Tetrahedron: *Asymmetry* 23 (2012) 117–123

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Stereoselective total synthesis of clonostachydiol

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ARTICLE INFO

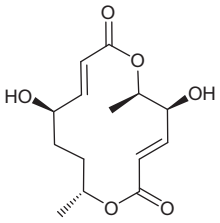
Article history:
Received 1 December 2011
Accepted 20 January 2012
Available online 17 February 2012

ABSTRACT

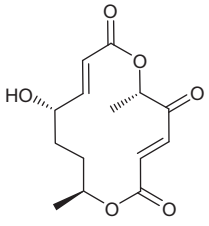
A simple and efficient stereoselective synthesis of clonostachydiol was achieved using ethyl (*R*)-3-hydroxybutanoate **5** and methyl (*R*)-2-hydroxypropanoate **12** as readily available starting materials. The key steps involved in the synthesis were MacMillan α-hydroxylation, Horner–Wadsworth–Emmons (HWE) olefination, a Grignard reaction, and Hoveyda–Grubbs IInd generation catalyzed ring closing metathesis (RCM).

1. Introduction

Naturally occurring macrodiolides have continued to attract synthetic chemists as well as biologists during recent years.[1] Generally, the fungi derived from marine sources produce pharmacologically active metabolites.[2,3] Clonostachydiol **1** belongs to the colletol family;[4] it is a 14-membered macrocyclic bislactone isolated from the marine algae-derived fungus *Clonostachys cylindrospora*.[5] Clonostachydiol **1** was first synthesized and its absolute stereochemistry determined by Rao et al.[6] while a second synthesis was reported by Yadav et al.[7] Clonostachydiol **1** is found to exhibit various biological activities such as being cytotoxic and the anthelmintic action in vivo.



clonostachydiol **1**



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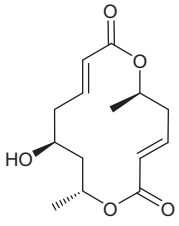
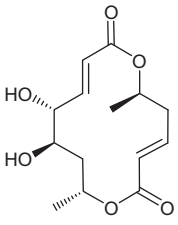


colletol **3**



colletodiol **4**

In a continuation of our interest toward the total synthesis of lactone containing molecules,[8] the promising biological properties and interesting structural features of clonostachydiol **1** prompted us to attempt the synthesis of this molecule. Recently we have accomplished the synthesis of macrolides such as stagonolides A, B,[9a] G,[9b] and herbarumin-I.[9c] Herein we report a simple and efficient approach for the total synthesis of clonostachydiol **1** in a concise manner.

2. Results and discussion

According to the retrosynthetic analysis shown in Scheme 1, the target clonostachydiol **1** can be synthesized by ring closing metathesis (RCM) of compound **20**, which in turn could be derived from fragments **11** and **16** via esterification reaction. Compounds **11** and **16** could be synthesized by starting from ethyl (*R*)-3-hydroxybutanoate **5** and methyl (*R*)-2-hydroxypropanoate **12**, respectively.

The synthesis of α,β-unsaturated acid **11** was achieved from ethyl (*R*)-3-hydroxybutanoate in six steps as depicted in Scheme 2. Initially, the commercially available alcoholic ester **5** was protected as its silyl ether **6** in a 94% yield with TBSCl and imidazole. The silyl ester **6** was converted in a two-step process into α,β-unsaturated ester **7** via controlled reduction using DIBAL-H at −78 °C, followed by the Wittig reaction of the resultant aldehyde with a C_2 ylide. The olefinic functionality in compound **7** was selectively reduced with $NaBH_4$[10] in the presence of $NiCl_2.6H_2O$ to its saturated ester **8** in a

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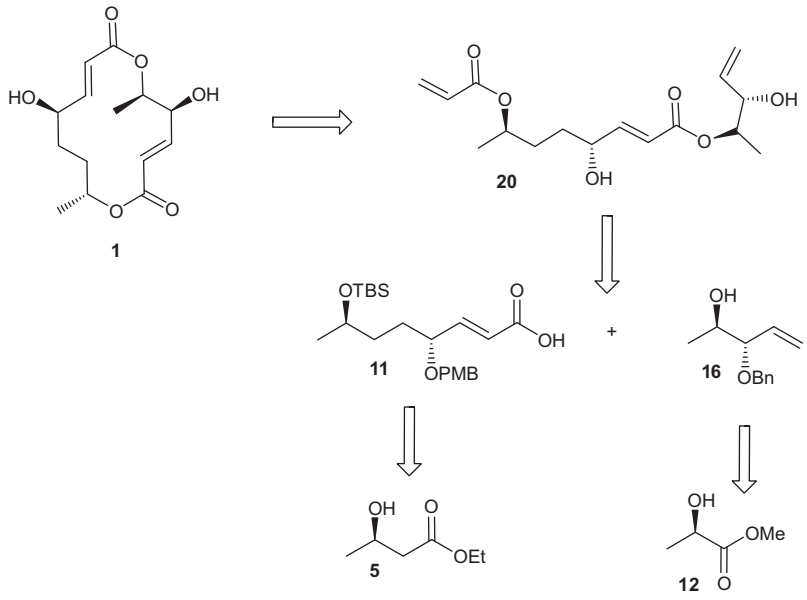
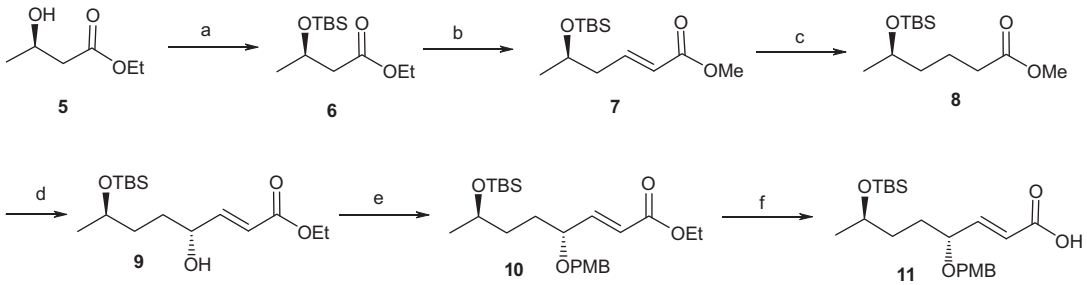
doi:10.1016/j.tetasy.2012.01.014



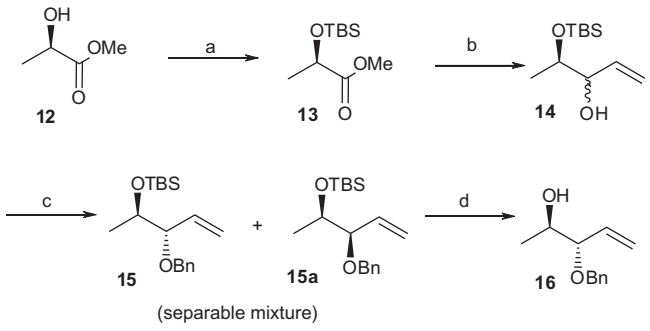
Scheme 1. Retrosynthetic analysis of clonostachydiol.



Scheme 2. Reagents and conditions: (a) TBS-Cl, imidazole, DCM, 0 °C to rt, 6 h, 94%; (b) (i) DIBAL-H, DCM, −78 °C, 0.5 h, 91%, (ii) Ph_3PCHCO_2Me, DCM, rt, 8 h, 88%; (c) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 1 h, 91%; (d) (i) DIBAL-H, DCM, −78 °C, 0.5 h, 92%, (ii) nitrosobenzene, L-proline, DMSO, 20 °C, 25 min, then triethyl phosphonoacetate, DBU, LiCl, 0 °C 1 h, then MeOH, $CuSO_4{\cdot}5H_2O$, rt, overnight, 60% (one pot); (e) PMB imidate, PTSA(cat), DCM, 0 °C to rt, 8 h, 82%; (f) $LiOH{\cdot}H_2O$, THF, H_2O (1:1), 87% 8 h.

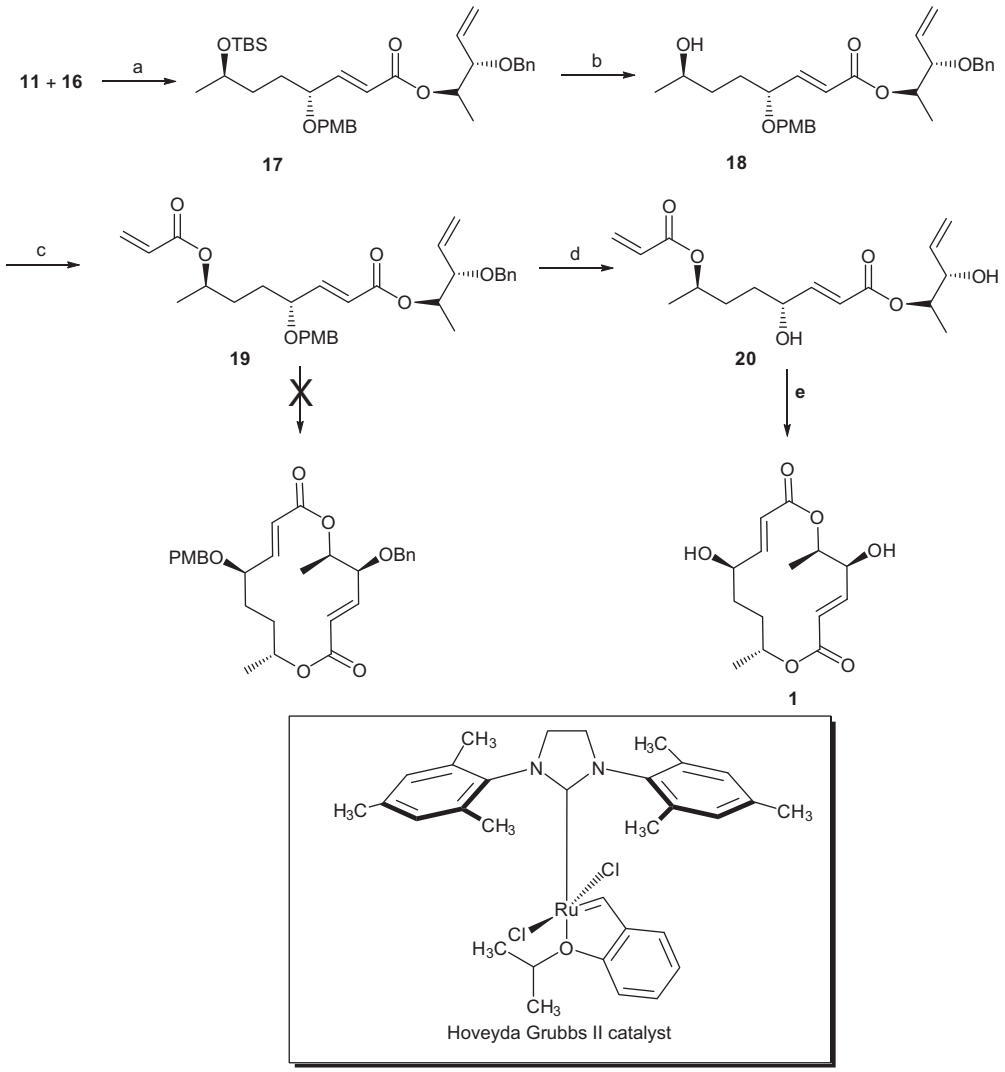
91% yield. Ethyl ester **8** was reduced with DIBAL-H at −78 °C to give an aldehyde (suitable for MacMillan α-hydroxylation) in a 92% yield. The thus obtained aldehyde was subjected to the crucial MacMillan α-hydroxylation[11] using nitrosobenzene (PhNO) and 40% of L-proline in DMSO, followed by rapid Horner–Wadsworth–Emmons Wittig reaction using DBU to furnish the unstable anilinoxy compound, which was further treated with 20 mol % of $CuSO_4{\cdot}5H_2O$ in methanol at room temperature to cleave the *O*–*N* bond providing γ-hydroxy α,β-unsaturated ester **9**[12] in a 60% yield and with high diastereoselectivity (de = 98%). The newly generated hydroxyl group in **9** was protected with PMB imidate derived from *p*-methoxy benzylalcohol to provide the a PMB-ether **10** in a 82% yield (Scheme 2). The ethyl ester **10** was hydrolyzed with $LiOH{\cdot}H_2O$ to furnish α,β-unsaturated acid **11** in a 87% yield (Scheme 2).

The synthesis of the other key fragment **16** was started from the commercially available methyl (*R*)-2-hydroxypropanoate (Scheme 3). The secondary hydroxyl group in **12** was protected with TBSCl in the presence of imidazole to give silyl ether **13** in a 93% yield followed by the reduction of the ethyl ester in **13** using DIBAL-H to give an aldehyde in 90% yield, which upon reaction with vinyl magnesium bromide[13] gave an inseparable mixture of **14** in 85% yield (86:14 dr determined by chiral HPLC), which was separated by conversion into its benzyl ethers (benzyl bromide/NaH) **15** and **15a** in 73% and 11% yields, respectively. The silylether in the major diastereomer **15** was deprotected with TBAF in THF to give the secondary alcohol **16** in a 90% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) TBS-Cl, imidazole, DCM, 0 °C to rt, 6 h, 93%; (b) (i) DIBAL-H, DCM, −78 °C, 0.5 h, 90%; (ii) vinylmagnesium bromide, Et_2O −78 °C 2 h, 85%; (c) NaH, BnBr, TBAI, THF, 0 °C to rt, 8 h, 73.1%; (d) TBAF, THF, 0 °C to rt, 8 h, 90%.

With the key fragments **11** and **16** in hand in sufficient quantities, alcohol **16** was esterified with acid **11** under classical conditions (DCC and DMAP) in dichloromethane to give ester **17** in an 81% yield (Scheme 4). Next, the TBS ether in ester **17** was removed using PTSA in methanol to give secondary alcohol **18** in an 88% yield. The secondary alcohol in **18** was esterified with acryloyl



Scheme 4. Reagents and conditions: (a) DCC, DMAP, DCM, 0 °C, 12 h, 81%; (b) PTSA, MeOH, 0 °C, 0.5 h, 88%; (c) TEA, acryloylchloride, DCM, 0 °C, 0.5 h, 87%; (d) $TiCl_4$, DCM, 0 °C 1 h, 82%; (e) Hoveyda–Grubbs-II, toluene, 80 °C 0.5 h, 80%.

chloride in the presence of TEA in dichloromethane to afford acrylester **19** in an 87% yield. However, the ring closing metathesis of diprotected olefin **19** with Hoveyda Grubbs-II catalyst was not successful. In order to favor the substrate for ring closing metathesis, both the benzyl and PMB ethers in compound **19** were removed using $TiCl_4$ in dichloromethane to afford the diol olefin **20** in an 82% yield, which was subjected to an RCM protocol with Hoveyda Grubbs-II[14] catalyst (10 mol %) in toluene at 80 °C to give exclusively the *trans*-clonostachydiol **1** in an 80% yield (Scheme 4).

3. Conclusion

In conclusion, we have achieved the total synthesis of clonostachydiol **1** in a stereocontrolled manner involving high yielding steps, and using easily accessible chemicals. The crucial steps involved in the synthesis are the MacMillan α-hydroxylation protocol, a diastereoselective Grignard reaction and ring closing metathesis for the synthesis of this marine derived natural product.

4. Experimental

General: Reactions were conducted under N_2 in anhydrous solvents such as DCM, THF, DMSO, CH_3CN, Et_2O, toluene, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Yields refer to after chromatography and spectroscopically (^1H, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or a double-ended needle. Evaporation of the solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300 spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as an internal standard. Mass spectra were obtained on MS-EI, MS-ESI, HRMS mass spectrometers of Agilent Technologies 1100 Series. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. IR (FT-IR) spectra were recorded either on KBr pellets or neat as thin film or in $CHCl_3$. Optical rotations were recorded on a JASCO DIP–360 digital polarimeter at 25 °C.

4.1. Ethyl (*R*)-3-(*tert*-butyldimethylsilyloxy) butanoate 6

To a solution of ethyl (*R*)-3 hydroxybutanoate **5** (2 g, 15.13 mmol) in dry DCM (50 mL) was added imidazole (1.54 g, 22.69 mmol), and the mixture was stirred for 10 min at 0 °C. To this solution *tert*-butyldimethylsilyl chloride (2.73 g, 18.15 mmol)

was added at 0 °C, and the mixture was stirred at room temperature for 6 h. After completion of the reaction, the mixture was diluted with ice-water and extracted into DCM (3 × 75 mL). The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography using hexane/ethyl acetate (97:3) to give pure compound **6** (3.5 g, 94%) as a colorless liquid. $[\alpha]_D^{25} = -30.5$ (*c* 2.0, $CHCl_3$) [Lit.[15a] = -28 (*c* 1.1, $CHCl_3$)]; IR (neat, cm^{-1}): ν_{max} 2957, 2932, 2897, 2858, 1739, 1376, 1254, 1184, 1087, 1003, 834, 776; ^1H NMR (300 MHz, $CDCl_3$): δ 4.31–4.17 (m, 1H), 4.09 (q, *J* = 6.8 Hz, 2H), 2.49–2.25 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6 Hz, 3H), 0.86 (s, 9H), 0.04 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 65.7, 60.0, 44.8, 25.5, 23.7, 17.8, 14.0, −4.6, −5.2; ESI/MS (*m*/*z*): 269 ($M+Na^+$).

4.2. Methyl (*R,E*)-4-(*tert*-butyldimethylsilyloxy)hex-2-enoate 7

To a cooled (−78 °C) stirred solution of compound **6** (2.5 g, 10.14 mmol) in dry DCM (50 mL) was added DIBAL-H (1.0 M, 10.1 mL, 10.1 mmol) and the reaction mixture was stirred for 0.5 h. After completion of the reaction, the reaction was quenched with saturated sodium potassium tartarate (20 mL) and stirred for 0.5 h. The reaction mixture was then extracted into DCM (3 × 75 mL). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue (1.86 g, 91%) was used in the next step without purification. To a stirred solution of crude aldehyde (1.8 g, 8.89 mmol) in dry DCM (30 mL) was added methyl (triphenylphosphorylidene) acetate (3.87 g, 11.56 mmol) and the mixture was stirred at room temperature for 8 h. After completion of the reaction, the solvent was removed under vacuum and the residue was purified by column chromatography (hexane/ethylacetate, 95:5) to afford pure compound **7** (2.02 g, 88%) as a colorless liquid. $[\alpha]_D^{25} = -9.8$ (*c* 1.8, $CHCl_3$) [Lit.[15a] = -9.0 (*c* 1.0, $CHCl_3$)]; IR (neat, cm^{-1}): ν_{max} 2955, 2932, 2892, 2858, 1727, 1659, 1259, 1172, 836, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 6.97–6.85 (m, 1H), 5.80 (dt, *J* = 15.8, 1.5 Hz, 1H), 3.97–3.85 (m, 1H), 3.71 (s, 3H), 2.34–2.27 (m, 2H) 1.16 (d, *J* = 6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 146.2, 122.7, 67.5, 51.3, 42.3, 25.7, 23.6, 17.9, −4.6, −4.9; ESI/MS (*m*/*z*): 281 ($M+Na^+$).

4.3. Methyl (*R*)-5-(*tert*-butyldimethylsilyloxy)hexanoate 8

To a cooled (0 °C) stirred solution of compound **7** (1.5 g, 5.80 mmol) in methanol (30 mL) was added $NiCl_2{\cdot}6H_2O$ (0.4 g, 1.74 mmol). To this solution sodium borohydride (0.661 g, 17.41 mmol) was added portionwise at 0 °C, and the mixture was stirred at room temperature for 1 h. After completion of the reaction, the mixture was quenched with ice-pieces and concentrated, extracted into EtOAc (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate, 95:5) to give compound **8** (1.37 g, 91%) as a colorless liquid. $[\alpha]_D^{25} = -13.3$ (*c* 2.9, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2956, 2932, 2858, 1743, 1370, 1252, 1168, 834, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 3.85–3.73 (m, 1H), 3.66 (s, 3H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.75–1.51 (m, 2H), 1.46–1.35 (m, 2H), 1.12 (d, *J* = 6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 68.1, 51.3, 38.9, 34.0, 25.8, 23.6, 21.1, 18.0, −4.4, −4.8 ESI/MS (*m*/*z*): 283 ($M+Na^+$).

4.4. Ethyl (4*R*,7*R, E*)-7-(*tert*-butyldimethylsilyloxy)-4-hydroxyoct-2-enoate 9

To a cooled (−78 °C) stirred solution of ester compound **8** (1.3 g, 4.99 mmol) in dry DCM (30 ml) was added DIBAL-H (1.0 M, 4.99 mL, 4.99 mmol) and the reaction was stirred for 0.5 h. After completion of the reaction, the reaction was quenched with saturated sodium potassium tartarate (20 mL) and stirred for 0.5 h. The reaction mixture was then extracted into DCM (3 × 75 mL). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethylacetate, 94:6) to give the aldehyde compound (1.05 g, 92%) as a colorless oil.

To a solution of the thus obtained aldehyde (1.0 g, 4.33 mmol) were added nitrosobenzene (0.464 g, 4.33 mmol) and L-proline (0.2 g, 1.73 mmol) in anhydrous DMSO (14.5 mL) at 20 °C. The reaction mixture was stirred vigorously for 25 min under nitrogen, and then cooled to 0 °C. Next, a cooled (0 °C) premixed solution of triethyl phosphonoacetate (2.57 mL, 13.02 mmol), DBU (1.94 mL, 13.02 mmol) and LiCl (0.553 g, 13.02 mmol) in CH_3CN (14.5 mL) was added quickly (1–2 min). The resulting mixture was allowed to warm to room temperature over 1 h, and reaction was quenched by the addition of pieces of ice. The acetonitrile was evaporated under vacuum and the reaction mixture was diluted with water (100 mL) and extracted into Et_2O (3 × 100 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give a crude product, which was dissolved in methanol (20 mL) and reacted with $CuSO_4{\cdot}5H_2O$ (0.216 g, 0.869 mmol). The reaction mixture was then stirred at room temperature overnight and then quenched with a cold saturated NH_4Cl solution (15 mL). The mixture was filtered on a Celite pad and washed thoroughly with ethyl acetate (100 mL), concentrated and extracted into ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified by using silica gel flash column chromatography using hexane/ethylacetate (85:15) as eluent to give compound **9** as a brown liquid (0.822 g, Yield 60%). $[\alpha]_D^{25} = -13.1$ (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3432, 2956, 2932, 2858, 1720, 1657, 1467, 1370, 1256, 1174, 1044, 834, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 6.93 (dd, *J* = 15.6, 4.6 Hz, 1H), 6.06 (dd, *J* = 15.6, 2.4 Hz, 1H), 4.30–4.24 (m, 1H), 4.20 (q, *J* = 7 Hz, 2H), 3.97–3.89 (m, 1H), 1.78–1.52 (m, 4H), 1.29 (t, *J* = 7 Hz, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.9 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 150.2, 120.1, 71.1, 68.4, 60.3, 35.3, 32.2, 25.9, 23.0, 14.3, −4.4, −4.7 ESI/MS (*m*/*z*): 339 ($M+Na^+$).

4.5. Ethyl (4*R*,7*R*,*E*)-7-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2-enoate 10

To a cooled (0 °C) solution of alcohol **9** (0.8 g, 2.52 mmol) in dry DCM (30 mL) was added PMB imidate (0.858 g, 3.03 mmol) followed by PTSA (catalytic amount) and the reaction was stirred at room temperature for 8 h. After completion of the reaction, it was quenched with triethylamine, diluted with water (30 mL), and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane /ethyl acetate, 95: 5) to give compound **10** (0.902 g, 82%) as a brown liquid. $[\alpha]_D^{25} = -13.8$ (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2955, 2930, 2856, 1721, 1655, 1513, 1464, 1250, 1172, 1039, 832, 773; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.3 Hz, 2H), 6.86–6.75 (m, 3H), 5.95 (d, *J* = 15.6 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.93–370 (m, 5H), 1.72–1.42 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 159.1, 148.3, 130.1, 129.2, 121.9, 113.7, 77.7, 70.5, 68.3, 60.3, 55.1, 34.9, 31.0, 25.8, 23.8, 18.0, 14.1, −4.4, −4.7. ESI/MS (*m*/*z*): 459 ($M+Na^+$).

4.6. (4*R*,7*R*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2-enoic acid 11

To a solution of ester **10** (0.7 g, 1.6 mmol) in THF (4 mL) and H_2O (4 mL) was added $LiOH{\cdot}H_2O$ (0.192 g, 8.015 mmol). This solution was allowed to stir for 8 h at room temperature. The reaction mixture was concentrated, the residue was diluted with H_2O (10 mL), and acidified with $KHSO_4$, the aqueous layer was extracted into EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethylacetate, 70:30) to give compound **11** (0.570 g, 87%) as a brown liquid: $[\alpha]_D^{25} = -29.6$ (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3440, 2932, 2858, 1700, 1652, 1513, 1249, 1043, 830, 771; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.94 (dd, *J* = 15.8, 6 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.99 (d, *J* = 15.8 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.3 (d, *J* = 11.3 Hz, 1H), 3.97–3.89 (m, 1H), 3.82–3.70 (m, 4H), 1.75–1.45 (m, 4H), 1.11 (d, *J* = 6 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 159.2, 151.2, 130.0, 129.3, 121.1, 113.8, 77.6, 70.7, 68.4, 55.2, 34.9, 30.9, 25.8, 23.8, 18.0, −4.4, −4.7 ESI/MS (*m*/*z*): 431 ($M+Na^+$).

4.7. Methyl (*R*)-2-(*tert*-butyldimethylsilyloxy)propanoate 13

To a solution of methyl (*R*)-2-hydroxylpropanoate **12** (2 g, 19.21 mmol) in dry DCM (60 mL) was added imidazole (1.96 g, 28.815 mmol), and the mixture was stirred for 10 min at 0 °C. To this solution *tert*-butyldimethylsilyl chloride (3.47 g, 23.05 mmol) was added at 0 °C and the mixture was stirred at room temperature for 6 h. After completion of the reaction, the mixture was diluted with cold water and extracted into DCM (3 × 75 mL). The combined extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using hexane/ethyl acetate (97:3) to give pure **13** (3.9 g, 93%) as a colorless oil. $[\alpha]_D^{25} = +25.3$ (*c* 2.8, $CHCl_3$) [Lit.[15b] +27.2 (*c* 1.89, CCl_4)]; IR (neat, cm^{-1}): ν_{max} 2944, 2894, 2859, 1753, 1255, 1146, 838, 778; ^1H NMR (300 MHz, $CDCl_3$): δ 4.25 (q, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (d, *J* = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 67.5, 50.6, 25.0, 20.5, 17.5, −5.6, −6.0; ESI/MS (*m*/*z*): 241 ($M+Na^+$).

4.8. (3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)pent-1-en-3-ol 14

To a cooled (−78 °C) stirred solution of ester compound **13** (2.5 g, 11.44 mmol) in dry DCM (50 mL) was added slowly DIBAL-H (1.0 M, 11.44 mL, 11.44 mmol) and stirred for 0.5 h. After completion, the reaction was quenched with saturated sodium potassium tartarate (30 mL) and stirred for 0.5 h and then extracted into DCM (3 × 100 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 97:3) to give the aldehyde (1.94 g, 90%) as a colorless liquid. The thus obtained aldehyde (1.9 g, 10.08 mmol) in anhydrous Et_2O (50 mL) was added dropwise to vinylmagnesium bromide (1.0 M, 15.13 mL, 15.13 mmol) at −78 °C and the reaction mixture was stirred for 2 h. After completion of the reaction, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted into Et_2O (3 × 100 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography using hexane/ethyl acetate (95: 5) to give pure **14** (1.85 g, 85%) as a colorless oil. IR (neat, cm^{-1}): ν_{max} 3409, 3084, 2956, 2931, 2891, 2859, 1380, 1254, 1091, 931, 835, 772; ^1H NMR (300 MHz, $CDCl_3$): δ 5.85–5.71 (m, 1H), 5.31–5.13 (m, 2H), 4.02–3.93 (m, 1H), 3.86–3.76 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 116.3, 76.6, 71.2, 25.7, 17.9, 17.6, −4.5, −4.9; ESI/MS (*m*/*z*): 239 ($M+Na^+$).

4.9. (2*R*,3*S*)-3-(Benzyloxy)pent-4-en-2-yloxy *tert*-butyldimethylsilane 15

To a cooled (0 °C) solution of compound **14** (1 g, 4.62 mmol) in dry THF (30 mL) was added NaH (60%) (0.277 g, 6.93 mmol) and stirred for 10 min. To this mixture, benzylbromide (0.68 mL, 5.54 mmol), and TBAI (cat amount) were added and stirred at room temperature for 8 h. After completion of the reaction, the reaction mixture was quenched with cold water (30 mL), extracted into EtOAc (3 × 75 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 98:2) to give compound **15** (1.04 g, 73.1%) as a colorless liquid. $[\alpha]_D^{25} = -10.3$ (*c* 3, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3071, 3031, 2956, 2930, 2890, 2858, 1462, 1252, 1112, 834, 776; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.17 (m, 5H), 5.84–5.70 (m, 1H), 5.31–5.17 (m, 2H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.86–3.77 (m, 1H), 3.50 (dd, *J* = 7.5, 4.5 Hz, 1H), 1.14 (d, *J* = 6 Hz, 3H), 0.86 (s, 9H), 0.02 (d, *J* = 4.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 136.5, 128.2, 127.6, 127.3, 118.6, 85.2, 71.0, 70.4, 26.1, 20.4, 18.3, −4.3; ESI/MS (*m*/*z*): 329 ($M+Na^+$).

4.10. (2*R*,3*S*)-3-(Benzyloxy)pent-4-en-2-ol 16

To a cooled (0 °C) solution of benzyl protected compound **15** (0.7 g, 4.5 mmol) in dry THF (10 mL) was added TBAF (1 M in THF, 4.58 mL, 4.58 mmol) and stirred for 8 h at room temperature. After completion of the reaction, the reaction mixture was diluted with water and extracted into EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 83:17) to give pure compound **16** 0.395 g (90%) as a colorless liquid. $[\alpha]_D^{25} = +18.9$ (*c* 3.3, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3446, 3073, 3029, 2977, 2928, 2871, 1637, 1452, 1078, 928, 741, 669; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H), 5.89–5.74 (m, 1H), 5.43–5.23 (m, 2H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.35 (d, *J* = 11.9 Hz, 1H), 3.90–3.80 (m, 1H), 3.64 (dd, *J* = 8.1, 3.8 Hz, 1H), 1.11 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 134.5, 128.3, 127.6, 127.5, 120.2, 84.2, 70.2, 69.2, 17.9; ESI/MS (*m*/*z*): 215 ($M+Na^+$).

4.11. (4*R*,7*R*,*E*)-((2*R*,3*S*)-3-(Benzyloxy)pent-4-en-2-yl)7-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2-enoate 17

To a cooled (0 °C) solution of compound **11** (500 mg, 1.22 mmol), DCC (252 mg, 1.22 mmol), and DMAP (30 mg, 1.22 mmol) in dry DCM (10 mL) was added alcohol **16** (235 mg, 1.22 mmol) in 5 ml of dry DCM and stirred at the same temperature for 12 h. After completion of the reaction, the mixture was diluted with water (15 mL) and extracted into DCM (3 × 50 mL). The combined organic layer was dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethylacetate, 94:6) to give pure compound **17** (0.577 mg, 81%) as a colorless liquid. $[\alpha]_D^{25} = -14.3$ (*c* 0.17, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2929, 2857, 1720, 1612, 1512, 1460, 1251, 1169, 1066, 831, 773: ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.17 (m, 7H), 6.87–6.74 (m, 3H), 5.95 (d, *J* = 16.0 Hz, 1H), 5.85–5.71 (m, 1H), 5.38–5.26 (m, 2H), 5.10–4.98 (m, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 12.2 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 3.95–3.64 (m, 6H), 1.75–1.45 (m, 4H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.02 (d, *J* = 3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 159.1, 148.5,

138.3, 134.8, 130.1, 129.3, 128.2, 127.5, 122.1, 119.5, 113.7, 81.7, 77.8, 72.0, 70.5, 70.4, 68.4, 55.1, 35.0, 31.0, 25.8, 23.8, 15.2, -4.4, -4.7; ESI/MS (m/z): 605 ($M+Na^+$).

4.12. (4*R*,7*R*,*E*)-((2*R*,3*S*)-3-(Benzyloxy)pent-4-en-2-yl)7-hydroxy-4-(4-methoxybenzyloxy)oct-2-enoate 18

To a cooled (0 °C) solution of **17** (500 mg, 0.857 mmol) in MeOH (10 mL) was added PTSA (147 mg, 0.857 mmol) and stirred at the same temperature for 0.5 h. After completion of the reaction, the mixture was quenched with solid sodium bicarbonate, filtered, and MeOH was evaporated under reduced pressure to afford a crude product, which was purified by column chromatography on silica gel (hexane/ethylacetate, 70:30) to give alcohol **18** (352 mg, 88%) as a colorless liquid: $[\alpha]_D^{25} = +6.2$ (c 0.4, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3448, 2925, 2860, 1716, 1613, 1512, 1445, 1250, 1172, 1068; ^1H NMR (30 0 MHz, $CDCl_3$): δ 7.33–7.17 (m, 7H), 6.86–6.75 (m, 3H), 5.96 (d, J = 16.6 Hz, 1H), 5.85–5.71 (m, 1H), 5.38–5.26 (m, 2H), 5.08–4.99 (m, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 11.3 Hz, 1H), 3.86–3.64 (m, 5H), 3.99–3.90 (m, 1H), 1.79–1.37 (m, 4H), 1.29 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 159.1, 148.1, 138.2, 134.6, 129.7, 129.3, 128.2, 127.5, 122.2, 119.5, 113.7, 81.7, 77.6, 72.0, 70.6, 70.3, 67.6, 55.1, 34.6, 31.0, 23.4, 15.2; ESI/MS (m/z): 491 ($M+Na^+$).

4.13. (4*R*,7*R*,*E*)-((2*R*,3*S*)-3-(Benzyloxy)pent-4-en-2-yl)7-(acryloyloxy)-4-(4-methoxybenzyl- oxy)oct-2-enoate 19

To a cooled (0 °C) solution of alcohol **18** (300 mg, 0.640 mmol) in dry DCM (10 mL) were added triethylamine (0.22 mL, 1.6 mmol) and acryloyl chloride (0.1 mL, 1.28 mmol) and stirred at the same temperature for 0.5 h. After completion of the reaction, the reaction mixture was quenched with saturated sodium bicarbonate (10 mL) and extracted into DCM (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 90:10) to acryl ester **19** (291 mg, 87%) as a colorless liquid: $[\alpha]_D^{25} = +2.5$ (c 0.2, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2925, 2855, 1719, 1613, 1513, 1272, 1248, 1200, 1065, 985, 756; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.15 (m,7H), 6.82 (d, J = 8.9 Hz, 2H), 6.76 (dd, J = 15.8, 5.9 Hz, 1H), 6.35 (d, J = 17.8 Hz, 1H), 6.06 (dd, J = 17.8, 10.8 Hz, 1H), 5.94 (d, J = 15.8 Hz, 1H), 5.82–5.72 (m, 2H), 5.35–5.25 (m, 2H), 5.06–4.99 (m, 1H), 4.97–4.89 (m, 1H), 4.63 (d, J = 11.8, 1H), 4.48 (d, J = 11.8, 1H), 4.41 (d, J = 11.8, 1H), 4.26 (d, J = 11.8, 1H), 3.94–3.81 (m, 2H), 3.79 (s, 3H), 1.72–154 (m, 4H), 1.28 (d, J = 5.9 Hz, 3H), 1.24 (d, J = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 165.3, 159.2, 147.9, 138.2, 134.7, 130.3, 129.9, 129.3, 128.7, 128.2, 127.5, 122.4, 119.5, 113.7, 81.6, 77.3, 72.0, 70.8, 70.6, 70.3, 55.1, 31.4, 30.7, 19.9, 15.2; ESI/MS (m/z): 545 ($M+Na^+$).

4.14. (4*R*,7*R*,*E*)-((2*R*,3*S*)-3-Hydroxypent-4-en-2-yl)7-(acryloyloxy)-4-hydroxyoct-2-enoate 20

To a cooled (0 °C) solution of **19** (250 mg, 0.478 mmol) in dry DCM (7 mL) was added a solution of $TiCl_4$ (0.21 mL, 1.915 mmol) in dry DCM (2 mL) under N_2 and the mixture was stirred at the same temperature for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated sodium bicarbonate (10 mL), and extracted into DCM (3 × 20 mL). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 55:45) to give pure compound **20** (123 mg, 82%) as a colorless gummy liquid: $[\alpha]_D^{25} = -10.8$ (c 0.65, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3450, 2922, 2852, 1712, 1639, 1276, 1202, 1050, 985, 761; ^1H NMR (300 MHz, $CDCl_3$): δ 6.95 (dd, J = 15.8, 4.5 Hz, 1H), 6.40 (dd, J = 17.3, 1.5 Hz, 1H), 6.16–6.03 (m, 2H), 5.92–5.79 (m, 2H), 5.42–5.23 (m, 2H), 5.09–4.97 (m, 2H), 4.40–4.23 (m, 2H), 1.80–1.51 (m, 4H), 1.28 (d, J = 6.0 Hz, 3H), 1.24 (d, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 166.0, 150.3, 135.6, 130.7, 128.7, 120.3, 117.4, 74.7, 73.5, 70.9, 70.6, 32.2, 31.6, 20.0, 14.4; ESI/MS (m/z): 335 ($M+Na^+$).

4.14.1. Clonostachydiol 1

A solution of compound **20** (30 mg, 0.096 mmol) in dry toluene (110 mL) was bubbled with a nitrogen flow, after which Hoveyda Grubbs II generation catalyst (6 mg, 0.009 mmol) was added at once and the resulting mixture was heated under nitrogen at 80 °C for 0.5 h. After completion of the reaction, the mixture was cooled to room temperature and the solvent was evaporated in vacuo. The crude residue was purified by column chromatography on silica gel (hexane/ethylacetate, 50:50) to give compound **1** (21.8 mg, 80%) as a white solid, mp 165 °C, (Lit.[5] mp 164 °C); $[\alpha]_D^{25} = +101.6$ (c 0.5, MeOH), [Lit.[5] = +103 (c 1.0, MeOH)]. IR (neat, cm^{-1}): ν_{max} 3407, 2979, 2920, 2851, 1711, 1639, 1461, 1370, 1225, 1179, 1049, 978; ^1H NMR (300 MHz, DMSO-d_6): δ 6.68 (dd, J = 15.8, 4 Hz, 1H), 6.48 (dd, J = 15.8, 7.9 Hz, 1H), 5.91 (d, J = 15.8 Hz, 1H), 5.78 (dd, J = 15.8, 2 Hz, 1H), 5.68 (d, J = 5 Hz, 1H), 5.07–4.99 (m, 2H), 4.77–4.66 (m, 1H), 4.49–4.42 (m, 1H), 3.92–4.0 (m, 1H), 1.87–1.77 (m, 1H), 1.61–1.53 (m, 1H), 1.51–140 (m, 2H), 1.34 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 6.5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 164.1, 150.8, 145.4, 123.8, 120.3, 77.2, 73.7, 70.4, 70.1, 30.6, 27.4, 18.6, 18.0;ESI/MS (m/z): 307 ($M+Na)^+$; HRMS Calcd for $C_{14}H_{20}O_6Na$ ($M+Na^+$) 307.1152. Found: 307.1157.

Acknowledgments

The authors D.R., S.R., S.P.R. and K.V. are thankful to MOES and the CSIR-UGC, New Delhi, India, respectively, for the financial support and Dr. J. S. Yadav Director, the Indian Institute of Chemical Technology (IICT) for his encouragement.

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