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Asymmetric Synthesis of (+)-Altholactone: A Styryllactone Isolated from Various *Goniothalamus* Species

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

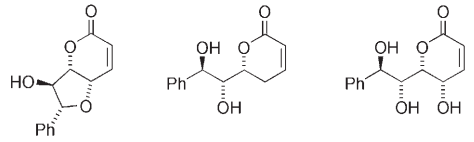
Abstract: The asymmetric total synthesis of (+)-altholactone (**1**), a member of the styryllactone family of natural products displaying cytotoxic and antitumor activities, is described. Key steps include a RAMP-hydrazone α-alkylation (RAMP = (*R*)-1-amino-2-methoxymethylpyrrolidine) of 2,2-dimethyl-1,3-dioxan-5-one, a boron-mediated aldol reaction, a six- to five-membered ring acetonide shuffling, an oxidative 1,5-diol to δ-lactone conversion and a stereoselective ring-closure to generate the annulated tetrahydrofuran moiety with inversion of configuration.

Keywords: aldol reaction · altholactone · asymmetric synthesis · hydrazones · natural products

Introduction

Trees and shrubs of the genus *Goniothalamus* growing in South East Asia have long been known as a source of diverse secondary metabolites such as the styryllactones. Many of these natural products show outstanding ranges of biological activities and have been used in folk medicine. (+)-Altholactone (**1**, Figure 1), a tetrahydrofurano-2-pyrone of the styryllactone family of natural products, has been isolated from an unnamed *Polyalthia* (Annonaceae) species[1] and also from various members of the *Goniothalamus* family.[2] This class of natural products shares a common 5,6-dihydro-2*H*-pyran-2-one[3] structural unit, other members of the group including acetoxygoniothalamine, goniodiol (**2**), and goniotriol (**3**).[4] (+)-Altholactone (**1**) is known to be cytotoxic in vitro and shows in vivo antitumor activity.[2,5]

Because of the intriguing structures of the styryllactone family and their broad range of important biological activities, many synthetic methods to synthesise this core structure have been employed.[6] Most syntheses are based on the chiral pool concept, employing enantiopure starting materials such as carbohydrates,[7] glyceraldehyde,[8] hydroxy acids,[9] and amino acids.[10] Asymmetric syntheses[11] and chemoenzymatic approaches[12] are rather rare.



(+)-altholactone (**1**) (+)-goniodiol (**2**) (+)-goniotriol (**3**)

Figure 1. Typical natural products of the styryllactone family.

Results and Discussion

In continuation of our efforts to develop efficient asymmetric syntheses of natural products and biologically active compounds[13] based on 2,2-dimethyl-1,3-dioxan-5-one (**4**)[14,15] by the SAMP/RAMP hydrazone methodology,[16] we now wish to report a new and efficient asymmetric synthesis of (+)-altholactone (**1**). As is depicted in Scheme 1, this tetrahydrofurano-2-pyrone structure can retrosynthetically be traced back to the dioxanone **4**, benzaldehyde and a protected 3-bromopropanol.

The commercially available and easy to prepare dioxanone **4** was first converted into the corresponding RAMP-hydrazone **5** (Scheme 2) in 90% yield by treatment with the chiral hydrazine auxiliary (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP). After metallation with *tert*-butyllithium

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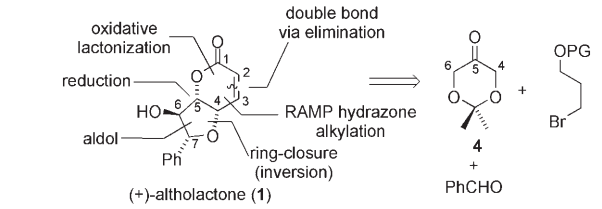
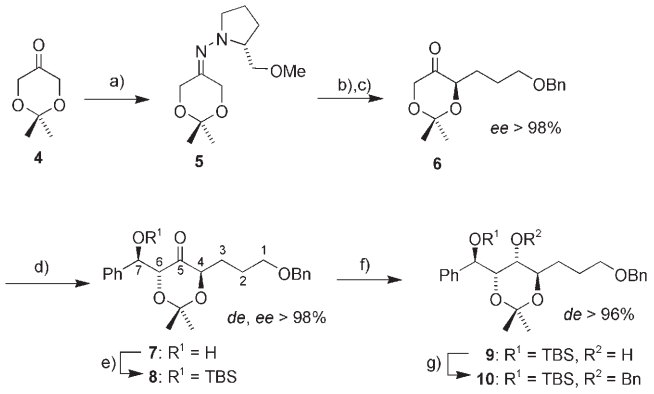


Scheme 1. Retrosynthetic analysis of (+)-altholactone (**1**).



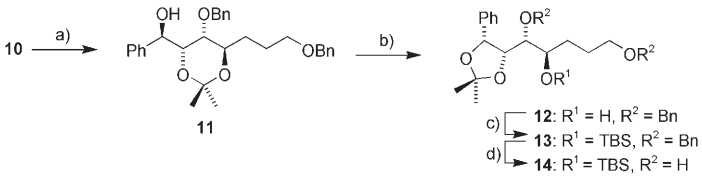
Scheme 2. a) RAMP, benzene, reflux (90%); b) 1) *t*BuLi, THF, −78°C; 2) $Br(CH_2)_3OBn$, −100°C→RT; c) oxalic acid, Et_2O, RT (82% over two steps); d) Cy_2BCl, Et_3N, Et_2O, −78°C, then H_2O_2, MeOH, pH 7 buffer, RT (68%); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT (90%); f) L-selectride, THF, −78°C (88%); g) BnBr, KH, THF, RT (90%). Tf = trifluoromethanesulfonyl.

and trapping of the aza-enolate with 3-benzyloxy-1-bromopropane at low temperature, the resulting α-alkylated hydrazone was hydrolysed[17] with a saturated aqueous solution of oxalic acid. The alkylated dioxanone **6** was obtained after purification by flash chromatography in 82% yield over the two steps and with an excellent enantiomeric excess (*ee*) of >98% as determined by chiral stationary phase GC.

We had next envisaged the use of our organocatalytic C_3+C_n biomimetic strategy[18] for carbohydrate synthesis in a proline-catalysed *anti*-selective aldol reaction to form **7** from the dioxanone **4.**[19] Because no satisfying results in terms of yield and stereoselectivity could be obtained in this special case of an organocatalytic aldol reaction between **6** and benzaldehyde, we switched to the boron-mediated aldol variant,[20] which afforded the desired *anti*-aldol **7** in 68% yield and with excellent diastereoselectivity (*de* > 98%) as determined by ^1H and ^{13}C NMR spectroscopy. As had been hoped, the relative configuration between C-6 and C-4 (see altholactone numbering) also turned out to be *anti*, as was easily determined by ^{13}C NMR[21] from the acetonide methyl group chemical shifts ($\delta = 23.5$ and 23.6 ppm). Gratifyingly, our strategy to control the relative and absolute configurations of the remaining stereocentres diastereoselectively through the first one created with the highly reliable SAMP/RAMP-hydrazone methodology had worked out.

Because of the sensitivity of the aldol addition product **7** and in order to achieve a high diastereoselectivity in the subsequent reduction step, it was necessary to protect the hydroxy group as the corresponding *tert*-butyldimethylsilyl (TBS) ether **8** under standard conditions (90% yield). Selective reduction of the ketone function with L-selectride afforded the alcohol **9** in 88% yield and with an excellent diastereoselectivity of *de* >96%, as determined by ^1H NMR and ^{13}C NMR spectroscopy, in favour of the *anti* relative configuration with respect to centre C-7 (Scheme 2).

In our synthetic strategy we had to discriminate between the several secondary alcohol groups in a specific way including an acetonide shuffling. Thus, benzylation of alcohol **9** yielded the corresponding dibenzyl ether **10** in 90% yield, and subsequent removal of the TBS protecting group with tetra-*n*-butylammonium fluoride (TBAF) gave the alcohol **11** (Scheme 3) in 95% yield. Treatment of the alcohol acetonide **11** under equilibrating acidic conditions furnished a readily separable mixture of the five-membered ring acetal acetonide **12** and starting material. The acetonide **12** was protected as the corresponding TBS ether **13** in 99% yield, whereas acetonide **11** was recycled. Simultaneous double debenzylation of **13** under standard hydrogenolysis conditions over 10% palladium on carbon provided a 99% yield of the diol **14** (Scheme 3), which was used in an oxidation/in situ cyclisation sequence with 2-iodoxybenzoic acid (IBX)[22] to afford the corresponding lactol. This was oxidised to the δ-lactone **15** (Scheme 4) with tetra-*n*-propylammonium perruthenate (TPAP)/N-methylmorpholine N-oxide (NMO)[23] in 77% yield over two steps. A exploratory attempt to reach lactone **15** in one step from diol **14** with use of TPAP/NMO had initially been envisaged, but the reaction gave the corresponding aldehyde without any observed cyclisation.

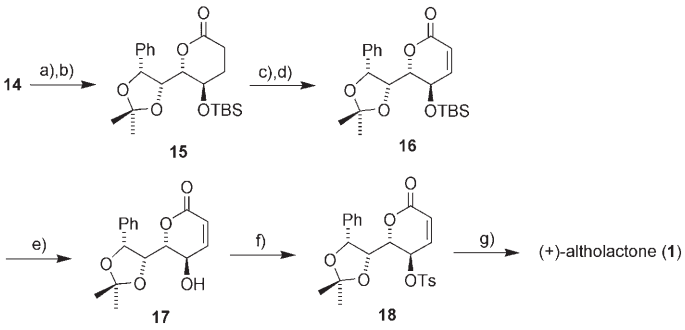


Scheme 3. a) TBAF, THF, RT (95%); b) 1. *p*-TsOH (cat.), acetone, RT. 2. 0.25 equiv 2,2-DMP, PPTS (cat.) [**12** (36%), **11** (59%)]; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT (99%); d) H_2, 10% Pd/C, EtOAc, RT (99%). TsOH = *p*-toluenesulfonic acid. 2,2-DMP = 2,2-dimethoxypropane. PPTS = pyridinium *p*-toluenesulfonate.

Abstract in German: *Die asymmetrische Totalsynthese von (+)-Altholacton (**1**), einem Mitglied der Styryllacton-Familie von Naturstoffen mit cytotoxischen und antitumor-Aktivitäten, wird beschrieben. Unter den Schlüsselschritten sind eine RAMP-Hydrazon-α-Alkylierung (RAMP = (R)-1-Amino-2-methoxymethylpyrrolidin) von 2,2-Dimethyl-1,3-dioxan-5-on, eine Bor-unterstützte Aldol-Reaktion, eine Sechs- zu Fünfring Acetonid-Verschiebung, eine oxidative 1,5-Diol zu δ-Lacton-Überführung und ein stereoselektiver Ringschluß zur Generierung der annulierten Tetrahydrofuran-Gruppierung unter Inversion der Konfiguration.*

The introduction of the α,β-double bond into the δ-lactone **15** was achieved through an α-selenylation/elimination sequence[24] with PhSeCl and H_2O_2, which provided **16** in 86% yield over two steps (calculated on the recovered starting material).

In order to construct the tetrahydrofuran ring of the target molecule through a ring-closure, the TBS protecting group was removed with tetrabutylammonium fluoride in 74% yield to afford the alcohol **17**, which was transformed into the corresponding tosylate **18** in 95% yield. Removal of the acetonide protecting group under acidic conditions with Amberlyst 15[25] and simultaneous ring-closure with complete inversion of configuration led to the target molecule (+)-altholactone (**1**) in 93% yield (Scheme 4).



Scheme 4. a) IBX (2.2 equiv), DMSO, RT; b) TPAP (5 mol%)/NMO (1.5 equiv), CH_2Cl_2, RT (77% over two steps); c) LDA, PhSeCl, THF, −78°C; d) 30% H_2O_2, CH_2Cl_2, 0°C [**16** (60%) and **15** (31%) over two steps]; e) TBAF, THF, RT (74%); f) TsCl, DMAP, CH_2Cl_2, RT (95%); g) Amberlyst 15, MeOH, RT (93%). DMAP = 4-(dimethylamino)pyridine.

Conclusion

In summary, an efficient highly diastereo- and enantioselective synthesis of (+)-altholactone (**1**) in eighteen steps and 13.7% overall yield from the commercially available starting dioxanone **4** has been achieved. The first key step of the asymmetric synthesis is a RAMP-hydrazone α-alkylation of the dihydroxy acetone C_3-building block **4**, which generates the first stereocentre with virtually complete asymmetric induction (*ee* > 98%), subsequently allowing the remaining three stereogenic centres to be diastereoselectively controlled. This was accomplished by a boron-mediated *anti*-selective aldol reaction, a ketone reduction with L-selectride, and a tetrahydrofuran ring-closure with complete inversion of configuration under acidic conditions. Our new route to the styryllactone family is flexible in terms both of stereoselectivity and of structural variations for further bioactivity screening. For instance, the enantiomer (−)-altholactone should be available simply by replacing the chiral auxiliary RAMP by its enantiomer SAMP in the first key step of the synthesis, and the aldehyde component of the aldol reaction may be varied. In addition, a Mitsunobu inversion of our intermediate alcohol **17** and a hydride displacement of the tosyl group in **18** should give rise to (+)-goniotriol (**3**) and (+)-goniodiol (**2**), respectively. These reactions are currently under investigation in our laboratories.

Experimental Section

Solvents were purified and dried prior to use. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium and under argon. Dichloromethane, dimethyl sulfoxide (DMSO) and triethylamine were distilled over calcium hydride and stored under argon. Acetone was distilled over P_4O_{10} and stored under argon. Methanol was distilled over magnesium. Diethyl ether, pentane and ethyl acetate were distilled over KOH, CaH_2 and K_2CO_3, respectively, prior to use. Analytical glass-backed TLC plates (silica gel 60 F_{254}) and silica gel (60, 40–63 μm) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Optical rotations were measured on a Perkin–Elmer P241 polarimeter and with solvents of Merck UVASOL quality. Microanalyses were performed with a Heraeus CHN-O-RAPID, Vario EL elemental analyser. ^{1}H and ^{13}C NMR spectra were obtained on Varian VXR 300, Gemini 300 (both 300 and 75 MHz), Varian Inova 400 (400 MHz and 100 MHz) or Varian Unity 500 (500 and 125 MHz) instruments with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer 1760 FT/IR spectrometer. Mass spectroscopic analyses were obtained on a Varian MAT 212 (EI, 70 eV, 1 mA) and a Finnigan MAT SSQ 7000 (CI, 100 eV) instrument (relative intensities are reported in brackets). High-resolution mass spectra were recorded on a Finnigan MAT 95 machine. Melting points were measured with a Büchi 510 apparatus and are uncorrected. ^{13}C NMR spectra of all compounds for which only HRMS data are given below are shown in the Supporting Information (compounds **7**, **12**, **14**, **16**, **17**, **18** and **1**).

(*R*)-(−)-1-(2,2-Dimethyl-1,3-dioxan-5-ylidenamino)-2-methoxymethylpyrrolidine (5): In a flask fitted with a Dean–Stark trap and a reflux condenser, dioxanone **4** (8.45 g, 64.93 mmol, 1.0 equiv) and (*R*)-1-amino-2-methoxymethylpyrrolidine (8.48 g, 65.14 mmol, 1.0 equiv) in benzene (80 mL) were heated at reflux for 20 h. After the system had cooled, Et_2O (200 mL) was added and the mixture was washed with H_2O (2× 10 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude hydrazone was purified by distillation under reduced pressure to give RAMP-hydrazone **5** as a yellow oil (14.16 g, 90%). B.p. 106–109°C (1 mbar); $[\alpha]_D^{23} = -230.0$ (neat) and −307.74 ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.21$–4.58 (m, 4H; CH_2CN), 3.35 (s, 3H; OCH_3), 3.04–3.46 (m, 4H; NCHH, NCH, CH_2OCH$_3$), 2.50 (q, ^3J(H,H) = 8.5 Hz, 1H; NCHH), 1.93–2.06 (m, 1H; NCHCHHCH$_2$), 1.80–1.89 (m, 2H; NCH$_2$CHH, NCHCHHCH$_2$), 1.60–1.71 (m, 1H; NCH$_2$CHH), 1.43 [s, 3H; C(CH_3)], 1.40 ppm (s, 3H; C(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.0$ (*C*N), 99.9 [*C*(CH$_3$)$_2$], 75.4 (*C*H$_2$OCH$_3$), 66.6 (N*C*H), 62.6 (*C*H$_2$CN), 60.3 (*C*H$_2$CN), 59.2 (O*C*H$_3$), 55.4 (N*C*H$_2$), 26.7 (NHCH*C*H$_2$CH$_2$), 24.5 [C(*C*H$_3$)], 23.2 [C(*C*H$_3$)], 22.7 ppm (NCH$_2$*C*H$_2$); IR (film): $\tilde{\nu} = 2982$, 2937, 2874, 1451, 1376, 1221, 1150, 1094, 1068, 836 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 243 (100) [*M*+H]$^+$, 242 (19), 211 (8) [*M*+H−CH$_3$OH]$^+$, 197 (19), 185 (52) [*M*+H−(CH$_3$)$_2$CO]$^+$; elemental analysis (%) calcd for $C_{12}H_{22}N_2O_3$ (242.31): C 59.48, H 9.15, N 11.56; found: C 59.47, H 9.36, N 11.34.

(*R*)-(+)-4-(3-Benzyloxypropyl)-2,2-dimethyl-1,3-dioxan-5-one (6): A dry, argon-flushed 500 mL Schlenk round-bottomed flask containing a magnetic stirring bar was charged with RAMP-hydrazone **5** (4.88 g, 20.14 mmol, 1.0 equiv) and anhydrous THF (80 mL). *t*BuLi (14.9 mL, 15% in *n*-pentane, 22.15 mmol, 1.1 equiv) was then added dropwise at −78°C. After stirring for 2 h at this temperature, the mixture was cooled to −100°C and 1-benzyloxy-3-bromopropane (5.55 g, 22.15 mmol, 1.1 equiv) in anhydrous THF (4 mL) was slowly added. After further stirring for 2 h at −100°C, the mixture was allowed to warm up to room temperature over 15 h. The mixture was quenched with buffer solution (pH 7, 4 mL) and then diluted with Et_2O (80 mL). The organic layer was washed with buffer solution (pH 7, 20 mL) and brine (2×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under re-

duced pressure. A solution of the resulting crude hydrazone in Et_2O (100 mL) was vigorously stirred at room temperature with a saturated aqueous solution of oxalic acid (80 mL) for 20 h. The aqueous layer was separated and extracted with Et_2O, and the organic extracts were combined, washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, PE/Et_2O 80:20) to afford the alkylated product **6** (4.60 g, 82% over two steps) as a colourless liquid. $[\alpha]_D^{23} = +150.96$ ($c = 1$, $CHCl_3$); *ee* = 98% (CSP-GC, Lipodex G, 25 m × 0.25 mm); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$–7.34 (m, 5H; Ar-*H*), 4.50 (s, 2H; CH_2Ph), 4.24 (ddd, ^3J(H,H) = 8.4, 4.2, 1.5 Hz, 1H; C*H*CH$_2$), 4.24 [dd, ^3J(H,H) = 17.1, 1.5 Hz, 1H; C(O)C*H*HO], 3.97 [d, ^3J(H,H) = 17.1 Hz, 1H; C(O)CH*H*O], 3.49 (td, ^3J(H,H) = 6.4, 1.2 Hz, 2H; CH_2OCH$_2$), 1.93–2.03 (m, 1H; CHC*H*H), 1.68–1.83 (m, 2H; CH$_2$CH_2CH$_2$), 1.57–1.65 (m, 1H; CHCH*H*), 1.42 ppm [s, 6H; C(CH_3)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 209.6 [*C*(O)], 138.5 (Ar-*C*), 128.4, 127.7, 127.6 (Ar-*C*H), 100.8 [*C*(CH$_3$)$_2$], 74.4 (*C*H), 72.9 (O*C*H$_2$Ph), 69.9 [C(O)*C*H$_2$O], 66.6 (CH$_2$CH$_2$*C*H$_2$), 25.4 (CH*C*H$_2$), 25.3 (CH$_2$*C*H$_2$CH$_2$), 24.0 [C(*C*H$_3$)], 23.6 ppm [C(*C*H$_3$)]; IR (film): $\tilde{\nu} = 3030$, 2987, 2936, 2860, 2361, 2335, 1746 (C=O), 1453, 1376, 1225, 1176, 1104, 740, 700 cm^{-1} (C$_6$H$_5$); MS (100 eV, CI): *m*/*z* (%): 279 (2.6) [*M*+H]$^+$, 261 (20) [*M*+H−H$_2$O]$^+$, 221 (66) [*M*+H−(CH$_3$)$_2$CO]$^+$, 203 (71) [*M*+H−H$_2$O−(CH$_3$)$_2$CO]$^+$, 171 (69), 129 (10), 113 (41), 91 (100) [C$_7$H$_7$]$^+$, 71 (14); elemental analysis (%) calcd for $C_{16}H_{22}O_4$ (278.34): C 69.04, H 7.97; found: C 68.81, H 7.96.

(4*R*,6*R*)-(+)-4-(3-Benzyloxypropyl)-6-[(*R*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxan-5-one (7): Et_3N (1.7 mL, 12.09 mmol, 1.7 equiv) was added by syringe at −78 °C to a stirred solution of dicyclohexylboryl chloride (10.7 mL, 10.67 mmol, 1.5 equiv) in Et_2O (70 mL), followed 10 min later by slow addition of a solution of ketone **6** (1.98 g, 7.11 mmol, 1.0 equiv) in Et_2O (15 mL). Stirring was continued for an additional 30 min at −78 °C, after which the mixture was allowed to warm to 0 °C and stirred for 1 h. The resulting suspension was cooled to −78 °C, after which a solution of freshly distilled benzaldehyde (1.1 mL, 10.67 mmol, 1.5 equiv) in Et_2O (20 mL) was added dropwise. Stirring was continued for 1 h at −78 °C, after which the flask was sealed and placed in a freezer (−24 °C) for 20 h. The mixture was quenched with phosphate buffer (pH 7, 140 mL) and extracted with Et_2O (280 mL). The combined organic extracts were concentrated under reduced pressure, and the residue was dissolved in a mixture of phosphate buffer (pH 7) and MeOH (1:1, 86 mL) and cooled to 0 °C, after which aqueous hydrogen peroxide (H_2O_2, 30% in H_2O, 22.0 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, poured into phosphate buffer (pH 7, 140 mL) and extracted with CH_2Cl_2 (560 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, PE/Et_2O 70:30) to afford aldol **7** (1.86 g, 68%) as a pale yellow oil. $[\alpha]_D^{23} = +76.02$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$–7.37 (m, 10H; Ar-*H*), 4.86 [d, ^3J(H,H) = 7.1 Hz, 1H; PhC*H*(OH)], 4.46 (d, ^3J(H,H) = 1.6 Hz, 2H; CH_2Ph), 4.29 [dd, ^3J(H,H) = 7.1, 1.4 Hz, 1H; C(O)C*H*CH(OH)], 4.09 (ddd, ^3J(H,H) = 8.2, 4.1, 1.4 Hz, 1H; C*H*CH$_2$), 3.76 (s, 1H; O*H*), 3.43 (td, ^3J(H,H) = 6.3, 1.6 Hz, 2H; CH_2OCH$_2$), 1.87–1.97 (m, 1H; CHC*H*H), 1.66–1.75 (m, 2H; CH$_2$CH_2CH$_2$), 1.56–1.65 (m, 1H; CHCH*H*), 1.30 (s, 3H; CH_3), 1.21 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.1$ [*C*(O)], 139.2, 138.2 (Ar-*C*), 128.1, 127.7, 127.7, 127.4, 127.3, 127.0 (Ar-*C*H), 101.2 [*C*(CH$_3$)$_2$], 75.8 (Ph*C*H(OH)], 74.1 (*C*HCH$_2$), 72.7 (O*C*H$_2$Ph), 72.6 [C(O)*C*HCH(OH)], 69.6 (CH$_2$CH$_2$*C*H$_2$), 25.5 (CH*C*H$_2$), 25.2 (CH$_2$*C*H$_2$CH$_2$), 23.6 [C(*C*H$_3$)], 23.5 ppm [C(*C*H$_3$)]; IR (film): $\tilde{\nu} = 3474$ (br, OH), 3031, 2986, 2930, 2861, 2360, 1737 (C=O), 1497, 1453, 1378, 1226, 1171, 1104, 900, 747, 700 cm^{-1} (C$_6$H$_5$); MS (100 eV, CI): *m*/*z* (%): 385 (1.4) [*M*+H]$^+$, 367 (25) [*M*+H−H$_2$O]$^+$, 309 (22) [*M*+H−H$_2$O−(CH$_3$)$_2$CO]$^+$, 305 (13), 261 (26), 221 (25), 171 (13), 107 (100) [C$_7$H$_7$O]$^+$, 91 (7) [C$_7$H$_7$]$^+$, 71 (23), 69 (17), 61 (18); HRMS: *m*/*z*: calcd for $C_{20}H_{22}O_4$ [*M*−(CH$_3$)$_2$CO]: 326.1518; found: 326.1518.

(4*R*,6*R*)-(+)-4-(3-Benzyloxypropyl)-6-[(*R*)-(*tert*-butyldimethylsilyloxy)-(phenyl)methyl]-2,2-dimethyl-1,3-dioxan-5-one (8): 2,6-Lutidine (360 μL, 3.10 mmol, 3.0 equiv) was added at 0 °C to a stirred solution of the hydroxy ketone **7** (397 mg, 1.03 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL), followed by dropwise addition of TBSOTf (360 μL, 1.5 mmol, 1.55 equiv). The stirring was continued for 3–4 h at room temperature (TLC monitoring), after which the reaction was quenched with aqueous NH_4Cl solution (10 mL). The mixture was poured into aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (30 mL). The aqueous phase was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a colourless syrup. Purification by flash chromatography on silica gel (PE/Et_2O 90:10) gave the TBS-protected product **8** (463 mg, 90%) as a colourless oil. $[\alpha]_D^{23} = +65.76$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$–7.52 (m, 10H; Ar-*H*), 5.28 [d, ^3J(H,H) = 3.3 Hz, 1H; PhC*H*(OSi)], 4.65 (s, 2H; CH_2Ph), 4.56 [dd, ^3J(H,H) = 3.3, 1.1 Hz, 1H; C(O)C*H*CH(OSi)], 4.13 (ddd, ^3J(H,H) = 8.2, 4.1, 1.1 Hz, 1H; C*H*CH$_2$), 3.62 (t, ^3J(H,H) = 6.3 Hz, 2H; CH_2OCH$_2$), 2.00–2.09 (m, 1H; CHC*H*H), 1.77–1.94 (m, 2H; CH$_2$CH_2CH$_2$), 1.64–1.75 (m, 1H; CHCH*H*), 1.54 [s, 3H; C(CH_3)], 1.52 [s, 3H; C(CH_3)], 1.06 [s, 9H; SiC(CH_3)$_3$], 0.26 [s, 3H; Si(CH_3)], −0.09 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 207.7$ [*C*(O)], 140.3, 138.5 (Ar-*C*), 128.3, 127.6, 127.6, 127.5, 127.3 (Ar-*C*H), 101.0 [*C*(CH$_3$)$_2$], 79.1 [C(O)*C*HCH(OSi)], 74.1 [2C; *C*HCH$_2$, Ph*C*H(OSi)], 72.9 (O*C*H$_2$Ph), 69.9 (CH$_2$CH$_2$*C*H$_2$), 25.7 [SiC(*C*H$_3$)$_3$], 25.4 (CH$_2$*C*H$_2$CH$_2$), 25.0 (CH*C*H$_2$), 24.2 [C(*C*H$_3$)], 23.9 [C(*C*H$_3$)], 18.2 [Si*C*(CH$_3$)$_3$], −5.0, −4.8 ppm [Si(*C*H$_3$)$_2$]; IR (film): $\tilde{\nu} = 3746$, 3673, 2985, 2932, 2857, 2362, 2336, 1747 (C=O), 1652, 1559, 1541, 1456, 1376, 1252, 1225, 1171, 1101, 1070, 838, 779, 738, 700 (C$_6$H$_5$), 669 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 499 (3.0) [*M*+H]$^+$, 481 (4) [*M*+H−H$_2$O]$^+$, 441 (1) [*M*+H−(CH$_3$)$_2$CO]$^+$, 425 (10), 383 (9), 367 (16), 309 (9), 277 (7), 222 (20), 221 (100), 91 (4) [C$_7$H$_7$$^+$]; elemental analysis (%) calcd for $C_{29}H_{42}O_5Si$ (498.73): C 69.84, H 8.49; found: C 69.89, H 8.56.

(4*R*,5*R*,6*R*)-(−)-6-(3-Benzyloxypropyl)-4-[(*R*)-(*tert*-butyldimethylsilyloxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxan-5-ol (9): L-selectride (1.0 M in THF, 5.2 mL, 5.20 mmol, 1.5 equiv) was added dropwise at −78 °C to a stirred solution of the TBS-protected aldol adduct **8** (1.73 g, 3.47 mmol, 1.0 equiv) in absolute THF (35 mL). The stirring was continued for 5 h at this temperature, after which the reaction was quenched with aqueous NH_4Cl solution (20 mL). The mixture was poured into aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (30 mL). The aqueous portion was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product as a yellow liquid. Purification by flash chromatography on silica gel (PE/Et_2O 80:20) gave alcohol **9** (1.53 g, 88%) as a colourless oil. $[\alpha]_D^{23} = -73.20$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.56$–7.70 (m, 10H; Ar-C*H*), 5.26 [d, ^3J(H,H) = 6.1 Hz, 1H; PhC*H*(OSi)], 4.80 (s, 2H; CH_2Ph), 4.10 [ddd, ^3J(H,H) = 6.1, 3.0, 1.1 Hz, 1H; C(O)C*H*CH(OSi)], 3.79 (t, ^3J(H,H) = 6.9 Hz, 2H; CH_2OCH$_2$), 3.99 (d, ^3J(H,H) = 4.6 Hz, 1H; O*H*), 3.96 [dd, ^3J(H,H) = 5.5, 4.6, 3.0 Hz, 1H; CHC*H*(OH)], 3.88 (dd, ^3J(H,H) = 5.5, 1.1 Hz, 1H; C*H*CH$_2$), 1.94–2.11 (m, 3H; CH$_2$CH_2CH$_2$, CHC*H*H), 1.81–1.88 (m, 1H; CHCH*H*), 1.65 [s, 3H; C(CH_3)], 1.43 [s, 3H; C(CH_3)], 1.21 [s, 9H; SiC(CH_3)$_3$], 0.41 [s, 3H; Si(CH_3)], −0.16 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.9$, 138.4 (Ar-*C*), 128.1, 127.9, 127.4, 127.4, 127.3, 126.5 (Ar-*C*H), 100.7 [*C*(CH$_3$)$_2$], 75.8 [Ph*C*H(OSi)], 75.0 (*C*HCH$_2$), 73.4 [C(O)*C*HCH(OSi)], 73.2 [*C*H(OH)], 72.7 (O*C*H$_2$Ph), 70.1 (CH$_2$CH$_2$*C*H$_2$), 30.3 (CH*C*H$_2$), 25.9 (CH$_2$*C*H$_2$CH$_2$), 25.7 [SiC(*C*H$_3$)$_3$], 24.8 [C(*C*H$_3$)], 23.8 [C(*C*H$_3$)], 18.1 [Si*C*(CH$_3$)$_3$], −5.2, −4.7 ppm [Si(*C*H$_3$)$_2$]; IR (film): $\tilde{\nu} = 3746$, 3673, 3471 (br, OH), 2985, 2932, 2857, 2362, 2336, 1992, 1699, 1652, 1559, 1541, 1457, 1377, 1252, 1226, 1171, 1099, 1067, 996, 838, 780, 736, 699 (C$_6$H$_5$), 669 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 501 (4.8) [*M*+H]$^+$, 409 (11) [*M*+H−C$_7$H$_8$]$^+$, 367 (11), 351 (28) [*M*+H−C$_7$H$_8$−(CH$_3$)$_2$CO]$^+$, 312 (10), 311 (56), 294 (20), 293 (100), 221 (41), 207 (10), 203 (49), 191 (28), 181 (12), 179 (25), 91 (20) [C$_7$H$_7$]$^+$, 71 (18); elemental analysis (%) calcd for $C_{29}H_{44}O_5Si$ (500.74): C 69.56, H 8.86; found: C 69.31, H 9.17.

(4*R*,5*R*,6*R*)-(−)-5-Benzyloxy-6-(3-benzyloxypropyl)-4-[(*R*)-(*tert*-butyldimethylsilyloxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxan (10): A solution of the alcohol **9** (695 mg, 1.39 mmol, 1.0 equiv) in absolute THF (10 mL) was added dropwise at 0 °C to a stirred solution of potassium hydride (30% in mineral oil, 557 mg, 4.16 mmol, 3.0 equiv), previously washed with distilled cyclohexane, in THF (4 mL). Stirring at this temperature was continued for 30 min, after which freshly distilled benzyl bromide

(660 μL, 5.55 mmol, 4.0 equiv) was added dropwise. The stirring was continued overnight at room temperature, after which the reaction was quenched with H_2O (30 mL). The mixture was poured into H_2O (20 mL) and extracted with Et_2O (50 mL). The aqueous portion was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a yellow liquid. Purification by flash chromatography on silica gel (PE/Et_2O 90:10) gave the benzyl-protected product **10** (738 mg, 90%) as a colourless oil. $[\alpha]_D^{22}=-1.65$ ($c=1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.42$–7.62 (m, 15H; Ar-C*H*), 5.11 [d, $^3J(H,H)=9.3$ Hz, 1H; PhC*H*(OSi)], 4.91 (d, $^3J(H,H)=11.8$ Hz, 1H; CHOC*H*HPh), 4.83 (d, $^3J(H,H)=11.8$ Hz, 1H; CHOCH*H*Ph), 4.70 (s, 2H; CH_2OCH_2Ph), 4.11 [dd, $^3J(H,H)=9.3$, 2.2 Hz, 1H; C*H*CH(OSi)], 3.98 (dd, $^3J(H,H)=5.0$, 3.3 Hz, 1H; C*H*CH_2), 3.96 (dd, $^3J(H,H)=5.0$, 2.2 Hz, 1H; CHC*H*OCH_2Ph), 3.64 (t, $^3J(H,H)=6.3$ Hz, 2H; CH_2OCH_2), 1.95–2.02 (m, 1H; CH_2C*H*HCH_2), 1.77–1.87 (m, 3H; CH_2CH*H*CH_2, CHCH_2), 1.45 [s, 3H; C(CH_3)], 1.08 [s, 3H; C(CH_3)], 1.05 [s, 9H; SiC(CH_3)$_3$], 0.18 [s, 3H; Si(CH_3)], −0.25 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=142.8$, 139.0, 138.6 (Ar-*C*), 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.4, 127.4 (Ar-CH), 100.7 [*C*(CH$_3$)$_2$], 80.7 (*C*HCH_2), 74.8 [*C*HCH(OSi)], 73.9 (*C*HOCH_2Ph), 72.9 (CH_2OCH_2Ph), 72.7 (CHO*C*H_2Ph), 72.4 [*C*H(OSi)], 70.0 (*C*H_2OCH_2), 31.8 (CH*C*H_2), 26.1 ($CH_2CH_2CH_2$), 26.1 [SiC(*C*H$_3$)$_3$], 25.0 [C(*C*H$_3$)], 23.6 [C(*C*H$_3$)], 18.2 [Si*C*(CH$_3$)$_3$], −4.7, −4.0 ppm [Si(*C*H$_3$)$_2$]; IR (film): $\tilde{\nu}=$ 3031, 2988, 2930, 2857, 1456, 1372, 1249, 1222, 1093, 1030, 839, 758, 699 cm^{-1} (C_6H_5); MS (100 eV, CI): *m*/*z* (%): 591 (5.0) [*M*+H]$^+$, 575 (11), 533 (7) [*M*+H−(CH$_3$)$_2$CO]$^+$, 516 (14), 515 (36) [*M*+H−(CH$_3$)$_2$CO−H$_2$O]$^+$, 459 (10), 425 (15) [*M*+H−(CH$_3$)$_2$CO−PhCH$_2$OH]$^+$, 409 (14), 407 (11), 402 (12), 401 (42), 383 (36), 367 (13), 351 (24), 319 (12), 317 (13), 301 (13), 297 (35), 295 (11), 294 (17), 293 (69), 277 (21), 251 (29), 249 (11), 233 (12), 222 (20), 221 (100), 215 (11), 203 (14), 191 (34), 181 (33), 173 (13), 161 (14), 91 (52) [C_7H_7]$^+$, 71 (13); elemental analysis (%) calcd for $C_{36}H_{50}O_5Si$ (590.86): C 73.18, H 8.53; found: C 73.39, H 8.72.

(4*S*,5*R*,6*R*)-(−)-5-Benzyloxy-6-(3-benzyloxypropyl)-4-[(*R*)-hydroxy-(phenyl)methyl]-2,2-dimethyl-1,3-dioxan (11): Tetra-*n*-butylammonium fluoride (TBAF, 1.0 M in THF, 7.1 mL, 7.11 mmol, 2.0 equiv) was added dropwise at 0 °C to a stirred solution of **10** (2.10 g, 3.55 mmol, 1.0 equiv) in absolute THF (40 mL). Stirring was continued at room temperature overnight, after which the reaction was quenched with H_2O (30 mL). The mixture was poured into H_2O (20 mL) and diluted with Et_2O (20 mL). The aqueous phase was extracted with Et_2O (3×20 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a pale brown syrup. Purification by flash chromatography on silica gel (PE/Et_2O 70:30) gave the alcohol **11** (1.60 g, 95%) as a colourless oil. $[\alpha]_D^{23}=-9.78$ ($c=1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.20$–7.37 (m, 15H; Ar-C*H*), 4.90 [dd, $^3J(H,H)=7.9$, 5.1 Hz, 1H; PhC*H*(OH)], 4.58 (d, $^3J(H,H)=11.4$ Hz, 1H; CHOCH*H*Ph), 4.51 (d, $^3J(H,H)=11.4$ Hz, 1H; CHOC*H*HPh), 4.44 (s, 2H; CH_2OCH_2Ph), 3.91 [dd, $^3J(H,H)=7.9$, 3.5 Hz, 1H; C*H*CH(OH)], 3.72 (td, $^3J(H,H)=6.4$, 6.2 Hz, 1H; C*H*CH_2), 3.59 (dd, $^3J(H,H)=6.2$, 3.5 Hz, 1H; CHC*H*OCH_2Ph), 3.40 (td, $^3J(H,H)=$ 6.2, 1.7 Hz, 2H; CH_2OCH_2), 2.94 (d, $^3J(H,H)=5.1$ Hz, 1H; O*H*), 1.71–1.80 (m, 1H; CH_2C*H*HCH_2), 1.55–1.69 (m, 2H; CH_2CH*H*CH_2, CHC*H*H), 1.40–1.53 (m, 1H; CHCH*H*), 1.29 [s, 3H; C(CH_3)], 1.02 ppm [s, 3H; C(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=142.1$, 138.4, 138.2 (Ar-*C*), 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 127.5, 127.4, 126.5 (Ar-CH), 100.8 [*C*(CH$_3$)$_2$], 81.1 (*C*HOCH$_2$Ph), 73.6 [*C*HCH(OH)], 73.3 (CHO*C*H_2Ph), 72.9 (*C*HCH_2), 72.7 (CH_2OCH_2Ph), 72.4 [*C*H(OH)], 69.7 (*C*H_2OCH_2), 30.9 (CH*C*H_2), 25.8 ($CH_2CH_2CH_2$), 24.6 [C(*C*H$_3$)], 23.6 ppm [C(*C*H$_3$)]; IR (film): $\tilde{\nu}=$3747, 3673, 3649, 3436 (br, OH), 3086, 3063, 3031, 2987, 2931, 2862, 2362, 2336, 1652, 1559, 1541, 1497, 1456, 1375, 1220, 1170, 1093, 910, 736, 700 (C_6H_5), 616, 513 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 477 (1.0) [*M*+H]$^+$, 459 (2) [*M*+H−H$_2$O]$^+$, 420 (29), 419 (100) [*M*+H−(CH$_3$)$_2$CO]$^+$, 401 (13) [*M*+H−H$_2$O−(CH$_3$)$_2$CO]$^+$, 383 (5), 311 (11), 294 (9), 293 (41), 205 (18), 203 (15), 191 (26), 181 (14), 149 (11), 91 (19) [C_7H_7]$^+$; elemental analysis (%) calcd for $C_{30}H_{36}O_5$ (476.60): C 75.60, H 7.61; found: C 75.53, H 8.03.

(1*R*,2*R*)-(−)-1,5-Dibenzyloxy-1-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]pentan-2-ol (12): A catalytic amount of *p*-toluenesulfonic acid was added at room temperature under argon to a stirred solution of acetonide **11** (272 mg, 0.57 mmol, 1.0 equiv) in absolute acetone (6 mL). The stirring was continued for 24 h at this temperature, after which 2,2-dimethoxypropane (2,2-DMP, 20 μL, 0.14 mmol, 0.25 equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) were added. The stirring was continued for 1 h, after which the reaction was quenched with pH 7 buffer (2 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mixture of two acetonides (1.6:1 ratio) as a colourless syrup. Purification by flash chromatography on silica gel (PE/Et_2O 50:50) gave acetonide alcohol **12** (97 mg, 36%) as a pale pink oil, together with recovered starting material **11** (160 mg, 59%). $[\alpha]_D^{22}=-123.75$ ($c=1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.15–7.28 (m, 15H; Ar-C*H*), 5.17 (d, $^3J(H,H)=6.9$ Hz, 1H; PhC*H*), 4.58 (dd, $^3J(H,H)=6.9$, 4.1 Hz, 1H; C*H*CHPh), 4.42 (s, 2H; CH_2OCH_2Ph), 4.24 (d, $^3J(H,H)=11.3$ Hz, 1H; CHOC*H*HPh), 3.85 (d, $^3J(H,H)=$ 11.3 Hz, 1H; CHOCH*H*Ph), 3.44 (dd, $^3J(H,H)=5.7$, 4.1 Hz, 1H; C*H*CH_2), 3.39 (td, $^3J(H,H)=5.4$, 1.9 Hz, 2H; CH_2OCH_2Ph), 2.96 (t, $^3J(H,H)=4.1$ Hz, 1H; C*H*OCH_2Ph), 2.77 (d, $^3J(H,H)=6.4$ Hz, 1H; O*H*), 1.65–1.72 (m, 1H; CH_2C*H*HCH_2), 1.59 [s, 3H; C(CH_3)], 1.45–1.54 (m, 2H; CHC*H*H, CH_2CH*H*CH_2), 1.40–1.43 (m, 1H; CHCH*H*), 1.40 ppm [s, 3H; C(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=138.6$, 138.3, 137.7 (Ar-*C*), 128.4, 128.2, 128.1, 127.7, 127.7, 127.6, 127.5, 127.3, 127.1 (Ar-CH), 109.2 [*C*(CH$_3$)$_2$], 79.4 (*C*HOCH$_2$Ph), 79.3 (PhCH*C*H), 79.2 (PhC*H*), 73.0 (CH_2OCH_2Ph), 72.1 (CHO*C*H_2Ph), 70.9 (*C*HCH_2), 70.3 (*C*H_2OCH_2), 30.4 ($CH_2CH_2CH_2$), 26.7 [C(*C*H$_3$)], 26.5 (CH*C*H_2), 25.4 ppm [C(*C*H$_3$)]; IR (film): $\tilde{\nu}=$3428 (br, OH), 3061, 3031, 2928, 2863, 1495, 1454, 1374, 1248, 1217, 1094, 880, 741, 701 cm^{-1} (C_6H_5); MS (100 eV, CI): *m*/*z* (%): 477 (1.0) [*M*+H]$^+$, 459 (2) [*M*+H−H$_2$O]$^+$, 420 (30), 419 (100) [*M*+H−(CH$_3$)$_2$CO]$^+$, 383 (5), 311 (16), 309 (12), 299 (25), 293 (38) [*M*+H−(CH$_3$)$_2$CO−PhCH$_2$OH−H$_2$O]$^+$, 203 (23), 192 (13), 191 (99), 181 (44), 179 (50) [*M*+H−2H$_2$O−(CH$_3$)$_2$CO−2PhCH$_2$OH]$^+$, 119 (24), 107 (14), 101 (21), 91 (78) [C_7H_7]$^+$, 71 (43); HRMS: *m*/*z*: calcd for $C_{19}H_{22}O_3$ [*M*−$C_{11}H_{14}O_2$]: 298.1569; found: 298.1570.

(1*S*,2*R*)-(−)-1,5-Dibenzyloxy-2-(*tert*-butyldimethylsilyloxy)-1-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-pentane (13): 2,6-Lutidine (120 μL, 1.03 mmol, 3.0 equiv) was added at 0 °C to a stirred solution of alcohol **12** (163 mg, 0.34 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL), followed by slow addition of TBSOTf (120 μL, 0.51 mmol, 1.5 equiv). The stirring was continued for 2 h at room temperature, after which the reaction was quenched with aqueous NH_4Cl solution (10 mL). The mixture was poured into aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (20 mL). The aqueous portion was extracted with CH_2Cl_2 (2×10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a colourless syrup. Purification by flash chromatography on silica gel (PE/Et_2O 80:20) gave the TBS-protected product **13** (200 mg, 99%) as a colourless oil. $[\alpha]_D^{22}=-$ 276.26 ($c=1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.45–7.62 (m, 15H; Ar-C*H*), 5.34 (d, $^3J(H,H)=6.9$ Hz, 1H; PhC*H*), 4.81 (d, $^3J(H,H)=11.4$ Hz, 1H; CHOC*H*HPh), 4.75 (dd, $^3J(H,H)=6.9$, 6.0 Hz, 1H; PhCHC*H*), 4.73 (s, 2H; CH_2OCH_2Ph), 4.37 (d, $^3J(H,H)=11.4$ Hz, 1H; CHOCH*H*Ph), 3.77 (dd, $^3J(H,H)=7.7$, 3.6 Hz, 1H; C*H*CH_2), 3.66 (td, $^3J(H,H)=5.8$, 1.1 Hz, 2H; CH_2OCH_2Ph), 3.54 (dd, $^3J(H,H)=6.0$, 3.6 Hz, 1H; C*H*OCH_2Ph), 1.90 [s, 3H; C(CH_3)], 1.73–1.96 (m, 4H; $CH_2CH_2CH_2$, CHCH_2), 1.71 [s, 3H; C(CH_3)], 1.08 [s, 9H; SiC(CH_3)$_3$], 0.09 [s, 3H; Si(CH_3)], 0.00 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=139.3$, 138.7, 138.7 (Ar-*C*), 128.5, 128.4, 128.0, 127.9, 127.7, 127.6, 127.5, 127.5, 127.1 (Ar-CH), 108.8 [*C*(CH$_3$)$_2$], 81.0 (*C*HOCH$_2$Ph), 80.2 (PhCH*C*HCH), 79.3 (PhC*H*), 73.8 (CHO*C*H_2Ph), 73.3 (*C*HCH_2), 72.9 (CH_2OCH_2Ph), 70.6 (*C*H_2OCH_2Ph), 28.8 (CH*C*H_2), 27.0 [C(*C*H$_3$)], 26.1 [SiC(*C*H$_3$)$_3$], 25.8 ($CH_2CH_2CH_2$), 25.5 [C(*C*H$_3$)], 18.2 [Si*C*(CH$_3$)$_3$], −4.8, −4.2 ppm [Si(*C*H$_3$)$_2$]; IR (film): $\tilde{\nu}=$3063, 3029, 2933, 2858, 1495, 1458, 1372, 1253, 1215, 1101, 880, 836, 754, 700 cm^{-1} (C_6H_5); MS (100 eV, CI): *m*/*z* (%): 591 (1.0) [*M*+H]$^+$, 533 (21) [*M*+H−(CH$_3$)$_2$CO]$^+$, 499 (3), 426 (12), 425 (33) [*M*+H−(CH$_3$)$_2$CO−PhCH$_2$OH]$^+$, 414 (15), 413 (47), 409 (11), 401 (13), 367 (21), 307 (15), 294 (25), 293 (100), 265 (11), 216

(13), 215 (74), 187 (15), 181 (12), 91 (26) $[C_7H_7]^+$; elemental analysis (%) calcd for $C_{36}H_{50}O_5Si$ (590.86): C 73.18, H 8.53; found: C 72.81, H 8.92.

(1*S*,2*R*)-(−)-2-(*tert*-Butyldimethylsilyloxy)-1-[(4*S*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]pentane-1,5-diol (14): A solution of compound **13** (200 mg, 0.34 mmol, 1.0 equiv) and palladium on carbon (10%, 20 mg) in EtOAc (5 mL) was stirred overnight at room temperature under hydrogen. The reaction mixture was filtered through a short pad of Celite, with elution with EtOAc, and the filtrate was concentrated under reduced pressure to give the crude product as a colourless syrup. Purification by flash chromatography on silica gel (PE/EtOAc 50:50) gave the debenzylated diol **14** (138 mg, 99%) as a colourless oil. $[\alpha]_D^{22} = -171.80$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.47 (m, 5H; Ar-C*H*), 5.32 (d, $^3J(H,H) = 7.4$ Hz, 1H; PhC*H*), 4.62 (dd, $^3J(H,H) = 7.4$, 3.5 Hz, 1H; PhCHC*H*), 3.59 [t, $^3J(H,H) = 6.2$ Hz, 2H; CH_2(OH)], 3.49 (dd, $^3J(H,H) = 6.4$, 3.7 Hz, 1H; C*H*CH$_2$), 3.27 [dd, $^3J(H,H) = 6.4$, 3.5 Hz, 1H; C*H*(OH)], 2.27 [s, 2H; 2×O*H*], 1.75 [s, 3H; C(CH_3)], 1.66–1.73 (m, 1H; CHC*H*H), 1.57 [s, 3H; C(CH_3)], 1.47–1.54 (m, 3H; CH$_2$CH_2CH$_2$, CHCH*H*), 0.94 [s, 9H; SiC(CH_3)$_3$], 0.02 [s, 3H; Si(CH_3)], 0.00 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.8$ (Ar-*C*), 128.4, 128.1, 127.0 (Ar-*C*H), 108.5 [*C*(CH$_3$)$_2$], 79.0 (PhC*H*), 77.5 [PhCH*C*HCH(OH)], 71.4 (*C*HCH$_2$), 71.3 [*C*H(OH)], 62.8 [*C*H$_2$(OH)], 28.5 (CH*C*H$_2$), 27.3 (CH$_2$*C*H$_2$CH$_2$), 26.6 [C(*C*H$_3$)], 25.8 [SiC(*C*H$_3$)$_3$], 24.4 [C(*C*H$_3$)], 18.0 [Si*C*(CH$_3$)$_3$], −4.9, −4.5 ppm [Si(*C*H$_3$)$_2$]; IR (film): $\tilde{\nu} =$ 3434 (br, OH), 2936, 2861, 1464, 1378, 1256, 1215, 1164, 1100, 1050, 887, 837, 758, 701 cm^{-1} (C_6H_5); MS (100 eV, CI): *m*/*z* (%): 411 (1.0) $[M+H]^+$, 353 (2) $[M+H-(CH_3)_2CO]^+$, 335 (14) $[M+H-(CH_3)_2CO-H_2O]^+$, 319 (13), 317 (24) $[M+H-(CH_3)_2CO-2H_2O]^+$, 277 (16), 217 (14), 216 (17), 215 (100), 203 (50), 175 (20), 91 (3) $[C_7H_7]^+$, 71 (14); HRMS: *m*/*z*: calcd for $C_{21}H_{35}O_5Si$ $[M-CH_3]$: 395.2254; found: 395.2253.

(5*R*,6*S*)-(−)-5-(*tert*-Butyldimethylsilyloxy)-6-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]tetrahydropyran-2-one (15): A solution of diol **14** (825 mg, 2.01 mmol, 1.0 equiv) in DMSO (15 mL) was added dropwise at room temperature to a stirred solution of *o*-iodoxybenzoic acid (IBX, 1.24 g, 4.42 mmol, 2.2 equiv) in freshly distilled DMSO (5 mL). The stirring at this temperature was continued for 3 h, after which the reaction was quenched with H_2O (20 mL) at 0°C. The reaction mixture was filtered through a short pad of Celite, and the solids were washed with Et_2O. The aqueous phase was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a colourless syrup.

Tetrapropylammonium perruthenate (TPAP, 36 mg, 0.10 mmol, 5 mol%) was then added in one portion at room temperature under argon to a stirred mixture of the crude lactol (1.08 g), *N*-methylmorpholine-*N*-oxide (NMO, 364 mg, 3.01 mmol, 1.5 equiv) and powdered molecular sieves (4 Å, 1.01 g, 0.5 g per mmol lactol) in CH_2Cl_2 (4 mL). Upon completion (20 minutes) the reaction mixture was filtered through a short pad of silica, which was washed with EtOAc, and the filtrate was concentrated under reduced pressure to give the crude product as a colourless syrup. Purification by flash chromatography on silica gel (PE/Et_2O 70:30) gave lactone **15** (625 mg, 77% over two steps) as a colourless solid. M.p. 107–108°C; $[\alpha]_D^{23} = -111.81$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.27–7.48 (m, 5H; Ar-C*H*), 5.42 (d, $^3J(H,H) = 7.4$ Hz, 1H; PhC*H*), 4.40 (d, $^3J(H,H) = 7.4$ Hz, 1H; PhCHC*H*CHO), 3.87 (td, $^3J(H,H) = 6.9$, 4.4 Hz, 1H; C*H*CH$_2$), 3.52 [d, $^3J(H,H) = 6.6$ Hz, 1H; C*H*OC(O)], 2.43 [ddt, $^3J(H,H) = 49.4$, 17.6, 6.6 Hz, 2H; CH$_2$C*H*$_2$C(O)], 2.03 (m, 1H; CHC*H*H), 1.67 (dd, $^3J(H,H) = 6.9$, 6.6 Hz, 1H; CHCH*H*), 1.62 [s, 3H; C(CH_3)], 1.47 [s, 3H; C(CH_3)], 0.83 [s, 9H; SiC(CH_3)$_3$], 0.02 [s, 3H; Si(CH_3)], 0.00 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.1$ [*C*(O)], 135.6 (Ar-*C*), 128.1, 127.8, 126.6 (Ar-*C*H), 109.6 [*C*(CH$_3$)$_2$], 80.1 [*C*HOC(O)], 79.1 (Ph*C*H), 76.7 (PhCH*C*HCHO), 65.6 (*C*HCH$_2$), 26.9 (CH*C*H$_2$), 26.9 [CH$_2$*C*H$_2$C(O)], 26.2 [C(*C*H$_3$)], 25.6 [SiC(*C*H$_3$)$_3$], 25.2 [C(*C*H$_3$)], 17.8 [Si*C*(CH$_3$)$_3$], −5.0, −4.5 ppm [Si(*C*H$_3$)$_2$]; IR (KBr): $\tilde{\nu} = 2945$, 2361, 2338, 1726 (C=O), 1462, 1379, 1256, 1213, 1170, 1086, 1015, 919, 840, 780, 699 (C_6H_5), 538 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 407 (28) $[M+H]^+$, 391 (11), 350 (24), 349 (100) $[M+H-(CH_3)_2CO]^+$, 333 (11), 292 (12), 291 (61), 229 (21), 221 (13), 217 (19); elemental analysis (%) calcd for $C_{22}H_{34}O_5Si$ (406.59): C 64.99, H 8.43; found: C 64.92, H 8.71.

(5*R*,6*S*)-(−)-5-(*tert*-Butyldimethylsilyloxy)-6-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5,6-dihydropyran-2-one (16): A solution of lactone **15** (62 mg, 0.15 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over 15 minutes at −78°C to a stirred solution of lithium diisopropylamide (LDA, 1.9 mL, 0.60 mmol, 4.0 equiv), prepared from a mother solution of LDA [diisopropylamine (330 μL) and *n*-BuLi (790 μL) in THF (5 mL)]. After the system had been stirred at this temperature for 45 minutes, a solution of PhSeCl (89 mg, 0.45 mmol, 3.0 equiv) in THF (3 mL) was slowly added. The stirring was continued for 1 h at −78°C. The reaction mixture was then allowed to warm to room temperature and quenched with NH_4Cl (2 mL). The organic phase was washed with NH_4Cl (20 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a yellow syrup.

The crude α-selenylated product (189 mg) was dissolved in CH_2Cl_2 (2 mL), and pyridine (30 μL, 2.2 equiv) was added at 0°C, followed by a solution of 30% H_2O_2/H_2O (1:1, *v*/*v*, 400 μL, 1.52 mmol, 10.0 equiv). The stirring was continued for 30 minutes at this temperature, after which the reaction mixture was poured into H_2O (20 mL) and CH_2Cl_2 (20 mL). The reaction mixture was washed with H_2O (20 mL) and brine (10 mL), and the organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a brown syrup. Purification by flash chromatography on silica gel (PE/Et_2O 80:20) gave the unsaturated lactone **16** (37 mg, 60%) as a pale yellow solid, together with remaining starting material (19 mg, 31%). M.p. 113°C; $[\alpha]_D^{23} = -98.41$ ($c =$ 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–7.50 (m, 5H; Ar-C*H*), 6.57 [dd, $^3J(H,H) = 9.9$, 1.6 Hz, 1H; C(O)CH=C*H*], 5.72 [dd, $^3J(H,H) =$ 9.9, 2.2 Hz, 1H; C(O)C*H*], 5.44 (d, $^3J(H,H) = 7.4$ Hz, 1H; PhC*H*), 4.56 [td, $^3J(H,H) = 9.9$, 1.9 Hz, 1H; C*H*(OSi)], 4.47 (d, $^3J(H,H) = 7.4$ Hz, 1H; PhCHC*H*CHO), 3.55 [dd, $^3J(H,H) = 9.9$, 0.8 Hz, 1H; C*H*OC(O)], 1.67 [s, 3H; C(CH_3)], 1.49 [s, 3H; C(CH_3)], 0.90 [s, 9H; SiC(CH_3)$_3$], 0.16 [s, 3H; Si(CH_3)], 0.12 ppm [s, 3H; Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 161.9 [*C*(O)], 149.6 [C(O)CH=*C*H], 135.3 (Ar-*C*), 128.0, 127.7, 126.6 (Ar-*C*H), 119.2 [C(O)*C*H], 109.7 [*C*(CH$_3$)$_2$], 79.7 [*C*HOC(O)], 78.8 (Ph*C*H), 75.3 (PhCH*C*HCHO), 63.7 (*C*HCH=CH), 26.3 [C(*C*H$_3$)], 25.6 [SiC-(*C*H$_3$)$_3$], 25.5 [C(*C*H$_3$)], 17.9 [Si*C*(CH$_3$)$_3$], −5.1, −4.6 ppm [Si(*C*H$_3$)$_2$]; IR (KBr): $\tilde{\nu} = 3017$, 2933, 2859, 1739 (C=O), 1465, 1376, 1254, 1218, 1163, 1106, 1061, 1008, 974, 917, 871, 839, 757, 701 (C_6H_5), 666 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 405 (53) $[M+H]^+$, 348 (26), 347 (100) $[M+H-(CH_3)_2CO]^+$, 331 (5) $[M+H-(CH_3)_2CO-H_2O]^+$, 289 (11), 215 (8), 97 (9), 91 (1) $[C_7H_7]^+$; HRMS: *m*/*z*: calcd for $C_{21}H_{29}O_5Si$ $[M-CH_3]$: 389.1784; found: 389.1784.

(5*R*,6*R*)-(−)-6-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxy-5,6-dihydropyran-2-one (17): Tetra-*n*-butylammonium fluoride (TBAF, 1.0 M in THF, 1.4 mL, 1.44 mmol, 2.0 equiv) was added dropwise at 0°C to a solution of compound **16** (290 mg, 0.72 mmol, 1.0 equiv) in absolute THF (7 mL). Stirring at room temperature was continued for 1 h, after which the reaction was quenched with H_2O (10 mL). The mixture was poured into H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a yellow syrup. Purification by flash chromatography on silica gel (PE/EtOAc 50:50) gave alcohol **17** (153 mg, 74%) as a colourless solid. M.p. 164°C; $[\alpha]_D^{23} = -106.34$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.52 (m, 5H; Ar-C*H*), 6.68 [dd, $^3J(H,H) = 9.9$, 2.0 Hz, 1H; C(O)CH=C*H*], 5.80 [dd, $^3J(H,H) = 9.9$, 2.0 Hz, 1H; C(O)C*H*], 5.47 (d, $^3J(H,H) = 7.3$ Hz, 1H; PhC*H*), 4.61 (dd, $^3J(H,H) = 7.3$, 1.1 Hz, 1H; PhCHC*H*CHO), 4.54 [ddd, $^3J(H,H) = 9.3$, 7.1, 2.0 Hz, 1H; C*H*(OH)], 3.68 [dd, $^3J(H,H) = 9.3$, 1.1 Hz, 1H; C*H*OC(O)], 2.05 (d, $^3J(H,H) = 7.1$ Hz, 1H; O*H*), 1.67 [s, 3H; C(CH_3)], 1.51 ppm [s, 3H; C(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.9$ [*C*(O)], 148.2 [C(O)CH=*C*H], 135.3 (Ar-*C*), 128.3, 128.1, 126.9 (Ar-*C*H), 120.3 [C(O)*C*H], 110.1 [*C*(CH$_3$)$_2$], 79.6 [*C*HOC(O)], 79.1 (Ph*C*H), 76.0 (PhCH*C*HCHO), 63.2 (*C*HCH=CH), 26.3 [C(*C*H$_3$)], 25.5 ppm [C(*C*H$_3$)]; IR (KBr): $\tilde{\nu} = 3852$, 3744, 3678, 3621, 3463 (br, OH), 2361, 1708 (C=O), 1646, 1548, 1460, 1378, 1227, 1084, 970, 904, 808, 743, 673 (C_6H_5), 559 cm^{-1}; MS (100 eV, CI): *m*/*z* (%): 291 (39) $[M+H]^+$, 275 (24), 234 (13), 233 (100) $[M+H-(CH_3)_2CO]^+$, 232 (12), 215 (61) $[M+H-$

$(CH_3)_2CO-H_2O]^+$, 149 (10), 148 (14), 97 (10), 91 (6) $[C_7H_7^+]$; HRMS: *m/z*: calcd for $C_{15}H_{15}O_5$ $[M-CH_3]$: 275.0919; found: 275.0920.

(5*R*,6*R*)-(−)-6-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-toluenesulfonyloxy-5,6-dihydropyran-2-one (18): 4-Dimethylaminopyridine (DMAP, 60 mg, 0.48 mmol, 3.0 equiv) and *p*-toluenesulfonyl chloride (46 mg, 0.24 mmol, 1.5 equiv) were added at room temperature to a stirred solution of alcohol **17** (47 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). Stirring at this temperature was continued for 3 h. The organic phase was washed with H_2O (10 mL) and brine (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product as a brown syrup. Purification by flash chromatography on silica gel (PE/EtOAc 70:30) gave tosylate **18** (68 mg, 95%) as colourless crystals. M.p. 50–51 °C; $[\alpha]_D^{23}=-88.90$ ($c=1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.79$ (m, 2H; Ar-C*H*), 7.28–7.44 (m, 7H; Ar-C*H*), 6.59 [dd, $^3J(H,H)=9.9$, 2.7 Hz, 1H; C(O)CH=C*H*], 5.89 [dd, $^3J(H,H)=9.9$, 1.6 Hz, 1H; C(O)C*H*], 5.32 (d, $^3J(H,H)=7.4$ Hz, 1H; PhC*H*), 5.18 [ddd, $^3J(H,H)=8.2$, 2.7, 1.6 Hz, 1H; C*H*(OTs)], 4.14 (d, $^3J(H,H)=7.4$ Hz, 1H; PhCHC*H*CHO), 3.81 [d, $^3J(H,H)=8.2$ Hz, 1H; C*H*OC(O)], 2.49 (s, 3H; CH_3), 1.55 [s, 3H; C(C*H*$_3$)], 1.34 ppm [s, 3H; C(C*H*$_3$)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.6$ [*C*(O)], 145.8 (Ar-*C*), 141.9 [C(O)CH=*C*H], 134.9, 132.6 (Ar-*C*), 130.2, 128.3, 128.2, 128.1, 126.7 (Ar-*C*H), 122.8 [C(O)*C*H], 110.1 [*C*(CH$_3$)$_2$], 78.7 (Ph*C*H), 76.8 [*C*HOC(O)], 75.9 (PhC*H*CHCHO), 70.6 (*C*HCH=CH), 26.0 [C(*C*H$_3$)], 25.0 [C(*C*H$_3$)], 21.8 ppm (*C*H$_3$); IR (KBr): $\tilde{\nu}=3853$, 3744, 3670, 3620, 3417, 2925, 2354, 1708 (C=O), 1548, 1250, 1105, 1022, 820, 758, 679 (C_6H_5), 564 cm^{-1}; MS (100 eV, CI): *m/z* (%): 233 (10), 232 (33) $[M+H-(CH_3)_2CO-OTs]^+$, 173 (17), 172 (40), 155 (11), 136 (10), 126 (11), 108 (14), 107 (57), 105 (34), 97 (100), 96 (14), 95 (28), 91 (59) $[C_7H_7]^+$, 79 (29), 77 (30), 68 (13), 65 (11).

(1*R*,6*S*,8*R*,9*R*)-(+)-9-Hydroxy-8-phenyl-2,7-dioxabicyclo[4.3.0]non-4-en-3-one [(+)-altholactone] (1): Amberlyst 15 (128 mg, 200% in weight) was added at room temperature to a stirred solution of acetonide **18** (64 mg, 0.14 mmol, 1.0 equiv) in MeOH (2 mL). Stirring was continued for 2 h, and subsequently the reaction mixture was filtered through a short pad of Celite, and the solids were washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude product as a yellow syrup. Purification by flash chromatography on silica gel (Et_2O) gave (+)-altholactone (**1**, 31 mg, 93%) as a colourless solid. M.p. 114 °C (lit.:[2a] 110 °C); $[\alpha]_D^{25}=+104.10$ ($c=1$, $CHCl_3$), $[\alpha]_D^{25}=+177.46$ ($c=0.5$, EtOH) (lit.:[1,2a] $[\alpha]_D^{20}=+188$, $[\alpha]_D^{25}=+184.7$, c=0.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.27$–7.36 (m, 5H; Ar-C*H*), 7.00 [dd, $^3J(H,H)=9.9$, 4.9 Hz, 1H; C(O)CH=C*H*], 6.21 [d, $^3J(H,H)=9.9$ Hz, 1H; C(O)C*H*], 4.92 [dd, $^3J(H,H)=5.2$, 2.2 Hz, 1H; C*H*OC(O)], 4.74 (d, $^3J(H,H)=5.8$ Hz, 1H; PhC*H*), 4.63 (t, $^3J(H,H)=5.2$ Hz, 1H; C*H*CH=CH), 4.44 [dd, $^3J(H,H)=5.8$, 2.2 Hz, 1H; C*H*(OH)], 2.55 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=161.3$ [*C*(O)], 140.3 [C(O)CH=*C*H], 137.9 (Ar-*C*), 128.5, 128.2, 125.9 (Ar-*C*H), 123.4 [C(O)*C*H], 86.4 [*C*HOC(O)], 85.9 (Ph*C*H), 83.5 [*C*H(OH)], 68.1 ppm (*C*HCH=CH); IR (KBr): $\tilde{\nu}=3438$ (OH), 2926, 2859, 2279, 1724 (C=O, α,β-unsaturated δ-lactone), 1456, 1378, 1259, 1088, 816, 759, 706 cm^{-1} (C_6H_5); MS (100 eV, CI): *m/z* (%): 233 (100) $[M+H]^+$, 215 (10) $[M+H-H_2O]^+$, 137 (2), 127 (4), 119 (5), 109 (7), 107 (5) $[M+H-H_2O-PhCH_2OH]^+$, 97 (16), 91 (8) $[C_7H_7]^+$, 79 (1); HRMS: *m/z*: calcd for $C_{13}H_{12}O_4$ [*M*]: 232.0735; found: 232.0733.

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