Tetrahedron: *Asymmetry* 20 (2009) 1536–1540

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Stereoselective total synthesis of dodoneine ☆

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ARTICLE INFO

Article history:
Received 12 May 2009
Accepted 29 May 2009
Available online 24 June 2009

ABSTRACT

The stereoselective total synthesis of the naturally occurring bioactive dihydropyranone dodoneine has been achieved involving the Sharpless asymmetric epoxidation, 1,3-*syn* diastereoselective reduction and Grubb's ring-closing metathesis as key steps.

1. Introduction

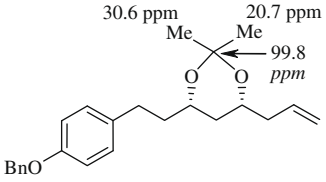
Naturally occurring 5,6-dihydropyran 2-ones possess various important biological properties including antifungal, antibacterial and cytotoxic activities.[1] Dodoneine [(*R*)-6-[(*S*)-2-hydroxyl-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one] **1**, a member of this group, has recently been isolated from *Tapinanthus dodoneifolius*, a parasitic medicinal plant that grows on the Sheanut trees in Loumbila, West Africa.[2] The structure of **1** was determined from spectroscopic data and X-ray diffraction analysis of a crystalline derivative. The compound exhibits a releasing effect on preconstricted rat aortic rings. Considering the structure as well as activity we were interested in its synthesis. While our work on the synthesis of **1** was in progress two synthetic works on the molecule have recently appeared.[3] Herein we report our alternative approach for the stereoselective synthesis of **1**.

2. Results and discussion

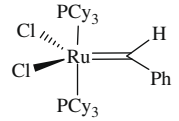
Retrosynthetic analysis (Scheme 1) suggests that compound **1** can be obtained from the intermediate **2** (by Grubbs' ring-closing metathesis) which can be prepared from the homoallylic alcohol **3** (by acylation with acryloyl chloride). Compound **3** can in turn be prepared from allylic alcohol **6** by Sharpless asymmetric epoxidation followed by reduction, protection, oxidation and allylation. Compound **6** can easily be obtained from 4-hydroxy benzaldehyde **7**.

We initiated our synthesis with **7** by converting it into a benzyl ether, followed by 2C-Wittig homologation with (carboethoxymethylene) triphenyl phosphorane and reduction of the resulting ester with $LiAlH_4$ to form alcohol **8** (Scheme 2). Swern oxidation of **8** and 2C-Wittig homologation produced ester **9**. Reduction of **9** with DIBAL-H afforded the unsaturated alcohol **6** which underwent epoxidation under Sharpless asymmetric epoxidation conditions[4] using (+)-DIPT to furnish epoxy alcohol **5**. The reductive opening of this epoxide with Red-Al formed the 1,3-diol **10**, which was converted into a di-TBS ether by treatment with TBS-Cl and subsequently into mono-TBS ether **11** by reaction with PTSA. Swern oxidation of **11** yielded aldehyde **4**, which was treated with allyl magnesium bromide to provide a diastereomeric mixture (*syn*:*anti* 42:58 by ^{1}H NMR analysis) of a homoallylic alcohol **12**, which in turn was oxidized with Dess–Martin periodinane reagent to form allyl ketone **13**. At this stage the diastereoselective reduction of this ketone to prepare *syn*-1,3-diol derivative was studied. The best result was obtained with $LiAlH_4$–LiI at −100 °C to form the product with a ratio of *syn*- and *anti*-isomers of 94:6, as determined by chiral HPLC.[5]

The selectivity was less (*syn*:*anti*, 4:1) when the reaction was carried out at −78 °C. Reduction with DIBAL-H was also less impressive. The *syn*-diol derivative **3** was separated by column chromatography and its structure determined from spectroscopic (IR, ^{1}H NMR and MS) analysis. From a minor amount of **3**, the deprotection of the TBS ether with TBAF and subsequent formation of the acetonide **A** with 2,2-DMP confirmed the *syn*-stereoselectivity of **3.** The structure of **A** (with *cis*-stereochemistry) was determined from its spectroscopic data, especially the ^{13}C NMR values which appear at δ 20.7 and 30.6 for two methyl groups of the acetonide moiety.[6] The alcohol **3** underwent acylation with acrolyl chloride to produce the diene ester **2**. In the intramolecular metathesis reaction,[7] in the presence of 5 mol % Grubbs' catalyst of the 1st generation (**B**), compound **2** yielded the α-β-unsaturated lactone **14**. The cleavage of the TBS and benzyl groups of **14** with $TiCl_4$ furnished the compound **1**, which was purified by column chromatography. The physical and spectroscopic properties of the compound were identical to those reported for natural dodoneine.[2]



A



Grubbs' Catalyst (1st generation)

B

☆ Part 29 in the series, 'Synthetic studies on natural products'.

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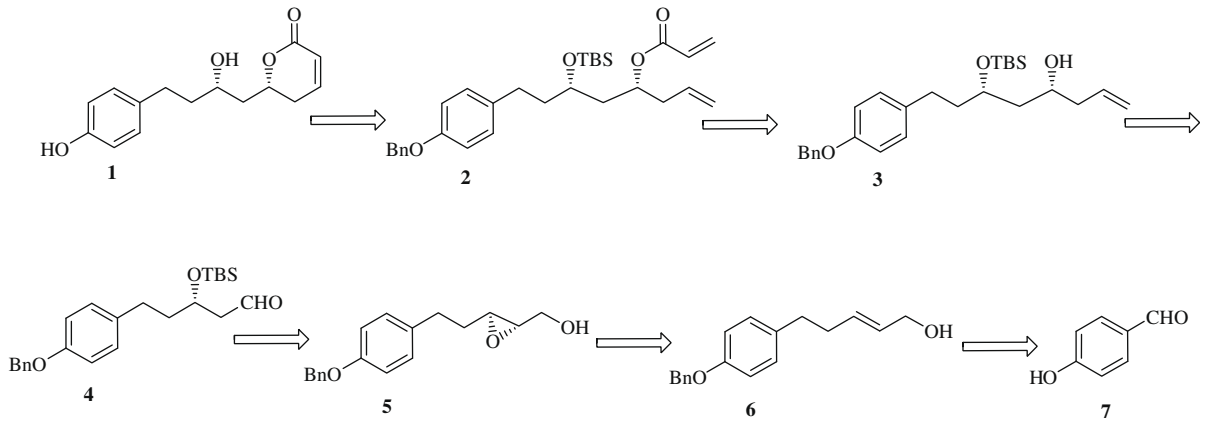
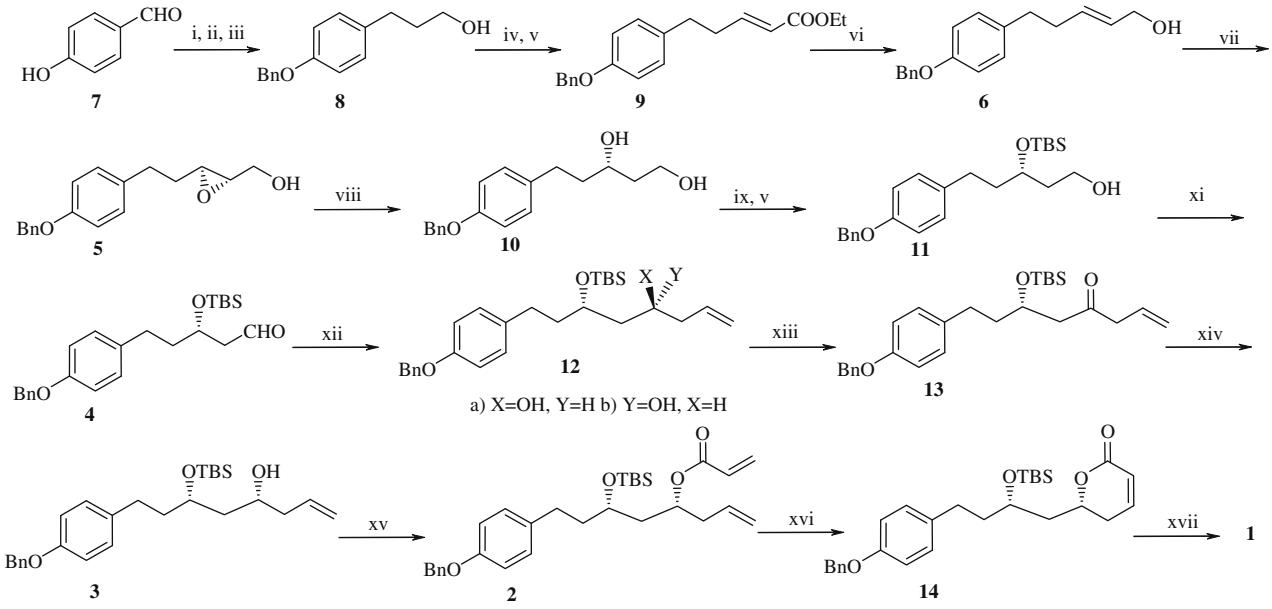
doi:10.1016/j.tetasy.2009.05.036



Scheme 1.



Scheme 2. Reagents and conditions: (i) NaH, BnBr, THF, 0 °C to rt, 4 h, 82%; (ii) $PPh_3CHCOOEt$, CH_2Cl_2, rt, 6 h, 80%; (iii) $LiBH_4$, H_2O, Et_2O, 0 °C, 24 h, 91%; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 0.5 h, 82%; (v) $PPh_3CHCOOEt$, CH_2Cl_2, rt, 24 h, 81%; (vi) DIBAL-H, CH_2Cl_2, −78 °C to −10 °C, 0.5 h, 79%; (vii) $Ti(^iOPr)_4$ (1.0 equiv), (+)-DIPT (1.1 equiv), TBHP (2.5 equiv), CH_2Cl_2, −20 °C, 12 h, 92%; (viii) Red-Al (3.0 equiv), THF, 0 °C, 0.5 h, 82%; (ix) TBSCl, imidazole, DMF, rt, 12 h, 88%; (x) PTSA(0.05 equiv), MeOH, 0 °C, 81%; (xi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 0.5 h, 82%; (xii) $CH_2{=}CHCH_2MgBr$, Et_2O, 0 °C, 1 h, 74%; (xii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h, 88%; (xiv) $LiAlH_4$–LiI, Et_2O, −100 °C, 30 min 94%; (xv) acryloyl chloride, Et_3N, 0 °C to rt, 30 min 96%; (xvi). Grubbs' first generation catalyst, CH_2Cl_2, 50 °C, 24 h, 85%; (xvii). $TiCl_4$, DCM, 0 °C, 89%.

3. Conclusion

In conclusion, the asymmetric total synthesis of dodoneine has been accomplished by using a Sharpless asymmetric epoxidation, a 1,3-*syn*-diasteroselective reduction and Grubb's metathesis as key steps.

4. Experimental

4.1. General

All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a positive pressure of dry nitrogen atmosphere where necessary. All reactions were performed in pre-dried apparatus under a nitrogen atmosphere unless otherwise stated. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) performed on Merck Silica Gel 60 F_{254} plates. Column chromatography was carried out using silica gel 60–120 mesh (Qingdao Marine Chemical, China). NMR spectra were recorded on Gemini 200 MHz spectrometer with tetramethylsilane as internal standard using $CDCl_3$. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). Yields were of purified compounds and were not optimized. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C.

4.1.1. 4-(Benzyloxy)benzaldehyde

To a stirred suspension of NaH (3.77 g, 163.91 mmol) in THF (70 mL) a solution of **7** (10 g, 81.96 mmol) in THF (20 mL) was added dropwise at 0 °C under a nitrogen atmosphere. After stirring for 15 min, benzyl bromide (90.16 mmol, 10.7 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was quenched with saturated aq NH_4Cl (50 mL) at 0 °C and extracted with ethylacetate (3 × 50 mL). The combined organic

extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 5:5) to afford pure 4-(benzyloxy) benzaldehyde (14.24 g, 82%) as a white solid. IR (neat): 3423, 1739, 1686, 1506, 1255 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.83 (2H, d, J = 8.0 Hz), 7.50–7.32 (5H, m), 7.06 (2H, d, J = 8.0 Hz), 5.16 (2H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.6, 164.8, 137.2, 132.4, 130.1, 128.8, 128.2, 127.5, 115.0, 70.2. ESIMS: m/z 213 $[M+H]^+$. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.25; H, 5.66. Found: C, 79.17; H, 5.61.

4.1.2. (*E*)-Ethyl 3-(4-(benzyloxy)phenyl) acrylate

To a stirred solution of 4-(benzyloxy) benzaldehyde (5.0 g, 23.58 mmol) in dry CH_2Cl_2 (50 mL) ethyl (triphenyl phosphornylidene) acetate (13.3 g, 38.21 mmol) was added and the mixture was stirred at ambient temperature for 8 h. It was then concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (*E*)-ethyl 3-(4-(benzyloxy) phenyl) acrylate (5.32 g, 80%) as a colourless solid. IR (neat): 1712, 1632, 1570, 1509, 1249 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.64 (1H, d, J = 16.0 Hz), 7.49–7.30 (5H, m), 6.95 (2H, d, J = 8.0 Hz), 6.31 (1H, d, J = 16.0 Hz), 5.08 (2H, s), 4.22 (2H, q, J = 7.0 Hz), 1.32 (3H, t, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.2, 160.8, 144.9, 136.2, 129.9, 128.2, 128.0, 127.0, 116.2, 115.0, 70.2, 60.1, 13.3. ESIMS: m/z 283 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.60; H, 6.38. Found: C, 76.55; H, 6.32.

4.1.3. 3-(4-(Benzyloxy)phenyl)propan-1-ol

To a solution of (*E*)-ethyl 3-(4-(benzyloxy) phenyl) acrylate (2 g, 7.0 mmol) in dry THF (20 mL) at 0 °C $LiBH_4$ (0.446 g, 21.23 mmol) was added with stirring under nitrogen atmosphere and the stirring was continued for 36 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 0 °C and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 3:7) to afford pure **8** (1.561 g, 91%) as a colourless crystalline solid. IR (neat): 3324, 1608, 1510, 1242 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.22 (5H, m), 7.08 (2H, d, J = 8.0 Hz), 6.87 (2H, d, J = 8.0 Hz), 4.88 (2H, s), 3.59 (2H, t, J = 7.0 Hz), 3.00 (1H, br s), 2.59 (2H, t, J = 7.0 Hz), 1.85–1.72 (2H, m).^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.5, 137.2, 134.0, 129.0, 128.2, 127.8, 127.1, 114.1, 69.8, 61.1, 34.0, 20.2. ESIMS: m/z 243 $[M+H]^+$. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.44. Found: C, 79.28; H, 7.39.

4.1.4. 3-(4-(Benzyloxy) phenyl) propanal

To a solution of oxaloyl chloride (9.69 mmol, 0.8 mL) in dry CH_2Cl_2 (15 mL) at −78 °C, DMSO (20.6 mmol, 1.4 mL) was added dropwise with stirring under nitrogen atmosphere. After 15 min. compound **8** (1.561 g, 6.4 mmol) was added into the reaction mixture and subsequently after stirring for 0.5 h at −78 °C, Et_3N (32.2 mmol, 4.5 mL) was added and the mixture was stirred for another 0.5 h at −78 °C and then for 0.5 h at 0 °C. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 0 °C and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The aldehyde, thus obtained (0.813 g, 82%), was used directly after flash column chromatography for the next reaction.

4.1.5. (*E*)-Ethyl 5-(4-(benzyloxy) phenyl) pent-2-enoate

To a solution of aldehyde (0.813 g, 3.38 mmol) in dry CH_2Cl_2 (10 mL) ethyl (triphenyl phosphornylidene) acetate (1.76 g, 5.0 mmol) was added and the mixture was stirred at ambient temperature for 8 h. It was concentrated in vacuo and the residue was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure **9** (0.850 g, 81%) as a yellow solid. IR (neat): 1715, 1601, 1511, 1455, 1249 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.49–7.30 (5H, m), 7.09 (2H, d, J = 8.0 Hz), 6.99–6.87 (3H, m), 5.82 (1H, d, J = 16.0 Hz), 5.00 (2H, s), 4.15 (2H, q, J = 7.0 Hz), 2.68 (2H, t, J = 7.0 Hz), 2.50–2.41 (2H, m), 1.22 (3H, t, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.3, 157.3, 148.0, 133.1, 129.4, 128.2, 127.6, 127.1 114.5, 114.1, 69.9, 60.0, 33.8, 33.2, 13.8. ESIMS: m/z 311 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}O_2$: C, 77.42; H, 7.10. Found: C, 77.39; H, 6.99.

4.1.6. (*E*)-5-(4-(Benzyloxy) phenyl) pent-2-en-1-ol

To a solution of **9** (0.850 g, 2.74 mmol) in dry CH_2Cl_2 (10 mL) cooled to −78 °C DIBAL-H (1.4 M, 4.9 mL, 6.85 mmol) was added dropwise and the mixture was stirred at that temperature for 1 h. The reaction mixture was then quenched by slow addition of dry methanol (10 mL) and was brought to room temperature. Saturated aq sodium potassium tartrate solution (10 mL) was added to the reaction mixture and stirred until two layers separated (2 h). Dichloromethane was evaporated under reduced pressure and the remaining aq layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 3:7) afforded pure **6** (0.580 g, 79%) as a yellow solid. IR (neat): 3386, 1606, 1510, 1455, 1241 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.49–7.26 (5H, m), 7.09 (2H, d, J = 8.0 Hz), 6.90 (2H, d, J = 8.0 Hz), 5.70–5.61 (2H, m), 5.01 (2H, s), 4.02 (2H, d, J = 6.0 Hz), 2.60 (2H, t, J = 7.0 Hz), 2.32–2.22 (2H, m), 2.11 (1H, br s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.8, 137.2, 134.1, 132.2, 129.7, 129.3, 128.5, 127.8 127.2, 114.5, 70.0, 63.2, 34.8, 34.3. ESIMS: m/z 269 $[M+H]^+$. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.60; H, 7.46. Found: C, 80.52; H, 7.41.

4.1.7. ((2*S*,3*S*)-3-(4-(Benzyloxy) phenethyl) oxiran-2-yl) methanol

To a suspension of the powder of activated 4 Å (0.116 g) molecular sieves in dry CH_2Cl_2 (10 mL) Ti (O^iPr)$_4$ (2.16 mmol, 0.6 mL) and (+)-DIPT (2.38 mmol, 0.5 mL) were added sequentially at −20 °C. After stirring for 30 min allylic alcohol (0.580 g, 2.16 mmol) in dry CH_2Cl_2 (8 mL) was added and stirring was continued for another 30 min at the same temperature. Then TBHP (5.4 mmol, 1.5 mL) was added and after stirring for another 3 h at the same temperature, the reaction mixture was quenched by addition of water (10 mL). It was allowed to remain at room temperature by stirring for 30 min. After re-cooling at 0 °C, an aq solution of NaOH (30% W/V, 10 mL, saturated with brine) was added to it and the mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 4:6) to afford pure **5** (0.565 g, 92%) as a colourless solid. $[\alpha]_D^{25} = -5.4$ (c 0.5, $CHCl_3$). IR (neat): 3418, 1608, 1510, 1239 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.50 (5H, m), 7.30 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 5.25 (2H, s), 4.02 (1H, dd, J = 12.0, 2.0 Hz), 3.73 (1H, dd, J = 12.0, 3.0 Hz), 3.17 (1H, m), 3.02 (1H, m), 2.99–2.81 (2H, m), 2.11–2.01 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.1, 137.2, 133.5, 129.8, 128.4, 127.9, 127.7, 114.9, 70.0, 61.8, 58.8, 55.2, 33.5, 31.2. ESIMS: m/z 285$[M+H]^+$. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.06; H, 7.04. Found: C, 76.14; H, 7.01.

4.1.8. (*S*)-5-(4-(Benzyloxy) phenyl) pentane-1,3-diol

To a stirred solution of **5** (0.565 g, 1.98 mmol) in dry THF (8 mL) under a N_2 atmosphere at 0 °C was added Red-Al solution in

toluene (1.8 mL, 5.9 mmol of 70% w/w) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aq NH_4Cl (10 mL) solution and then extracted with EtOAc (30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 5:5) to afford pure **10** (0.466 g, 82%) as a colourless solid. $[\alpha]_D^{25} = -1.4$ (*c* 0.5, $CHCl_3$). IR (neat): 3330, 1611, 1512, 1455, 1247 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.66–7.51 (5H, m), 7.28 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 5.21 (2H, s), 4.14–3.92 (3H, m), 2.92–2.74 (2H, m), 2.68 (2H, br s), 2.01–1.90 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.2, 137.8, 134.1, 129.0, 128.3, 127.3, 127.1, 114.8, 71.4, 70.0, 61.2, 39.2, 38.5, 31.0. ESIMS: *m/z* 287 $[M+H]^+$. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.52; H, 7.69. Found: C, 75.41; H, 7.65.

4.1.9. (*S*)-5-(4-(Benzyloxy)phenethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane

Imidazole (0.443 g, 6.5 mmol) and TBDMS-Cl (0.490 g, 3.25 mmol) were added sequentially to a solution of **10** (0.466 g, 1.62 mmol) in dry DMF (6 mL) at 0 °C. After stirring for 5 min, DMAP (catalytic amount) was added to the reaction mixture and stirring was continued for 12 h at room temperature. The reaction mixture was quenched with saturated aq NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 1:9) afforded pure di-TBS compound (0.736 g, 88%) as a viscous solid. $[\alpha]_D^{25} = +7.0$ (*c* 0.5, $CHCl_3$). IR (neat): 1611, 1511, 1465, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.51 (5H, m), 7.32 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 5.23 (2H, s), 4.05 (1H, m), 3.92–3.85 (2H, m), 2.84–2.71 (2H, m), 2.03–1.89 (4H, m), 1.05 (18H, s), 0.24 (6H, s), 0.18 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.4, 137.0, 135.1, 129.7, 129.0, 128.1, 128.0, 115.1, 70.2, 69.5, 60.2, 40.5, 40.0, 31.1, 25.2, 17.7, −4.2, −5.0. ESIMS: *m/z* 487 $[M+H]^+$. Anal. Calcd for $C_{30}H_{50}O_3Si_2$: C, 70.04; H, 9.73. Found: C, 70.23; H, 9.70.

4.1.10. (*S*)-5-(4-(Benzyloxy) phenyl)-3-(*tert*-butyldimethylsilyloxy) pentan-1-ol

A solution of di-TBS compound (0.736 g, 1.431 mmol) in MeOH (5 mL) was treated with PTSA (0.013 g, 0.07 mmol) at 0 °C. After stirring for 20 min the reaction mixture was quenched with saturated aq $NaHCO_3$. The solvent was removed in vacuo and the residue was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The remaining mass was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure **11** (0.463 g, 81%) as a viscous liquid. $[\alpha]_D^{25} = -33.0$ (*c* 0.6, $CHCl_3$). IR (neat): 3444, 1613, 1510, 1459, 1243 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.53 (5H, m), 7.30 (2H, d, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 5.23 (2H, s), 4.18 (1H, m), 4.05 (1H, m), 3.94 (1H, m), 2.81–2.74 (2H, m), 2.08–1.98 (4H, m), 1.07 (9H, s), 0.29 (6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.0, 137.3, 131.7, 129.5, 128.9, 128.2, 128.0, 115.1, 71.1, 70.2, 60.0, 39.1, 38.1, 29.5, 27.0, 17.6, −4.3. ESIMS: *m/z* 400$[M+H]^+$. Anal. Calcd for $C_{24}H_{36}O_3Si$: C, 72.00; H, 9.00. Found: C, 71.87; H, 8.94.

4.1.11. (*S*)-5-(4-(Benzyloxy) phenyl)-3-(*tert*-butyldimethylsilyloxy) pentanal

To a solution of oxaloyl chloride (0.06 mL, 0.75 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C, DMSO (0.1 mL, 1.6 mmol) was added dropwise with stirring under nitrogen atmosphere. After 15 min compound **8** (0.200 g, 0.5 mmol) was added to the reaction mixture. After stirring for 0.5 h at −78 °C, Et_3N (0.3 mL) was added and the mixture was stirred for another 0.5 h at −78 °C and then for 0.5 h at 0 °C. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) at 0 °C and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The aldehyde **4** thus obtained (0.163 g, 82%) was used directly after flash column chromatography for the next reaction.

4.1.12. (*S*)-8-(4-(Benzyloxy) phenyl)-6-(*tert*-butyldimethylsilyloxy) oct-1-en-4-ol

To a solution of aldehyde 4 (0.163 g, 0.4 mmol) in dry ether (4 mL) at 0 °C allyl magnesium bromide (0.2 mL, 1.63 mmol) was added slowly with stirring under nitrogen atmosphere. After 10 min. the reaction mixture was quenched with saturated NH_4Cl (5 mL) and was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 2:8) afforded pure **12** (0.133 g, 74%) as a viscous liquid.

4.1.13. (*S*)-8-(4-(Benzyloxy) phenyl)-6-(*tert*-butyldimethylsilyloxy) oct-1-en-4-one

To a solution **12** (0.133 g, 0.3 mmol) in dry CH_2Cl_2 (3 mL) were added $NaHCO_3$ (0.05 g, 0.6 mmol) and DMP (256 mg, 0.6 mmol) at 0 °C. The reaction mixture was stirred for 30 min while warming to room temperature. A portion of aq $Na_2S_2O_3$ solution (5 mL) was added to quench the reaction and the aq layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:9) to afford pure **13** (0.116 g, 88%) as a viscous liquid. $[\alpha]_D^{25} = +1.8$ (*c* 0.6, $CHCl_3$). IR (neat): 1716, 1612, 1511, 1479, 1245 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.62–7.50 (5H, m), 7.29 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 6.05 (1H, m), 5.38–5.25 (2H, m), 5.22 (2H, s), 4.28–4.13 (2H, m), 4.06–3.95 (4H, m), 2.82–2.71 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 207.5, 157.0, 136.2, 135.0, 130.3, 129.5, 129.1, 130.7, 126.5, 119.9, 115.1, 70.2, 69.4, 49.9, 39.6, 30.0, 25.8, 19.2, −4.5. ESIMS: *m/z* 439 $[M+H]^+$. Anal. Calcd for $C_{27}H_{38}O_3Si$: C, 73.97; H, 8.68. Found: C, 73.84; H, 8.62.

4.1.14. (4*R*,6*S*)-8-(4-(Benzyloxy) phenyl)-6-(*tert*-butyldimethylsilyloxy)oct-1-en-4-ol

To a stirred solution of ketone **13** (0.116 g, 0.26 mmol) in ether (3 mL) was added LiI (0.354 g, 2.64 mmol) and the resulting mixture was stirred at −40 °C for 5 min. The mixture was cooled to −78 °C, and $LiAlH_4$ (0.100 g, 2.64 mmol) was added. The mixture was stirred for 30 min and quenched with aq 10% potassium sodium tartrate solution (5 mL). The layers were separated and the aq layer was extracted with ether (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The remaining mass was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure **3** (0.109 g, 94%) as a viscous liquid. $[\alpha]_D^{25} = -0.1$ (*c* 0.6, $CHCl_3$). IR (neat): 3456, 1611, 1511, 1461, 1245 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.22 (5H, m), 7.03 (2H, d, *J* = 8.0 Hz), 6.82 (2H, d, *J* = 8.0 Hz), 5.76 (1H, m), 5.13–5.05 (2H, m), 5.01 (2H, s), 3.94 (1H, m), 3.75 (1H, m), 2.61–2.50 (2H, m), 2.21–2.15 (2H, m), 1.87–1.72 (2H, m), 1.65–1.56 (2H, m), 0.92 (9H, s), 0.06 (6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.5, 137.9, 136.1, 134.7, 129.8, 129.0, 128.1, 127.8, 118.0, 114.9, 72.6, 70.2, 68.1, 42.9, 40.0, 31.5, 26.4, 18.1, −3.2, −4.4. ESIMS: *m/z* 441 $[M+H]^+$. Anal. Calcd for $C_{27}H_{40}O_3Si$: C, 73.64; H, 9.09. Found: C, 73.50; H, 9.01.

4.1.15. (4*R*,6*S*)-8-(4-(Benzyloxy)phenyl)-6-(*tert*-butyldimethylsilyloxy)oct-1-en-4-yl acrylate

To a stirred solution of **3** (0.050 g, 0.11 mmol) in dry CH_2Cl_2 (2 mL) were added acryloyl chloride (0.02 g, 0.22 mmol) and Et_3N

(0.057 g, 0.56 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was diluted with water (3 mL) and extracted into CH_2Cl_2 (2 × 10 mL).The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The gummy mass was purified by column chromatography (ethyl acetate/hexane, 1:9) to afford pure **2** (0.053 g, 96%) as a colourless solid. $[\alpha]_D^{25} = -2.0$ (*c* 0.25, $CHCl_3$). IR (neat): 3431, 1724, 1611, 1511, 1242 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.31 (5H, m), 7.12 (2H, d, *J* = 8.0 Hz), 6.91 (2H, d, *J* = 8.0 Hz), 6.40 (1H, m), 6.14 (1H, m), 5.89–5.68 (2H, m), 5.21–5.03 (3H, m), 5.02 (2H, s), 3.80 (1H, m), 2.70–2.51 (2H, m), 2.48–2.31 (2H, m), 1.94–1.70 (4H, m), 0.92 (9H, s), 0.04 (6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.2, 157.1, 137.4, 134.8, 133.6, 131.0, 130.7, 129.0, 128.9, 128.2, 127.8, 127.4, 118.1, 114.5, 71.4, 70.2, 69.0, 41.1, 38.9, 29.9, 26.0, 18.2, -3.8. ESIMS: *m/z* 495$[M+H]^+$. Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.87; H, 8.50. Found: C, 72.75; H, 8.43.

4.1.16. (*R*)-6-((*S*)-4-(4-(Benzyloxy)phenyl)-2-(*tert*-butyldimethylsilyloxy)butyl)-5,6-dihydro-2*H*-pyran-2-one

To a stirred solution of Grubbs' catalyst (1st generation, 5 mol %) in dry CH_2Cl_2 (1 mL) at 55 °C was added compound **2** (0.053 g, 0.10 mmol) dissolved in CH_2Cl_2 (2 mL). The resulting mixture was heated for 12 h. After completion of the reaction, the contents were cooled and the solvent was removed under reduced pressure to yield a crude product, which was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to afford pure **14** (0.042 g, 85%) as a colourless solid. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.46–7.24 (7H, m), 7.05 (1H, m), 6.84 (2H, d, *J* = 8.0 Hz), 6.02 (1H, d, *J* = 10.0 Hz), 5.04 (2H, s), 4.58 (1H, m), 4.12 (1H, m), 2.68–2.52 (2H, m), 2.38–2.29 (2H, m), 1.96–1.61 (4H, m), 0.86 (9H, s), 0.05 (6H, s). ESIMS: *m/z* 467$[M+H]^+$. Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.10; H, 8.16. Found: C, 72.28; H, 8.11.

4.1.17. (*R*)-6-((*S*)-2-Hydroxy-4-(4-hydroxyphenyl) butyl)-5,6-dihydro-2*H*-pyran-2-one

To a stirred solution of **14** (0.042 g, 0.09 mmol) in dry CH_2Cl_2 (2 mL) under a N_2 atmosphere at 0 °C $TiCl_4$ (0.02 mL, 0.19 mmol,) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aq $NaHCO_3$ solution (5 mL) and then extracted with $CHCl_3$ (2 × 5 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. The mixture was concentrated and the crude residue was purified by column chromatography (ethyl acetate/hexane, 3:7) to afford pure **1** (0.021 g, 89%) as a colourless solid. $[\alpha]_D^{25} = +39.3$ (*c* 0.35, $CHCl_3$) {lit.[2] $[\alpha]_D^{25} = +40.2$ (*c* 0.4, $CHCl_3$)}, IR (neat): 3417, 1700, 1513, 1454, 1258 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.01 (2H, d, *J* = 8.0 Hz), 6.82 (1H, m), 6.70 (2H, d, *J* = 8.0 Hz), 5.95 (1H, d, *J* = 10.0 Hz), 4.84 (1H, br s), 4.61 (1H, m), 3.99 (1H, m), 3.82 (1H, br s), 2.71–2.51 (2H, m), 2.37–2.22 (2H, m), 2.00–1.66 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.8, 154.6, 145.2, 145.0, 133.6, 129.5, 129.2, 129.0, 120.5, 115.0, 75.2, 66.1, 42.4, 39.6, 36.2, 30.5. HRMS: *m/z* 285.1111 $[M+Na]^+$ (Calcd for $C_{15}H_{18}O_4Na$: 285.1102).

4.1.18. (3*S*,5*R*)-1-(4-(Benzyloxy) phenyl) oct-7-ene-3,5-diol

To a stirred solution of **3** (0.050 g, 0.11 mmol) in dry THF (2 mL) at 0 °C, TBAF (0.03 mL, 0.1 mmol, 1 M in THF solution) was added with stirring under a N_2 atmosphere. After 2 h the reaction mixture was quenched with saturated ammonium chloride solution (3 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 3:7) afforded pure (3*S*,5*R*)-1-(4-(benzyloxy) phenyl)oct-7-ene-3,5-diol (0.035 g, 95%) as a viscous liquid which was used directly for the acetonide protection reaction.

4.1.19. (4*R*,6*S*)-4-Allyl-6-(4-(benzyloxy)phenethyl)-2,2-dimethyl-1,3-dioxane

To a stirred solution of (3*S*,5*R*)-1-(4-(benzyloxy) phenyl)oct-7-ene-3,5-diol (0.035 g, 0.1 mmol) in dry DCM (2 mL) 2,2-dimethoxy propane (0.02 mL, 0.12 mmol) was added at 0 °C. Then CSA (0.01 mmol) was added with stirring under a N_2 atmosphere. After stirring for further 2 h, the reaction mixture was quenched with saturated aq $NaHCO_3$ solution (3 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with water and brine dried over Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:9) to afford pure **A** (0.034 g, 89%) as a yellow solid. $[\alpha]_D^{25} = -7.1$ (*c* 0.15, $CHCl_3$) IR (neat): 1611, 1510, 1379, 1238 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.43–7.21 (5H, m), 7.02 (2H, d, *J* = 8.0 Hz), 6.82 (2H, d, *J* = 8.0 Hz), 5.74 (1H, m), 5.06 (2H, m), 5.02 (2H, s), 3.82–3.63 (2H, m), 2.71–2.52 (2H, m), 2.25 (1H, m), 2.11(1H, m), 1.75 (1H, m), 1.60 (1H, m), 1.48–1.28 (2H, m), 1.32 (6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.2, 137.2, 134.5, 134.2, 129.5, 128.6, 127.8, 127.2, 117.1, 114.5, 98.8, 70.1, 68.9, 67.5, 40.8, 38.2, 36.2, 30.1, 30.0, 20.0. HRMS: *m/z* 367.2285 $[M+H]^+$ (Calcd for $C_{24}H_{31}O_3$: 367.2273).

Acknowledgements

The authors thank CSIR and UGC, New Delhi for financial assistance.

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