Tetrahedron: *Asymmetry* 21 (2010) 106–111

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

First stereoselective total synthesis of (−)-stagonolide A

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ARTICLE INFO

Article history:
Received 23 November 2009
Accepted 21 December 2009
Available online 11 January 2010

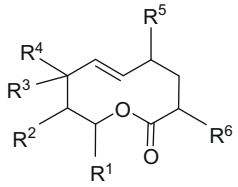
ABSTRACT

The first stereoselective total synthesis of the nonenolide (−)-stagonolide A is described. Olefin metathesis and epoxide opening reaction are the key steps involved.

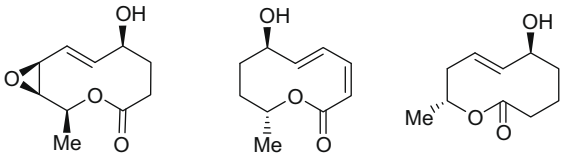
1. Introduction

Ten-membered macrolides with significant biological properties continue to attract the attention of both biologist and chemists.[1] The scarcity coupled with complexity of the natural materials poses a great challenge for synthetic chemist. Herbarumin I–III[2] are recent examples with potent phytotoxic properties, and have been well addressed by several groups.[3] Our own interest in these types of natural products has allowed us to accomplish the total synthesis of herbarumin III[3l] in a concise manner. Stagonolides (Fig. 1) are other examples, which have been isolated recently from the fungus *Stagonospora cirsii*, a pathogen of Cirsium arvense causing necrotic lesions on leaves.[4] To the best of our knowledge, there are no reports so far on the total synthesis of the toxic metabolite stagonolide A, and in continuation of our investigations for concise synthetic routes for the total synthesis of biologically active lactone containing natural products, we herein report the first stereoselective total synthesis of stagonolide A.

Interestingly, we observed that both herbarumin I and stagonolide A have a similar skeleton but differ by the presence of an oxidized carbon in stagonolide (C7). Retrosynthetically, we identified lactone **10** as the key intermediate, which can be manipulated further by acetonide deprotection and selective allyl alcohol oxidation to give the target compound stagonolide A. The macrolactone **10** can be synthesized by coupling two fragments **11** and **12** via an olefin metathesis followed by macrolactonization or esterification followed by an olefin metathesis. While the 5-hexenoic acid fragment is commercially available, the second fragment with three stereogenic centers **11** can be easily synthesized from *trans*-2-hexenol (a non-carbohydrate route) or D-ribose (chiral pool strategy) (Scheme 1).



R^1 = α-$CH_2CH_2CH_3$, R^2 = β-OH, R^3 = α-H, R^4 = β-OH,
R^5 = H, R^6 = H : Herbarumin I **1**
R^1 = α-$CH_2CH_2CH_3$, R^2 = β-OH, R_3 = α-H, R^4 =β-OH,
R_5 = H, R^6 = β-OH : Herbarumin II **2**
R^1 = α-$CH_2CH_2CH_3$, R^2 = H, R^3 = α-H, R^4 = β-OH,
R_5 = H, R^6 = H : Herbarumin III **3**
R^1= α-$CH_2CH_2CH_3$, R^2 = β-OH, R^3 + R^4 = O, R^5 = H,
R^6 = H : Stagonolide A **4**
R^1 = α-$CH_2CH_2CH_3$, R^2 = α-OH; R^3 = β-H, R^4 = α-H,
R^6 = H : Stagonolide B **5**
R^1 = α-Me, R^2 = H, R^3 = α-OH, R^4 = β-H, R^5 = β-OH,
R^6 = H : Stagonolide C **6**



Stagonolide D **7** Stagonolide E **8** Stagonolide F **9**

Figure 1.

2. Results and discussion

Initially we started with the commercially available *trans*-2-hexenol, which was epoxidized under Sharpless conditions[5] to provide chiral epoxy alcohol **15**. The epoxy alcohol was converted to epoxy chloride **16** with triphenylphosphine and CCl_4 and then subjected to our earlier reported procedure to give chiral propargyl alcohol **17**.[6] The newly generated chiral secondary alcohol was protected as TBS ether **18** and the terminal acetylene was then treated with *n*-BuLi followed by quenching with ethyl chloroformate to yield α,β-unsaturated ester **19**. The *cis* reduction under Lindlar's condition gave *Z* olefin **13**, which was subjected to dihydr-

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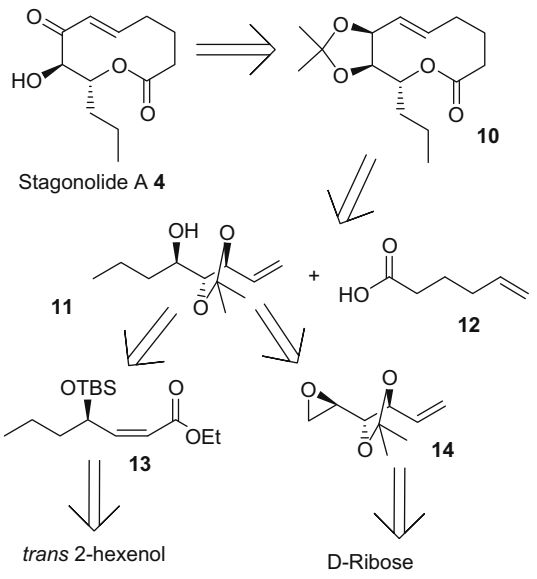
doi:10.1016/j.tetasy.2009.12.015



Scheme 1. Retrosynthesis.

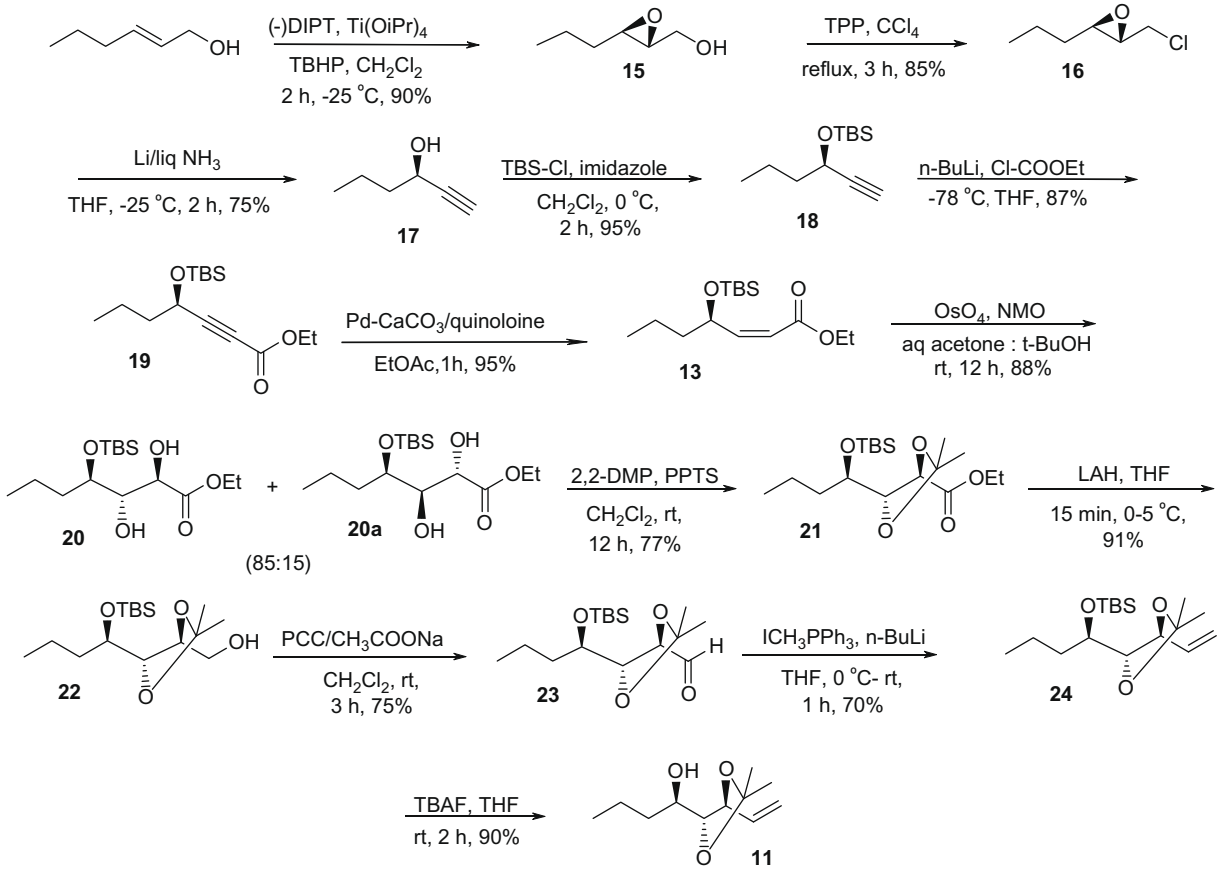
oxylation with OsO_4 to give the polyhydroxylated ester **20** along with undesired **20a** as an easily separable diastereomeric mixture (85:15).[7] Isopropylidination of the desired major diol **20** with 2,2-DMP in CH_2Cl_2 yielded ester **21**, which was reduced with $LiAlH_4$ to afford alcohol **22**. Oxidation of **22** with PCC provided aldehyde **23**, which was subsequently treated with iodomethyltriphenylphosphine in the presence of *n*-BuLi to give the 1-C homologated product **24**. Silyl deprotection with TBAF yielded the key fragment **11** with the required stereogenic centers (Scheme 2).

Alternatively, in a concise manner, we also synthesized the key intermediate **11** utilizing a chiral pool synthetic strategy. This synthesis is a departure from the prior work at the readily available epoxide intermediate **14**.[8] The epoxide **14** is treated with ethyl magnesium bromide in the presence of copper iodide to give the key intermediate **11**.

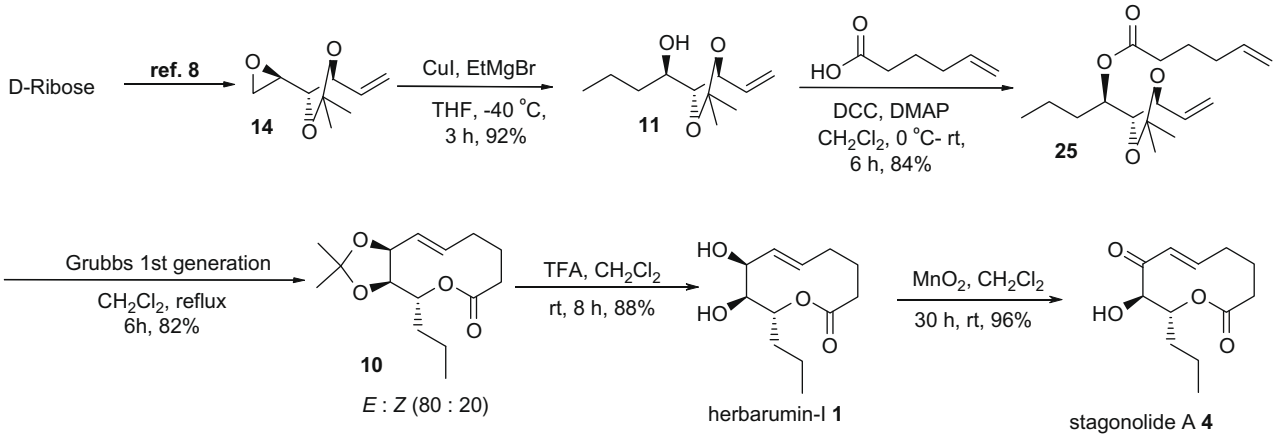
Coupling of alcohol **11** with 5-hexenoic acid under standard DCC, DMAP conditions gave ester **25** which in turn allowed us to proceed further for the metathesis reaction. We observed that 1st generation Grubb's catalyst works efficiently to produce the desired lactone ring **10** as a diastereomeric mixture *E*/*Z* (8:2).[9] The diastereomers were not separated at this stage due to very close R_f values but were separated after performing the next reaction. The major diastereomer was found to be the desired *E*-isomer based on the comparison of the crude data with earlier literature[3b] and was characterized fully after deprotection of the acetonide moiety. Thus, we proceeded further for acetonide deprotection by TFA in CH_2Cl_2 to give the easily separable diastereomers to provide herbarumin I **1**, whose analytical data were compared with those of the natural product[2] and the synthetic products from earlier reports.[3b] Further oxidation of herbarumin I with MnO_2 yielded the new nonenolide stagonolide A **4** in a good yield (Scheme 3). The spectroscopic data were found to be identical to those of the natural product.[4a]

3. Conclusion

In conclusion, the first total synthesis of stagonolide A has been achieved in nine steps with an overall yield of 24%. Two synthetic



Scheme 2.



Scheme 3.

routes for the synthesis of the key intermediate **11** with three stereogenic centers have been provided, which could be utilized for the synthesis of herbarumin I and stagonolide A. The key reactions involved are the epoxide opening, the generation of chiral propargyl alcohol from a chiral epoxy chloride, Lindlar's reduction, and Grubb's olefin metathesis. Application of this strategy to the preparation of other analogues toward investigation for biological activity is currently being pursued.

4. Experimental

4.1. General

The reactions were carried out under an N_2 atmosphere in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. THF used was freshly distilled over benzophenone prior to use. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Yields refer to isolated yields. Air-sensitive reagents were transferred by a syringe or a double-ended needle. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker Avance 300 spectrometers. Chemical shifts are reported relative to TMS as an internal standard. 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. Optical rotations were recorded on JASCO DIP-360 digital polarimeter.

4.1.1. (2*R*,3*R*)-(3-Propyl-oxiranyl)-methanol 15

A mixture of D-(−)-diisopropyl tartrate (15.92 mL, 75 mmol) and $Ti(O^iPr)_4$ (17.85, 60 mmol) in CH_2Cl_2 (100 mL) containing 4 Å molecular sieves was stirred for 15 min at −25 °C under a nitrogen atmosphere. After 15 min at the same temperature, *t*-BuOOH (150 mL, 4 M in toluene, 600 mmol) was added over a period of 10 min and the mixture was stirred for 30 min. A solution of *trans*-2-hexene-1-ol (30 g, 300 mmol) in dry CH_2Cl_2 (100 mL) was slowly added at −25 °C. The mixture was stirred for 1 h at −25 °C and then to this was added 10% NaOH (50 mL) followed by aq satd NaCl solution (100 mL) at 0 °C. The reaction mixture was warmed to room temperature for 1 h and diluted with CH_2Cl_2. The mixture was filtered through Celite and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phases were washed with water and brine solution and were concentrated under reduced pressure. Purification by silica gel column chromatography (30% EtOAc/hexane) provided the epoxy alcohol **15** (31.5 g, 90%) as a colorless oil; $[\alpha]_D^{28} = +40.5$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3406, 2961,2872, 1462, 1223, 1068, 897 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J* = 6.8 Hz, 3H), 1.35–1.58 (m, 4H), 2.48 (br s, 1H), 2.80–2.92 (m, 2H), 3.53 (dd, *J* = 12.8, 4.5 Hz, 1H), 3.83 (dd, *J* = 12.8, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 18.9, 33.3, 55.8, 58.5, 61.8. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.12; H, 10.38.

4.1.2. (2*R*,3*R*)-*trans*-3-Propyloxiranemethylchloride 16

A stirred solution of alcohol **15** (1.0 g, 8 mmol), triphenyl phosphine (Ph_3P) (3.39 g, 12 mmol), and $NaHCO_3$ (362 mg, 4 mmol) in CCl_4 (15 mL) under nitrogen atmosphere was refluxed for 3 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (5% EtOAc/hexane) to yield the epoxy chloride **16** (0.91 mg, 85%) as a yellow oil. $[\alpha]_D^{27} = +10.0$ (*c* 2.8, $CHCl_3$); IR (neat) ν_{max}: 1637, 1219, 913, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.22–1.37 (m, 2H), 1.43–1.59 (m, 2H), 2.78–2.83 (m, 1H), 2.91–2.96 (m, 1H), 3.38 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.61 (dd, *J* = 11.0, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 19.0, 33.3, 44.7, 57.0, 58.8. Anal. Calcd for $C_6H_{11}OCl$: C, 53.54; H, 8.24. Found: C, 54.56; H, 8.26.

4.1.3. (3*R*)-Hex-1-yn-3-ol 17

To a solution of $LiNH_2$ [prepared from lithium (1.03 g, 148 mmol) in liquid NH_3 (50 mL) at −35 °C, and catalytic amount of ferric nitrate] was added epoxy-choloride **16** (2.5 g, 18.5 mmol) in THF (100 mL) and was allowed to stir for 2 h. The reaction was quenched with solid NH_4Cl and allowed to warm to room temperature. The reaction mixture was diluted with water and extracted with diethyl ether (2 × 10 mL). The combined organic phase was washed with water and brine, and evaporated in vacuo. The crude product was purified by silica gel column chromatography (10% EtOAc/hexane) to give yellow liquid **17** (1.36 g, 75%). $[\alpha]_D^{27} = +15.8$ (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 3421, 2959, 2855, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.31–1.48 (m, 2H), 1.53–1.72 (m, 2H), 2.39 (d, *J* = 2.0 Hz, 1H), 3.02–3.13 (br s, 1H), 4.30 (td, *J* = 6.4, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 18.1, 39.4, 61.7, 72.5, 85.0. Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.32; H, 10.65.

4.1.4. (3*R*)-3-*tert*-Butyldimethylsilyloxy-hex-1-yne 18

Imidazole (2.7 g, 40 mmol) was added to a solution of alcohol **17** (2.0 g, 20 mmol) in dry CH_2Cl_2 (100 mL) and the mixture was stirred at 0 °C under nitrogen. After 30 min TBDMSCl (4.6 g, 30 mmol) was added to the reaction mixture and stirred at the same temperature for 2 h. After complete consumption of the starting material, the reaction was quenched with the addition of water, and the reaction mixture was extracted with CH_2Cl_2

(2 × 25 mL). The organic extract was washed with water and brine. The organic layer was concentrated using a rotaevaporator to give the crude product, which was purified by silica gel column chromatography (5% EtOAc/hexane) to provide TBS protected ether **18** as a colorless oil, yield (4.0 g, 95%). $[\alpha]_D^{29} = +27.9$ (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3311, 2958, 2933, 2859, 1466, 1255, 1114, 1084, 896, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.13 (s, 3H), 0.88–0.95 (m, 12H), 1.35–1.54 (m, 2H), 1.58–1.73 (m, 2H), 2.36 (d, *J* = 2.26 Hz, 1H), 4.34 (td, *J* = 6.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.0, −4.5, 13.7, 18.2, 18.4, 25.7, 40.7, 62.5, 71.8, 85.7. Anal. Calcd for $C_{12}H_{24}OSi$: C, 67.86; H, 11.39. Found: C, 67.95; H, 11.52.

4.1.5. (4*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-hept-2-ynoicacid ethyl ester 19

n-Butyllithium (10.5 mL, 1.6 M in hexane 16.9 mmol) was added to a stirred solution of alkyne **18** (3 g, 11.4 mmol) in THF (100 mL) at −78 °C. After 30 min, ethyl chloroformate (3 mL, 21 mmol) was added at the same temperature for 30 min. After completion of the reaction (judged by TLC analysis), the reaction was quenched with saturated aqueous NH_4Cl solution and the reaction mixture was extracted with ethyl acetate. (2 × 30 mL). The extract was washed with water and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give ester **19** (2.7 g, 87%) as a yellow liquid. $[\alpha]_D^{30} = +8.0$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2959, 2933, 2860,1716,1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.15 (s, 3H), 0.90 (s, 9H), 0.95 (t, *J* = 6.8 Hz, 3H), 1.33 (t, *J* = 6.8 Hz, 3H), 1.38–1.54 (m, 2H), 1.65–1.77 (m, 2H), 4.21 (q, *J* = 6.8 Hz, 2H), 4.44 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, −4.6, 13.5, 13.9, 18.0, 18.2, 25.6, 39.8, 61.8, 62.3, 76.5, 88.7, 153.5; MS-ESI: *m/z* 307 (M^++Na); HRMS (ESI): *m/z* calcd for $C_{15}H_{28}O_3NaSi$: 307.1705, found: 307.1704.

4.1.6. (4*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-hept-2-enoic acid ethylester 13

To a stirred solution of alkyne **19** (2 g, 7 mmol) in EtOAc (15 mL) were added Pd–$CaCO_3$ (50 mg) and 10 mL ethyl acetate/quinoline (10:3) and the mixture was stirred under a hydrogen atmosphere for 1 h at room temperature. The resultant mixture was filtered through a short pad of Celite. The filter cake was washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to afford unsaturated ester **13** (1.9 g, 95%) as a pale yellow liquid; $[\alpha]_D^{30} = -14.8$ (*c* 1.9, $CHCl_3$); IR (neat): ν_{max} 2957, 2932, 2859, 1721, 1465, 1410, 1187 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.81–0.91 (m, 12H), 1.24 (td, *J* = 7.1, 0.9 Hz, 3H), 1.28–1.58 (m, 4H), 4.12 (qd, *J* = 7.1, 0.9 Hz, 2H), 5.22–5.31 (m, 1H), 5.63 (dt, *J* = 12.8, 7.7 Hz, 1H); 6.10 (dt, *J* = 12.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.6, 13.9, 14.1, 18.0, 18.3, 25.7, 39.7, 59.9, 68.5, 117.1, 153.7, 165.7; MS-ESI: *m/z* 309 (M^++Na); HRMS (ESI): *m/z* calcd for $C_{15}H_{30}O_3NaSi$: 309.1861, found: 309.1867.

4.1.7. (2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxy-heptanoicacid ethylester 20

4-Methylmorpholine *N*-oxide (NMO) (2 g, 17.4 mmol) and OsO_4 (8.74 mL, 0.1 M in *t*-BuOH, 0.4 mmol) were added to a stirred solution of unsaturated ester **13** (2.5 g, 1 mmol) in *t*-BuOH, water, acetone (24 mL, 1:1:1) at room temperature and were stirred for 12 h. The reaction was quenched with solid sodium sulfite. The solvent was removed under reduced pressure and the compound was extracted with ethyl acetate. (3 × 20 mL) The combined organic layer was washed with water and brine and dried over sodium sulfate. Purification by column chromatography over silica gel (15% EtOAc/hexane) provided diol **20** as a yellow liquid (2.2 g, 88%). $[\alpha]_D^{27} = -4.5$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3451, 2957, 2931, 2858, 1733, 1638, 1255, 1070, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.83–0.92 (m, 12H), 1.20–1.48 (m, 6H), 1.58–1.72 (m, 1H), 2.70 (d, *J* = 8.8 Hz, 1H), 3.21 (d, *J* = 7.9 Hz, 1H), 3.48–3.56 (m, 1H), 3.88–3.95 (m, 1H), 4.02 (t, *J* = 7.8 Hz, 1H), 4.15–4.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.2, 14.0 (2 C), 17.9, 18.2, 25.7, 35.8, 61.4, 71.0, 71.9, 73.5, 173.7; MS-ESI: *m/z* 343 (M^++Na); HRMS (ESI): *m/z* calcd for $C_{15}H_{32}O_5NaSi$: 343.1916, found: 343.1927.

4.1.8. (2*R*,3*S*,4*R*)-5-[1-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-2,2dimethyl-[1,3]dioxolane-4-carboxylic acid ethyl ester 21

Pyridinium *p*-toluenesulfonate (PPTS) (39 mg, 0.15 mmol) was added to the stirred solution of diol **20** (500 mg, 1.56 mmol) in dry CH_2Cl_2 (100 mL) under nitrogen at room temperature. 2,2-Dimethoxy propane (1 g, 3 mmol) was added to the reaction mixture and stirred at room temperature for 12 h. The solvent was removed under reduced pressure, purified by silica gel column chromatography gel (5% EtOAc/hexane) to give a colorless liquid **21** (100 mg, 77%). $[\alpha]_D^{30} = +25.8$ (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 2958, 2933, 2858, 1756, 1733, 1251, 1104, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):δ 0.04 (s, 3H), 0.06 (s, 3H), 0.84–0.91 (m, 12H), 1.21–1.54 (m, 10H), 1.58 (s, 3H), 3.61 (td, *J* = 8.4, 2.0 Hz, 1H), 4.06–4.27 (m, 3H), 4.43 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7, −3.9, 13.9, 14.0, 18.4, 18.6, 25.5, 25.9, 26.5, 36.1, 60.9, 71.2, 76.0, 81.8, 110.5, 170.2; MS-ESI: *m/z* 361 (M^++H); HRMS (ESI): *m/z* calcd for $C_{18}H_{36}O_5NaSi$: 383.2229, found: 383.2229.

4.1.9. (2*S*,3*S*,4*R*)-5-[1-(*tert*-Butyl-dimethyl-silanyloxy]-2,2-dimethyl-[1,3]dioxolan-4-yl-methanol 22

To the stirred solution of compound **21** (1.2 g, 3.3 mmol) in dry THF (10 mL) was added $LiAlH_4$ (164 mg, 4.3 mmol) under nitrogen at −15 °C for 15 min. The reaction was quenched with saturated Na_2SO_4 (3 mL) and stirred at rt for 1 h. The reaction mixture was filtered through Celite and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with water and brine and concentrated under reduced pressure. Residue was purified by chromatography over silica gel (20% EtOAc/hexane) to give alcohol as a yellow liquid **22** (950 mg, 91%). $[\alpha]_D^{28} = +39.1$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}3455, 2956, 2932, 2857, 1464, 1250, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87–0.97 (m, 12H), 1.24–1.57 (m, 10H), 2.05 (br s, 1H), 3.54 (m, 2H), 3.70–3.79 (m, 1H), 3.98–4.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.6, −4.0, 14.0, 18.3, 19.0, 25.3, 25.9, 28.0, 36.2, 61.5, 70.8, 77.5, 80.2, 108.2; MS-ESI: *m/z* 341 (M^++Na); HRMS (ESI): *m/z* calcd for $C_{16}H_{34}O_4NaSi$: 341.2124, found: 341.2120.

4.1.10. (2*R*,3*S*,4*R*)5-[1-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-2,2dimethyl-[1,3]dioxolane-4-carbaldehyde 23

At first, PCC (311 mg, 1.4 mmol) and anhydrous sodium acetate (118 mg, 1.4 mmol) were added to a solution of alcohol **22** (400 mg, 1.2 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 3 h. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (10% EtOAc/hexane) to give aldehyde **23** (306 mg, 88%) as a colorless liquid. $[\alpha]_D^{30} = -13.6$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 2957, 2932, 2858, 1738, 1465, 1253, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.76–0.98 (m, 12H), 1.37 (s, 3H), 1.38–1.56 (m, 4H), 1.57 (s, 3H), 4.04 (td, *J* = 2.3 Hz, 1H), 4.32 (d, *J* = 3.2 Hz, 1H), 4.36 (d, 2.0, *J* = 2.4 Hz, 1H), 9.56 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.1, 14.1, 18.0, 19.1, 25.1, 25.8, 27.1, 36.7, 70.8, 80.6, 82.7, 110.0, 198.8; MS-ESI: *m/z* 317 (M^++H).

4.1.11. *tert*-(3*S*,4*S*,5*R*)-Butyl-[-(2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl-butoxyl-dimethyl-silane 24

To a stirred solution of iodomethyltriphenylphosphine (383 mg, 0.94 mmol) in THF (10 mL) was added *n*-BuLi (0.29 mL, 1.6 M, 0.47 mmol) dropwise at 0 °C. After 30 min, aldehyde **23** (100 mg, 0.31 mmol) was added and the reaction mixture was allowed to warm to room temperature over 15 min. The resultant mixture was quenched with saturated aqueous NH_4Cl, diluted with ethyl-acetate (2 × 5 mL). The combined organic layer was washed with water and then brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (10% EtOAc/hexane) to give compound **24** (78 mg, 70%) as a yellow liquid. $[\alpha]_D^{27} = -19.6$ (*c* 12.5, $CHCl_3$); IR (neat): ν_{max} 2956, 2933, 2860, 1465, 1374, 1251, 1078,773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 3H),1.37–1.46 (m, 2H), 1.47 (s, 3H), 1.54–1.71 (m, 2H), 3.80–3.89 (m, 1H), 4.07 (t, *J* = 7.0 Hz, 1H), 4.55 (t, *J* = 7.0, 6.4 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.31 (br d, *J* = 17.2 Hz, 1H), 5.96 (ddd, *J* = 17.2, 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.3, −3.7, 14.3, 16.6, 25.3, 25.9, 27.8, 29.6, 36.0, 70.3, 79.0, 79.6, 108.0, 117.6, 134.9; MS-ESI: *m/z* 337 (M^++Na); HRMS (ESI): *m/z* calcd for $C_{17}H_{34}O_3NaSi$: 337.2174, found: 337.2174.

4.1.12. (*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butan-1-ol (11) from 24

To a stirred solution of TBS ether **24** (75 mg, 0.23 mmol) in THF (5 mL) at 0 °C, TBAF (0.47 mL, 0.47 mmol, 1 M solution in THF) was added dropwise at the same temperature. The mixture was allowed to stir at room temperature over 3 h. The resultant mixture was quenched with water and diluted with diethyl ether (5 mL). The organic layer was washed with water and then with brine, respectively. The combined organic layers was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (15% EtOAc/hexane) to give compound **11** (42 mg, 90%) as a yellow liquid.

4.1.13. Synthesis of compound 11 from 14

To a solution of an epoxide **14** (600 mg, 3.5 mmol) in THF (8 mL) at −40 °C was added CuI (0.134, 0.7 mmol) and stirred at the same temperature for 15 min. After this time, the pre cooled ethyl magnesium bromide (10.5 ml of 1 M solution in THF, 10.5 mmol) was added by a cannula. The resulting mixture was stirred at −40 °C for 3 h and the reaction was quenched by the addition of aqueous NH_4Cl solution and warmed to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to provide the crude product. Silica gel column chromatography (15% EtOAc/hexane) afforded the pure product **11** (649 mg, 92%) as a colorless oil. $[\alpha]_D^{30} = +8.8$ (*c* 1.6, CH_2Cl_2); lit.[3a] $[\alpha]_D^{20} = +8.8$ (*c*.1.2, CH_2Cl_2). IR (neat): ν_{max} 3467, 2983, 2959, 2932, 2873, 1642, 1217, 1065, 872 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.37 (m, 1H), 1.37 (s, 3H),1.45 (m, 1H), 1.48 (s, 3H), 1.57 (m, 1H), 1.69 (m, 1H), 1.80 (br s, 1H), 3.67 (dt, *J* = 2.6, 2.3 Hz, 1H), 3.97 (dd, *J* = 8.1, 6.4 Hz, 1H), 4.63 (t, *J* = 7.4 Hz, 1H), 5.31 (d, *J* = 10.4 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 6.04 (ddd, *J* = 17.2, 10.4, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 18.3, 25.3, 27.8, 35.8, 69.7, 78.9, 80.7, 108.6, 118.9, 134.7; MS-ES: *m/z* 223 (M^++Na); HRMS (ESI): *m/z* calcd for $C_{11}H_{20}O_3Na$, 223.1305, found 223.1304.

4.1.14. (*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butyl hept-6-enoate 25

A solution of 5-hexenoic acid (792 mg, 5.5 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C. A sample of DCC (1.34 g, 6.5 mmol) was added in several portions and a white precipitate formed quickly. After 15 min stirring, alcohol **11** (1 g, 5.0 mmol) was added as a solution in 9 mL CH_2Cl_2 along with a small amount of DMAP (15 mg). The cooling bath was removed and stirring was continued for 6 h. The solution was filtered and the solvent was removed under reduced pressure. The resulting oil purified by column chromatography (2% EtOAc/hexane) to give **25** (1.24 g, 84%) as colorless oil; $[\alpha]_D^{30} = +19.7$ (*c* 1.5, CH_2Cl_2): IR (neat): ν_{max} 2961, 2933, 2873, 1738, 1642, 1459, 1376, 1246, 1217, 1169, 1100, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.23–1.35 (m, 2H), 1.36 (s, 3H), 1.47 (s, 3H), 1.53–1.75 (m, 4H), 2.07 (q, *J* = 7.0 Hz, 2H), 2.16–2.33 (m, 2H), 4.17 (t, *J* = 7.4 Hz, 1H), 4.60 (t, *J* = 7.4 Hz, 1H), 4.92 (q, *J* = 7.4 Hz, 1H), 4.95–5.06 (m, 2H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.68–5.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 17.9, 23.9, 25.2, 27.5, 33.0, 33.4, 33.7, 71.5, 78.4, 78.9, 108.7, 115.3, 118.5, 133.2, 137.6, 172.5; MS-ES: *m/z* 297 (M^++1); HRMS (ESI); *m/z* calcd for $C_{17}H_{28}O_4Na$ 319.1885, found 319.1872.

4.1.15. Synthesis of herbarumin-1 1 via 10

A degassed solution of Grubbs' first generation catalyst (0.055 g, 0.06) in CH_2Cl_2 (30 mL) was added over 30 min to a refluxing solution of compound **25** (0.1 g, 0.33) in CH_2Cl_2 (180 mL) and was stirred for 8 h at reflux. After the starting material was completely consumed (judged by TLC), the reaction was stopped and allowed to cool to room temperature. The solvent was removed under reduced pressure to give a dark brown colored residue. The crude product was purified by silica gel column chromatography (7% EtOAc/hexane) to afford *E*/*Z* (4:1) mixture of **10** (0.074 g, 82%) as a colorless liquid.

The diastereomeric mixture of compound **10** (70 mg, 0.26 mmol) and trifluoroacetic acid (0.03 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature for 8 h until TLC showed complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography (25% EtOAc/hexane) to obtain Herbarumin-1 (30 mg, 88%), as a low melting solid along with a mixture of *E*/*Z* diastereomers 22.4 mg. $[\alpha]_D^{31} = +11.2$ (*c* 0.7, EtOH); Lit.[3b] $[\alpha]_D^{20} = +10.8$ (*c* 0.51, EtOH); IR (neat): ν_{max} = 3451, 2959, 2929, 1730, 1455, 1206, 1061, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.20–1.40 (m, 2H), 1.50–1.54 (m, 1H), 1.72 (m, 1H), 1.82–2.00 (m, 4H), 2.16 (br s, 1H), 2.38–2.50 (m, 3H), 3.51 (dd, *J* = 9.8, 1.9 Hz, 1H), 4.42 (br s, 1H,), 4.94 (dt, *J* = 9.6, 2.4 Hz, 1H), 5.45–5.57 (m, 1H),5.61 (d, *J* = 15.9, Hz, 1H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 18.0, 24.6, 33.3, 33.7, 34.4, 70.2, 73.3, 73.7, 120.8, 130.6, 176.4; MS-ES: *m/z* 251 (M^++Na); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_4Na$, 251.1259, found 251.1248.

4.1.16. Stagonolide A

To a solution of herbarumin-1 (30 mg, 0.13 mmol) in CH_2Cl_2 (6.0 mL) was added manganese dioxide (229 mg, 2.6 mmol) at room temperature. After being stirred at the same temperature for 20 h, the reaction mixture was filtered through a pad of Celite. The solvent was concentrated under reduced pressure and the resulting residue was purified by column chromatography (10% EtOAc/hexane) to obtain stagonolide A (28.5 mg, 96%, based on recovery of starting material) as a colorless crystalline solid. Mp = 71–72 °C. $[\alpha]_D^{32} = -60$ (*c* 0.2, EtOH); IR (neat): ν_{max} = 3417, 2960, 2930, 2869, 1727, 1692, 1632, 1438, 1398, 1152, 1075, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.24–1.50 (m, 2H), 1.58–1.73 (m, 1H), 1.86–2.03 (m, 3H), 2.05 (m, 1H), 2.13 (dd, *J*= 14.0, 2.3 Hz, 1H), 2.44 (d, *J* = 5.7 Hz, 1H), 2.47–2.55 (m, 1H), 4.05 (dd, *J* = 9.5, 6.2 Hz, 1H), 4.65 (dt, *J* = 9.6, 2.4 Hz, 1H), 6.24–6.37 (m, 1H), 6.42 (d, *J* = 16.0, Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 13.7, 18.0, 25.0, 33.5, 34.0, 34.2, 74.5, 76.5, 131.9, 143.1, 174.1, 199.6; MS-ES: *m/z* 249 (M^++Na); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}O_4Na$, 249.1102, found 249.1095.

Acknowledgment

B.K. and G.M.R. thank CSIR, New Delhi, for financial assistance.

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