Chemoselectivity and Unusual Internal Acetal Formation in the Synthesis of a Glycosidation Precursor

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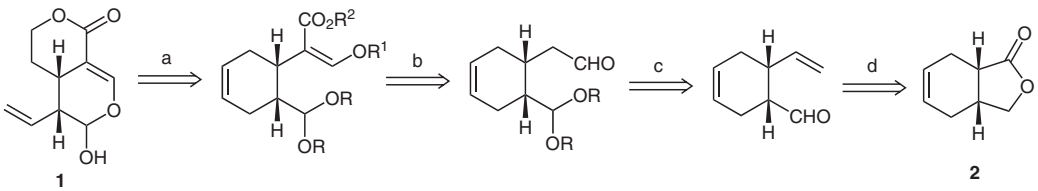
Abstract: Chemoselective deprotection of a *tert*-butyldimethyl (TBS) silyl ether group in the presence of an acetal moiety within an advanced iridoid precursor using scandium trifluoromethanesulfonate at 25 °C unexpectedly leads to internal acetal formation in high yield (70%). The same reaction at 0 °C resulted in spontaneous lactonisation of the diol intermediate, which was further elaborated to an iridoid glycosidation precursor.

Key words: iridoids, glycosidation, scandium triflate, chemoselective deprotection

The secoiridoid aglycone **1** is also the aglycone of more frequently reported secoiridoids including, sweroside.[1] Most published syntheses of complex secoiridoids rely on an advanced secoiridoid precursor as a starting point. This is exemplified by the synthesis of bakankosin[2] and huntereoside,[3] which were both derived from the natural product secologanin. The susceptibility of the hemiacetal in sweroside aglycone **1** to epimerisation to give the thermodynamically favoured *trans*-isomer has frequently been reported, particularly upon de- and reglycosidation.[4–7] This precluded the use of readily available sweroside or secologanin as starting materials. Thus in view of the aforementioned, we sought an alternative synthetic approach to sweroside aglycone **1**, initially in racemic form. We devised a retrosynthetic scheme as outlined in Scheme 1. Transformation (a) consists of a series of functional-group interconversions involving elimination, a coupled oxidative endocyclic double-bond cleavage–termini reduction followed by lactonisation and deprotection of the enolic and acetal moieties with concomitant ring closure. An enolate-mediated process is reflected in the C–C bond-formation step (b), so utilising the carbonyl functionality available at this point. The aldehyde would be protected as an enol ether after the homologation process. Transformation (c) comprises firstly acetal formation, followed by regioselective functionalisation of the exocyclic olefin to install the requisite carbonyl group. For process (d), opening of the heterocyclic moiety is required first, to allow access to both termini. Homologative olefination and oxidation of the 'northern' and 'southern' termini, respectively, complete this step.

The starting material **2** was prepared according to a literature procedure[8] in which phthalic anhydride was directly reduced with $NaBH_4$ in cold *N*,*N*-dimethylformamide (DMF) to give the lactone as a single product, which could be purified by vacuum distillation (Scheme 2).

The next step was to conduct homologation studies on lactone **2**. Both stepwise[9] and one-pot procedures[10] have been described for the diisobutylaluminium hydride (DIBAL-H) reduction of **2** to the corresponding lactol followed by a Wittig reaction with a methylphosphorane to give the homologated olefin. In the event, the reduction procedure was found to be less selective than that described and reduction of the product lactol to the corresponding diol was observed prior to complete consumption of starting lactone. The reaction of **2** with 1.5 equivalents of DIBAL-H showed complete consumption of starting material and a 3:1 distribution of the required lactol **3** and the diol. It was later noted that very fast addition of DIBAL-H to a rapidly stirring solution of **2** minimised over-reduction and amount of stoichiometric hydride could be used to give **3** in 92% yield. Protection of the hydroxyl group as a *tert*-butyldiphenylsilyl (TPS) ether gave **4**. Hydroboration–oxidation using 9-borabicyclononane (9-BBN-H) and hydrogen peroxide provided a single product **5** with the expected chemo- and regioselectivity (Scheme 2).



Scheme 1 Synthetic plan for the racemic synthesis of sweroside aglycone

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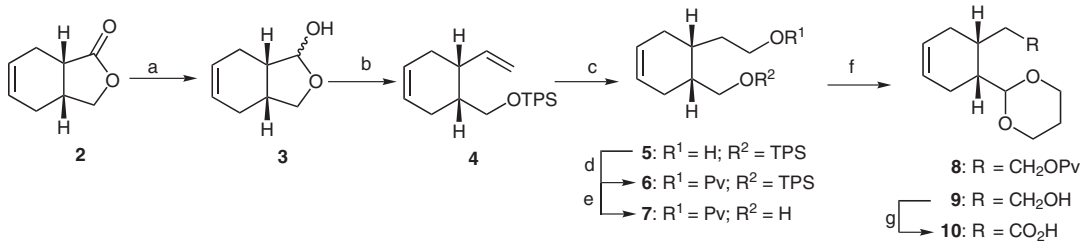


Scheme 2 *Reagents and conditions*: (a) (i) DIBAL-H (1.5 mol equiv, slow addition), toluene, –78 °C, 72%; (ii) DIBAL-H (1.1 mol equiv, fast addition), toluene, –78 °C, 92%; (b) (i) $Ph_3P^+MeI^-$, *n*-BuLi, THF, 0–25 °C, 89%; (ii) TPSCl, imidazole, DMF, 99%; (c) 9-BBN, THF, then NaOH (1 M), H_2O_2, 99%; (d) PvCl, DMAP, pyridine, 99%; (e) TBAF, THF, 96%; (f) (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, 0 °C; (iv) $TMSO(CH_2)_3OTMS$, TMSOTf, –78 °C, 91% (over 2 steps); (g) (i) LAH, THF, 0 °C, 95%; (ii) CrO_3 (8 M), acetone, 0 °C, 50%.

Treatment of **5** with pivaloyl chloride in pyridine afforded the pivaloate ester **6**. The desilylation was chemoselective, leaving the pivaloate ester intact, to give **7**. A TLC monitoring of the Dess–Martin and Swern oxidations of **6** indicated the formation of a single product. The NMR spectra of the crude extracts from these reactions verified the presence of a single diastereomer. Previous experience had highlighted the epimerisable nature of the aldehyde α-proton to give a *trans*-ring junction, and crude aldehyde was thus protected without purification and further characterisation. The mild acetal-formation procedure developed by Noyori[11] was applied and provided the dioxane derivative, **8** as a single diastereomer. Over two steps the procedure using the Dess–Martin oxidation delivered 69% of **8**, whilst the Swern oxidation afforded 91%. Epimerisation was noted (by NMR) if the aldehyde protection reaction temperature exceeded –78 °C.

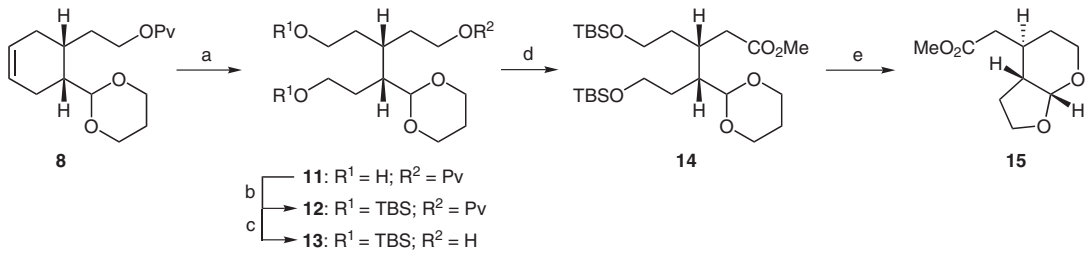
Treatment of **8** with an excess of LAH in THF at 0 °C delivered the alcohol **9**. Oxidation of the alcohol to acid **10** was achieved using a Jones oxidation at 0 °C, but was accompanied by considerable decomposition, presumed to be due to hydrolysis of the acetal in the harshly acidic reaction conditions. Ruthenium tetroxide oxidation also produced mixtures, presumably due to interaction between the reagent and the cyclohexenyl olefin. The oxidation was thus delayed until after cleavage of this olefin, when chemoselective reaction could be assured.

Ozonolysis of **8** in methanol at –78 °C followed by reduction with excess $NaBH_4$ gave diol **11** (Scheme 3). The high polarity of **11** made purification on silica gel difficult and the crude material was therefore silylated to give **12**.

Pivaloate ester **12** underwent deprotection with LAH as before to give **13**. Oxidation with ruthenium tetroxide, prepared in situ using catalytic ruthenium dioxide with sodium periodate as the co-oxidant,[12] gave a carboxylic acid which was converted into its methyl ester **14** and then characterized (Scheme 3).[13] When the oxidation was performed at ambient temperatures, as described, TLC analysis showed evidence of numerous side reactions. The optimum reaction temperature was found to be 0 °C. Spectroscopic and analytical data confirmed the assigned structure.

Chemoselective deprotection of the silyl ethers was more difficult than had been anticipated. Treatment of **14** with TBAF at 0 °C showed a single polar product on TLC. The ^{1}H NMR spectrum of the product post chromatography was dominated by four signals (δ = ca. 0.96, 1.36, 1.65, and 3.45 ppm) which indicated the presence of a tetrabutylammonium species. The absence of a resonance relating to the ester methoxy protons indicated that hydrolysis of the ester may have accompanied silyl deprotection and that the resulting acid was isolated as an ammonium salt. Buffering the TBAF with an equimolar amount of acetic acid,[14,15] gave the same result. Attempts to isolate a free acid or a lactonised species resulted in decomposition. Deprotection using HF·pyridine gave multiple products. A procedure using trimethylsilyltrifluoromethane sulfonate for the chemoselective desilylation of TBS ethers under mild conditions has been reported.[16] Application of those conditions to our system gave multiple products, from which the major product **15** was isolated (Scheme 3).

The ^{1}H NMR spectrum of the product carried a signal implying the presence of an acetal moiety (doublet, δ = 5.12 ppm), but the absence of any methylene signals relating to propanediol showed that the starting acetal was no longer



Scheme 3 *Reagents and conditions*: (a) O_3, MeOH, –78 °C, then $NaBH_4$, 25 °C; (b) TBSCl, imidazole, MeCN, 93%; (c) LAH, THF, 0 °C, 86%; (d) (i) RuO_2 (cat.), $NaIO_4$, CCl_4–MeCN–H_2O, 0 °C; (ii) MeI, K_2CO_3, DMF, MeCN, 91% (over 2 steps); (e) TMSOTf (3.0 mol equiv), CH_2Cl_2, –78 °C, then MeOH (excess), –78 °C followed by $NaHCO_3$ (aq), 27% or $Sc(OTf)_3$, H_2O, MeCN, 25 °C, 70%.

present. The IR and ^{1}H NMR spectra contained no evidence of hydroxyl functionality and MS–FAB results proposed a parent molecular ion with *m/z* = 200. All of these data confirm the assigned structure.[17] The *cis* stereochemistry at the ring junction is proposed on the basis of the observed coupling of the acetal proton that (J = 3.6 Hz) implied a gauche relationship with its partner. In hydrindane-like systems, relationship of the bridgehead protons in a *trans* system would be antiperiplanar and a larger coupling than that observed would be expected.

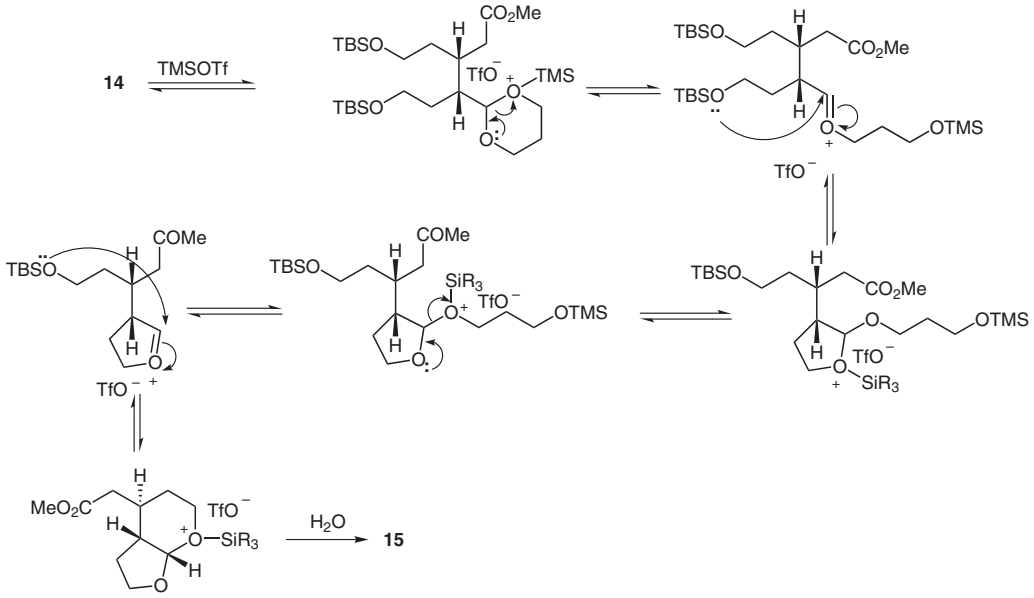
Since **14** was treated with TMSOTf under aprotic conditions, and the addition of methanol, followed by aqueous sodium bicarbonate ten minutes later took place at –78 °C, a straightforward hydrolytic cleavage of the acetal moiety, followed by internal acetal formation was unlikely. In addition, examples cited in the original work showed isopropylidene ketal protecting groups to be stable to these reagents at –40 °C.[16] Although a difference in the rates of hydrolysis of these moieties could be expected, this degree of selectivity was unlikely. A mechanism for this reaction is depicted in Scheme 4. The proposed reaction mechanism invokes silylation of the acetal oxygen by TMSOTf, leading to an oxycarbenium intermediate. In this form, the acetal is potentiated towards attack by a nucleophilic silyloxy moiety. Following silyl exchange, a further oxycarbenium intermediate intercepts the second silyloxy function, resulting in formation of the internal acetal.

The mild, water-stable Lewis acid, scandium triflate, has been used catalytically to cleave TBS ethers at ambient temperatures.[18] Treatment of **14** with 0.5 mol% $Sc(OTf)_3$, in the presence of an excess of water, in acetonitrile delivered a 70% yield of **15**. TLC monitoring of this reaction indicated that **15** was formed via a polar species assumed to be the desired diol with the acetal still intact. Under these reaction conditions, acetal hydrolysis catalysed by the Lewis acid, followed by internal acetal formation with the desilylated alcohols to give **15**, is feasible.

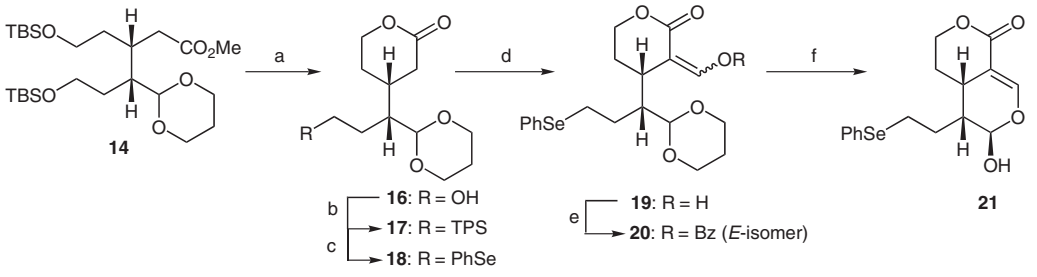
At 0 °C, complete reaction to the polar material could be achieved prior to formation of **15**. Spontaneous lactonisation of the diol intermediate provided **16**, which was isolated in 94% yield (Scheme 5).

The structure of **16** was confirmed by reacting it with TPSCl and imidazole in acetonitrile to give the product of monosilylation, **17**.[19]

The primary alcohol **16** was converted into the selenide **18** by reaction with phenylselenocyanate and



Scheme 4 Proposed mechanism for internal acetal formation



Scheme 5 *Reagents and conditions*: (a) $Sc(OTf)_3$, H_2O, MeCN, 0 °C, 94%; (b) TPSCl, imidazole, MeCN, 97%; (c) PhSeCN, *n*-Bu_3P, THF, 72%; (d) Bredereck's reagent, THF, reflux, 86%; (e) BzCl, pyridine, CH_2Cl_2, 87%; (f) CAN (0.1 mol equiv), MeCN, HCl–borate buffer (pH 8), 60 °C, 65%.

tributylphosphine[20] (Scheme 5). The one-carbon homologation step was performed using *tert*-butoxybis(dimethylamino)methane, or Bredereck's reagent, under mild conditions. The formylated product **19** was present as a mixture of tautomers for which the NMR spectra were too complex to be easily assigned. The formation of **19** was, however, confirmed by the detection of the parent molecular ion in the mass spectrum. For complete characterisation, **19** was benzoylated to give the enoate ester **20** (Scheme 5). The ^{1}H NMR chemical shift for 1′-H (δ = 8.36 ppm) was used to assign **20**[21] as the *E*-isomer on the basis of the literature analogy.[22]

Deprotection of the acetal moiety in **19** accompanied by the closure to the dihydropyran ring was required to provide the glycosidation precursor **21**. Owing to the sensitive nature of the chiral centre α to the carbonyl group to be exposed, conventional acid hydrolysis was not considered for the deprotection reaction.[23] Instead, a procedure employing catalytic ceric ammonium nitrate in a buffered medium[24] was used. The major product from this reaction proved to be unstable, and decomposition was observed during chromatography on silica gel. However, the NMR spectra of a sample obtained by flash chromatography allowed it to be identified as **21**, for which the connectivities depicted were confirmed by 2D (COSY and HSQC) spectroscopy. The absence of signals associated with the methylene groups of the dioxane moiety in both the ^{1}H and ^{13}C spectra confirmed that deprotection had occurred.[25]

In conclusion, this study has unraveled an unusual acetal-forming reaction mediated by TMSOTf and $Sc(OTf)_3$ under aprotic conditions. The usefulness of $Sc(OTf)_3$ as a mild Lewis acid at low temperature for the chemoselective cleavage of TBS ether in the presence of an acetal moiety to deliver the desired lactone for further elaboration into an advance iridoid glycosidation precursor has also been demonstrated.

Acknowledgment

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(13) **Methyl (3*R**,4*R**)-6-(*tert*-Butyldimethylsilanyloxy)-3-(2-*tert*-butyldimethylsilanyloxyethyl)-4-(1,3-dioxan-2-yl)hexanoate(14)**
Sodium metaperiodate (10% solution in H_2O, 100 mL) and RuO_2 (60 mg, 0.5 mmol) were added sequentially to a vigorously stirred solution of **13** (21.32 g, 44.8 mmol) in CCl_4–MeCN (1:1, 100 mL) at 0 °C. Stirring was continued at this temperature for 18 h. The resulting mixture was poured into CH_2Cl_2–H_2O (1:1, 1000 mL) and the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the acid (27.21 g), which was dissolved in MeCN (400 mL). *N*,*N*-Dimethylformamide (50 mL) was added, followed by K_2CO_3 (12.36 g, 89.6 mmol) and IMe (3.3 mL, 53.8 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure and the residual aqueous slurry was added to EtOAc (800 mL). The organic phase was washed with H_2O and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a residue (29.32 g), which was purified by chromatography on silica gel (800 g) using EtOAc–hexane (1:9) as eluent, to yield the ester **14** (20.54 g, 91%) as a gum. IR ($CHCl_3$): ν_{max} = 1729 (CO) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 [6 H, s, $Si(CH_3)_2$], 0.04 [6 H, s, $Si(CH_3)_2$], 0.87 [9 H, s, $SiC(CH_3)_3$], 0.88 [9 H, s, $SiC(CH_3)_3$], 1.23–1.31 (1 H, m, 5″-H_A), 1.38–1.80 (5 H, m, 4-H, 5-H_2, 1′-H_2), 1.93–2.07 (1 H, m, 5″-H_B), 2.16 (1 H, dd, *J* = 15.6, 7.9 Hz, 2-H_A), 2.25–2.37 (1 H, m, 3-H), 2.57 (1 H, dd, *J* = 15.6, 5.7 Hz, 2-H_B), 3.63 (3 H, s, OCH_3), 3.55–3.79 (6 H, m, 6-H_2, 2′-H_2, 4″-H_A, 6″-H_A), 4.00–4.10 (2 H, m, 4″-H_B, 6″-H_B), 4.45 (1 H, d, *J* = 3.9 Hz, 2″-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 and –5.1 [2 × $Si(CH_3)_2$], 18.4 and 18.5 [2 × $SiC(CH_3)_3$], 26.0 (C-5″), 26.1 and 26.2 [2 × $SiC(CH_3)_3$], 29.4 (C-1′ or C-5), 32.6 (C-3), 35.7 (C-1′ or C-5), 36.8 (C-2), 42.1 (C-4), 51.5 (OCH_3), 61.8 and 62.9 (C-2′, C-6), 66.9 and 67.0 (C-4″, C-6″), 104.4 (C-2″) and 174.2 (C-1). HRMS: *m/z* calcd for $C_{25}H_{52}O_6Si_2$ [M]: 504.3303; found [M$^+$]: 504.3268.
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(17) **Methyl (4′*S**,4′a*R**,7′aR*)-{Hexahydrofuro[2,3-*b*]pyran-4-yl}acetate (15)**
Water (0.22 mL, 12.6 mmol) followed by a solution of scandium trifluoromethanesufonate (6.2 mg, 0.013 mmol) in MeCN (5 mL) were added to a stirred solution of **14** (1.27 g, 2.52 mmol) in MeCN (20 mL). The reaction was stirred for 40 min at 25 °C after which sat. aq NH_4Cl was added. The resulting mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and the solvent was removed in vacuo. Chromatography of the residue (750 mg) on silica gel (70 g) using EtOAc–hexane (3:7) as eluent, yielded the acetal **15** (354 mg, 70%) as an oil. IR ($CHCl_3$): ν_{max} = 1732 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (1 H, dtd, *J* = 13.7, 2 × 8.3, 3.6 Hz, 3′-H_A), 1.70–1.91 (3 H, m, 3′-H_B, 4′a-H, 5′-H_A), 1.96 (1 H, dtd, *J* = 12.1, 8.3, 2 × 7.2 Hz, 5′-H_B), 2.04–2.16 (1 H, m, 4′-H), 2.26 (1 H, dd, *J* = 15.1, 8.8 Hz, 2-H_A), 2.47 (1 H, dd, *J* = 15.1, 5.4 Hz, 2-H_B), 3.60 (1 H, ddd, *J* = 11.6, 6.2, 3.6 Hz, 2′-H_A), 3.65 (3 H, s, OCH_3), 3.76 (1 H, ddd, *J* = 11.6, 8.3, 3.5 Hz, 2′-H_B), 3.83 (1 H, td, *J* = 2 × 8.0, 5.2 Hz, 6′-H_A), 4.02 (1 H, q, *J* = 3 × 8.0 Hz, 6′-H_B), 5.12 (1

H, d, J = 3.6 Hz, 7′a-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 (C-3′), 27.8 (C-5′), 31.2 (C-4′), 39.2 (C-2), 41.1 (C-4′a), 51.5 (OCH_3), 60.2 (C-2′), 65.6 (C-6′), 100.2 (C-7′), 172.1 (C-1). HRMS: *m/z* calcd for $C_{10}H_{16}O_4$ [M]: 200.1049; found [M$^+$]: 200.1061.

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(19) **(2′*R**,4*R**)-4-[4-*tert*-Butyldiphenylsilanyloxy-1-(propan-1,3-dioxy)butan-2-yl]tetrahydropyran-2-one (17)**
tert-Butyldiphenylsilyl chloride (0.13 mL, 0.49 mmol) and imidazole (33 mg, 0.49 mmol) were added to a stirred solution of **16** (40 mg, 0.16 mmol) in MeCN. The solution was stirred for 2 h, diluted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and the solvent was removed to give the crude product (280 mg). Chromatography on silica gel (20 g) using EtOAc–hexane (3:7) as eluent afforded the silyl ether **17** (75 mg, 97%). IR ($CHCl_3$): ν_{max} = 1731 (CO) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 [9 H, s, $C(CH_3)_3$], 1.24–1.31 (1 H, m, 2″-H_A), 1.46–1.58 (1 H, m, 3′-H_A), 1.60–1.81 (4 H, m, 5-H_2, 2′-H, 3′-H_B), 1.97 (1 H, qt, J = 3 × 12.6, 2 × 4.9 Hz, 2″-H_B), 2.26–2.40 (2 H, m, 3-H_A, 4-H), 2.61–2.73 (1 H, m, 3-H_B), 3.54–3.73 (3 H, m, 4′-H_A, 1″-H_A, 3″-H_A), 3.74–3.83 (1 H, m, 4′-H_B), 3.98–4.07 (2 H, m, 1″-H_B, 3″-H_B), 4.15 (1 H, td, J = 2 × 11.1, 3.7 Hz, 6-H_A), 4.32 (1 H, ddd, J = 11.1, 4.8, 3.7 Hz, 6-H_B), 4.43 (1 H, d, J = 3.5 Hz, 1′-H), 7.33–7.45 (6 H, m, ArH), 7.63–7.70 (4 H, m ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1 [$C(CH_3)_3$], 23.7 (C-2″), 24.9 [$C(CH_3)_3$], 25.0 (C-3′), 26.7 (C-5), 29.2 (C-4), 31.8 (C-3), 40.9 (C-2′), 60.5 (C-4′), 64.9 and 64.9 (C-1″ and C-3″) 66.7 (C-6), 100.9 (C-1′), 125.6 (0) and 125.6 (2), 127.6, 131.7 (6) and 131.8 (1), 133.5 (4) and 133.5 (9) (ArC), 170.0 (C-2). HRMS–FAB: *m/z* calcd for $C_{12}H_{19}O_5Na$ [M]: 505.2386; found [M$^+$ + Na]: 505.2372.

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(21) **(2′*R**,3*E*,4*S**)-4-[4-Phenylselanyl-1-(propan-1,3-dioxy)butan-2-yl]-3-benzoyloxymethylenetetrahydropyran-2-one (20)**
Formyl lactone **19** (80 mg, 0.19 mmol) was dissolved in CH_2Cl_2–pyridine (2:1, 3 mL). Benzoyl chloride (0.05 mL, 0.43 mmol) was added and the solution was stirred at 25 °C for 90 min. The pyridine was removed under reduced pressure by azeotrope formation with toluene (3 × 30 mL). The resulting material was dissolved in CH_2Cl_2, washed with brine, and the aqueous phase was extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) to give the benzoylated product (270 mg) which was purified by chromatography on silica gel (20 g) using EtOAc–hexane (1:9) to elute excess benzoyl chloride followed by elution with EtOAc–hexane (3:2) to yield the enol benzoate **20** (85 mg, 86%). IR ($CHCl_3$): ν_{max} = 1715, 1749 (CO) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.34 (1 H, m, 2‴-H_A), 1.68–1.79 (1 H, m, 3″-H_A), 1.83–1.93 (1 H, m, 5-H_A), 2.02 (1 H, qt, J = 3 × 12.4, 2 × 5.0 Hz, 2‴-H_B), 2.09–2.24 (2 H, m, 5-H_B, 3″-H_B), 2.24–2.33 (1 H, m, 2″-H), 2.98–3.13 (2 H, m, 4″-H_2), 3.32–3.41 (1 H, m, 4-H), 3.63–3.74 (2 H, m, 1‴-H_A, 3‴-H_A), 4.02–4.13 (3 H, m, 6-H_A, 1‴-H_B, 3‴-H_B), 4.39 (1 H, ddd, J = 11.3, 6.2, 3.9 Hz, 6-H_B), 4.57 (1 H, d, J = 3.3 Hz, 1″-H), 7.16–8.14 (10 H, m, ArH), 8.36 (1 H, d, J = 1.7 Hz, 1′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (C-5), 25.6 (C-2‴), 26.6 (C-4″), 28.6 (C-3″), 33.0 (C-4), 45.1 (C-2″), 66.4 (C-6), 66.8 and 66.9 (C-1‴, C-3‴), 102.5 (C-1″), 116.7 (C-3), 126.8, 127.8, 128.4, 128.8, 129.0, 130.1, 130.2, 130.3, 132.5, 133.5 and 134.2 (ArC), 144.1 (C-1′), 162.0 (ArC=O), 167.4 (C-2). HRMS: *m/z* calcd for $C_{26}H_{28}O_6{}^{80}Se$ [M]: 516.1051; found [M$^+$]: 516.1053.

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(25) **(4a*S**,5*R**,6*R**)-6-Hydroxy-5-(2-phenylselanylethyl)-4,4a,5,6-tetrahydro-3*H*-pyrano[3,4-*c*]-pyran-1-one (21)**
Borate–HCl buffer (pH 8, 2 mL) followed by CAN (18 mg, 0.03 mmol) were added to a stirred solution of **19** (150 mg, 0.36 mmol) in MeCN (2 mL). The resulting mixture was stirred at 60 °C for 24 h and then cooled and diluted with CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil (140 mg). Flash chromatography on silica gel (12 g) using EtOAc–hexane (1:1) as eluent afforded the hemiacetal **21** (82 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.55 (1 H, m, 1′-H_A), 1.56–1.82 (3 H, m, 4-H_2 and 1′-H_B), 2.06–2.18 (1 H, m, 5-H), 2.70–3.20 (3 H, m, 4a-H, 2′-H_2), 4.18–4.32 (1 H, m, 3-H_A), 4.35–4.47 (1 H, m, 3-H_B), 5.46 (1 H, d, J = 1.8 Hz, 6-H), 7.20–7.29 (3 H, m, ArH), 7.43–7.50 (2 H, m, ArH), 7.55 (1 H, d, J = 2.2 Hz, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (C-4), 25.1 (C-1′), 25.6 (C-2′), 27.8 (C-4a), 36.9 (C-5), 68.2 (C-3), 94.1 (C-6), 103.5 (C-8a) 127.2, 129.2 and 132.9 (ArC), 153.3 (C-8), 166.3 (C-1).