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The first total synthesis of (+)-goniothalesacetate and syntheses of (+)-altholactone, (+)-gonioheptolide A, and (−)-goniofupyrone by an asymmetric acetate aldol approach†

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The first stereoselective total synthesis of (+)-goniothalesacetate and total synthesis of several bioactive styryl lactones, (+)-altholactone, (+)-gonioheptolide A, and (−)-goniofupyrone have been achieved from an advanced intermediate, which can be derived from L-(+)-DET.

Introduction

Styryl lactones, despite their restricted occurrence in the plant kingdom, are reported to possess cytotoxic, anti-tumour, pesticidal, teratogenic and embryotoxic activities.[1] Therefore they make up an interesting group from a pharmacological point of view. (+)-Goniothalesacetate, (+)-altholactone, (+)-gonioheptolide A, and (−)-goniofupyrone are representatives of the styryl lactones (**1–4**, Fig. 1). Goniothalesacetate (**1**) was isolated along with other compounds from the stems of a southern Taiwan tree *Goniothalamus amuyon*.[2] The seeds were reported to be useful in the treatment of edema and rheumatism.[3] The structure of the compound was determined on the basis of standard spectroscopic methods and the absolute stereochemistry was established from the NOESY spectrum and by the preparation of *R* & *S*-MTPA esters. Goniothalesacetate has five contiguous stereocenters and its structure was determined as (2*R*,3*R*,4*S*,5*S*,6*R*)methyl 3-(3-acetoxy-4-hydroxy-5-phenyloxolan-2-yl)-3-methoxypropanoate. (+)-Altholactone (**2**), a styryl lactone, tetrahydrofuro[3,2-*b*]pyran-5-one was first isolated in 1977 from a *Polyalthia* species (Annonaceae) by Loder and co-workers[4] and later, in 1985 from the bark of *Goniothalamus giganteus* by El-Zayat *et al.*[5] The flowers of this plant undulate like waves and their scent is sweet and very strong. Altholactone has also been isolated from the Malaysian plant *G. malayanus* and found to induce apoptosis *via* oxidative stress in human HL-60 leukemia cells[6a] and displays promising antimicrobial activity.[6b] (+)-Altholactone (**2**) is a bicyclic compound presenting an α,β-unsaturated δ-lactone (5-oxygenated-5,6-dihydro-2*H*-pyran-2-one) and a disubstituted furanic motif with a bicyclic *cis* ring junction.

This natural product exhibits a very interesting cytotoxicity to mice during the P388 *in vivo* antileukemic screening (toxic at 45 mg kg^{-1} and 118% T/C at 25 mg kg^{-1}) and is lethal to brine shrimp, *Artemia salina* (LC_{50} = 234 μg mL^{-1}, 9KB cytotoxicity ED_{50} = 2 μg mL^{-1}).[5] Additionally, it was known to possess broad spectrum immune modulating activity by inhibiting the activation of pro-inflammatory cytokines in RAW 264.7 cell lines.[7] Altholactone induces reactive oxygen species-mediated apoptosis in bladder cancer T24 cells through mitochondrial dysfunction, MAPK-p38 activation and Akt suppression.[8] Therefore, this lactone has been the target of synthetic efforts by several groups.[9] In 1993, gonioheptolide A (**3**) was isolated from the bark extract of *Goniothalamus giganteus*.[10] Later in 1999, the structure of gonioheptolide A[11] was unambiguously revised as (1′*R*,2*S*,3*S*,4*S*,5*R*)-3,4-dihydroxy-2-[(19-

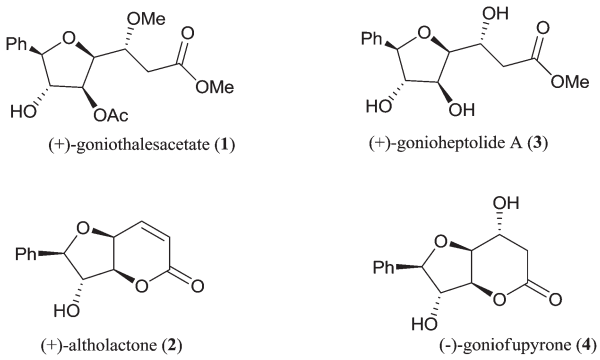

Fig. 1 Chemical structures of styryl lactones **1–4**.

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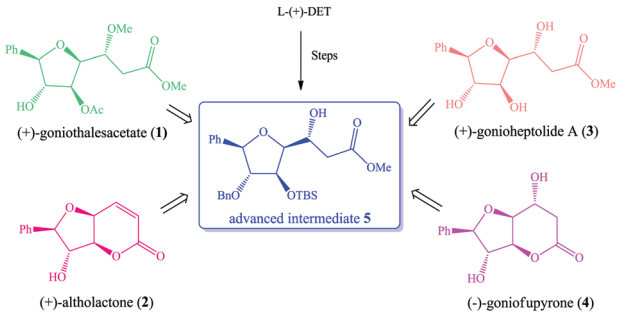


Scheme 1 Retrosynthesis.

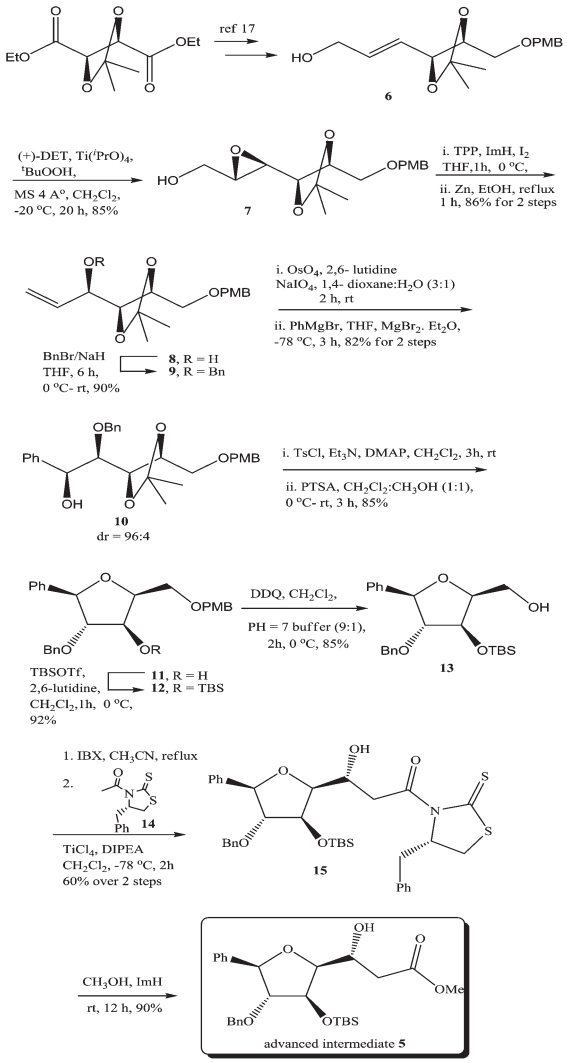
hydroxy-29-methoxycarbonyl)ethyl]-5-phenyltetrahydrofuran by its racemic synthesis from (±)-goniofupyrone. The absolute configuration of (+)-gonioheptolide A was established in 2007 [12] by its total synthesis. It showed marginal cytotoxicity to certain human solid tumor cells in culture.[13] Goniofupyrone (**4**) was also isolated from the stem bark of *Goniothalamus giganteus* (Annonaceae) and is significantly cytotoxic to human tumor cells.[14] Its absolute stereochemistry was determined by its synthesis.[15]

Even though, several total syntheses of **2**,[9] **3** [12] and **4** [9,14] have been reported, to the best of our knowledge, no total synthesis of goniothalesacetate **1** has been reported yet. As part of our continuing efforts, in the preparation of biologically active styryl lactones,[16] we now disclose the first stereoselective total synthesis of (+)-goniothalesacetate and total syntheses of (+)-altholactone, (+)-gonioheptolide A and (−)-goniofupyrone from L-(+)-DET *via* an advanced intermediate.

The retrosynthetic analysis of **1**–**4** is shown in Scheme 1. We envisaged that the four target molecules (+)-goniothalesacetate, altholactone, gonioheptolide A and goniofupyrone (**1**–**4**) could be prepared from the common intermediate **5**. C2 and C6 chiral centers in the intermediate **5** could be obtained from Grignard and asymmetric acetate aldol reactions respectively.

Results and discussion

The synthesis of the key intermediate **5** is illustrated in Scheme 2. The known allylic alcohol[17] **6** prepared in 6 steps from L-(+)-DET was subjected to Sharpless asymmetric epoxidation[18] using (+)-DET and TBHP to yield the required epoxy alcohol **7** with good stereoselectivity in 85% yield. Iodination under standard conditions followed by zinc reduction[19] of the derived iodo-epoxide afforded secondary allylic alcohol **8** in 86% yield for the two steps. The resulting secondary hydroxyl was protected as its Bn ether to obtain **9** in 90% yield. Oxidative cleavage of the olefin in compound **9** under Jin's one-pot conditions[20] using OsO_4–$NaIO_4$ and 2,6-lutidine in dioxane–water (3 : 1) furnished the corresponding aldehyde. Due to its inherent lack of stability, aldehyde was used in the next step without further purification. Treatment of the above aldehyde with PhMgBr, generated from PhBr and Mg by the



Scheme 2 Synthesis of advanced intermediate **5**.

Grignard reaction in the presence of $MgBr_2{\cdot}OEt_2$,[21] afforded 1,2-*syn* diol **10** in 82% yield and with a diastereomeric ratio of 96 : 4 (determined by chiral HPLC).[22] Following a modification of the Mosher method,[23] the newly created stereogenic center in compound **10** bearing the hydroxyl group was assigned. The syntheses of both the (*S*)- and (*R*)-MTPA esters of **10** were achieved using MTPA acid with DCC as the coupling reagent. The chemical shifts of both the (*S*)- and (*R*)-MTPA esters of **10** were assigned by ^{1}H NMR. From the equation given in Fig. 2, the $\Delta\delta$ values were calculated for as many protons as possible.

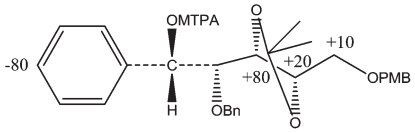


Fig. 2 $\Delta\delta = (\delta S - \delta R) \times 10^3$ for (*S*)- and (*R*)-MTPA esters of compound **10**.

The carbon chain bearing protons showing $\Delta\delta$ negative values should be placed on the left hand side of the model (Fig. 2) whilst those where $\Delta\delta$ has positive values should be placed on the right hand side. From this the center was found to have the *S*-configuration which thus establishes the absolute stereochemistry of **10**. Next, the hydroxyl group was tosylated in **10** and followed by the removal of acetonide under acidic conditions using PTSA in CH_2Cl_2 : MeOH (1 : 1) resulted in the desired 2,5-*syn* tetrahydrofuran **11** in 85% yield over two steps. The secondary hydroxy group was protected as the corresponding silyl ether **12** by treatment with *tert*-butyl(dimethyl)-silyl triflate and 2,6-lutidine in 92% yield. Next, the removal of the PMB group with DDQ under buffer conditions obtained the free alcohol **13**. To extend the two carbon side chains with a chiral center, it was thought worthwhile to adopt a diastereoselective asymmetric acetate aldol reaction.

Accordingly, oxidation of the alcohol using IBX furnished the corresponding aldehyde, which was immediately treated with (4*S*)-3-acetyl-4-benzyl-1,3-thiazolidine-2-thione **14** [24] in the presence of titanium(IV) chloride and ethyl(diisopropyl)amine, yielding *syn* isomer **15** as the major diastereomer in a 97 : 3 ratio (by crude ^{1}H NMR analysis) (Scheme 2). The resulting aldol adduct was immediately converted to methyl ester using imidazole in methanol to obtain the pure compound **5** after column chromatography. This advanced intermediate **5** can be utilized for the synthesis of four styryl lactones.

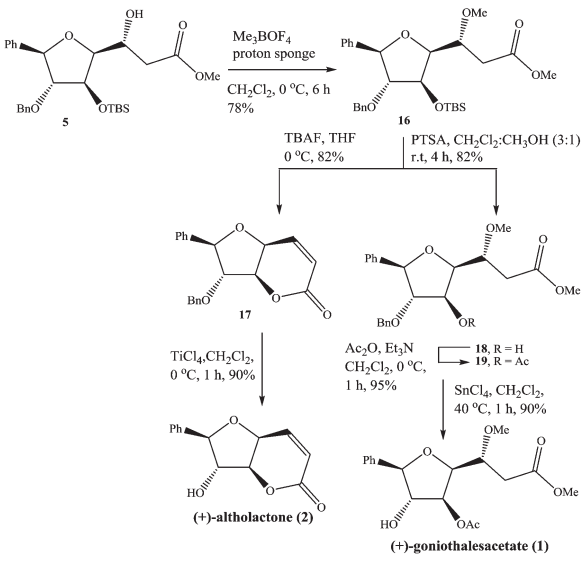
Synthesis of (+)-goniothalesacetate (1) and (+)-altholactone (2)

Synthesis of goniothalesacetate (**1**) was accomplished in 4 steps from an intermediate **5** (Scheme 3). Accordingly, the free secondary hydroxyl group in **5** was methylated using Meerwein salt to give *O*-methylated compound **16**. Our next task was the removal of the TBS group. However, a three step sequence occurred (TBS deprotection, β-methoxy elimination, cyclization) in a one-pot reaction by using TBAF in THF to furnish a bicyclic compound **17**, which can be later utilized in the synthesis of altholactone (**2**). Alternatively, a silyl group removal in compound **16** was achieved by treatment with PTSA in DCM : MeOH (1 : 1) to afford the alcohol **18** in 82% yield, which was subsequently acetylated with acetic anhydride and NEt_3 to give acetate compound **19**. Benzyl ether deprotection in **19** could not be achieved under $TiCl_4$ conditions, which led to the complete decomposition of the starting material. Finally, the cleavage of the Bn group occurred smoothly with $SnCl_4$ (CH_2Cl_2, 40 °C) to furnish synthetic (+)-goniothalesacetate (**1**) in 90% yield, whose spectroscopic properties (^{1}H, ^{13}C NMR, IR, HRMS) as well as specific rotation ($[\alpha]_D$) were in full accordance with those reported for natural (+)-**1**.[2]

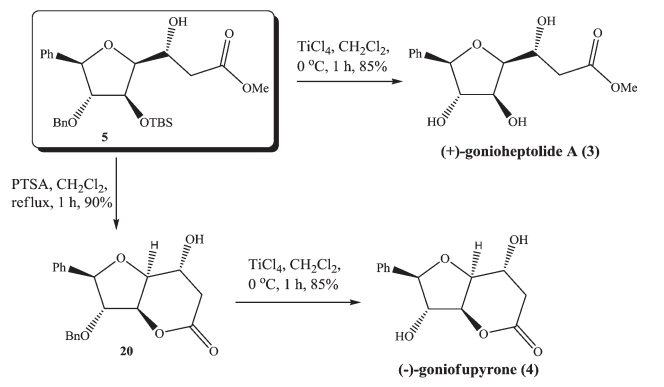
The above bicyclic compound **17** formed during the synthesis of goniothalesacetate (refer Scheme 3) was converted into the target compound **2**. Accordingly, the removal of the benzyl group with $TiCl_4$ [25] in **17** led to the formation of altholactone (**2**)[9] in 90% yield. The physical and spectroscopic data of synthetic **2** were identical to the reported values of the natural product.

Synthesis of (+)-gonioheptolide A (3) and synthesis of (−)-goniofupyrone (4)

With enough compound **5** in hand, we extended our work to the synthesis of gonioheptolide **3**, which was accomplished in a single step (Scheme 4). Thus, global deprotection of Bn and TBS groups in **5** was achieved with $TiCl_4$ to afford (+)-gonioheptolide A (**3**) in 85% yield. The synthesis of goniofupyrone **4** was accomplished in two steps from an intermediate **5** (Scheme 4). The treatment of **5** with PTSA/DCM deprotection of the TBS group and cyclization occurred in one-pot to furnish the lactone **20** in 90% yield. Finally, removal of the benzyl group with $TiCl_4$ in **20** led to the formation of (−)-goniofupyrone (**4**)[9,14] in 85% yield. The physical and spectroscopic data of synthetic **3** and **4** were identical to the reported values of the natural products.



Scheme 3 Synthesis of goniothalesacetate (**1**) & altholactone (**2**).



Scheme 4 Synthesis of gonioheptolide A (**3**) & goniofupyrone (**4**).

Conclusion

We have reported the first stereoselective total synthesis of (+)-goniothalesacetate and total syntheses of (+)-altholactone, (+)-gonioheptolide A and (−)-goniofupyrone using Grignard and asymmetric acetate aldol reactions as the key steps.

Experimental section

General

All reactions were performed under an inert atmosphere. All glassware apparatus used for the reactions were perfectly oven/flame dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates (250 μm thickness). Optical rotations $[\alpha]_D^{25}$ were measured using a polarimeter and given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wave number (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, and HRMS mass spectrometers. High resolution mass spectra (HRMS) [ESI+] were recorded using either a TOF or a double focusing spectrometer. ^{1}H NMR spectra were recorded at 300, 400, 500 and ^{13}C NMR spectra were recorded at 75 and 125 MHz in $CDCl_3$ solution unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The diastereomeric purity was determined by HPLC.

((2*S*,3*R*)-3-((4*R*,5*S*)-5-((4-Methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)methanol (7)

To a freshly flame dried double necked round bottom flask equipped with activated molecular sieves (4 Å) (5 g) and dry CH_2Cl_2 (30 mL) at −20 °C were added $Ti(O^iPr)_4$ (1.14 mL, 3.89 mmol) and D-(+)-diisopropyl tartrate (0.86 g, 3.89 mmol) and the mixture was stirred for 30 min. To this reaction mixture, allyl alcohol **6** (6.0 g, 19.4 mmol) after an interval of 30 min, TBHP (5.9 mL, 29.20 mmol, 5 M solution in CH_2Cl_2) was then added and the stirring was continued till the completion of the reaction (8 h). The reaction mixture was warmed to 0 °C and then filtered through Celite. The filtrate was quenched with water (1 mL) and 15% aqueous NaOH solution (1 mL) and stirred vigorously for 1 h. The biphasic solution was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography (7 : 3 hexane–EtOAc) to afford the pure epoxide **7** (5.36 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ = −7.5 (*c* 0.18, $CHCl_3$); **IR** (neat): 3452, 2987, 2868, 1612, 1513, 1248, 1089 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27–7.23 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.50 (s, 3H), 4.15–4.11 (m, 1H), 3.84 (dd, J = 12.9, 2.1 Hz, 1H), 3.81 (s, 3H), 3.77 (dd, J = 8.2, 5.0 Hz, 1H), 3.66 (dd, J = 9.9, 4.8 Hz, 1H), 3.59–3.52 (m, 2H), 3.10–3.06 (m, 2H), 1.41 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.3, 129.6, 129.5, 113.7, 110.0, 78.7, 76.4, 73.0, 69.7, 60.5, 55.6, 55.2, 54.5, 26.9, 26.5. HRMS (ESI): m/z calcd for $C_{17}H_{24}O_6Na$ $[M + Na]^+$: 347.1450, found = 347.1465.

(*R*)-1-((4*S*,5*S*)-5-((4-Methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (8)

To a stirred solution of **7** (5.1 g, 15.7 mmol) in Et_2O–MeCN (3 : 1, 20 mL) were added TPP (6.2 g, 23.6 mmol) and imidazole (2.14 g, 31.5 mmol) at 0 °C and the mixture was stirred for 5 min. I_2 (6.0 g, 23.6 mmol) was then added at 0 °C and the mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to afford the crude iodo compound. This was used for the next step without further purification. To a stirred solution of the above iodo compound in EtOH (20 mL) was added activated Zn dust (3.66 g, 56.4 mmol) and the mixture was stirred at reflux for 1–2 h. The mixture was passed through a short pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluent: PE–EtOAc, 8 : 2) to afford **8** (4.16 g, 86%) as a colorless liquid. $[\alpha]_D^{25}$ = +10.7 (*c* 0.24, $CHCl_3$); **IR** (neat): 3454, 2987, 2867, 1612, 1513, 1248, 1081 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27–7.23 (m, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.89–5.81 (m, 1H), 5.35 (dt, J = 17.2, 1.5 Hz, 1H), 5.22 (dt, J = 10.6, 1.5 Hz, 1H), 4.5 (s, 2H), 4.19–4.08 (m, 2H), 3.86 (dd, J = 7.9, 4.4 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, J = 10.0, 5.3 Hz, 1H), 3.53 (dd, J = 10.0, 4.8 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.2, 136.7, 129.6, 129.3, 116.8, 113.7, 109.5, 80.9, 76.0, 73.1, 72.0, 69.8, 55.2, 27.0 (2C). HRMS (ESI): m/z calcd for $C_{17}H_{24}O_5Na$ $[M + Na]^+$: 331.1504, found = 331.1516.

(4*S*,5*S*)-4-((*R*)-1-(Benzyloxy)allyl)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolane (9)

To a suspension of NaH (60%, 0.7 g, 28.4 mmol) in dry THF (20 mL) was added dropwise a solution of alcohol **8** (3.50 g, 11.3 mmol) in THF (20 mL) at 0 °C. To this reaction mixture TBAI (0.01 g) and benzyl bromide (1.94 mL, 11.3 mmol) were added subsequently and stirring was continued for 2 h at the same temperature and 6 h at room temperature. The reaction mixture was quenched by using crushed ice flakes until a clear solution (biphasic) was formed. The reaction mixture was extracted with ethyl acetate (2 × 30 mL). The organic extracts were washed with water (1 × 50 mL), brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (10% EtOAc/hexane) afforded the pure product **9** (4.08 g, 90% yield) as a colorless liquid. $[\alpha]_D^{25}$ = −22.7 (*c* 0.22, $CHCl_3$); **IR** (neat): 2986, 2865, 1611, 1513, 1086 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38–7.21

(m, 7H), 6.86 (d, J = 8.6 Hz, 2H), 5.81–5.67 (m, 1H), 5.36–5.26 (m, 2H), 4.67 (d, J = 12.2 Hz, 1H), 4.49 (s, 2H), 4.42 (d, J = 12.2 Hz, 1H), 4.16–4.08 (m, 1H), 3.94–3.84 (m, 2H), 3.80 (s, 3H), 3.57 (dd, J = 10.5, 3.2 Hz, 1H), 3.46 (dd, J = 10.5, 6.2 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.0, 134.2, 129.2, 128.2 (2C), 127.5 (2C), 127.4, 119.7, 113.6, 109.6, 80.0, 79.0, 76.7, 72.9, 70.3, 70.2, 55.1, 27.1, 26.9. HRMS (ESI): m/z calcd for $C_{24}H_{34}O_5N$ $[M + NH_4]^+$: 416.2417, found = 416.2431.

(1*S*,2*R*)-2-(Benzyloxy)-2-((4*R*,5*S*)-5-((4-methoxybenzyloxy)-methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-phenylethanol (10)

To a solution of **9** (2.4 g, 5.52 mmol) in 1,4-dioxane/water (3 : 1; 12 mL), 2,6-lutidine (1.7 mL, 16.58 mmol), and OsO_4 (2.82 mL, 0.05 mmol) followed by $NaIO_4$ (5.20 g, 24.8 mmol) were sequentially added at room temperature, and the mixture was stirred for 2 h. After the completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were quickly washed with 1 N HCl (2 × 5 mL) to remove excess 2,6-lutidine followed by brine (2 × 5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude aldehyde.

To a suspension of Mg (0.26 g, 11.0 mmol) in anhydrous THF (10 mL) phenyl bromide (1.72 mL, 11.0 mmol) was added dropwise under a nitrogen atmosphere at room temperature. The suspension was stirred for half an hour at room temperature.

In another R.B. flask the crude aldehyde **9a** (2.2 g, 5.5 mmol) dissolved in CH_2Cl_2 (10 mL) under nitrogen conditions was added at 0 °C to a stirred suspension of $MgBr_2{\cdot}Et_2O$ (1.83 g, 7.15 mmol) in CH_2Cl_2. After stirring for 20 min, the flask was cooled to −78 °C and the phenyl Grignard generated above was added slowly at −78 °C and the reaction was stirred further at this temperature for 1 h. The solvent was then removed *in vacuo*, after which the residue was diluted with CH_2Cl_2 and allowed to warm to 0 °C. Then, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The compound was purified by silica gel column chromatography (20% EtOAc/hexane) to provide **10** (2.1 g, 82%) as yellow oil. $[\alpha]_D^{25}$ = +24.3 (c 0.27, $CHCl_3$); **IR** (neat): 3474, 2987, 2932, 1611, 1513, 1248, 1085 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43–7.24 (m, 9H), 7.18–7.14 (m, 3H), 6.85 (d, J = 8.6 Hz, 2H), 4.92–4.89 (m, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.44–4.39 (m, 3H), 4.23 (td, J = 10.5, 5.2 Hz, 1H), 3.82–3.79 (m, 4H), 3.60 (dd, J = 5.0, 3.0 Hz, 1H), 3.50 (dd, J = 10.0, 5.2 Hz, 1H), 3.41 (dd, J = 9.9, 5.2 Hz, 1H), 3.09 (d, J = 3.9 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.1, 141.2, 137.6, 129.8, 129.2, 128.3, 128.2, 128.1, 127.8, 127.5, 126.4, 113.7, 109.1, 81.6, 79.6, 75.5, 74.9, 74.2, 73.0, 69.9, 55.2, 26.9, 26.8. HRMS (ESI) m/z calcd for $C_{29}H_{34}O_6Na$ $[M + Na]^+$: 501.2220, found = 501.2247.

(*R*)-MTPA ester of compound 10

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.41 (m, 1H), 7.40–7.35 (m, 4H), 7.33–7.15 (m, 9H), 7.06 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.23 (d, J = 9.1 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.35 (d, J = 11.6 Hz, 1H), 4.31 (d, J = 7.9 Hz, 2H), 4.05 (td, J = 10.6,5.3 Hz, 1H), 3.81–3.77 (m, 4H), 3.40 (s, 3H), 3.30–3.26 (m, 2H), 3.13 (dd, J = 9.6, 5.8 Hz, 1H), 1.39 (s, 3H), 1.20 (s, 3H).

(*S*)-MTPA ester of compound 10

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.34 (m, 1H), 7.34–7.26 (m, 11H), 7.17–7.13 (m, 2H), 7.03 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 6.15 (d, J = 9.3 Hz, 1H), 4.81 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.30 (ABq, J = 25.4, 11.9 Hz, 2H), 4.12 (m, 1H), 3.82–3.78 (m, 4H), 3.37 (s, 3H), 3.33–3.27 (m, 2H), 3.14 (dd, J = 9.7, 6.1 Hz, 1H), 1.45 (s, 3H), 1.24 (s, 3H).

(2*S*,3*R*,4*S*,5*R*)-4-(Benzyloxy)-2-((4-methoxybenzyloxy)methyl)-5-phenyltetrahydrofuran-3-ol (11)

To a stirred mixture of compound **10** (1.8 g, 3.76 mmol), triethylamine (1.04 mL, 7.53 mmol) and DMAP (cat, 10 mol%) in CH_2Cl_2 (20 mL) at 0 °C was added tosyl chloride (0.86 g, 4.51 mmol) in CH_2Cl_2 (2 mL) over 15 min. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$. The organic layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 20 mL), brine solution (2 × 20 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product which was used for the next reaction without further purification.

To a stirred solution of compound **10a** (2.1 g, 3.30 mmol) in MeOH : DCM (1 : 1) 5 ml PTSA was added (10 mol%) and the reaction mixture was stirred at r.t. for 3 h. MeOH and DCM were removed under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: PE–EtOAc, 7 : 3) to afford the acid **11** (1.16 g, 72%) as a viscous liquid; yield: $[\alpha]_D^{25}$ = +3.4 (c 0.52, $CHCl_3$); **IR** (neat): 3443, 2908, 1611, 1511, 1247, 1032 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45–7.42 (m, 2H), 7.34–7.24 (m, 10H), 6.89 (d, J = 8.6 Hz, 2H), 4.79 (d, J = 4.7 Hz, 1H), 4.64–4.52 (m, 4H), 4.42 (dd, J = 4.5, 2.3 Hz, 1H), 3.96 (dd, J = 10.5, 4.4 Hz, 1H), 3.94–3.89 (m, 3H), 3.81 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.3, 140.2, 137.7, 129.4, 128.3, 127.7, 127.6, 127.5, 126.3, 113.8, 92.0, 84.7, 79.2, 77.9, 73.6, 72.0, 68.6, 55.2. HRMS (ESI) m/z calcd for $C_{26}H_{28}O_5Na$ $[M + Na]^+$: 443.1812, found = 443.1829.

((2*S*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-2-((4-methoxybenzyloxy)methyl)-5-phenyltetrahydrofuran-3-yloxy)(*tert*-butyl)dimethylsilane (12)

A solution of compound **11** (0.72 g, 1.64 mmol) in CH_2Cl_2 (10 mL) was treated with 2,6-lutidine (0.57 mL, 4.93 mmol) at 0 °C and stirred for 20 min. Next, TBSOTf (0.45 mL, 1.97 mmol) was added, and following the completion of the reaction as indicated by TLC, the mixture was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to yield a viscous

liquid, which on purification by silica gel column chromatography (EtOAc–hexane, 1 : 9) afforded the silyl-protected ether **12** (0.81 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$ = +31.2 (*c* 0.28, $CHCl_3$); **IR** (neat): 2929, 2858, 1611, 1513, 1250, 1093 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.54–7.30 (m, 12H), 6.98 (d, *J* = 8.5 Hz, 2H), 5.0 (d, *J* = 2.3 Hz, 1H), 4.72–4.58 (m, 4H), 4.46–4.36 (m, 2H), 3.95–3.84 (m, 6H), 0.90 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.1, 140.9, 137.6, 130.3, 129.5, 128.4, 128.0, 127.7, 127.5, 127.2, 126.6, 113.7, 92.0, 86.2, 81.3, 77.0, 73.1, 71.8, 68.1, 55.2, 25.5, 17.9, −4.8, −5.3. HRMS (ESI): *m*/*z* calcd for $C_{32}H_{46}O_5NSi$ $[M + NH_4]^+$: 552.3139, found = 552.3113.

((2*S*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)methanol (13)

To an ice-bath cooled solution of compound **12** (0.7 g, 1.31 mmol) in 10 mL aq. CH_2Cl_2 ($CH_2Cl_2 : H_2O$, 9 : 1), DDQ (0.32 g, 1.44 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was washed with 5% aq. $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (2 × 10). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (15% EtOAc/hexane) to afford alcohol **13** (0.46 g, 85% yield) as a liquid. $[\alpha]_D^{25}$ = +29.0 (*c* 0.20, $CHCl_3$); **IR** (neat): 3451, 2931, 2858, 1606, 1460, 1072 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46–7.44 (m, 2H), 7.35–7.24 (m, 8H), 4.88 (d, *J* = 3.9 Hz, 1H), 4.51 (ABq, *J* = 20.2, 11.5 Hz, 2H), 4.38 (dd, *J* = 4.4, 2.3 Hz, 1H), 4.25–4.21 (m, 1H), 4.01 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.92–3.87 (m, 2H), 0.83 (s, 9H), 0.07 (s, 3H), −0.04 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 140.5, 137.4, 128.4, 128.3, 127.8, 127.6, 126.6, 91.8, 85.1, 81.5, 77.9, 72.1, 62.3, 25.5, 17.8, −4.8, −5.2. HRMS (ESI) *m*/*z* calcd for $C_{24}H_{34}O_4NaSi$ $[M + Na]^+$: 437.2096, found = 437.2118.

(*R*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((2*S*,3*S*,4*R*,5*R*)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)-3-hydroxypropan-1-one (15)

To a stirred solution of **13** (0.24 g, 1.04 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under argon, freshly distilled $TiCl_4$ (0.11 mL, 1.06 mmol) was added slowly. After 15 min, DIPEA (0.2 mL, 1.16 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was cooled to −78 °C and stirred for another 1 h before the addition of aldehyde **14** (0.43 g dissolved in 5 mL of dry CH_2Cl_2, 1.04 mmol). The reaction was continued for further 15 min at −78 °C prior to quenching with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (2 × 50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100–200 mesh, 20–30% EtOAc in hexane) of the crude residue resulted in aldol adduct **15** (0.41 g, 60% over 2 steps) as a white solid. Attempts toward crystallization from 20% EtOAc/hexane gave a yellow oil. $[\alpha]_D^{25}$ = +10.9 (*c* 0.45, $CHCl_3$); **IR** (neat): 3455, 2928, 2856, 1695, 1456, 1255, 1042 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2H), 7.37–7.25 (m, 13H), 4.96 (d, *J* = 3.3 Hz, 1H), 4.73–4.68 (m, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.37 (dd, *J* = 4.1, 1.9 Hz, 1H), 3.91 (dd, *J* = 3.5, 2.1 Hz, 1H), 3.63–3.53 (m, 2H), 3.27–3.19 (m, 2H), 3.08–2.98 (m, 2H), 2.89 (dd, *J* = 16.4, 11.5 Hz, 2H), 0.78 (s, 9H), 0.07 (s, 3H), −0.15 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 201.1, 171.5, 140.5, 137.3, 136.4, 129.4, 129.2, 128.9, 128.8, 128.4, 128.2, 127.9, 127.7, 127.5, 127.2, 127, 126.5, 113.9, 91.3, 85.1, 83.2, 78, 72, 68.5, 67.2, 42.5, 36.5, 31.9, 25.5, 17.7, −4.5, −5.1. HRMS (ESI): *m*/*z* calcd for $C_{36}H_{46}O_5NS_2Si$ $[M + H]^+$: 664.2564, found = 664.2581.

(*R*)-Methyl 3-((2*S*,3*S*,4*R*,5*R*)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)-3-hydroxypropanoate (5)

Imidazole (0.41 g, 6.0 mmol) was added to a stirred solution of compound **15** (0.40 g, 0.60 mmol) in MeOH (10 mL). After stirring overnight the yellow solution became colorless and then EtOAc (10 mL) and saturated $NaHCO_3$ (10 mL) solutions were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (petroleum ether/EtOAc, 8 : 2) provided methyl ester **5** (0.26 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ = +4.1 (*c* 0.32, $CHCl_3$); **IR** (neat): 3449, 2929, 2857, 1741, 1457, 1255, 1078 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48–7.44 (m, 2H), 7.35–7.24 (m, 8H), 4.89 (d, *J* = 3.9 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.51–4.46 (m, 2H), 4.39 (dd, *J* = 4.4, 2.7 Hz, 1H), 4.10–4.08 (m, 1H), 3.91 (dd, *J* = 3.9, 2.4 Hz, 1H), 3.72 (s, 3H), 2.74–2.61 (m, 2H), 0.81 (s, 9H), 0.08 (s, 3H), −0.09 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.0, 140.4, 137.3, 129.2, 128.8, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 126.5, 126.4, 91.3, 84.6, 82.1, 78.3, 72.1, 67.7, 51.7, 37.9, 25.5, 17.7, −4.6, −4.2. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{39}O_6Si$ $[M + H]^+$: 487.2490, found = 487.2510.

(*R*)-Methyl 3-((2*S*,3*S*,4*R*,5*R*)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-phenyltetrahydrofuran-2-yl)-3-methoxypropanoate (16)

To a solution of alcohol **5** (0.1 g, 0.20 mmol) in DCM (5 mL) at 0 °C was added Proton Sponge (0.13 g, 0.60 mmol) followed by trimethyloxonium tetrafluoroborate (0.09 g, 0.60 mmol). The reaction mixture was stirred for 6 h, before being quenched with $NaHCO_3$ (5 mL), filtered through Celite, and extracted with DCM (2 × 5 mL). The combined organic extracts were washed with 1 N HCl (6 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 9 : 1) afforded methyl ether **16** (0.08 g, 78%) as a colourless oil. $[\alpha]_D^{25}$ = +8.2 (*c* 0.25, $CHCl_3$); **IR** (neat): 2953, 1740, 1650, 1076 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45–7.42 (m, 2H), 7.35–7.21 (m, 8H), 4.95 (d, *J* = 3.2 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.22 (dd, *J* = 3.5, 1.9 Hz, 1H), 4.14–4.07 (m, 2H), 3.87 (dd, *J* = 3.0, 1.9 Hz, 1H), 3.71 (s, 3H), 3.57 (s, 3H), 2.60–2.55 (m, 2H), 0.80 (s, 9H), 0.02 (s, 3H), −0.19 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.6, 141, 137.5, 128.4, 128.1, 127.9, 127.7, 127.3, 126.4, 90.7, 85.7, 84.3, 77.1, 76.8, 71.8, 59.3, 51.6, 36.7, 25.6, 17.8, −4.3, −5.2. HRMS (ESI) *m*/*z* calcd for $C_{28}H_{40}O_6SiNa$ $[M + Na]^+$: 523.2481, found = 523.2481.

(*R*)-Methyl 3-((2*R*,3*S*,4*S*,5*R*)-4-(benzyloxy)-3-hydroxy-5-phenyltetrahydrofuran-2-yl)-3-methoxypropanoate (18)

To a stirred solution of compound **16** (0.052 g, 0.10 mmol) in MeOH : DCM (1 : 2, 5 mL) was added PTSA (10 mol%) and the reaction mixture was stirred at r.t. for 4 h. The MeOH was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: PE–EtOAc, 8 : 2) to afford the acid **18** (0.032, 82%) as a viscous liquid; yield. $[\alpha]_D^{25}$ = +25.0 (*c* 0.15, $CHCl_3$); **IR** (neat): 3449, 2924, 2854, 1738, 1636, 1215, 1098 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44–7.42 (m, 2H), 7.35–7.26 (m, 8H), 4.81 (d, *J* = 4.2 Hz, 1H), 4.60 (ABq, *J* = 18.7, 11.7 Hz, 2H), 4.35–4.32 (m, 1H), 4.21–4.17 (m, 1H), 4.13 (dd, *J* = 4.7, 3.9 Hz, 1H), 3.91 (dd, *J* = 4.1, 1.6 Hz, 1H), 3.71 (s, 3H), 3.51 (s, 3H), 2.82 (dd, *J* = 18.3, 6.2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.0, 140.2, 137.6, 128.4, 128.3, 127.8, 127.6, 126.2, 92.1, 84.9, 81.8, 77.1, 72.1, 58.0, 51.9, 35.9. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{26}O_6Na$ $[M + Na]^+$: 409.1606, found = 409.1621.

(*R*)-Methyl 3-((2*S*,3*S*,4*R*,5*R*)-3-acetoxy-4-(benzyloxy)-5-phenyltetrahydrofuran-2-yl)-3-methoxypropanoate (19)

Anhydrous Et_3N (0.018 mL, 0.13 mmol), Ac_2O (0.006 mL, 0.06 mmol), and DMAP (10 mg) were added to a solution of alcohol **18** (20 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated $NaHCO_3$. The organic layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (10% EtOAc/hexane) to afford **19** (21 mg, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +30.4 (*c* 0.12, $CHCl_3$); **IR** (neat): 2927, 1741, 1646, 1231, 1097 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 10H), 5.24 (dd, *J* = 3.5, 1.1 Hz, 1H), 4.89 (d, *J* = 3.9 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.27 (dd, *J* = 7.8, 3.5 Hz, 1H), 4.14–4.08 (m, 1H), 3.84 (dd, *J* = 4.0, 1.1 Hz, 1H), 3.71 (s, 3H), 3.56 (s, 3H), 2.55–2.51 (m, 2H), 2.02 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.4, 170.1, 140.0, 139.2, 128.4, 128.3, 127.8, 127.7, 127.6, 125.8, 89.9, 85.8, 82.4, 77.2, 76.5, 72.1, 59.3, 51.8, 36.8. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{28}O_7Na$ $[M + Na]^+$: 451.1711, found = 451.1727.

(*R*)-Methyl 3-((2*S*,3*S*,4*R*,5*R*)-3-acetoxy-4-hydroxy-5-phenyltetrahydrofuran-2-yl)-3-methoxypropanoate (1)

To a stirred solution of compound **19** (9 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $SnCl_4$ (1 M solution in DCM, 0.04 mL, 0.04 mmol) at 40 °C and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ (5 mg) and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (70% EtOAc/hexane) to afford **1** (7 mg, 90%) as a colorless yellow oil. $[\alpha]_D^{25}$: +3.02 (*c* 0.32, CH_3OH); lit[2] $[\alpha]_D^{25}$: +1.03 (*c* 0.39, CH_3OH); **IR** (neat): 3451, 2923, 2853, 1740, 1632, 1237, 1046 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.38–7.28 (m, 3H), 5.0 (dd, *J* = 5.1, 2.6 Hz, 1H), 4.71 (d, *J* = 6.1 Hz, 1H), 4.31 (dd, *J* = 6.9, 5.2 Hz, 1H), 4.08 (dd, *J* = 3.7, 2.8 Hz, 1H), 4.05 (td, *J* = 6.9, 1.1 Hz, 1H), 3.72 (s, 3H), 3.55 (s, 3H), 2.60–2.58 (m, 2H), 2.08 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.5, 171.4, 139.4, 128.3, 127.8, 125.9, 84.9, 83.5, 81.9, 80.9, 77.2, 59.2, 51.8, 36.5. **^{1}H NMR** (300 MHz, CD_3OD): δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.27 (tt, *J* = 6.5, 1.2 Hz, 1H), 5.08 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.70 (d, *J* = 6.1 Hz, 1H), 4.26 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.03 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.99 (td, *J* = 7.3, 4.4 Hz, 1H), 3.69 (s, 3H), 3.51 (s, 3H), 2.58 (d, *J* = 4.6 Hz, 1H), 2.56 (d, *J* = 7.6 Hz, 1H), 1.98 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.2, 171.8, 141.7, 129.3, 127.1, 88.1, 83.3, 82.9, 81.2, 78.2, 59.3, 52.3, 37.5, 20.7. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{22}O_7Na$ $[M + Na]^+$: 361.1257, found = 361.1247.

(2*R*,3*R*,3a*R*,7a*S*)-3-(Benzyloxy)-2-phenyl-3,3a-dihydro-2*H*-furo[3,2-*b*]pyran-5(7a*H*)-one (17)

To a solution of **16** (30 mg, 0.06 mmol) in anhydrous THF (5 mL) was added TBAF (0.12 mL, 0.12 mmol, 1 M solution in THF) dropwise at 0 °C, and the mixture was stirred for 2 h. H_2O (5 mL) was added, and the mixture was extracted with ethyl acetate (2 × 5 mL). The org. extracts were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. After the evaporation of the solvent, the residue was purified by column chromatography (30% EtOAc/hexane) to furnish the bicyclic compound **17** (15 mg, 82% yield) as a colorless solid. M.P. 89–91 °C; $[\alpha]_D^{25}$ = +11 2.7 (*c* 0.29, $CHCl_3$); **IR** (neat): 2920, 1734, 1639, 1245, 1096 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 10H), 7.0 (dd, *J* = 9.9, 5.2 Hz, 1H), 6.25 (d, *J* = 9.9 Hz, 1H), 5.01 (dd, *J* = 4.7, 1.3 Hz, 1H), 4.85 (d, *J* = 5.4 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.62–4.57 (m, 2H), 4.24 (dd, *J* = 5.3, 1.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 160.1, 139.4, 138.2, 136.8, 128.6, 128.5, 128.3, 128.1, 127.7, 126.2, 124.2, 90.7, 85.3, 84.2, 72.6, 68.7. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{19}O_4$ $[M + H]^+$: 323.1270, found = 323.1277.

(2*R*,3*R*,3a*S*,7a*S*)-3-Hydroxy-2-phenyl-3,3a-dihydro-2*H*-furo[3,2-*b*]pyran-5(7a*H*)-one (2)

To a stirred solution of compound **17** (10 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $TiCl_4$ (1 M solution in DCM, 0.06 mL, 0.06 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ (20 mg) and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (40% EtOAc/hexane) to afford **2** (6.4 mg, 90%) as a colorless solid. M.p. 108–110 °C; $[\alpha]_D^{25}$: +115.6 (*c* 0.52, $CHCl_3$); lit.[4] $[\alpha]_D^{25}$: +118.6 (*c* 0.5, $CHCl_3$); **IR** (neat): 3433, 2923, 1729, 1638, 1251, 1093 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 6.99 (dd, *J* = 9.9, 5.0 Hz, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 4.92 (dd, *J* = 5.0, 2.2 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H), 4.63 (t, *J* = 5.0 Hz, 1H), 4.44 (dd, *J* = 6.1, 2.2 Hz, 1H), 3.36 (Brs, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 161.4, 140.4, 138.1, 128.6, 128.3,

126.1, 123.5, 86.4, 85.9, 83.5, 68.1. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}O_4$ $[M + H]^+$: 233.0804, found = 233.0808.

(2*R*,3*R*,3a*S*,7*R*,7a*S*)-3-(Benzyloxy)-7-hydroxy-2-phenyltetrahydro-2*H*-furo[3,2-*b*]pyran-5(6*H*)-one (20)

A stirred solution of **5** (25 mg, 0.05 mmol) in DCM (5 mL) was treated with *p*-TSA (10%, 0.25 mmol) for 3 h at 40 °C. After the completion of the reaction (indicated by TLC), the reaction mixture was diluted with DCM (5 mL) and then solid $NaHCO_3$ (0.34 g, 4.0 mmol) was added and stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3 × 10 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using EtOAc as the eluent yielded **20** (14 mg, 81%) as a colourless oil. $[\alpha]_D^{25}$ = +38.35 (*c* 0.19, $CHCl_3$); **IR** (neat): 3432, 2922, 1741, 1496, 1055 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 10H), 5.07 (dd, *J* = 4.8, 1.8 Hz, 1H), 4.82 (d, *J* = 6.1 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.44 (dt, *J* = 7.6, 3.8 Hz, 1H), 4.33–4.31 (m, 1H), 4.09 (dd, *J* = 6.1, 1.9 Hz, 1H), 2.91 (dd, *J* = 16.7, 3.6 Hz, 1H), 2.67 (dd, *J* = 16.1, 5.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 168.4, 138.1, 136.8, 128.6, 128.5, 128.3, 128.0, 127.7, 126, 90.4, 84.9, 84.2, 77.0, 72.6, 65.8, 35.2. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{24}O_5N$ $[M + NH_4]^+$: 358.1641, found = 358.1649.

(*R*)-Methyl 3-((2*S*,3*S*,4*S*,5*R*)-3,4-dihydroxy-5-phenyltetrahydrofuran-2-yl)-3-hydroxypropanoate (3)

To a stirred solution of compound **5** (11 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $TiCl_4$ (1 M solution in DCM, 0.04 mL, 0.044 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ (20 mg) and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (80% EtOAc/hexane) to afford **3** (5.4 mg, 85%) as a colorless oil; $[\alpha]_D^{25}$: −2.80 (*c* 0.29, $CHCl_3$); lit[12] $[\alpha]_D^{25}$: −5.0 (*c* 0.3, $CHCl_3$); **IR** (neat): 3405, 2924, 1727, 1440, 1044 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48–7.44 (m, 1H), 7.37–7.27 (m, 4H), 4.58 (d, *J* = 6.5 Hz, 1H), 4.45–4.38 (m, 1H), 4.35–4.30 (m, 1H), 4.10–4.06 (m, 2H), 3.71 (s, 3H), 2.86 (dd, *J* = 16.4, 8.6 Hz, 1H), 2.65 (dd, *J* = 16.6, 4.1 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.2, 139.4, 128.5, 128, 126.4, 84.4, 83.8, 79.8, 67.8, 52.0, 37.6. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}O_6Na$ $[M + Na]^+$: 305.0985, found = 305.0995.

(2*R*,3*R*,3a*S*,7*R*,7a*S*)-3,7-Dihydroxy-2-phenyltetrahydro-2*H*-furo[3,2-*b*]pyran-5(6*H*)-one (4)

To a stirred solution of compound **20** (9 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $TiCl_4$ (1 M solution in DCM, 0.05 mL, 0.05 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ (20 mg) and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to afford **4** (5.84 mg, 87%) as a colorless oil. $[\alpha]_D^{25}$: −6.52 (*c* 0.34, $CHCl_3$); lit.[12] $[\alpha]_D^{25}$: −5.0 (*c* 0.3, $CHCl_3$); **IR** (neat): 3393, 2923, 1734, 1452, 1049 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32–7.24 (m, 5H), 4.94 (dd, *J* = 5.0, 2.3 Hz, 1H), 4.62 (d, *J* = 6.2 Hz, 1H), 4.33–4.24 (m, 2H), 4.17 (dd, *J* = 6.2, 2.3 Hz, 1H), 3.91 (Brs, 1H), 2.79 (dd, *J* = 17, 3.5 Hz, 1H), 2.62 (dd, *J* = 16.7, 4.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 170.6, 137.9, 128.6, 128.3, 125.9, 87, 85.4, 83.3, 75.8, 65.3, 34.8. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{15}O_5$ $[M + H]^+$: 251.0908, found = 233.0900.

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