Tetrahedron: *Asymmetry* 20 (2009) 205–209

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Chemoenzymatic asymmetric synthesis of harzia lactone A stereomers

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ARTICLE INFO

Article history:
Received 18 November 2008
Accepted 19 January 2009
Available online 14 February 2009

ABSTRACT

A facile chemoenzymatic synthesis of the harzia lactone A enantiomers was developed. A lipase-catalyzed acylation and an enantio-controlled substrate and reagent-controlled Sharpless' asymmetric dihydroxylation are the key features of the synthesis.

1. Introduction

Marine microorganisms have been a rich source of bioactive metabolites, especially those with unique structural features that might represent possible leads in the drug discovery processes.[1] The *Trichoderma* species, found in diverse ecological niches, including marine and freshwater environments, are prolific producers of secondary metabolites many of which show biological activity against infective agents. (+)-harzia lactone A **1** is one such marine metabolite, isolated from the culture broth of a strain of *T. harizanum* OUPS-N115. The naturally available (3*R*,5*R*)-**1** shows modest cytotoxicity against cultured P388 cells.[2] The absolute configuration of **1** was established by its synthesis from D-glucose[3a] and D-xylose,[3b] each in seven steps with yields of 15% and 24%, respectively. More recently, the synthesis of (3*S*,5*S*)-**1** from L-malic acid (40% overall yield),[3c] and of natural **1** via an L-proline-catalyzed sequential aminooxylation–olefination[3d] have been reported. Considering that the different stereomers of a compound can show different biological activities, we developed the first chemoenzymatic route of **1** which can provide easy access to all of its stereomers.

2. Results and discussion

For the synthesis, the racemic homoallylic alcohol **3** was prepared in reasonable yield by allylation of the commercially available, 2-phenylacetaldehyde **2** in the presence of Al-powder/$SnCl_2{\cdot}2H_2O$ in MeOH/H_2O/CH_3COOH.[4] For the resolution of **3**, we adopted a lipase catalyzed acylation strategy. To this end, several commercially available lipases and acylating agents (vinyl acetate, trifluoroethyl butyrate) were screened in various solvents. The best result was obtained with a combination of Novozyme 435/vinyl acetate in diisopropyl ether. The (*R*)-acetate **4** (47%, 97% ee) and (*S*)-**3** (44%, 87% ee) were obtained after 26 h. Compound (*S*)-**3** could be obtained with 96% ee and up to ~65% conversion in the acetylation. Alkaline hydrolysis of the acetate (*R*)-**4** with K_2CO_3/MeOH furnished alcohol (*R*)-**3**, which was easily converted to its antipode under Mitsunobu conditions[5] (*p*-benzoic acid/Ph_3P/DEAD/THF, 92%). The ees of the enantiomeric alcohols (*R*)-**3** and (*S*)-**3** were determined from the relative intensities of the methoxyl resonances of the corresponding MTPA esters, prepared using (*R*)-MTPA chloride.[6] The configurations of the alcohols were assigned from the NMR spectroscopic data of the corresponding (*R*)-MTPA esters,[7] and were finally confirmed by converting them to the target lactones and correlating their specific rotations with the reported values.[3b,3d]

Asymmetric dihydroxylation (ADH)[8] of (*S*)-**3** using the Ad-mix-α or β reagents, or OsO_4 (stoichiometric as well as catalytic) did not proceed with any diastereoselectivity, thus furnishing the *syn*/*anti* triols **5a** and **5b** in an almost 1:1 ratio. Hence, for economic reasons and easy isolation of the products, we carried out the dihydroxylation with the commercially available polymer-bound OsO_4 reagent producing a similar mixture of the triol epimers **5a**/**5b**, which were difficult to separate by column chromatography. Hence, we proceeded with the synthesis using the mixture. The 2,4-stereochemistry of the individual C-2 epimers was confirmed at a later stage (vide infra).

Monosilylation of the mixture of **5a**/**5b** with *tert*-butyldiphenylsilyl chloride (TPSCl) in the presence of 4,4′-dimethylaminopyridine (DMAP) produced compounds **6a** and **6b** that were separable by column chromatography. Next, the 1,3-diol functionality of compound **6a** was transformed into acetonide **7** with 2,2-dimethoxypropane (DMP)/pyridinium *p*-toluenesulfonate (PPTS). The 2,4-stereochemistry of **7** was determined[9] from the ^{13}C NMR resonances of the methyl and acetal carbons of the six-membered acetonide moiety. Desilylation of compound **7** gave alcohol **8**, which upon Swern's oxidation[10] afforded the aldehyde **9**. Finally, oxidation[11] of aldehyde **9** with $NaClO_2$ and acidic work-up furnished directly the lactone (3*R*,5*R*)-**1** (Scheme 1). The synthesis of (3*S*,5*S*)-**1** was also accomplished in an identical manner starting from (*R*)-**3**.

Overall, we developed a facile and operationally simple synthesis of both (3*R*,5*R*)- and (3*S*,5*S*)-**1**. However, the flexibility of our

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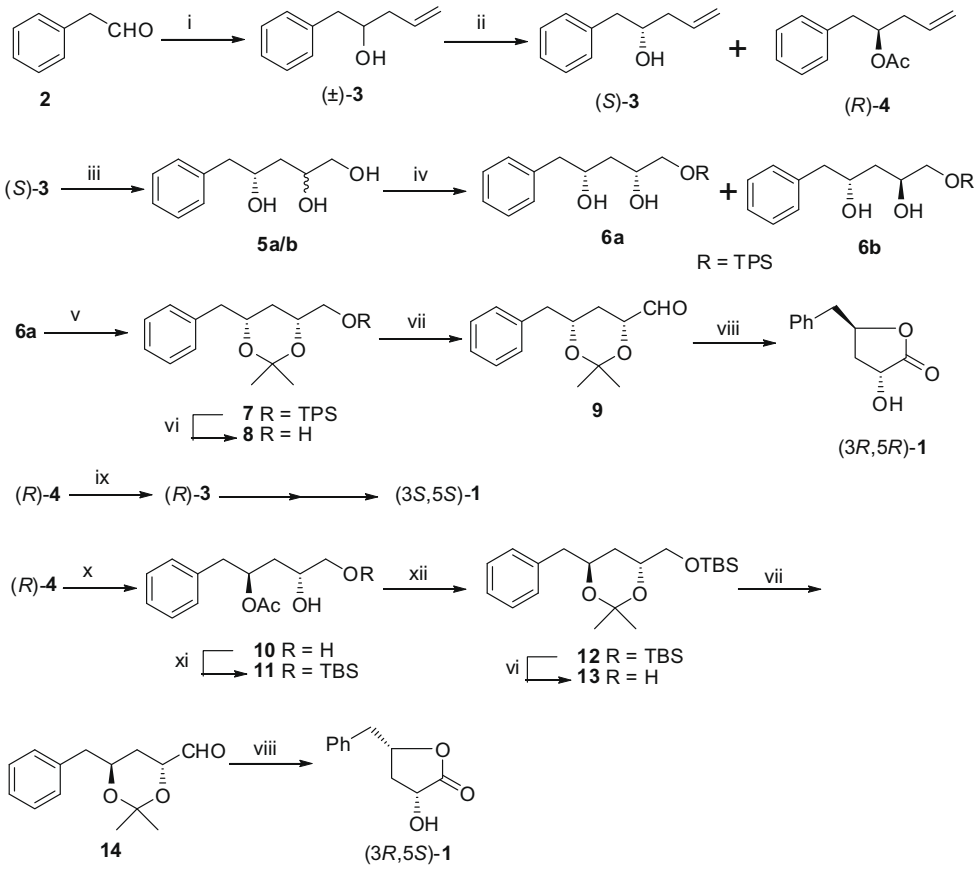
doi:10.1016/j.tetasy.2009.01.009



Scheme 1. (i) Allyl bromide/Al-powder/$SnCl_2{\cdot}2H_2O$/MeOH–H_2O–CH_3COOH/25 °C/18 h (84%), (ii) Novozyme 435/vinyl acetate/diisopropyl ether/25 °C/26 h (47% for **4**), (iii) Polymer bound-OsO_4/NMO/*tert*-BuOH–H_2O/ δ /12 h (86%), (iv) TBDPSCl/TEA/DMAP/CH_2Cl_2/0 °C/25 h (77%), (v) DMP/PPTS/CH_2Cl_2/25 °C/3 h (85%), (vi) Bu_4NF/THF/−78 °C/6 h (87% for **8**, 84% for **13**), (vii) $(COCl)_2$/DMSO/Et_3 N/CH_2Cl_2/25 °C/0.5 h (95% for **8**, 89% for **14**), (viii) $NaClO_2$/NaH_2PO_4/DMSO/H_2O/25 °C/22 h; 3 N HCl (44% for (3*R*,5*R*)-**1**, 42% for (3*R*,5*S*)-**1**), (ix) K_2CO_3/ MeOH/25 °C/6 h (98%), (x) Ad-mix-β/*t*-BuOH–H_2O/0 °C/14 h (81%), (xi) TBSCl/ Et_3 N/DMAP/CH_2Cl_2/0 °C/18 h (75%), (xii) K_2CO_3/MeOH/25 °C/6 h (91%); DMP/PPTS/CH_2Cl_2/25 °C/3 h (88%).

method would also allow the synthesis of the other stereomers of **1**, which would facilitate the biological evaluation of the lactone comprehensively. Ironically, the non-selective dihydroxylation step that was the key to access all the stereomers of **1** is unsuitable for the synthesis of a single particular enantiomer. It is well known that the presence and nature of a chelating group in the vicinity of an alkene site dictates the stereochemistry of its ADH reaction with the Sharpless' regents.[8] Given that the ADH reaction with alcohol **3** was non-selective, we attempted the reaction with acetate **4**. Fortunately, the AD-mix β-catalyzed dihydroxylation of (*R*)-**4** proceeded with exclusive *anti*-selectivity to give **10** as an enantiomerically pure single product. The AD-mix-α reagent furnished a mixture of a *syn*/*anti* compound in a 6:4 ratio. The basis for its selectivity in many organic reactions is the involvement of attractive, non-covalent secondary interactions between the substrate and catalyst as suggested or strongly indicated by experiments.[12a–d] The incorporation of enzyme-like recognition elements into simple catalysts/substrates is clearly an appealing feature in organic synthesis, since attractive interactions can, in principle, reduce conformational degrees of freedom and enhance chiral discrimination in determining transition states selectivity.[12e] Our strategy of using the acetate, rather than the alcohol for achieving excellent enantioselectivity in ADH reaction illustrates this.

Monosilylation of diol **10** with *tert*-butyldimethylsilyl chloride (TBSCl) furnished compound **11**, which on deacetylation followed by reaction with DMP/PPTS afforded ketal **12**. This was converted to (3*R*,5*S*)-**1** as described above for the synthesis of the other stereomers of **1**. So far only one synthesis of the different stereomers of **1** has been reported.[3b] Our strategy provides a simple alternative for these stereomers.

3. Experimental

3.1. General experimental details

All the chemicals (Fluka and Lancanster) were used as received. Other reagents were of AR grade. All anhydrous reactions were carried out under an Ar atmosphere using freshly dried solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrophotometer. The ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker Ac-200 spectrometer. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter.

3.2. (±)-1-Phenylpent-4-en-2-ol 3

To a suspension of Al-powder (8.1 g, 0.3 mol) and $SnCl_2{\cdot}2H_2O$ (6.8 g, 0.03 mol) in MeOH/H_2O/CH_3COOH (50 mL–25 mL–0.5 mL) was added a mixture of **2** (36.0 g, 0.3 mol) and allyl bromide (54.4 g, 0.45 mol), and the mixture was stirred at room temperature for 18 h. After neutralization with aqueous saturated $NaHCO_3$, the mixture was filtered to remove the solid residue. The filtrate was diluted with water, extracted with EtOAc and the combined organic extracts were washed with brine and dried. Removal of the solvent in vacuo followed by purification with column chromatography on silica gel (0–5% EtOAc/hexane) afforded pure (±)-**3**.

Yield: 40.8 g (84%); colourless oil; IR: 3423, 3028, 1641 cm^{-1}; ^1H NMR: δ 2.24–2.39 (m, 3H), 2.75–2.82 (m, 2H), 3.85–3.91 (m, 1H), 5.15–5.21 (m, 2H), 5.85–5.93 (m, 1H), 7.24–7.38 (m, 5H); ^{13}C NMR: δ 40.8, 43.0, 71.4, 117.5, 126.1, 128.1, 129.2, 134.6, 138.3. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.59; H, 8.88.

3.3. (*R*)-2-Acetoxy-1-phenylpent-4-ene (*R*)-4

A mixture of (±)-**3** (2.24 g, 13.83 mmol), vinyl acetate (2.38 g, 27.6 mmol) and Novoyme 435 (1.10 g) in diisopropyl ether (20 mL) was agitated on an orbital shaker at 110 rpm for 26 h. The reaction mixture was filtered, and the solution was concentrated in vacuo to get a residue, which on chromatography (silica gel, 0–10% EtOAc/hexane) gave pure (*S*)-**3** and (*R*)-**4**. (*S*)-**3**: Yield: 0.986 g (44%); colourless oil; [$[\alpha]_D^{22} = +10.0$ (*c* 2.91, $CHCl_3$). (*R*)-**4:** Yield: 1.32 g (47%); colourless oil; $[\alpha]_D^{22} = -17.5$ (*c* 1.16, $CHCl_3$); IR: 1736, 1243 cm^{-1}; ^1H NMR: δ 1.98 (s, 3H), 2.27–2.42 (m, 2H), 2.87 (d, *J* = 6.4 Hz, 2H), 5.07–5.19 (m, 3H), 5.75–5.85 (m, 1H), 7.23–7.26 (m, 5H); ^{13}C NMR: δ 21.0, 37.8, 39.8, 73.6, 117.8, 126.4, 128.2, 129.3, 133.5, 137.3, 170.3. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.59; H, 8.04.

3.4. (*S*)-1-Phenylpent-4-en-2-ol (*S*)-3

Following the above-mentioned method, the esterification of (±)-**3** with vinyl acetate in diisopropyl ether in the presence of Novozyme 435 was carried out in up to ~65% conversion (~40 h) to give optically enriched (*S*)-**3**. Yield: 0.790 g (36%); $[\alpha]_D^{22} = +12.2$ (*c* 1.84, $CHCl_3$).

3.5. (*R*)-1-Phenylpent-4-en-2-ol (*R*)-3

A mixture of (*R*)-**4** (3.06 g, 15 mmol) and K_2CO_3 (4.15 g, 30 mmol) in MeOH (25 mL) was stirred at room temperature for 6 h. The mixture was filtered, concentrated in vacuo, water was added into it, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried. Removal of the solvent in vacuo followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) afforded pure (*R*)-**3**. Yield: 2.40 g (98%). $[\alpha]_D^{22} = -12.6$ (*c* 1.41, $CHCl_3$).

3.6. (2*R*/*S*,4*R*)-5-Phenylpentane-1,2,4-triol (2*R*,4*R*)-5a/(2*S*,4*R*)-5b

A mixture of (*S*)-**3** (1.94 g, 11.98 mmol), 4-methylmorpholine-N-oxide·H_2O (NMO) (3.24 g, 24 mmol) and polymer bound-OsO_4 (2.0 g, 0.6 mmol, catalyst loading 0.3 mmol/g) in *tert*-BuOH–H_2O (7–2 mL) was refluxed until completion of the reaction (cf. 12 h). The reaction mixture was filtered, and the catalyst was washed thoroughly with CH_2Cl_2. The filtrate was dried and concentrated in vacuo. Purification of the residue with column chromatography (silica gel, 0–7% MeOH/$CHCl_3$) afforded the triol **5a**/**5b**. Yield: 2.03 g (86%); white viscous liquid; $[\alpha]_D^{22} = +6.8$ (*c* 1.34, $CHCl_3$); IR: 3377 cm^{-1}; ^1H NMR: δ 1.39–1.54 (m, 2H), 2.60–2.70 (m, 2H), 3.24–3.42 (m, 2H), 3.72–4.10 (m, 2H), 7.16–7.21 (m, 5H); ^{13}C NMR: δ 38.3, 44.4, 66.4, 72.2, 72.7, 126.5, 128.5, 129.4, 137.9. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.16; H, 8.38.

3.7. (2*R*,4*R*)- and (2*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-5-phenylpentane-2,4-diol (2*R*,4*R*)-6a and (2*S*,4*R*)-6b

To a stirred and cooled (−30 °C) solution of the mixture of **5a**/**b** (1.96 g, 10 mmol), DMAP (catalytic) and Et_3N (2.64 mL, 19 mmol) in CH_2Cl_2 (25 mL) was dropwise added TPSCl (4.12 g, 15 mmol) in CH_2Cl_2 (25 mL). After stirring the mixture for 7 h at −30 °C, and for 18 h at room temperature, it was poured into ice cold water, and the organic layer was separated and the aqueous portion was extracted with $CHCl_3$. The combined organic extracts were washed with aqueous saturated NH_4Cl, water and brine, and dried. Removal of the solvent in vacuo followed by purification with column chromatography (silica gel, 0–20% EtOAc/hexane) afforded pure **6a** and **6b**. Compound **6a:** Yield: 1.82 g (42%); thick colourless liquid; $[\alpha]_D^{23} = -4.0$ (*c* 1.26, $CHCl_3$); IR: 3376 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.46–1.56 (m, 2H), 2.54–2.81 (m, 4H), 3.50–3.56 (m, 2H), 3.93–4.07 (m, 2H), 7.17–7.41 (m, 11H), 7.61–7.64 (m, 4H); ^{13}C NMR: δ 19.2, 26.8, 38.1, 44.2, 67.8, 72.8, 73.0, 126.4, 127.8, 128.4, 129.5, 129.9, 133.0, 135.5, 138.2. Anal. Calcd for $C_{27}H_{34}O_3Si$: C, 74.61; H, 7.88. Found: C, 74.67; H, 8.04. Compound **6b:** Yield 1.51 g (35%); $[\alpha]_D^{22} = +16.0$ (*c* 1.52, $CHCl_3$); IR: 3441 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.57 (m, 2H), 2.79 (d, *J* = 6.8 Hz, 2H), 3.00 (br s, 2H), 3.51 (d, *J* = 5.4 Hz, 2H), 4.00–4.12 (m, 2H), 7.14–7.37 (m, 1H); 7.64–7.79 (m, 4H); ^{13}C NMR: δ 19.3, 27.0, 37.6, 43.4, 68.1, 68.9, 73.3, 126.0, 127.7, 128.2, 129.3, 129.7, 129.8, 133.4, 133.9, 136.0, 138.1. Anal. Calcd for $C_{27}H_{34}O_3Si$: C, 74.61; H, 7.88. Found: C, 74.77; H, 7.71.

3.8. (2*R*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2,4-isopropanedioxy-5-phenylpentane (2*R*,4*R*)-7

A solution of **6a** (1.30 g, 3.0 mmol), DMP (0.625 g, 6.0 mmol) and PPTS (0.075 g, 0.3 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O, and the organic layer was washed with 10% aqueous $NaHCO_3$, water and brine, and dried. Removal of the solvent in vacuo followed by column chromatography (silica gel, 0–5% EtOAc/hexane) of the residue afforded pure **7**. Yield: 1.21 g (85%); colourless oil; $[\alpha]_D^{22} = -5.0$ (*c* 1.28, $CHCl_3$); IR: 1428, 1379 cm^{-1}; ^1H NMR: δ 1.17 (s, 9H), 1.29–1.68 (m containing a s at δ 1.50, 8H), 2.69–2.79 (m, 1H), 3.01–3.08 (m, 1H), 3.54–3.65 (m, 1H), 3.70–3.78 (m, 1H), 3.88–4.19 (m, 2H), 7.33–7.48 (m, 11H), 7.77 (m, 4H); ^{13}C NMR: δ 19.2, 19.7, 26.8, 30.0, 33.1, 43.0, 67.4, 69.7, 69.8, 98.4, 126.2, 127.5, 128.2, 129.4, 129.5, 133.6, 135.6, 137.8. Anal. Calcd for $C_{30}H_{38}O_3Si$: C, 75.90; H, 8.07. Found: C, 75.78; H, 8.15.

3.9. (2*R*,4*R*)-2,4-Isopropanedioxy-5-phenylpentan-1-ol (2*R*,4*R*)-8

To a cooled (−78 °C) and stirred solution of **7** (0.95 g, 2.0 mmol) in THF (5 mL) was added Bu_4NF (2.2 mL, 2.2 mmol, 1.0 M in THF). The reaction mixture was brought to room temperature and stirred until the reaction was complete (cf. TLC, 6 h). The mixture was poured into ice cold water and was extracted with EtOAc. The organic extract was washed with water and brine, and dried. Removal of the solvent followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) furnished **8**. Yield: 0.41 g (87%); colourless oil; $[\alpha]_D^{22} = -9.8$ (*c* 4.86, $CHCl_3$); IR: 3408 cm^{-1}; ^1H NMR: δ 1.29–1.33 (m, 2H), 1.43 (s, 6H), 2.62–2.66 (m, 1H), 2.90–2.99 (m, 2H), 3.46–3.51 (m, 2H), 3.87–4.05 (m, 2H), 7.17–7.27 (m, 5H); ^{13}C NMR: δ 19.8, 29.9, 31.6, 42.8, 65.8, 69.5, 69.6, 98.7, 126.2, 128.2, 129.3, 137.5. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.06; H, 8.44.

3.10. (2*R*,4*R*)-2,4-Isopropanedioxy-5-phenylpentanal (2*R*,4*R*)-9

To a cooled (−50 °C) and stirred solution of oxalyl chloride (0.244 g, 1.92 mmol) in CH_2Cl_2 (4 mL) was added dimethylsulfoxide (0.3 g, 3.84 mmol) in CH_2Cl_2 (2 mL). After five min, **8** (0.378 g, 1.6 mmol) in CH_2Cl_2 (3 mL) was added to the mixture, followed by Et_3N (0.81 g, 8 mmol). The mixture was stirred further for 15 min, brought to room temperature, H_2O was added into it, and stirring continued for 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated in vacuo to afford **9**. Yield: 0.355 g (95%); colourless oil; $[\alpha]_D^{22} = -6.8$ (*c* 1.26, $CHCl_3$); IR:

2714, 1717 cm^{-1}; ^1H NMR: δ 1.46 (s, 3H), 1.49 (s, 3H), 1.62–1.72 (m, 2H), 2.55–2.71 (m, 1H), 2.84–2.95 (m, 1H), 4.19–4.28 (m, 2H), 7.21–7.25 (m, 5H), 9.55 (s, 1H); ^{13}C NMR: δ 19.3, 30.3, 42.6, 69.3, 73.8, 99.0, 125.8, 126.1, 128.1, 129.3, 137.0, 200.9. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.96; H, 7.89.

3.11. (3*R*,5*R*)-3-Hydroxy-5-phenylmethyldihydrofuran-2-one (3*R*,5*R*)-1

To a mixture of **9** (0.374 g, 1.6 mmol) in DMSO (1.6 mL) and a solution of NaH_2PO_4 (52 mg) in water (0.6 mL) was dropwise added $NaClO_2$ (0.253 g, 2.24 mmol, 80% purity) in water (2.5 mL). After stirring the reaction mixture at room temperature for 22 h, it was acidified with aqueous 3 M HCl. The reaction mixture was extracted with EtOAc, and the organic extract washed with water and brine, and dried. Removal of the solvent in vacuo followed by column chromatography (silica gel, 0–25% EtOAc/hexane) afforded pure (*R*,*R*)-**1**. Yield: 0.135 g (44%); white solid; mp: 78–79 °C (lit.[3d] mp: 80 °C); $[\alpha]_D^{22} = +38.6$ (*c* 0.702, $CHCl_3$) {lit.[3d] $[\alpha]_D^{25} = +40$ (*c* 0.3, $CHCl_3$)}; IR: 3398, 1768 cm^{-1}; ^1H NMR: δ 2.24–2.33 (m, 2H), 2.95 (d, *J* = 6.0 Hz, 2H), 3.35 (br s, 1H), 4.07 (t, *J* = 7.2 Hz, 1H), 4.85–4.91 (m, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR: δ 34.4, 41.0, 67.0, 78.4, 127.1, 128.7, 129.5, 135.3, 177.7.

3.12. (3*S*,5*S*)-3-Hydroxy-5-phenylmethyldihydrofuran-2-one (3*S*,5*S*)-1

In analogy to the preparation of (3*R*,5*R*)-**1** from (*S*)-**3**, (3*S*,5*S*)-**1** was prepared from (*R*)-**3** in six steps and 22% yield. White solid; mp: 68 °C (lit.[3b] mp: 71–74 °C); $[\alpha]_D^{22} = -36.4$ (*c* 0.781, $CHCl_3$) {lit.[3b] $[\alpha]_D^{22} = -38.0$ (*c* 0.3, $CHCl_3$)}; IR: 3408, 1765 cm^{-1}; ^1H NMR: δ 2.22–2.35 (m, 2H), 2.68 (br s, 1H), 2.89 (d, *J* = 6.2 Hz, 2H), 3.95 (t, *J* = 7.2 Hz, 1H), 4.86–4.98 (m, 1H) and 7.17 (br s, 5H); ^{13}C NMR: δ 34.7, 41.5, 66.8, 78.1, 127.3, 128.9, 135.5, 177.2.

3.13. (2*R*,4*S*)-4-Acetoxy-5-phenylpentane-1,2-diol (2*R*,4*S*)-10

A solution of (*R*)-**4** (2.0 g, 10 mmol) in *tert*-BuOH/water (1:1, 25 mL) was added to a cooled (0 °C) and stirred suspension of AD mix-β (14.0 g) in the same solvent (120 mL). The mixture was stirred at 0 °C for 14 h, treated with solid Na_2SO_3 (14.0 g), stirred for a further 1 h at room temperature and extracted with $CHCl_3$. The organic extract was washed with water and brine, and dried. Solvent removal and column chromatography of the residue (silica gel, 0–7% MeOH/$CHCl_3$) afforded **10** as the sole product. Yield: 1.92 g (81%); colourless oil; $[\alpha]_D^{22} = +14.8$ (*c* 0.88, $CHCl_3$). IR: 3442, 1734 cm^{-1}; ^1H NMR: δ 1.56–1.72 (m, 2H), 2.01 (s, 3H), 2.63 (br s, 2H), 2.87 (two overlapping d, *J* = 5.6 Hz, 2H), 3.46–3.72 (m, 2H), 4.08–4.18 (m, 1H), 5.21–5.27 (m, 1H), 7.19–7.34 (m, 5H); ^{13}C NMR: δ 20.8, 37.2, 40.9, 66.2, 68.0, 71.8, 126.3, 128.1, 129.2, 136.9, 171.6. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.38; H, 7.75.

3.14. (2*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-acetoxy 5-phenylpentane-2-ol (2*R*,4*S*)-11

To a stirred and cooled (−30 °C) solution of **10** (1.20 g, 5.0 mmol), DMAP (catalytic) and Et_3N (1.32 mL, 9.50 mmol) in CH_2Cl_2 (25 mL) was added TBSCl (1.12 g, 7.50 mmol) in CH_2Cl_2 (25 mL). After stirring the mixture for 18 h at 0 °C, it was poured into ice cold water and the organic layer was separated and the aqueous portion was extracted with $CHCl_3$. The combined organic extracts were washed with aqueous saturated NH_4Cl, water and brine, and dried. Removal of solvent in vacuo followed by purification with column chromatography (silica gel, 0–10% EtOAc/hexane) afforded pure **11**. Yield: 1.33 g (75%); colourless oil; $[\alpha]_D^{22} = +10.4$ (*c* 1.18, $CHCl_3$). IR: 3408, 1725 cm^{-1}; ^1H NMR: δ 0.05 (s, 6H), 1.09 (s, 9H), 1.52–1.68 (m, 2H), 1.99 (s, 3H), 2.28 (br s, 2H), 2.78–2.86 (m, 2H), 3.46–3.72 (m, 2H), 3.89–3.97 (m, 1H), 5.07–5.14 (m, 1H), 7.19 (br s, 5H); ^{13}C NMR: δ −5.3, 18.7, 20.8, 37.2, 40.9, 66.2, 68.0, 71.8, 126.3, 128.1, 129.2, 136.9, 171.6. Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15. Found: C, 64.87; H, 9.27.

3.15. (2*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-isoproanedioxy-5-phenylpentane (2*R*,4*S*)-12

A mixture of **11** (3.06 g, 15 mmol) and K_2CO_3 (4.15 g, 30 mmol) in MeOH (25 mL) was stirred at room temperature for 6 h. The mixture was filtered, concentrated in vacuo, and water was added after which the mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) afforded the corresponding alcohol. Yield: 1.04 g (91%).

A solution of the above-mentioned product (1.30 g, 3.0 mmol), DMP (0.625 g, 6.0 mmol) and PPTS (0.075 g, 0.3 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O, the organic layer was washed with 10% aqueous $NaHCO_3$, water and brine, and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0–5% EtOAc/hexane) of the residue afforded pure **12**. Yield: 0.990 g (88%); colourless oil; $[\alpha]_D^{22} = +7.5$ (*c* 0.860, $CHCl_3$). IR: 1484, 1383 cm^{-1}; ^1H NMR: δ 0.05 (s, 6H), 1.08 (s, 9H), 1.26–1.32 (m, 1H), 1.40–1.71 (m containing a s at δ 1.43, 7H), 2.63–2.69 (m, 1H), 2.84–3.0 (m, 1H), 3.44–3.50 (m, 1H), 3.56–3.70 (m, 1H), 3.74–3.81 (m, 1H), 3.88–4.12 (m, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR: δ −5.4, 18.2, 23.8, 24.0, 33.1, 42.9, 66.8, 69.7, 72.9, 100.2, 126.3, 128.4, 129.4, 138.2. Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.36; H, 9.60.

3.16. (2*R*,4*S*)-2,4-Isopropanedioxy-5-phenylpentan-1-ol (2*R*,4*S*)-13

As described for **8**, compound **12** (0.700 g, 2.0 mmol) was desilylated with Bu_4NF (2.2 mL, 2.2 mmol, 1.0 M in THF) in THF (5 mL) to furnish **13** after purification by column chromatography (silica gel, 0–10% EtOAc/hexane). Yield: 0.396 g (84%); colourless oil; $[\alpha]_D^{22} = +5.2$ (*c* 0.882, $CHCl_3$); IR: 3431 cm^{-1}; ^1H NMR: δ 1.22–1.36 (m, 2H), 1.53 (s, 3H), 1.58 (s, 3H), 2.24 (broad s, 1H), 2.52–2.75 (m, 2H), 3.43–3.47 (m, 2H), 3.78–3.93 (m, 2H), 7.20–7.26 (m, 5H); ^{13}C NMR: δ 23.7, 24.7, 38.6, 43.7, 69.4, 72.6, 75.3, 101.1, 126.1, 128.4, 129.2, 138.1. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.02; H, 8.65.

3.17. (2*R*,4*S*)-2,4-Isopropanedioxy-5-phenylpentanal (2*R*,4*S*)-14

Compound **13** (0.390 g, 1.65 mmol) was oxidized using oxalyl chloride (0.254 g, 1.92 mmol), dimethylsulfoxide (0.3 g, 3.84 mmol) and Et_3N (0.910 g, 9 mmol) in CH_2Cl_2 (15 mL) to give **14** after work-up, as described for **9**. Yield: 0.344 g (89%); colourless oil; $[\alpha]_D^{22} = +5.9$ (*c* 1.04, $CHCl_3$); IR: 2721, 1736 cm^{-1}; ^1H NMR: δ 1.44–1.65 (m, containing two s at δ 1.54 and δ 1.62, 8H), 2.51–2.68 (m, 1H), 2.78–2.88 (m, 1H), 3.99–4.10 (m, 1H), 4.19–4.24 (m, 1H), 7.32 (m, 5H), 9.52 (s, 1H); ^{13}C NMR: δ 23.6, 29.6, 44.7, 65.9, 71.0, 105.1, 126.4, 128.2, 129.3, 137.6, 202.3. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.91.

3.18. (3*R*,5*S*)-3-Hydroxy-5-phenylmethyldihydrofuran-2-one (3*R*,5*S*)-1

Oxidation of **14** (0.340 g, 1.45 mmol) with $NaClO_2$ (0.230 g, 2.0 mmol, 80% purity) and NaH_2PO_4 (50 mg) in DMSO (1.5 mL) and water (3.5 mL) followed by acidic work-up and purification furnished (3*R*,5*S*)-**1**. Yield: 0.116 g (42%); white solid; mp 99–

100 °C (lit.[3b] mp: 101–103 °C); $[\alpha]_D^{22} = +8.9$ (*c* 0.648, $CHCl_3$) {lit.[3b] $[\alpha]_D = +8.7$ (*c* 1.1, $CHCl_3$)}; IR: 3389, 1774 cm^{-1}; ^1H NMR: δ 2.17–2.25 (m, 2H), 2.93–3.07 (m, 2H), 3.77–3.86 (m, 1H), 4.54–4.68 (m, 2H), 7.17–7.32 (m, 5H); ^{13}C NMR: δ 36.3, 40.8, 68.7, 77.7, 128.3, 128.7, 129.5, 134.2, 179.1.

3.19. General procedure for preparation of the MTPA esters

A mixture of (*R*)-MTPA (25 mg) and $SOCl_2$ (0.250 mL) in toluene (2 mL) was refluxed for 3 h. After removing the excess $SOCl_2$ in vacuo, the resultant MTPA chloride was taken in methanol-free CH_2Cl_2 (0.5 mL), and added to a solution of the alcohol (15 mg), pyridine (0.1 mL) and 4,4-dimethylaminopyridine (1–2 crystals) in CH_2Cl_2 (0.250 mL). After stirring the mixture for 16 h at room temperature, the excess pyridine was removed by purging with N_2 gas, and the residue was subjected to preparative thin layer chromatography (silica gel, 10% EtOAc/hexane) to isolate the respective MTPA esters.

(*R*)-MTPA ester of (*R*)-**3:** ^1H NMR: δ 2.29–2.75 (m, 2H), 2.81–3.17 (m, 2H), 3.44 (major) and 3.56 (two s, 3H), 4.90–5.12 (m, 1H), 5.19–5.24 (m, 2H), 5.83–5.95 (m, 1H), 7.21–7.42 (m, 10H).

(*R*)-MTPA ester of (*S*)-**3** ^1H NMR: δ 2.31–2.91 (m, 2H), 2.84–3.27 (m, 2H), 3.47 and 3.57 (major) (two s, 3H), 4.81–5.15 (m, 1H), 5.25–5.34 (m, 2H), 5.85–5.91 (m, 1H), 7.21–7.43 (m, 10H).

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