Tetrahedron: *Asymmetry* 23 (2012) 1155–1160

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Stereoselective total synthesis of decarestrictine O

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ARTICLE INFO

Article history:
Received 28 May 2012
Accepted 29 June 2012

ABSTRACT

The stereoselective total synthesis of decarestrictine O, a polyketide natural product is described. The synthesis involves MacMillan α-hydroxylation, C_1-Wittig olefination, hydrolytic kinetic resolution and ring closing metathesis (RCM) as key steps. Improved efficiency was achieved by using the DIBAL mediated reductive transformation of trans-dimethyl L-tartrate acetonide into ε-hydroxy α,β-unsaturated ester in a single step.

1. Introduction

Decarestrictines are secondary metabolites,[1] belonging to the family of decanolides which are one of the most important classes of compounds due to their cholesterol inhibiting properties as described in cell line tests with HEP-G2 liver cells.[2] These properties are very important in treating coronary diseases, which have high prevalence all over the world and more importantly in India where the risk of these diseases is high due to genetic factors and higher fat food habits. Decarestrictines are ten membered lactones, which are isolated from various penicillium strains.[3] A common polyketide precursor of decanolides undergoes structural modifications leading to different members of the decarestrictine family. Fig. 1 depicts decarestrictine F, and decarestrictines A_1, A_2, D, N and O,[4,5] which can be isolated via fermentation of decarestrictine F at pH 1–2.5.

As part of an ongoing research programme aimed at developing the enantioselective synthesis of biologically active natural products, certain expertise is required in using different sequences of reactions such as MacMillan α-hydroxylations, hydrolytic kinetic resolutions, ring closing metathesis and so on. During these studies, our investigations into the stereoselective total synthesis of decarestrictine O **4** have become important due to its significant biological activity. However, only one synthetic approach has been

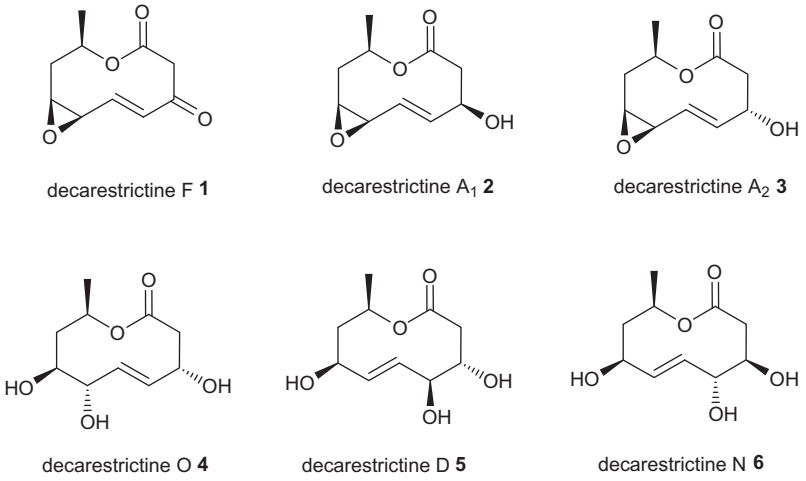

Figure 1.

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http://dx.doi.org/10.1016/j.tetasy.2012.06.027

reported so far for decarestrictine O,[6] which is a tedious and multistep (24 steps) synthesis. Herein, a successful, more concise synthetic route (19 steps) for decarestrictine O is reported employing MacMillan α-hydroxylation C_1-Wittig olefination, hydrolytic kinetic resolution and RCM as the key steps.

2. Results and discussion

Retrosynthetic analysis (Fig. 2) suggested that the target molecule **4** could be obtained from **21** via ring closing metathesis. Compound **21** could in turn be obtained via esterification of compound **15** with relevant acid **20**. Alcohol fragment **15** could be obtained from dimethyl L-tartrate **7** by using Macmillan α-hydroxylation and C_1-Wittig olefination reactions. Acid fragment **20** could be synthesized from 1-butenol by means of Jacobsen's hydrolytic kinetic resolution and opening of the corresponding epoxide with trimethylsulfoniumiodide.

The synthesis started with compound **7**, to make ε-hydroxy α,β-unsaturated ester **9,** which was synthesized from *trans*-dimethyl L-tartrate acetonide **8** in a single step as shown in Scheme 1, while eliminating an existing much longer process.[7] Compound **9** upon hydrogenation with Pd/C afforded compound **10**. Oxidation of alcohol **10** with IBX in a DMSO/CH_2Cl_2 system yielded the corresponding aldehyde which by C_1-Wittig olefination afforded ester **11** in 57% yield. The DIBAL-H reduction of ester **11** gave the corresponding alcohol **12** in 93% yield. Alcohol **12** upon oxidation with IBX in a DMSO/CH_2Cl_2 system yielded the corresponding aldehyde, which was subjected to the MacMillan α-hydroxylation using nitrosobenzene and 40 mol % of D-Proline in DMSO, followed by reduction with sodium borohydride to furnish the unstable anilinoxy compound, which was further treated with 30 mol % of $CuSO_4{\cdot}5H_2O$ in methanol at rt to cleave the O–N bond to provide diol **13** in 47% yield.[8] Selective protection of the primary hydroxyl group of diol **13** with tosyl chloride, triethylamine and a catalytic amount of dibutyl tinoxide has afforded the tosylate compound **14** in 80% yield. Tosylated compound **14** was then $LiAlH_4$ reduced with LAH in dry THF under reflux conditions to afford alcohol **15** in 79% yield.[9]

Following the steps shown in Scheme 2, the synthesis of acid fragment **20** was achieved by Jacobsen's hydrolytic kinetic resolu-

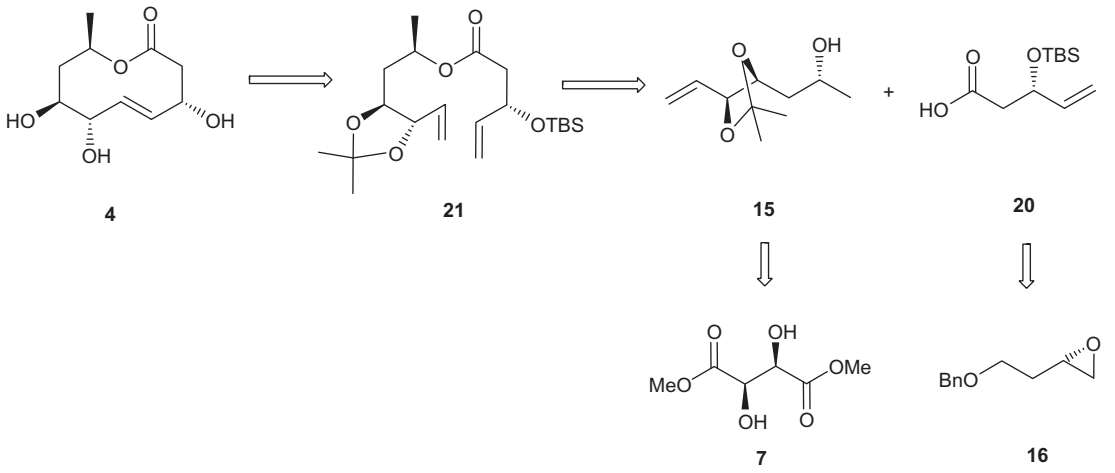
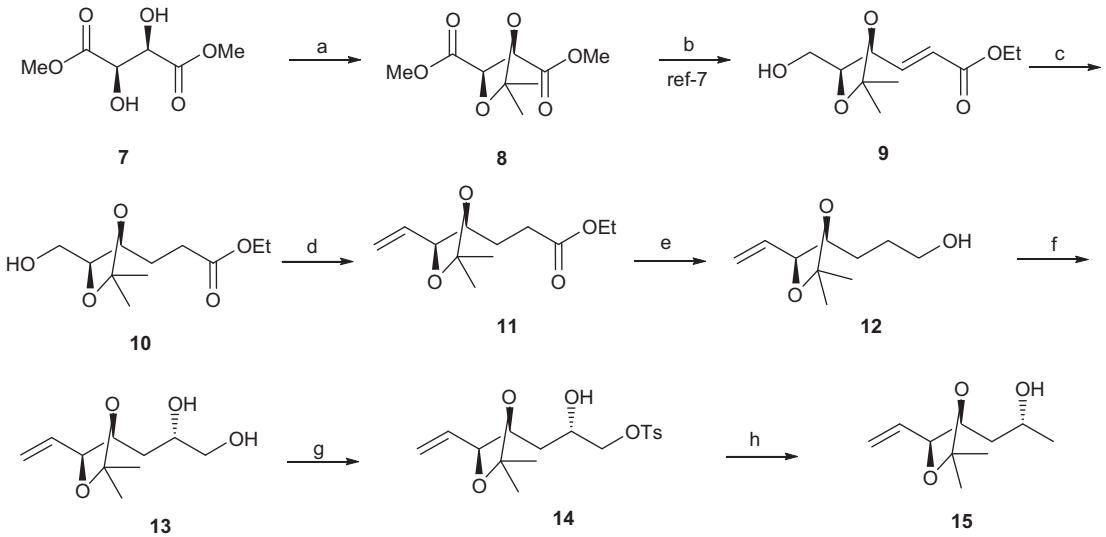


Figure 2.



Scheme 1. Reagents and conditions: (a) 2,2-DMP, cat. PTSA, benzene, reflux, 2 h; (b) DIBAL-H, $[(EtO)_2P(O)CHCO_2Et]^-Na^+$, −78 °C to rt; (c) H_2, Pd/C, EtOAc, 3 h; (d) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h; (ii) Ph_3PCH_2, *t*BuOK, THF, −10 °C to rt, 2 h; (e) DIBAL-H, −78 °C to rt, 1 h; (f) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h; (ii) PhNO, D-proline, DMSO, $NaBH_4$, MeOH, $CuSO_4.5H_2O$ −20 °C to rt over two steps; (g) TsCl, Et_3N, Dibutyl tin oxide (cat), dry CH_2Cl_2, 0 °C to rt, 12 h; (h) $LiAlH_4$, THF, reflux, 3 h.

tion of racemic epoxide **16** using the (*R*,*R*)-catalyst to give chiral epoxide (*S*)-**16**. Epoxide **16** was treated with trimethylsulfonium iodide in the presence of *n*-BuLi as a base in dry THF at −20 °C to provide allyl alcohol **17** in 87% yield.[10] The allylic alcohol was subsequently protected as the *tert*-butyldimethylsillyl ether with TBSCl and imidazole to afford compound **18** in 81% yield. Deprotection of the benzyl ether was achieved by using Li/naphthalene in dry THF at −20 °C to yield the corresponding alcohol **19**. The resulting alcohol was oxidized to the aldehyde with IBX in a dry DMSO/CH_2Cl_2 system, which upon oxidation with $NaClO_2$, NaH_2PO_4 and 2-methyl 2-Butene in *t*-BuOH/H_2O afforded the acid fragment **20** in 89% yield.[11]

With both the alcohol and acid fragments in hand, the coupling of these two fragments was successfully achieved by following the steps in Scheme 3. Thus, esterification of the free OH group of **15** with acid **20** in the presence of DCC and DMAP gave the diene ester **21** in 72% yield. The diene ester was then cyclized by ring closing metathesis.[12] The diene upon treatment with 5 mol % Grubbs II catalyst under high dilution condition (0.001 M in CH_2Cl_2), afforded the cyclic ester **22** in 60% yield. Deprotection of the TBS ether and acetonide group by using PTSA in methanol afforded the target molecule Decarestrictine O **4** in 65% yield. The physical data of the synthesized compound **4** are in full agreement with the reported data in the literature.[4,6]

3. Conclusion

In conclusion, the stereoselective total synthesis of Decarestrictine O has been achieved in 19 steps. The Macmillan α-hydroxylation, C_1-Wittig olefination, hydrolytic kinetic resolution and ring closing metathesis (RCM) are the key steps used in this endeavour.

4. Experimental

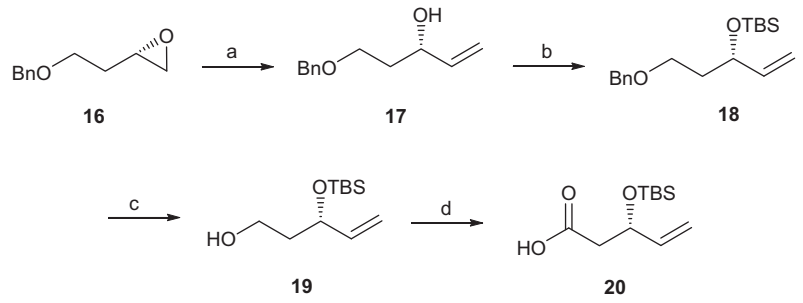
4.1. General

All reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, EtOAc and Et_2O. Preparative chromatographic separations were performed on silica gel (35–75 μm); reactions were monitored by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with a UV lamp, anisaldehyde or β-naphthol solution or alkaline $KMnO_4$ solution. All commercially available reagents were purchased and typically used as supplied.

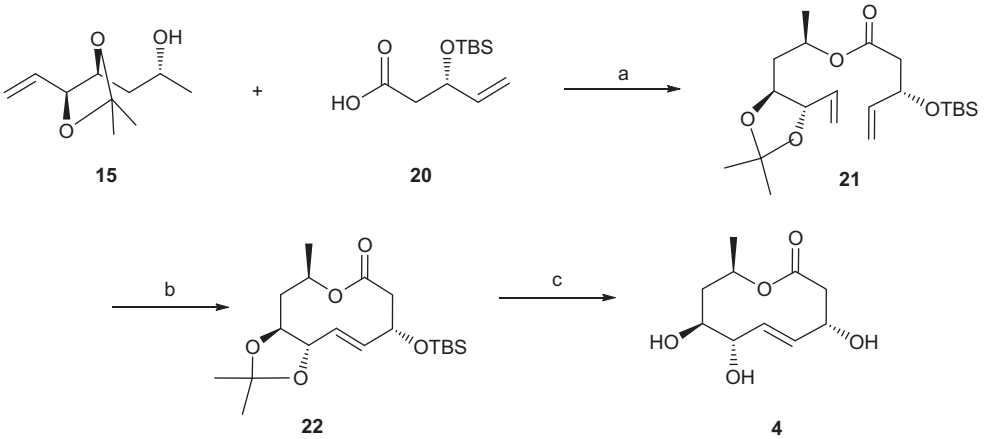
Optical rotations were measured at an ambient temperature (25 °C) on $CHCl_3$ solutions with a polarimeter using a 2 ml capacity cell with 100 mm path length. Infrared spectra were recorded using a thin film supported between NaCl plates or as a solid embedded in a KBr disc. ^1H and ^{13}C NMR spectra are recorded in a Fourier transform mode at the field strength specified either on a Bruker UXNMR FT-300 MHz (avance) or a Varian VXR-unity-400 MHz spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes; Chemical shifts in ppm are quoted relative to the residual signals of chloroform (δH 7.25 ppm or δC 77.0 ppm). Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in Hz. For low (MS) and high (HRMS) resolution mass spectra ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units.

4.1.1. (*E*)-Ethyl 3-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylate 9

To *trans*-dimethyl tartrate acetonide **8** (15 g, 68 mmol) in dry toluene (100 mL) was added DIBAL-H (80 mL, 1.7 M solution in



Scheme 2. Reagents and conditions: (a) $Me_3S^+I^-$, *n*-BuLi, THF, −20 °C, 3 h; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 81%; (c) Li/naphthalene, dry THF, −20 °C, 3 h, (d) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 6 h.



Scheme 3. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt; (b) Grubb's II catalyst, CH_2Cl_2, reflux, 16 h; (c) PTSA, MeOH, 0 °C to rt, 2 h.

toluene, 137 mmol) slowly at 0 °C via cannula. The reaction mixture was stirred for 1 h at 0 °C, then cooled to −78 °C and another 1 equiv of DIBAL (40 mL, 68 mmol) was slowly added, and stirred for 30 min. Next Horner–Emmons reagent was added, which was separately prepared from triethylphosphonoacetate (23.4 g, 104 mmol) and NaH (2.5 g, 104 mmol) in dry toluene The reaction mixture was left overnight (−78 °C to rt) and then quenched with a saturated sodium potassium tartrate solution. The reaction mixture was then stirred for 2 h and diluted with water (100 mL). The aqueous layer was extracted with ether. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The compound was purified by column chromatography to afford **9** (6.8 g, 42.5% yield) as a pale yellow liquid. R_f = 0.4 (silica gel, 60–120 mesh, 20% Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, J = 6.2 Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 2.52 (br s, OH), 3.33–3.51 (m, 1H), 3.58–3.67 (m, 2H), 4.13–4.18 (m, 2H), 4.39–4.47 (m, 1H), 5.64–6.01(m, 1H), 6.62–6.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 26.6, 27.1, 61.4, 62.3, 78.6, 81.0, 139.4, 166.7; IR (neat): υ 3453, 2985, 2933, 1727, 1375, 1040 cm^{-1}; $[\alpha]_D^{25} = -8.13$ (c 1.5, $CHCl_3$); ESI-MS: m/z: 253 [M+Na]$^+$.

4.1.2. Ethyl 3-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxan-4-yl) propanoate 10

To a stirred solution of compound **9** (7 g, 30.4 mmol) in EtOAc, was added 10% Pd/C (catalytic) and stirred under a hydrogen atmosphere for 3 h. Next, the reaction mixture was filtered through a small Celite pad and concentrated in vacuo. The compound was purified by flash column chromatography to afford the corresponding ester **10** (6.4 g, 92% yield) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, 3H, J = 6.98 Hz), 1.37 (s, 3H), 1.38 (s, 3H), 1.75–2.0 (m, 2H), 2.25 (br s, OH), 2.36–2.56 (m, 2H), 3.37–3.64 (m, 1H), 3.70–3.80 (m, 2H), 3.84–3.92 (m, 1H), 4.08–4.15 (q, 2H, J = 7.17 Hz, 14.35 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.11, 26.92, 27.18, 27.91, 30.56, 60.43, 61.86, 76.13, 80.98, 108.82, 173.20; IR (neat): υ 3453, 2985, 2933, 1731, 1375, 1219, 1166, 1070, 1040 cm^{-1}; $[\alpha]_D^{25} = +20.3$ (c 1.26, $CHCl_3$); ESI-MS: m/z: 233 (M+H), 250 (M+NH_4)

4.1.3. Ethyl 3-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-propanoate 11

To a stirred solution of IBX (10.86 g, 38 mmol) dissolved in DMSO (20 mL) was added compound **10** (6 g, 25.86 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After complete conversion, the reaction mixture was filtered through a Celite pad, washed with water, extracted with ether, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash column chromatography to afford the corresponding aldehyde.

To a stirred solution of Methyltriphenylphosponium iodide in dry THF was added potassium *tert*-butoxide at 0 °C. The mixture was then stirred for 30 min at the same temperature. Next was added the aldehyde (4 g, 17.4 mmol) dissolved in dry THF and the reaction mixture was stirred for 1 h at rt. After completion of reaction, a small amount of water was added and the compound was extracted with EtOAc, dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography to afford compound **11** (2.15 g, 57%) as a light yellow liquid. R_f = 0.7 (silicagel, 60–120 mesh, 30% Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (t, J = 7.55, 6.79 Hz, 3H), 1.37 (s, 6H), 1.75–1.99 (m, 2H), 2.35–2.54 (m, 2H), 3.64–3.71 (m, 1H), 3.96–4.01 (m, 1H), 4.07–4.14 (q, J = 6.79 Hz, 7.55 Hz, 2H), 5.22–5.38 (m, 2H), 5.72–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.08, 26.67, 26.82, 27.08, 30.54, 60.30, 79.42, 82.30, 108.68, 119.07, 134.92, 173.03; IR (neat): υ 3452, 2985, 2927, 1773, 1735, 1180 cm^{-1}; $[\alpha]_D^{25} = +18.75$ (c 0.8, $CHCl_3$); ESI-MS: m/z: 229 [M+H].

4.1.4. 3-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-1-ol 12

To a stirred solution of compound **11** (2 g, 18.5 mmol) in dry CH_2Cl_2 was added DIBAL-H (13.6 mL, 1.7 M, 23 mmol) dropwise at 0 °C. The mixture was then stirred for 1 h at room temperature. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with a saturated sodium potassium tartrate solution. The reaction mixture then became viscous, and was diluted with CH_2Cl_2 (20 mL), and stirred for 3 h. The two layers were separated, and the aqueous layer was washed with CH_2Cl_2 twice. The organic layer was dried over Na_2SO_4, the solvent was evaporated and the product purified by column chromatography to afford **12** (1.6 g, 93%) as a pale yellow liquid. R_f = 0.2 (silica gel, 60–120 mesh, 30% Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (d, J = 1.51 Hz, 6H), 1.53–1.75 (m, 4H), 3.65–3.71 (m, 3H), 3.96–4.01 (m, 1H), 5.25–5.38 (m, 2H), 5.78–5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.91, 27.21, 28.38, 29.43, 62.60, 80.55, 80.73, 108.71, 119.08, 135.05; IR (neat): υ 3419, 2986,2928, 1374, 1224,1050 cm^{-1}; $[\alpha]_D^{25} = -16.2$ (c 0.4, $CHCl_3$); ESI-MS: m/z 209 [M+Na]$^+$.

4.1.5. (*S*)-3-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxan-4-yl) propane-1,2-diol 13

To a stirred solution of IBX (3.16 g, 11.29 mmol) dissolved in DMSO (6 mL) was added compound **12** (1.4 g, 7.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After complete conversion, the reaction mixture was filtered through a Celite pad, washed with water and extracted with ether, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash column chromatography to afford the corresponding aldehyde.

Next, D-proline (0.187 g, 1.63 mmol) was dissolved in DMSO (10 mL), and the suspension stirred at room temperature for 10 min. Nitrosobenzene (0.581 g, 5.43 mmol) was then added in one portion at room temperature, turning the solution green. The reaction mixture was cooled to −20 °C, then the aldehyde (1 g, 5.43 mmol) dissolved in DMSO was added. The reaction mixture was stirred for 2 h, then sodium borohydride and methanol were added at 0 °C, the reaction mixture was stirred for 1 h, after which was added $CuSO_4{\cdot}2H_2O$ (0.405 g, 1.63 mmol). The reaction mixture was then stirred overnight at rt. The reaction mixture was filtered through a small Celite pad and concentrated in vacuo. The compound was purified by column chromatography to afford **13** (0.52 g, 47%) as a brown liquid. R_f = 0.3 (silicagel, 60–120 mesh, 60%, Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41(s, 6H), 1.56–1.65 (m, 1H), 1.78–1.86 (m, 1H), 3.49–3.55 (m, 1H), 3.65–3.70 (m, 1H), 3.86–4.07 (m, 3H), 5.25–5.39 (m, 2H), 5.73–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.59, 35.39, 66.0, 68.2, 70.17, 75.16, 115.26, 137.43; IR (neat): υ 3388, 2925, 2855, 1658, 1037 cm^{-1}; $[\alpha]_D^{25} = -2.5$ (c 0.2, $CHCl_3$); ESI-MS: m/z 225 [M+Na]$^+$.

4.1.6. (*S*)-3-(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxypropyl4-methyl benzenesulfonate 14

To a stirred solution of compound **13** (0.5 g, 2.47 mmol) in dry CH_2Cl_2 was added Et_3N (0.7 mL), and a catalytic amount of dibutyltin oxide. The reaction mixture was stirred for 15 min, then cooled to 0 °C, after which was added *para*-toluene sulfonyl chloride (0.564 g, 2.97 mmol). The reaction mixture was then stirred overnight. After completion of the reaction, a few mL of water was added and the compound extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated and the residue purified by column chromatography to afford **14** (0.71 g, 80%) as a pale yellow liquid. R_f = 0.2 (silicagel, 60–120 mesh, 30% Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 6H), 1.48–1.57 (m, 2H), 2.34 (s, 3H), 3.32–3.47 (m, 1H), 3.83–3.99 (m, 3H), 4.57 (m, 1H), 5.12–5.26 (m, 1H), 5.47–5.89 (m, 2H), 7.46 (m, 2H), 7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.29, 21.57, 30.83, 37.0, 66.97, 71.82,

74.72, 80.69, 117.20, 127.92, 129.18, 129.87, 138.75, 141.96; IR (neat): υ 3365, 2924, 2851, 1723, 1601, 1174 cm^{-1}; $[\alpha]_D^{25} = -65.3$ (*c* 0.4, $CHCl_3$); ESI-MS: *m*/*z* 379 $[M+Na]^+$.

4.1.7. (*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-2-ol 15

At first, $LiAlH_4$ was taken in dry THF at 0 °C, after which was added to a solution of compound **14** (0.7 g, 2 mmol) dissolved in THF at 0 °C. The reaction mixture was heated at reflux for 3 h, and then the reaction was quenched with water and 5 M NaOH solution. The reaction mixture was then filtered through a Celite pad. The solvent was evaporated in vacuo. The compound was purified by column chromatography to afford alcohol **15** (0.29 g, 80% yield) as a pale yellow liquid. R_f = 0.5 (silicagel, 60–120 mesh, 30% Hexane/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (s, 6H), 1.36 (d, *J* = 3.77 Hz, 3H), 1.56–1.71 (m, 2H), 3.83–4.06 (m, 3H), 5.17–5.33 (m, 2H), 5.67–5.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.54, 26.87, 27.21, 39.19, 65.11, 77.79, 82.27, 108.90, 119.23, 134.73; IR (neat): υ 3404, 2961, 2925, 1726, 1376, 1243 cm^{-1}; $[\alpha]_D^{25} = -12.25$ (*c* 0.4, $CHCl_3$); ESI-MS: *m*/*z* 209 $[M+Na]^+$.

4.1.8. (*S*)-2-(2-(Benzyloxy)ethyl)oxirane 16

The racemic epoxide of **16** (10 g, 56 mmol) and THF (0.5 mL) were added to (*R*,*R*)-Salen-CoIII catalyst (0.17 g, 0.28 mmol) and the solution was cooled to 0 °C. Then acetic acid (0.1 mL, 1.12 mmol) was added and after 5 min, water (0.5 mL, 30.8 mmol) was added. After another 5 min, the ice bath was removed and the reaction mixture was stirred at rt for 24 h. The reaction mixture was then concentrated in vacuo. The compound was purified by column chromatography to afford epoxide (*S*)-**16** (4.8 g) as a pale yellow liquid. R_f = 0.8 (silicagel, 60–120 mesh, 60% Hexane/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.67–1.78 (m, 1H), 1.82–1.93 (m, 1H), 2.45–2.47 (m, 1H), 2.71–2.74 (m, 1H), 2.98–3.04 (m, 1H), 3.55–3.60 (m, 2H), 4.49 (s, 1H), 7.21–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 32.99, 47.13, 50.09, 67.05, 73.10, 127.65, 128.44, 138.30; IR (neat): υ 2922, 2854, 772 cm^{-1}; $[\alpha]_D^{25} = +19.2$ (*c* 0.7, $CHCl_3$); ESI-MS: *m*/*z*: 179 [M+H].

4.1.9. (*S*)-5-(Benzyloxy)pent-1-en-3-ol 17

To a stirred solution of dry THF was added trimethylsulfoniumiodide (22.9 g, 112.35 mmol) at −20 °C. The reaction mixture was stirred for 20 min followed by the addition of *n*-BuLi (52 mL, 1.6 M, 84.26 mmol). After 40 min, epoxide **16** (5 g, 28 mmol) in THF was added dropwise. The reaction mixture was stirred at −20 °C for 3 h. The reaction mixture was quenched with a saturated solution of NH_4Cl. The two phases were separated and the aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue purified by column chromatography to afford pure allylic alcohol **17** (4.72 g, 87%) as a pale yellow liquid. R_f = 0.4 (silicagel, 60–120 mesh, 30% Hexane/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.68–1.75 (m, 2H), 2.70 (br s, OH), 3.56–3.75 (m, 2H), 3.78–3.86 (m, 1H), 4.5 (s, 2H), 5.03–5.10 (m, 2H), 5.73–5.86 (m, 1H), 7.21–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): 35.78, 68.75, 70.13, 73.16, 117.42, 127.54, 127.60, 128.33, 134.77, 137.85; IR (neat): υ 3425, 3067, 3030, 2922, 2855, 1640, 1363, 1093 cm^{-1}; $[\alpha]_D^{25} = -2.1$ (*c* 0.6, $CHCl_3$); ESI-MS: *m*/*z*: 215 $[M+Na]^+$.

4.1.10. (*S*)-(5-(Benzyloxy)pent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane 18

To a solution of **17** (3 g, 15.62 mmol) in dry CH_2Cl_2 (30 mL) were added a catalytic amount of DMAP (15 mg) and imidazole (3.18 g, 46.7 mmol) in one portion followed by TBSCl (3.5 g, 23.43 mmol) in one portion at 0 °C. The resulting mixture was then stirred for 4 h at rt. After completion of the reaction, the mixture was quenched by the addition of water (15 mL), diluted with CH_2Cl_2 (3 x 20 mL), washed with brine and dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the crude compound by column chromatography afforded TBS ether **18** (3.9 g, 81%) as a colourless oil. R_f = 0.8 (Silicagel, 60–120 mesh, 30% Hexane/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04 (s, 3H). 0.05 (s, 3H), 0.89 (s, 9H), 1.75–1.81 (m, 2H), 3.47–3.61 (m, 2H), 4.27–4.33 (m, 1H), 4.42–4.53 (m, 2H), 4.99–5.17 (m, 2H), 5.75–5.86 (m, 1H), 7.33-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.0, −4.39, 18.18, 25.83, 38.08, 66.67, 70.72, 72.96, 113.69, 127.48, 127.65, 128.29, 138.47, 141.56; IR (neat): υ 3068, 3032, 2954, 2930, 1725, 1644, 1464, 1254, 1092 cm^{-1}; $[\alpha]_D^{25} = 6.4$ (*c* 0.4, $CHCl_3$); ESI-MS: *m*/*z*: 329 $[M+Na]^+$.

4.1.11. (*S*)-3-(tert-butyldimethylsilyloxy)pent-4-en-1-ol 19

To a stirred solution of naphthalene powder (14.64 g, 114.3 mmol) in dry THF (50 mL) was added lithium metal (0.4 g, 57.7 mmol). The mixture was stirred for 3 h at room temperature then cooled to −20 °C and compound **18** (3.5 g, 11.43 mmol) in dry THF (10 mL) was added. After stirring for 2 h at −20 °C, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with ether (3 × 30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was evaporated, and the product purified by column chromatography to afford the corresponding alcohol **19** (2.1 g, 85.6%) as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.66–1.91(m, 2H), 3.67–3.86 (m, 2H), 4.39–4.45 (m, 1H), 5.08–5.25 (m, 2H), 5.79–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): −5.07, −4.42, 18.09, 25.79, 39.13, 60.06, 73.16, 114.36, 140.61; IR (neat): υ 3355, 2925, 2856, 1735, 1453, 1055 cm^{-1}; $[\alpha]_D^{25} = +4.7$ (*c* 0.6, $CHCl_3$); ESI-MS: *m*/*z*: 239 $[M+Na]^+$.

4.1.12. 3-(*tert*-Butyldimethyl silyloxy)pent-4-enoic acid 20

To a stirred solution of IBX (8.28 g, 29.58 mmol) in DMSO (30 mL) was added compound **19** (2.13 g, 9.86 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After complete conversion, the reaction mixture was filtered through a Celite pad, washed with water (30 mL), extracted with ether (3 × 40 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash column chromatography to afford the corresponding aldehyde.

To a stirred solution of the aldehyde (1.0 g, 4.6 mmol) in *t*-BuOH (10 mL) were added solutions of 2-methyl-2-butene (10 mL), $NaClO_2$ (0.63 g, 7 mmol) and NaH_2PO_4 (0.84 g, 7 mmol) in water (5 mL) and stirred over 6 h at room temperature. The solvent was removed under reduced pressure and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography to afford acid **20** (0.89 g, 89%) as a light yellow liquid. R_f = 0.2 (Silicagel, 60–120 mesh, 30% Hexane/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 2.55 (d, *J* = 6.79 Hz. 2H), 4.54–4.60 (m, 1H), 5.09–5.28 (m, 2H), 5.79–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.23, −4.48, 14.08, 29.64, 42.94, 70.54, 115.32, 139.32, 172.45; IR (neat): υ 2925, 2855, 1714, 1464, 835 cm^{-1}; $[\alpha]_D^{25} = +2.1$ (*c* 0.4, $CHCl_3$); ESI-MS: *m*/*z*: 253 $[M+Na]^+$.

4.1.13. (*S*)-((*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4yl)propan-2-yl)-3-(*tert*-butyl dimethyl silyloxy) pent-4-enoate 21

To a stirred solution of alcohol **15** (0.2 g, 1.07 mmol) in CH_2Cl_2 (10 mL) were added DCC (0.44 g, 2.15 mmol) and DMAP (0.26 g, 2.15 mmol) at 0 °C followed by compound **20** (0.29 g, 1.3 mmol). The reaction mixture was then stirred at room temperature for 2–3 h. After completion of reaction, the mixture was filtered through a Celite pad with ether and the resulting filtrate was evaporated in vacuo. The crude residue was purified by column chromatography to afford diene ester **21** (0.31 g, 72%) as a colourless

oil. R_f = 0.7 (SiO_2, 60–120 mesh, 30% Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.26 (d, J = 6.79 Hz, 6H), 1.38 (d, J = 5.28 Hz, 3H), 1.60–1.71 (m, 1H), 1.80–1.89 (m, 1H), 2.37–2.55 (m, 2H), 3.66–3.78 (m, 1H), 3.92–3.97 (m, 1H), 4.52–4.57 (m, 1H), 4.98–5.04 (m, 2H), 5.18–5.39 (m, 3H), 5.72–5.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.94, −4.45, 18.11, 20.62, 25.80, 26.92, 27.25, 38.43, 43.83, 68.92, 70.65, 77.23, 82.81, 108.91, 114.62, 119.19, 134.85, 140.21, 170.32; IR (neat): υ 3083, 2929, 2857, 1737, 1646, 1463, 1373, 1250 cm^{-1}; $[\alpha]_D^{25} = -5.25$ (c 0.4, $CHCl_3$); ESI-MS: m/z: 399 [M+H].

4.1.14. (3*S*,5*R*,9*S*,11*S*,*E*)-9-(*tert*-Butyl dimethyl silyloxy)-2,2,5-trimethyl-4,5,8,9-tetrahydro-3-(1,3)dioxolo(4,5)oxecin-7-one 22

Grubbs' II catalyst (0.88 mg, 5 mol %) was dissolved in CH_2Cl_2 (10 mL) and then added dropwise to a solution of the ester **21** (0.25 g, 0.628 mmol) in 700 mL of CH_2Cl_2. The reaction mixture was stirred at reflux at 45 °C for 12 h by which time all the starting material were consumed (TLC). The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography to afford compound **22** (0.14 g, 65%) as a colourless oil. R_f = 0.2 (Silicagel, 60–120 mesh, 10% Hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.92 (s, 9H), 1.21 (d, J = 6.23 Hz, 3H), 1.40 (s, 6H), 1.87–2.04 (m, 2H), 2.45 (d, J = 3.58 Hz, 2H), 3.58–3.65 (m, 1H), 4.06–4.12 (m, 1H), 4.66–4.68 (m, 1H), 4.93–5.0 (m, 1H), 5.59–5.68 (m, 1H), 5.88–5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.16, −4.95, 18.27, 21.80, 25.76, 26.97, 29.68, 38.56, 45.24, 67.93, 68.99, 81.62, 84.14, 107.89, 122.89, 138.09, 168.35; IR (neat): υ 2929, 2857, 1737, 1162, 1078 cm^{-1}; $[\alpha]_D^{25} = -8.1$ (c 0.4, $CHCl_3$); ESI-MS: m/z: 371 [M+H].

4.1.15. (4*S*,7*S*,8*S*,10*R*,*E*)-4,7,8-Trihydroxy-10-methyl-3,4,7,8,9,10-hexahydrooxecin-2-one 4

To a stirred solution of compound **22** (0.1 g, 0.27 mmol) in methanol (10 mL) was added a catalytic amount of *para*-toluenesulfonic acid at 0 °C. The reaction mixture was then stirred for 2 h at rt. After completion of the reaction, it was quenched with $NaHCO_3$ salt. The solvent was evaporated in vacuo, and the compound was purified by column chromatography to afford compound **4** (0.032 g, 65%) as a pale yellow liquid. R_f = 0.2 (silicagel, 60–120 mesh, 60% Hexane/EtOAc); ^{1}H NMR (500 MHz, acetone-d6): δ 1.28 (d, J = 6.7 Hz, 3H), 1.30 (m, 1H), 1.34–1.38 (dd, J = 3.2 Hz, 15.6 Hz, 1H), 2.24–2.30 (m, 1H), 2.89 (dd, J = 7.9 Hz, 13.3 Hz, 1H), 3.38–3.43 (m, 1H), 4.03 (br s, OH), 4.24 (m, 1H), 4.45 (m, 1H), 4.56 (br s, OH), 5.02 (m, 1H), 5.41 (dd, J = 8.1 Hz, 16.1 Hz, 1H), 5.54 (dd, J = 7.1 Hz, 16.3 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 21.18, 39.62, 45.18, 71.46, 73.2, 74.0, 76.88, 131.12, 135.7, 170.63; IR (neat): υ 3399, 2924, 1717, 1459 cm^{-1}; $[\alpha]_D^{25} = -19.6$ (c 0.20, CH_3OH); ESI-MS: m/z: 239 $[M+Na]^+$; HRMS m/z $[M+Na]^+$ found 239.0889; calculated 239.0895 for $C_{10}H_{16}O_5Na$.

Acknowledgements

K.A.L., N.M.R. and N.S. thank UGC and CSIR New Delhi respectively for award of research fellowships.

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