Hz, H3′), 5.54 (d, 1H, *J* 6.5 Hz, H3), 4.89 (d, 1H, *J* 6.5 Hz, H2), 4.50 (d, 1H, *J* 17.6 Hz, H5a), 4.31 (d, 1H, *J* 17.6 Hz, H5b), 1.45 (s, 3H, C*H*$_3$-isopropylidene), 1.43 (s, 3H, C*H*$_3$-isopropylidene), 0.82 (s, 9H, C(C*H*$_3$)$_3$), −0.02 (s, 3H, SiC*H*$_3$), −0.05 (s, 3H, SiC*H*$_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 203.5 (C1), 188.2 (C4), 140.8 (C1′), 135.1 (C3′), 134.7 (C2′), 128.1 (C4′), 111.5 (acetal-C), 80.8 (C3), 80.4 (C2), 68.2 (C5), 27.0 (*C*H$_3$-isopropylidene), 25.8 (C(*C*H$_3$)$_3$), 25.8 (*C*H$_3$-isopropylidene), 18.4 (*C*(CH$_3$)$_3$), −5.5 (Si*C*H$_3$), −5.7 (Si*C*H$_3$); HRMS: Found 384.1427. Calculated for $C_{18}H_{28}SSiO_5$ 384.1427; EIMS: *m*/*z* 384 (M^+, 32%), 154 (100%).

3.13. (3*S*,4*S*)2-*tert*-Butyldimethylsilyloxymethyl-3,4-*O*-isopropylidene-1-(thiophen-2-yl)-cyclobutane-1,2,3,4-tetraol (13)

The diketone **12** (120 mg, 0.313 mmol) in THF (2 mL) was added dropwise to a soln of SmI_2 (0.938 mmol, 3.0 equiv) in THF (12 mL) at −78 °C under argon. The reaction mixture was allowed to warm to room temperature over 24 h and then quenched by opening the flask to the atmosphere. The mixture was filtered through a thin pad of silica and then chromatographed to afford the cyclobutane derivative as a light yellow oil (10 mg, 0.026 mmol, 8%).

$[\alpha]_D$: −3.7 (*c* 1, EtOAc); TLC: R_f 0.42 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3600, 3440, 3040 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.27 (dd, 1H, *J* 3.6 and 1.2 Hz, H2′), 7.19 (dd, 1H, *J* 5.1 and 1.2 Hz, H4′), 6.95 (dd, 1H, *J* 5.1 and 3.6 Hz, H3′), 6.66 (d, 1H, *J* 5.9 Hz, H3), 6.62 (d, 1H, *J* 5.9 Hz, H2), 4.54 (s, 1H, OH), 3.89 (s, 1H, OH), 3.79 (d, 1H, *J* 10.5 Hz, H5a), 3.75 (d, 1H, *J* 10.5 Hz, H5b), 1.58 (s, 3H, C*H*$_3$-isopropylidene), 1.30 (s, 3H, C*H*$_3$-isopropylidene), 0.73 (s, 9H, C(C*H*$_3$)$_3$), −0.08 (s, 3H, SiC*H*$_3$), −0.24 (s, 3H, SiC*H*$_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 143.0 (C1′), 126.5 (C3′), 124.8 (C2′), 124.6 (C4′), 114.8 (acetal-C), 80.7 (C1), 80.1 (C2), 79.2 (C3), 73.4 (C4), 61.0 (C5), 25.7 (C*C*H$_3$), 25.2 (*C*H$_3$-isopropylidene × 2), 18.1 (*C*(CH$_3$)$_3$), −5.79 (Si*C*H$_3$), −5.95 (Si*C*H$_3$); HRMS: Found 386.157993. Calculated for $C_{18}H_{30}SSiO_5$ 386.158325; EIMS: *m*/*z* 386 (M^+, 17%), 136 (100%).

3.14. 2,3,5-Tri-*O*-benzyl-1-(1-butyl)-D-arabinitol (15)

A Grignard reaction (see compound **4**) using butylmagnesium bromide (7.10 mmol) on tri-*O*-benzyl-D-arabinofuranose (commercially available from Sigma–Aldrich, 299 mg, 0.711 mmol) afforded the desired product as a colourless oil after chromatography (3:1 hexanes–EtOAc) (326 mg, 0.682 mmol, 96%).

TLC: R_f 0.28 (3:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3582, 2956, 2880, 1396, 1368, 1142, 1100, 1027, 916 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.38–7.31 (m, 15H, aromatics), 4.82–4.55 (m, 6H, OC*H*$_2$Ph), 4.16–4.11 (m, 1H, H2), 3.96–3.56 (m, 5H, H1a, H1b, H3, H4, H5), 3.40 (br s, OH), 3.35 (d, OH), 2.99 (d, OH, *J* 5.4 Hz), 2.87 (br s, OH), 1.70–1.15 (m, 6H, (C*H*$_2$)$_3$CH$_3$), 0.94 (t, 3H, *J* 7.1 Hz, (CH$_2$)$_3$C*H*$_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C (major and minor isomers) 137.8 (*ipso*), 137.7 (*ipso*), 137.6 (***ipso***), 137.5 (***ipso***), 137.4 (***ipso***), Aromatics—128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 81.0 (C4), 80.4 (**C4**), 78.3 (C3), 77.8 (**C3**), 74.2 (C2), 73.5 (C5), 73.1 (C1 and **C2**), 73.0 (**C5**), 72.9 (**C1**), 71.0 (O*C*H$_2$Ph), 70.9 (**O*C*H$_2$Ph**), 70.7 (**O*C*H$_2$Ph**), 70.7 (O*C*H$_2$Ph), 70.4 (**O*C*H$_2$Ph**), 70.1 (O*C*H$_2$Ph), 33.9 (C6), 33.3 (**C6**), 27.8 (C7), 27.7 (**C7**), 22.6 (**C8**), 22.5 (C8), 14.0 (**C9**), 13.9 (C9); HRMS: Found 479.2796. Calculated for $C_{30}H_{39}O_5$ 479.2797; FABMS: 479 (MH^+).

3.15. 2,3,5-Tri-*O*-benzyl-1-(thiophen-2-yl)-D-arabinitol (16)

Reaction of tri-*O*-benzyl-D-arabinofuranose (288 mg, 0.686 mmol) with thiophen-2-yllithium (2.058 mmol, prepared from 173 mg thiophene and 1.0 equiv of *n*-BuLi) according to the procedure described for compound **2** afforded the product **16** as a colourless oil (335 mg, 0.665 mmol, 97%).

TLC: R_f 0.33 (3:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3560, 2880, 1459, 1396, 1358, 1097, 1069, 1031, 920, 833 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.40–7.23 (m, 30H, aromatics), 7.21–7.17 (m, 2H, *thiophene* aromatics), 7.04–6.93 (m, 4H, *thiophene* aromatics), 5.28 (br s, 1H), 5.23 (t, 1H, *J* 5.5 Hz), 4.67–4.50 (m, 12H), 4.35 (dd, 2H, *J* 34.8 and 11.1 Hz), 4.10–4.09 (m, 2H, H4), 3.98 (t, 1H, *J* 4.1 Hz), 3.89 (d, 1H, *J* 6.9 Hz), 3.73–3.59 (m, 4H), 3.45 (d, 1H, *J* 4.5 Hz, OH), 2.95 (d,

1H, *J* 5.7 Hz, OH), 1.80 (br s, OH × 2); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C (major and minor isomers) 145.9 (C1′), 145.8 (**C1′**), 137.8 (***ipso***), 137.7 (***ipso*** × 2), 137.6 (*ipso*), 137.5 (*ipso*), 137.4 (*ipso*), Aromatics—128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 126.6 (C3′), 126.5 (**C3′**), 124.7 (C2′), 124.6 (**C2′**), 124.2 (C4′), 124.2 (**C4′**), 83.3 (**C3**), 81.8 (C3), 78.5 (**C2**), 78.0 (C2), 73.7 (C4 and **C4**), 73.6 (C1), 73.5 (**C1**), 73.3 (**C5** and C5), 70.9 (**O*C*H$_2$Ph**), 70.8 (**O*C*H$_2$Ph**), 70.7 (**O*C*H$_2$Ph**), 70.1 (O*C*H$_2$Ph), 69.9 (O*C*H$_2$Ph), 69.7 (O*C*H$_2$Ph); HRMS: Found 504.1971. Calculated for $C_{30}H_{32}O_5S$: 504.1970; FABMS: 504 (M^+).

3.16. (3*S*,4*S*)-1,3,4-Tri-(benzyloxy)-2,5-nonanedione (17)[17]

Swern oxidation of **15** (50 mg, 0.105 mmol, see compound **2** for procedure) followed by column chromatography (5:1 hexanes–EtOAc) afforded the dione **17** as a white solid material (48 mg, 0.103 mmol, 98%).

Mp: 64–66 °C; TLC: R_f 0.31 (5:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3081, 3026, 2993, 2880, 1793, 1740, 1695, 140, 1333 1100, 1034, 913 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.42–7.16 (m, 15H, aromatics), 4.62–4.21 (m, 10H, OC*H*$_2$Ph × 3, H1a, H1b, H3, H4), 2.56 (dt, 1H, *J* 18.3 and 7.5 Hz, H6a), 2.29 (dt, 1H, *J* 18.3 and 7.5 Hz, H6b), 1.49–1.39 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.30–1.15 (m, 2H, $(CH_2)_2CH_2CH_3$), 0.84 (t, 3H, *J* 7.4 Hz, $(CH_2)_3CH_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 210.0 (C2), 206.6 (C5), 136.9 (*ipso*), 136.4 (*ipso*), 136.1 (*ipso*), Aromatics—128.5, 128.4, 128.3, 128.2, 128.2, 127.8, 84.5 (C4), 83.7 (C3), 74.3 (O*C*H$_2$Ph × 2), 74.2 (O*C*H$_2$Ph), 73.3 (C1), 39.4 (C6), 24.9 (C7), 22.2 (C8), 13.8 (C9); HRMS: Found 475.2485. Calculated for $C_{30}H_{35}O_5$ 475.2484; FABMS: 475 (MH^+).

3.17. (2*S*,3*S*)-2,3,5-Tri-(benzyloxy)-1-(thiophen-2-yl)-1,4-pentanedione (18)

The general procedure to perform a Swern oxidation (see compound **2**) was carried out to oxidise **16** (53 mg, 0.105 mmol), and the product was purified by column chromatography (3:1 hexanes–EtOAc) affording the title compound as an oil (36 mg, 0.072 mmol, 68%).

TLC: R_f 0.44 (3:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3074, 2873, 1733, 1692, 1688, 1660, 1500, 1413, 1358, 133, 1139, 1104, 1034, 920, 864 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.89 (dd, 1H, *J* 3.8 and 1.1 Hz, H3′), 7.66 (dd, 1H, *J* 5.1 and 1.2 Hz, H2′), 7.35–6.94 (m, 16H, aromatics), 4.89 (d, 1H, *J* 3.0 Hz), 4.72 (d, 1H, *J* 11.4 Hz), 4.32 (t, 1H, *J* 2.4 Hz), 4.66–4.22 (m, 7H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 205.9 (C4), 190.1 (C1), 141.1 (C1′), 136.9 (*ipso*), 136.5 (*ipso*), 135.9 (*ipso*), 134.8 (C2′), 134.1 (C4′), Aromatics—128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 126.6 (C3′), 83.8 (C2), 83.3 (C3), 74.4 (O*C*H$_2$Ph), 74.1 (O*C*H$_2$Ph), 73.5 (O*C*H$_2$Ph), 73.3 (C5); HRMS: Found 501.1735. Calculated for $C_{30}H_{29}SO_5$: 501.1736.

3.18. (3*R*,4*R*)-3,4-Di-*O*-benzyl-2-[(benzyloxy)methyl]-1-butyl-cyclobutane-1,2,3,4-tetraol (19)

(3*R*,4*R*)-1,3,4-Tri-(benzyloxy)-2,5-nonanedione (67 mg, 0.21 mmol) was dissolved in degassed THF (5 mL) and the solvent removed by vacuum distillation to ensure an oxygen-free system. The residue was dissolved in THF (6 mL) and added dropwise with stirring to a freshly prepared soln of SmI_2 in THF (6.3 mL of 0.1 M soln, 0.63 mmol, 3.0 equiv) at room temperature. The mixture was heated under reflux for 6 h, after which it was diluted with EtOAc (20 mL) and filtered through a thin pad of silica gel. The solvent was removed under diminished pressure and the residue purified by column chromatography, providing the product as an oil (15 mg, 0.032 mmol, 15%).

$[\alpha]_D$: −29.6 (*c* 3.0, $CHCl_3$); TLC: R_f 0.75 (3:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max}. 3070, 3016, 2934, 2872, 1723, 1704, 1685, 1458, 1272, 1109, 1026, 913 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.32–7.24 (m, 15H, aromatics), 4.65–4.43 (m, 6H, OC*H*$_2$Ph × 3), 3.83 (dd, 2H, *J* 33.3 and 6.0 Hz), 3.65 (dd, 2H, *J* 28.8 and 9.9 Hz), 2.85 (s, 1H, OH), 2.67 (s, 1H, OH), 1.41–1.24 (m, 6H, $(CH_2)_3CH_3$), 0.87 (t, 3H, *J* 6.9 Hz, $(CH_2)_3CH_3$); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 138.0 (*ipso*), 137.7 (*ipso*), 137.4 (*ipso*), 128.4 (*meta*), 128.3 (*meta*), 128.3 (*meta*), 127.9 (*ortho* and *para*), 127.8 (*ortho*), 127.7 (*para* and *ortho*), 127.6 (*para*), 81.7 (C3), 80.2 (C4), 76.2 (C1), 75.8 (C2), 73.7 (CH_2OBn), 72.1 (O*C*H$_2$Ph), 72.0 (O*C*H$_2$Ph) 71.8 (O*C*H$_2$Ph), 34.0 ($CH_2CH_2CH_2CH_3$), 25.5 ($CH_2CH_2CH_2CH_3$), 23.2 ($CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_3$); HRMS: Found 476.2566. Calculated for $C_{30}H_{36}O_5$ 476.2563; EIMS: *m*/*z* 477 (MH^+, 46%), 368 ($M^+ - C_7H_8O$, 16%), 296 ($M^+ - C_8H_{12}O - C_4H_9$, 58%), 85 (100%).

3.19. (3*R*,4*R*)-3,4-Di-*O*-benzyl-2-[(benzyloxy)methyl]-1-(thiophen-2-yl)-cyclobutane-1,2,3,4-tetraol (20)

(2*R*,3*R*)-2,3,5-Tri-(benzyloxy)-1-(thiophen-2-yl)-1,4-pentanedione (69 mg, 0.21 mmol) was subjected to identical cyclisation conditions as **19**. The residue was purified by column chromatography (4:1 hexanes–EtOAc), affording the desired product as a colourless oil (21 mg, 0.042 mmol, 20%).

$[\alpha]_D$: −11.1 (*c* 0.5, $CHCl_3$); TLC: R_f 0.27 (4:1 hexanes–EtOAc); IR ($CHCl_3$); ν_{max} 3441, 3038, 2930, 2879, 1538, 1523 1458, 1263, 1099 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 7.37–7.20 (m, 15H, aromatics), 7.05 (dd, 1H, *J* 3.6 and 3.3 Hz, H3′), 7.01 (d, 1H, *J* 3.6 Hz, H2′), 6.98 (d, 1H, *J* 3.3 Hz, H4′), 4.75–4.49 (m, 6H,OC*H*$_2$Ph × 3), 4.43 (d, 1H, *J* 6.6 Hz, H4), 4.04 (d,

1H, *J* 6.6 Hz, H3), 3.71 (s, 2H, CH_2OBn), 3.41(s, 1H, OH), 2.89 (s, 1H, OH); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 138.6 (*ipso*), 137.9 (*ipso*), 137.5 (C1′), 137.0 (*ipso*), Aromatics—128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 126.9, 126.8 (C4′), 125.1 (C2′), 124.6 (C3′), 83.4 (C4), 79.5 (C3), 75.0 (C2), 73.6 (C1), 72.6 (O*C*H_2Ph), 72.4 (O*C*H_2Ph × 2), 70.6 (*C*H_2OBn); HRMS: Found 502.1821. Calculated for $C_{30}H_{30}O_5S$ 502.2753; EIMS: *m/z* 502 (M^+, 34%), 501 (M^+-H, 100%), 484 (M^+-H_2O, 35%).

Acknowledgements

We gratefully acknowledge the financial assistance from the NRF (South Africa, through GUN2053664) and the RAU which made this work possible.

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