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Stereoselective synthesis of (+)-pericosine B and (+)-pericosine C using ring closing metathesis approach

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ABSTRACT

Stereoselective synthesis of (+)-pericosine B and (+)-pericosine C were achieved from D-ribose using RCM and RCEYM as key steps.

1. Introduction

Carbasugars[1] are the mimics of monosaccharides in biological systems in which the ring oxygen is replaced with a methylene group[2] and they have attracted considerable attention from biologists and chemists because of glycosidase inhibitory activity. Glycosidase enzymes are involved in numerous biological processes and their inhibition has enormous potential for the treatment of many diseases. Some of the carbasugar related compounds have been isolated from natural sources.[3] One among them is the pericosine family, pericosines A–E **1**–**5** have been isolated from *Periconia byssoides* OUPS-N133 fungus that was originally isolated from the sea hare, *Aplysia kurodai* (Fig 1).[4]

These compounds show interesting biological activities such as cytotoxicity against P388 lymphocytic leukemia cells, antitumor activity against murine P388 cells and selective growth inhibition against human cancer cell lines HBC-5 and SNB-75.[4,5] Hence various synthetic approaches to pericosine A–D,[6,7] have been developed and most of these syntheses start from shikimic acid or quinic acid. Shikimic acid and quinic acids are relatively expensive and are of limited availability,[8] therefore non-dependent shikimic acid or quinic acid routes are desirable for the synthesis of these natural products. As a part of ongoing program in our group on the synthesis of carbasugars we have developed a NHK-RCM strategy for the construction of carbocycles;[9] herein we are presenting the application of this approach to the synthesis of (+)-pericosine B **2** and an enyne metathesis strategy (RCEYM) for (+)-pericosine C **3** from the inexpensive starting material D-ribose (Scheme 1).

The (+)-pericosine C **3** is nothing but a C_6 epimer of (+)-pericosine B **2**. Therefore, it is logical to envisage a common strategy for their synthesis by appropriately tuning the reaction conditions to get both epimers at C_6. The chiral hydroxyl groups at C_3, C_4 and C_5 of **2** and **3** can be obtained from D-ribose. For instance, one carbon homologation at C-1, and a vinyl group or ethynyl group introduction at C-5 will give the RCM precursors **6** or **7** respectively which can be elongated to the cyclohexene cores of (+)-pericosine B **8** and (+)-pericosine C **9**. In our previous communication, we have studied and compared the stereoselectivities between the addition of organo chromium and organo magnesium nucleophiles onto α-alkoxy aldehydes,[9b] where organo chromium addition takes place via a Felkin–Anh model, in non-chelation mode. In the case of organo lithiums, the addition takes place in chelation mode, thus giving a reversal of stereochemistry at the newly generated stereocentre. Herein we have developed a common strategy for the synthesis of epimers **2** and **3** based on the above approach from D-ribose by the addition of appropriate nucleophiles onto C-5 of ribose.

Based on our retrosynthetic analysis, we have chosen D-ribose as a starting material and the compound **10** required for the synthesis is prepared from D-ribose in six steps by using our earlier procedure.[9b]

2. Results and discussion

Nucleophilic addition onto α-alkoxy aldehyde **10** with iodo compound **11** under Nozaki–Hiyama–Kishi (NHK) conditions[10] in DMF gave *anti* alcohol **12** as the major product along with *syn* **13** in the ratio of 3:1. The major isomer **12** was separated and subjected to ring closing metathesis using Grubbs 2nd generation catalyst in toluene at reflux to give cyclohexene derivative **14**.[11] The allylic alcohol in compound **14** was converted into a methyl ether **15** using NaH/MeI, which on treatment with PPTS in MeOH yielded **16** (Scheme 2).

The primary alcohol within compound **16** was oxidized using TEMPO/BAIB to give α,β-unsaturated aldehyde **17**. The aldehyde **17** was subjected to Pinnick oxidation[12] to give an acid, which on esterification with MeI and K_2CO_3 gave compound **18**. Global deprotection of the MOM and isopropylidene in compound **18** was achieved with TFA in methanol to give (+)-pericosine B **2** as a white solid whose physical and spectroscopic data were identical with the reported values.[7b,e]

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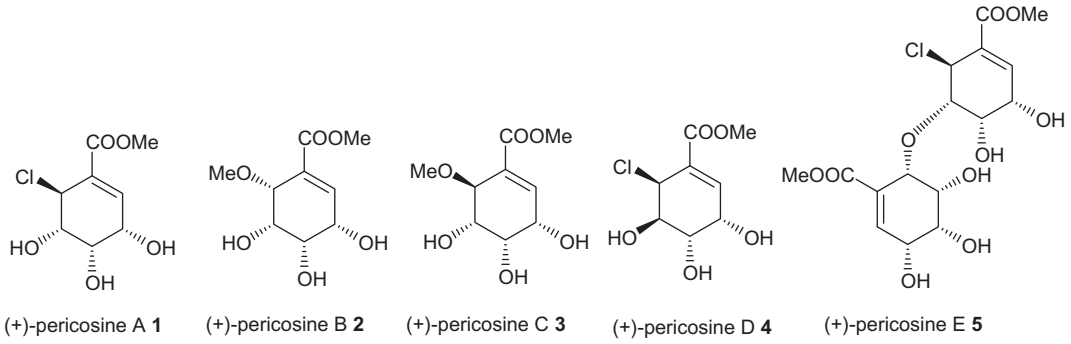
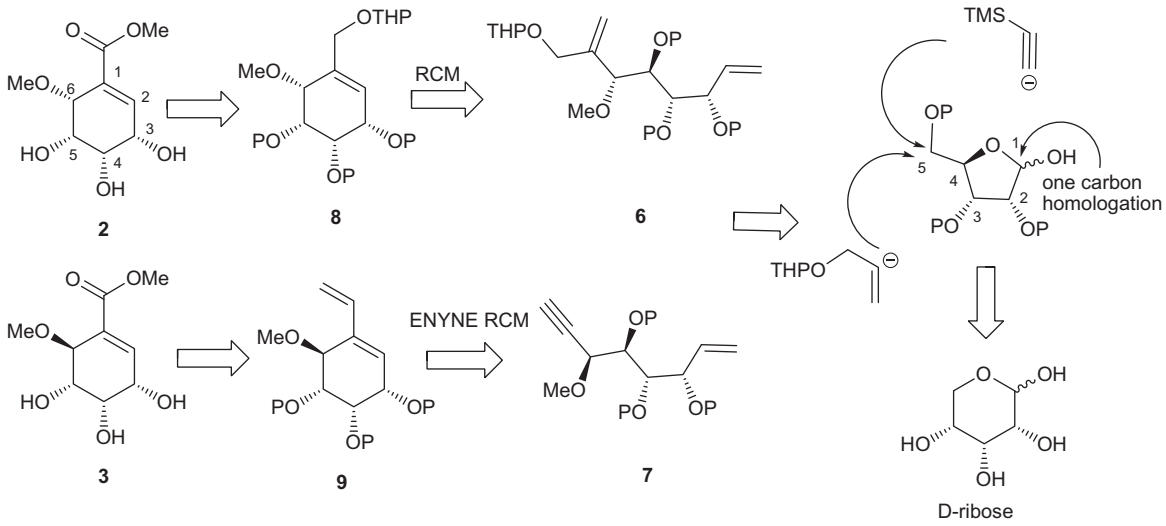


Figure 1. Structures of (+) pericosines A, B, C, D and E.



Scheme 1. Retrosynthetic analysis of (+) pericosine B and C.

For the synthesis of (+)-pericosine C **3**, we needed a reversal of stereochemistry at the newly generated stereogenic centre obtained during nucleophilic addition onto **10**. For this we envisaged to carry out an alkynylation on the α, β-*anti*-dialkoxyaldehyde **10** under the chelation mode and we assumed that the MOM protecting group in the alkoxy aldehyde should act as a bidentate ligand to give 1,2-*syn* selectivity during nucleophilic addition.[13]

When aldehyde **10** was treated with lithium trimethylsilylacetalide in THF it gave *syn* propargylic alcohol **19** as the major isomer along with *anti* propargylic alcohol **20** in a ratio of 4:1. Both isomers were separated by column chromatography. The *C*-Silyl group in major compound **19** was desilylated with K_2CO_3 in methanol to give **21(a)**, which on methylation with NaH and MeI afforded the required RCEYM precursor **21(b)**. The enyne **21(b)** was treated with 10 mol % Grubbs second generation catalyst in toluene at 80 °C under Mori's conditions and gave the cyclohexene derivative **22** in a 60% yield.[14] Oxidative cleavage of the terminal double bond in compound **22** was achieved with $OsO_4/NaIO_4$ to give α,β-unsaturated aldehyde **23**.[15] Aldehyde **23** was oxidized to an acid using Pinnick's protocol, followed by esterification with K_2CO_3/MeI in acetone and yielded the protected form of (+)-pericosine C **24**. Global deprotection of the isopropylidine and methoxy methyl groups in compound **24** was achieved with TFA in methanol to give (+)-pericosine C **3** (Scheme 3). The spectroscopic and physical data of (+)-pericosine C **3** were identical with the reported values.[6e]

To further confirm the stereochemistry of the newly generated stereogenic centre the minor isomer **13** was converted to compound **23** as shown in Scheme 4.

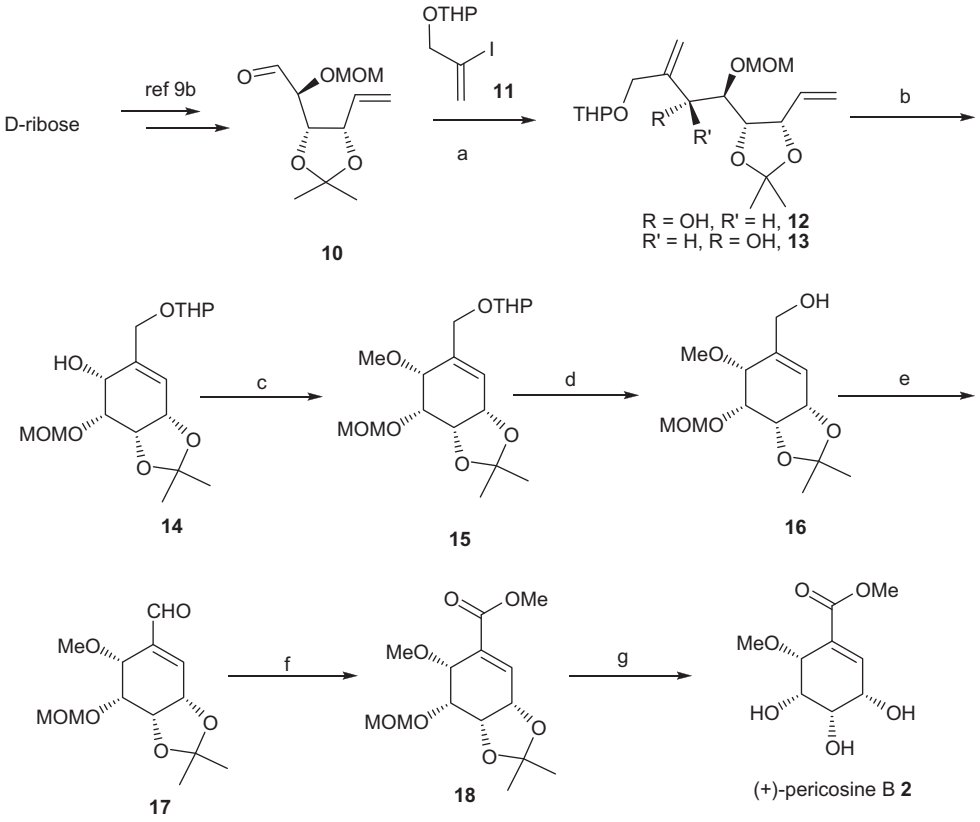
The minor isomer **13** was separated and subjected to ring closing metathesis using Grubbs 2nd generation catalyst in toluene at reflux to give cyclohexene derivative **25** (Scheme 4).[11] The allylic alcohol within compound **25** was converted to methyl ether **26(a)** using NaH, MeI and followed by THP deprotection with PPTS in MeOH to yield **26(b)**. The primary alcohol in compound **26(b)** was oxidized using TEMPO/BAIB to give α,β-unsaturated aldehyde **23** (Scheme 4). The spectroscopic data of compound **23** were identical with the compound obtained from alkenyl addition (Scheme 3).

3. Conclusion

In conclusion we successfully developed a common strategy based on ring closing metathesis for the synthesis of (+)-pericosine B and (+)-pericosine C. Our strategy may be useful to synthesize other pericosines and related structures.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as an eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz and 400 MHz or a Bruker Avance-300 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity



Scheme 2. Reagents and conditions: (a) $CrCl_2$, $NiCl_2$, DMF, **11**, 24 h, 72%; (b) 10 mol % Grubbs 2nd gen. cat. toluene, reflux, 12 h, 80%; (c) NaH, MeI, THF, 0 °C to rt, 3 h, 70%; (d) PPTS, MeOH, rt, 1 h, 65%; (e) BAIB, TEMPO (cat), DCM, 1 h, 62%; (f) (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, 0 °C to rt, 2 h; (ii) K_2CO_3, MeI, acetone, rt, 3 h, 80% (over 2 steps); (g) TFA, MeOH, 3 h, rt, 65%.

(s–singlet; d–doublet; t–triplet; q–quartet; m–multiplet), number of proton (s) and coupling constant (s) *J* (Hz). ^{13}C NMR data are expressed as chemical shifts in ppm. Optical rotations were measured with JASCO digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA). Doubling of peaks in NMR of compounds **12**, **13**, **14**, **15**, **25** and **26(a)** is because of diastereomers due to THP protection.

4.1. (1*R*,2*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-3-((tetrahydro-2*H*-pyran-2-yloxy)methyl) but-3-en-2-ol 12, (1*R*,2*S*)-1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-3-((tetrahydro-2*H*-pyran-2-yloxy)methyl) but-3-en-2-ol 13

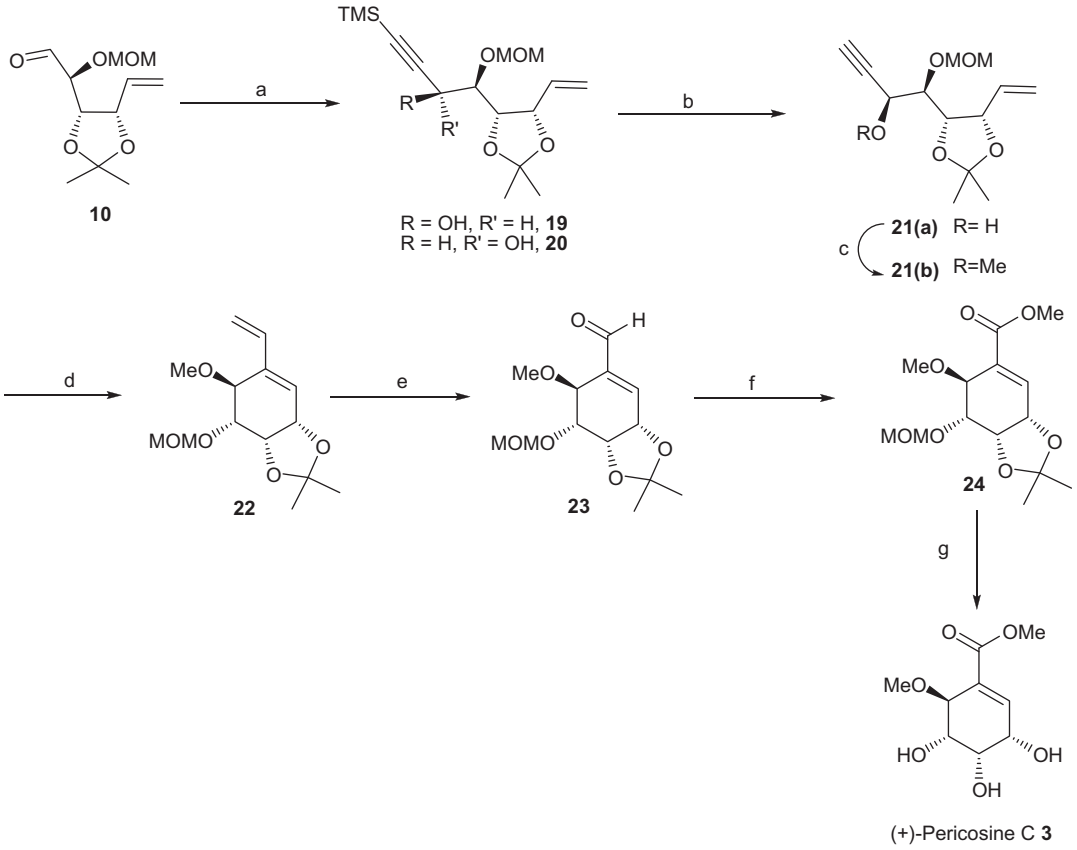
A mixture of $CrCl_2$ (1.33 g, 8.69 mmol) and a catalytic amount of $NiCl_2$ (0.028 g, 0.217 mmol) in dry DMF (7 mL) was stirred at 25 °C for 10 min under nitrogen atmosphere. To it a solution of aldehyde **10** (0.5 g, 2.17 mmol) in DMF (5 mL), **11** (0.76 mL, 8.69 mmol) was added at 25 °C successively. After stirring at room temperature for 24 h, the reaction mixture was diluted with ether, poured into water and extracted with ether repeatedly. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography using EtOAc/hexane (12:1) as an eluant provided alcohol **12** as a yellow oil (0.36 g, 54%) and **13** also as a yellow oil (0.06 g, 18%) in a ratio of 3:1 (0.42 g, 72%): Data for compound **12**: $[\alpha]_D^{24} = +122.3$ (*c* 0.3, $CHCl_3$): IR (neat) ν_{max}: 3471, 2938, 1377, 1214, 1030, 908, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.34 (s, 3H), 1.48 (s, 3H), 1.51–1.91 (m, 6H), 3.41 (s, 3H), 3.49 (m, 1H), 3.77–3.96 (m, 3H), 4.06–4.22 (m, 2H), 4.32–4.46 (m, 2H), 4.58–4.73 (m, 4H), 5.20–5.42 (m, 4H), 5.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): (19.3, 19.4)*, (25.3, 25.4)*, 27.9, 30.5, (56.4, 56.4)*, (61.9, 62.1)*, (67.7, 67.9)*, (73.2, 73.5)*, 77.2, 79.0, (82.0, 82.2)*, 97.7, 98.0, (98.7, 98.8)*, 108.5, (114.5, 115.0)*, (117.6, 117.6)*, (134.7, 134.8)*, (144.1, 144.3)*; ESI/MS (*m*/*z*): 395 $(M+Na)^+$; HRMS Calcd for $C_{19}H_{32}O_7Na$ $(M+Na)^+$ 395.2045, found 395.2048.

4.1.1. Data for compound 13

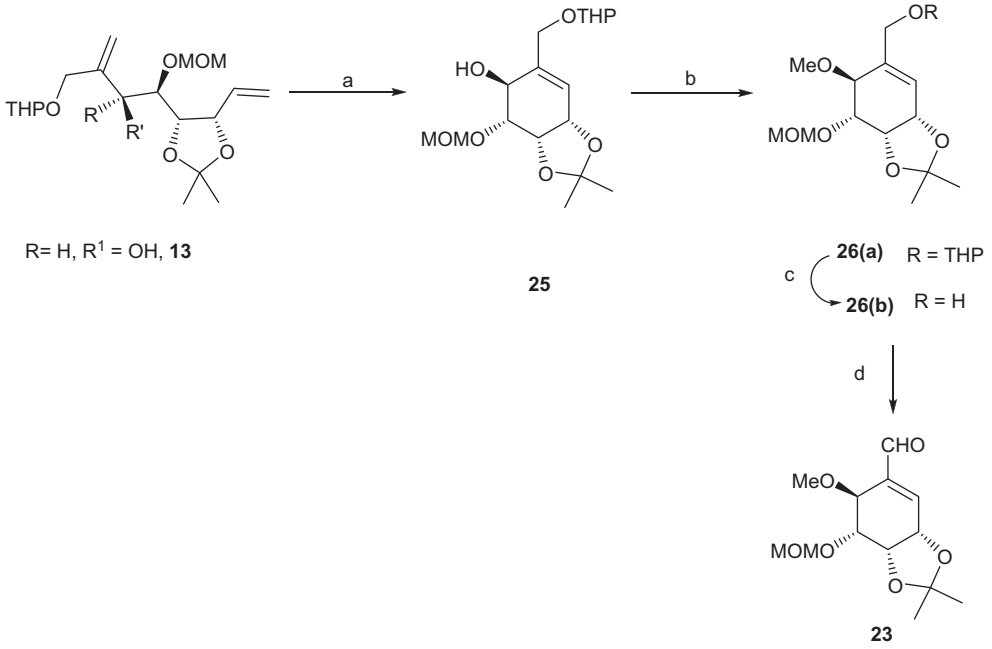
$[\alpha]_D^{24} = -14.3$ (*c* 2.1, $CHCl_3$): IR (neat) ν_{max}: 3471, 2938, 1377, 1214, 1030, 908, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.36 (s, 3H), 1.50 (s, 3H), 1.52–1.87 (m, 6H), 3.38 (s, 3H), 3.49 (m, 1H), 3.77–3.96 (m, 2H), 4.04 (m, 1H), 4.26–4.47 (m, 3H), 4.60–4.72 (m, 4H), 5.24–5.42 (m, 5H), 6.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): (19.2, 19.2)*, (25.2, 25.4)*, (27.7, 27.9)*, 30.5, 56.3, 61.9, (67.4, 67.6)*, 67.9, 72.1, 72.5, 78.4, 78.8, (97.5, 97.7)*, 98.3, 98.30, 108.4, 114.4, 114.554, 118.3, (134.6, 134.7)*, (145.0, 145.2)*; ESI/MS (*m*/*z*): 395 $(M+Na)^+$.

4.2. (3a*S*,4*R*,5*R*,7a*S*)-4-(Methoxymethoxy)-2,2-dimethyl-6-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol 14

To a solution of **12** (0.6 g, 1.7 mmol) in toluene (44 mL) Grubbs second generation catalyst (0.13 g, 0.16 mmol) was added at room temperature. The reaction mixture was refluxed for 12 h, toluene was removed under vacuum and purified by column chromatography using EtOAc/hexane (1:4) to provide cyclohexenol derivative **14** as an oily compound (0.44 g, 80%). $[\alpha]_D^{24} = -64.06$ (*c* 2.1, $CHCl_3$); IR (neat) ν_{max}: 2933, 2355, 1201, 1119, 1030, 908, 762 cm^{-1}; ^1H NMR (300 MHz): 1.36 (s, 3H), 1.43 (s, 3H), 1.48–1.91 (m, 6H), 3.14 (dd, 1H, *J* = 2.6, 10.7 Hz), 3.47 (s, 3H), 3.53 (br s, 1H), 3.75–3.87 (m, 2H), 4.05 (m, 1H), 4.16 (m, 1H), 4.31 (m, 1H), 4.53–4.66



Scheme 3. Reagents and conditions: (a) TMS–acetylene, *n*-BuLi, THF, −78 °C, 3 h, 85%; (b) K_2CO_3, MeOH, rt, 2 h, 85%; (c) NaH, MeI, THF, 0 °C to rt, 3 h, 70%; (d) 10 mol % Grubbs 2nd gen. cat. toluene, ethylene gas, 80 °C, 12 h, 65%; (e) (i) OsO_4, NMO, acetone/water, rt, 3 h; (ii) $NaIO_4$, 1 h, rt, 50% (over 2 steps); (f) (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, 0 °C to rt, 2 h; (ii) K_2CO_3, MeI, acetone, rt, 3 h, 80% (over 2 steps); (g) TFA, MeOH, rt, 3 h, 65%.



Scheme 4. Reagents and conditions: (a) 10 mol % Grubbs 2nd gen. cat. toluene, reflux, 12 h, 80%; (b) NaH, MeI, THF, 0 °C to rt, 3 h, 70%; (c) PPTS, MeOH, rt, 1 h, 65%; (d) BAIB, TEMPO (cat), DCM, 1 h, 65%.

(m, 3H), 4.78 (d, 1H, J = 6.9 Hz), 4.92 (d, 1H, J = 6.8 Hz), 5.67 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz): (19.2, 19.4)*, 25.3, 26.4, 28.0, 30.4, 55.7, (62.0, 62.2)*, 64.7, 66.8, 67.9, 71.6, 73.6, 76.0, (95.0, 95.1)*, 97.6, 99.0, 110.8, (122.2, 122.3)*, (137.9, 137.0)*; ESI/MS (m/z): 367 (M+Na)$^+$; HRMS Calcd for $C_{17}H_{28}O_7Na$ (M+Na)$^+$ 367.1732, found 367.1737.

4.3. (3a*S*,4*R*,5*R*,7a*S*)-5-Methoxy-4-(methoxymethoxy)-2,2-dimethyl-6-((tetrahydro2*H*-pyran-2-yloxy)methyl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole 15

To an ice-cooled, stirred solution of NaH (0.09 g, 60% w/v dispersion in mineral oil, 2.3 mmol) in THF (5 mL) were added compound **14** (0.4 g, 1.11 mmol) in THF (5 mL) and methyl iodide (0.1 mL, 1.7 mmol). The mixture was stirred at room temperature for 3 h, quenched with saturated NH_4Cl solution and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water and brine, then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on silica gel eluting with EtOAc/hexane (9:1) to give compound **15** (0.29 g, 70%) as a syrup. $[\alpha]_D^{24} = +31.9$ (c 0.6, $CHCl_3$): IR (neat) ν_{max}: 2933, 2355, 1201, 1119, 1030, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.31 (s, 3H), 1.41 (s, 3H), 1.44–1.88 (m, 6H), 3.35 (s, 3H), 3.41(2s, 3H), 3.45 (m, 1H), 3.74–3.80 (m, 2H), 3.90–4.01 (m, 2H), 4.13–4.30 (m, 2H), 4.51 (br s, 1H), 4.55 (m, 1H), 4.67 (d, 1H, J = 6.4 Hz), 4.75(d, 1H, J = 6.7 Hz), 5.80 (d, 1H, J = 9.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): (19.3, 19.3)*, 25.4, 25.6, 26.8, 30.5, 30.8, 55.5, 58.7, 62.1, 64.1, 66.9, 67.9, (69.0, 69.4)*, 69.9, (71.1, 71.5)*, 74.0, 77.2, (96.3, 96.6)*, 98.0, 98.8, (110.3, 110.3)*, (120.4, 120.7)*, (137.6, 137.8)*; ESI/MS (m/z): 381 (M+Na)$^+$: HRMS Calcd for $C_{18}H_{30}O_7Na$ (M+Na)$^+$ 381.1889, found 381.1879.

4.4. ((3a*S*,6*R*,7*R*,7a*S*)-6-Methoxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetra-hydrobenzo[*d*][1,3]dioxol-5-yl) methanol 16

To an ice cooled stirred solution of compound **15** (0.2 g, 0.55 mmol) in methanol (5 mL) catalytic amount of PPTS was added. The mixture was stirred for 1 h at 0 °C, methanol was removed under vacuo and purified by column chromatography using EtOAc/hexane (3:2) to give compound **16** (0.09 g, 65%) as a syrup. $[\alpha]_D^{24} = +62.9$ (c 0.5, $CHCl_3$): IR (neat) ν_{max}: 3470, 2926, 1376, 1123, 1031, 975, 907, 863 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.39 (s, 3H), 1.48 (s, 3H), 3.42 (s, 3H), 3.51 (s, 3H), 3.92 (br s, 1H), 4.17 (m, 1H), 4.24 (br s, 2H), 4.30 (m, 1H), 4.59 (m, 1H), 4.73 (d, 1H, J = 6.9 Hz), 4.88 (d, 1H, J = 6.9 Hz), 5.90 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz): 25.4, 26.6, 55.4, 57.8, 64.2, 68.9, 71.1, 74.2, 77.9, 96.7, 110.4, 120.5, 139.7; ESI/MS (m/z): 297 (M+Na)$^+$; HRMS Calcd for $C_{13}H_{22}O_6Na$ (M+Na)$^+$ 297.1314, found 297.1305.

4.5. (3a*S*,6*R*,7*R*,7a*S*)-6-Methoxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetra-hydrobenzo[*d*][1,3]dioxole-5-carbaldehyde 17

To an ice cooled stirred solution of alcohol **16** (0.1 g, 0.36 mmol) in CH_2Cl_2 (3 mL) TEMPO (0.005 g, 0.03 mmol) and BAIB (0.14 g, 0.43 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and extracted with DCM. The organic layer was washed with brine, separated, dried over anhydrous Na_2SO_4 and purified by column chromatography using EtOAc/hexane (3:7) to give compound **17** (0.06 g, 62%) as a syrup. $[\alpha]_D^{24} = -52.1$ (c 0.7, $CHCl_3$): IR (neat) ν_{max}: 2923, 1742, 1459, 1258, 1019 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): 1.38 (s, 3H), 1.41 (s, 3H), 3.46 (s, 3H), 3.52 (s, 3H), 3.74 (dd, 1H, J = 2.8, 4.5 Hz), 4.3 (d, 1H, J = 4.5 Hz), 4.60 (m, 1H), 4.72 (dd, 1H, J = 3.2, 5.6 Hz), 4.82 (s, 2H), 6.56 (dd, 1H, J = 0.7, 3.2 Hz), 9.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 25.9, 27.7, 55.8, 61.0, 69.2, 72.2, 72.7, 74.0, 95.0, 111.7, 139.3, 145.7, 192.9; ESI/MS (m/z): 295 (M+Na)$^+$; HRMS Calcd for $C_{13}H_{20}O_6Na$ (M+Na)$^+$ 295.1157, found 295.1154.

4.6. (3a*S*,6*R*,7*R*,7a*S*)-Methyl 6-methoxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-5-carboxylate 18

To an ice cooled stirred solution of compound **17** (0.06 g, 0.22 mmol) in t-BuOH (1.0 mL) were added (0.2 mL) of 2-methyl-2-butene, $NaClO_2$ (0.06 g, 0.68 mmol) and NaH_2PO_4 (0.10 g, 0.67 mmol) and then stirred for 2 h at room temperature. Then the reaction mixture was treated with aq 1 M HCl and extracted with EtOAc (2 × 50 mL). Organic layers were combined and washed with water and brine then dried over Na_2SO_4 and concentrated in vacuum. The crude acid was dissolved in acetone (2 mL), to it K_2CO_3 (0.09 g, 0.64 mmol) and methyl iodide (0.02 mL, 0.32 mmol) were added and then stirred for 3 h. Reaction mixture was filtered through a celite pad and washed with ethyl acetate and the filtrate was concentrated under vacuum. The residue was dissolved in EtOAc (50 mL), washed with water, brine and dried over Na_2SO_4. The solvent was removed on a rotary evaporator, the crude ester **18** was submitted to column chromatography and eluted using EtOAc/hexane (2:3) to give ester **18** (0.04 g) as a syrup in an 80% yield (over 2 steps). $[\alpha]_D^{24} = -39.8$ (c 0.8, $CHCl_3$): IR (neat) ν_{max}: 2921, 2363, 1693, 1516, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.39 (s, 3H), 1.43 (s, 3H), 3.49 (s, 3H), 3.60 (s, 3H), 3.78 (s, 3H), 3.80 (m, 1H), 4.38 (d, 1H, J = 4.5 Hz), 4.59 (m, 1H), 4.67 (dd, 1H, J = 3.3, 5.4 Hz), 4.87 (s, 2H), 6.80 (dd, 1H, J = 0.7, 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 26.1, 27.7, 52.1, 55.8, 61.2, 71.7, 72.6, 72.8, 73.2, 95.0, 111.5, 130.2, 137.0, 166.5; ESI/MS (m/z): 325 (M+Na)$^+$; HRMS Calcd for $C_{15}H_{24}O_7Na$ (M+Na)$^+$ 325.1263, found 325.1255.

4.7. (+)-Pericosine B 2

To a solution of compound **18** (0.04 g, 0.13 mmol) in methanol (1 mL), TFA (0.5 mL) was added and stirred the reaction mixture at room temperature for 3 h. Then the solvent was removed under vacuum to afford crude pericosine B, which was purified by column chromatography using MeOH/$CHCl_3$ (1:24) to give (+)-pericosine B **2** (0.018 g) as a white solid in a 65% yield, mp 85–87 °C. $[\alpha]_D^{24} = +29$ (c 0.12, EtOH); (lit.[7e] $[\alpha]_D^{20} = +22.3$ (c 0.82, EtOH)); IR (neat) ν_{max}: 3620, 2924, 2362, 1740, 1462, 1080 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): 3.58 (s, 3H), 3.75 (s, 3H), 3.79 (m, 1H), 3.81–3.96 (m, 2H), 4.15 (m, 1H), 4.25 (d, 1H, J = 4.1 Hz), 4.40 (d, 1H, J = 6.7 Hz), 6.70 (dd, 1H, J = 0.9, 2.4 Hz); ^{13}C NMR (acetone-d_6, 75 MHz): 51.9, 61.3, 69.3, 69.8, 72.5, 76.8, 130.3, 141.8, 166.7; ESI/MS (m/z): 241 (M+Na)$^+$; HRMS Calcd for $C_9H_{14}O_6Na$ (M+Na)$^+$ 241.0688, found 241.0682.

4.8. (1*R*,2*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-4-(trimethylsilyl)but-3-yn-2-ol 19, (1*R*,2*R*)-1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-4 (trimethylsilyl)but-3-yn-2-ol 20

To a solution of TMS-acetylene (1.8 mL, 13.04 mmol) in dry THF (10 mL) was added n-BuLi (7.6 mL, 12.17 mmol, 1.6 M solution in hexane) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. This reaction mixture was further cooled to −78 °C, to this aldehyde **10** (1 g, 4.34 mmol) in THF was added over 10 min. After stirring for 3 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Concentration and purification by silica gel column

chromatography using EtOAc/hexane (9:1) as eluent afforded propargylic alcohol **19** (0.97 g, 68%) and **20** (0.24 g, 17%) as yellow oils in the ratio 4:1 (1.21 g, 85%). Data for compound **19**: $[\alpha]_D^{24} = -16.5$ (*c* 1.4, $CHCl_3$); IR (neat) ν_{max}: 3529, 2956, 2173, 1643, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.19 (s, 9H), 1.39 (s, 3H), 1.50 (s, 3H), 3.12 (d, 1H, *–OH*, *J* = 10.9 Hz), 3.38 (s, 3H), 3.54 (dd, 1H, *J* = 3.3, 9.0 Hz), 4.43 (dd, 1H, *J* = 6.0, 9.0 Hz), 4.61–4.67 (m, 4H), 5.23 (d, 1H, *J* = 10.5 Hz), 5.36 (d, 1H, *J* = 15.8 Hz), 5.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −0.2, 25.1, 27.7, 56.1, 64.3, 77.2, 77.8, 78.8, 90.8, 97.7, 104.0, 109.1, 118.0, 133.8; ESI/MS (*m*/*z*): 351 $(M+Na)^+$; HRMS Calcd for $C_{16}H_{28}O_5NaSi$ $(M+Na)^+$ 351.1603, found 351.1588.

4.8.1. Data for compound 20

$[\alpha]_D^{24} = +29.3$ (*c* 2.2, $CHCl_3$); IR (neat) ν_{max}: 3418, 2987, 2173, 1644, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.18 (s, 9H), 1.40 (s, 3H), 1.50 (s, 3H), 3.53 (m, 1H), 3.55 (s, 3H), 4.21 (dd, 1H, *J* = 6.0, 9.6 Hz), 4.54–4.67 (m, 3H), 4.72 (t, 1H, *J* = 6.4 Hz), 4.90 (d, 1H, *J* = 11.8 Hz), 5.24 (d, 1H, *J* = 10.3 Hz), 5.39 (d, 1H, *J* = 17.5 Hz), 5.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −0.1, 25.2, 27.8, 56.2, 63.5, 76.3, 77.8, 78.4, 84.3, 90.8, 97.9, 103.2 108.8, 116.9, 133.6; ESI/MS (*m*/*z*): 351 $(M+Na)^+$; HRMS Calcd for $C_{16}H_{28}O_5NaSi$ $(M+Na)^+$ 351.1603, found 351.1590.

4.9. (1*R*,2*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-but-3-yn-2-ol 21a

To a stirred solution of silyl derivative **19** (0.95 g, 2.9 mmol) in dry MeOH (5 mL) was added K_2CO_3 (1.2 g, 8.6 mmol) under nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was filtered through a Celite pad and washed with ethyl acetate. Then MeOH was evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (3 × 50 mL), and the organic extract was washed with water, brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc/hexane (5:1) to give **21(a)** (0.63 g, 85%) as a liquid. $[\alpha]_D^{24} = +11.0$ (*c* 2.2, $CHCl_3$); IR (neat) ν_{max}: 3516, 2926, 2173, 1377, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.41 (s, 3H), 1.52 (s, 3H), 2.52 (d, 1H, *J* = 1.98 Hz), 3.41 (s, 3H), 3.55 (d, 1H, *J* = 11 Hz, *–OH*), 3.63 (dd, 1H, *J* = 3.3, 8.8 Hz), 4.55 (dd, 1H, *J* = 6.3, 8.8 Hz), 4.66 (d, 1H, *J* = 6.7 Hz), 4.72 (d, 1H, *J* = 6.7 Hz), 4.68–4.80 (m, 2H), 5.27 (d, 1H, *J* = 10.4 Hz), 5.40 (d, 1H, *J* = 17.1 Hz), 5.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 25.2, 27.6, 56.1, 64.2, 73.9, 77.4, 77.4, 78.6, 82.3, 97.9, 109.2, 117.8, 133.4; ESI/MS (*m*/*z*): 293 $(M+Na)^+$; HRMS Calcd for $C_{14}H_{22}O_5Na$ $(M+Na)^+$ 279.1208, found 279.1208.

4.10. (4*S*,5*S*)-4-((1*R*,2*S*)-2-Methoxy-1-(methoxymethoxy)but-3-ynyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane 21b

To an ice-cooled, stirred solution of NaH (0.18 g, 60% w/v dispersion in mineral oil, 4.68 mmol) in THF (5 mL) were added compound **21(a)** (0.65 g, 2.34 mmol) in THF (5 mL) and methyl iodide (0.25 mL, 3.8 mmol). The mixture was stirred at room temperature for 3 h. It was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with water and brine, then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on silica gel using EtOAc/hexane (9:1) to give compound **21(b)** (0.48 g, 70%) as a syrup. $[\alpha]_D^{24} = -8.9$ (*c* 1.1, $CHCl_3$); IR (neat) ν_{max}: 3257, 2926, 2854, 1375, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.35 (s, 3H), 1.46 (s, 3H), 2.45 (d, 1H, *J* = 1.8 Hz), 3.38 (s, 3H), 3.44 (s, 3H), 3.75 (dd, 1H, *J* = 3.02, 7.5 Hz), 4.20 (dd, 1H, *J* = 2.26, 3.02 Hz), 4.34 (dd, 1H, *J* = 6.4, 7.5 Hz), 4.61 (dd, 1H, *J* = 6.04, 6.4 Hz), 4.77 (d, 1H, *J* = 6.4 Hz), 4.88 (d, 1H, *J* = 6.4 Hz), 5.22 (d, 1H, *J* = 10.2 Hz), 5.35 (d, 1H, *J* = 16.9 Hz), 6.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 25.4, 27.8, 56.3, 57.3, 71.0, 75.6, 76.5, 77.7, 78.5, 80.5, 97.4, 108.2, 117.8, 134.5; ESI/MS (*m*/*z*): 293 $(M+Na)^+$; HRMS Calcd for $C_{14}H_{22}O_5Na$ $(M+Na)^+$ 293.1364, found 293.1351.

4.11. (3a*S*,4*R*,5*S*,7a*S*)-5-Methoxy-4-(methoxymethoxy)-2,2-dimethyl-6-vinyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole 22

To the solution of ene-yne **21** (**b**) (0.43 g, 1.6 mmol) in toluene (44 mL), Grubbs' second-generation catalyst (0.13 g, 0.16 mmol) was added at room temperature and the reaction mixture refluxed for 12 h under ethylene atmosphere. Toluene was removed under vacuum, and the crude was purified by column chromatography using EtOAc/hexane (1:9) to provide cyclohexene **22** (0.28 g, 65%) as a syrup. $[\alpha]_D^{24} = +2.1$ (*c* 0.9, $CHCl_3$); IR (neat) ν_{max}: 2919, 2851, 1462, 1374, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); 1.40 (s, 3H), 1.41 (s, 3H), 3.42 (s, 3H), 3.47 (s, 3H), 4.04 (dd, 1H, *J* = 3.02, 6.6 Hz), 4.25 (d, 1H, *J* = 6.6 Hz), 4.53 (dd, 1H, *J* = 3.02, 5.85 Hz), 4.67 (dd, 1H, *J* = 3.2, 5.85 Hz), 4.80 (d, 1H, *J* = 6.8 Hz), 4.86 (d, 1H, *J* = 6.8 Hz), 5.18 (d, 1H, *J* = 10.9 Hz), 5.48 (d, 1H, *J* = 17.5 Hz), 5.86 (d, 1H, *J* = 3.2 Hz), 6.38 (dd, 1H, *J* = 10.9, 17.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 26.1, 27.1, 55.5, 57.9, 72.2, 73.8, 74.2, 75.9, 97.0, 109.8, 115.4, 125.7, 135.8, 137.3; ESI/MS (*m*/*z*): 293 $(M+Na)^+$.

4.12. (3a*S*,6*S*,7*R*,7a*S*)-6-Methoxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetra-hydrobenzo[*d*][1,3]dioxole-5-carbaldehyde 23

4.12.1. Method A

To an ice cooled stirred solution of compound **22** (0.2 g, 0.74 mmol) in acetone/water (4:1), (5 mL) were added NMO (0.2 g, 1.48 mmol) and OsO_4 (in toluene) (0.003 g, 0.0.15 mmol), stirred for 3 h at 0 °C. To this reaction mixture $NaIO_4$ (0.31 g, 1.48 mmol) was added at 0 °C and stirred for 1 h. The solvent was removed and the residue was taken in EtOAc (75 mL) and washed with water and brine. The solvent was removed on a rotary evaporator, the crude aldehyde **23** was submitted to column chromatography and eluted using EtOAc/hexane (1:1) to give aldehyde **23** (0.1 g, 50%) as a syrup.

4.12.2. Method B

To an ice cooled stirred solution of alcohol **26(b)** (0.30 g, 0.7 mmol) in DCM (3 mL) TEMPO (0.001 g, 0.01 mmol) and BAIB (0.042 g, 0.13 mmol) were added. The reaction mixture was stirred at room temperature for 1 h extracted with DCM. The organic layer was washed with brine, separated, and dried over anhydrous Na_2SO_4, purification by column chromatography using EtOAc/hexane (3:7) gave compound **23** (0.026, 65%) as a syrup.

$[\alpha]_D^{24} = +78.2$ (*c* 1.5, $CHCl_3$); IR (neat) ν_{max}: 2923, 1742, 1459, 1258, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.41 (s, 3H), 1.43 (s, 3H), 3.35 (s, 3H), 3.46 (s, 3H), 4.08 (dd, 1H, *J* = 3.3, 5.2 Hz), 4.37 (d, 1H, *J* = 5.2 Hz), 4.60 (dd, 1H, *J* = 3.3, 6.4 Hz), 4.69 (d, 1H, *J* = 6.8 Hz), 4.80 (m, 1H), 4.81 (d, 1H, *J* = 6.8 Hz), 6.83 (d, 1H, *J* = 2.8 Hz), 9.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 25.4, 26.6, 55.6, 59.2, 71.1, 72.5, 72.5, 74.1, 97.1, 110.4, 140.0, 145.4, 192.3; ESI/MS (*m*/*z*): 295 $(M+Na)^+$; HRMS Calcd for $C_{13}H_{20}O_6Na$ $(M+Na)^+$ 295.1157, found 295.1162.

4.13. (3a*S*,6*S*,7*R*,7a*S*)-Methyl-6-methoxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-5-carboxylate 24

To an ice cooled stirred solution of compound **23** (0.1 g, 0.36 mmol) in *t*-BuOH (1.5 mL) were added 2-methyl-2-butene (0.4 mL), $NaClO_2$ (0.1 g, 1.1 mmol) and NaH_2PO_4 (0.17 g, 1.1 mmol) were added and stirred for 2 h at room temperature. Then the

reaction mixture was neutralized with aqueous 1 M HCl and extracted with EtOAc (2 × 50 mL). The organic layers were combined and washed with water and brine, then dried over Na_2SO_4 and concentrated in vacuum. The crude acid was dissolved in acetone (2 mL) to it were added K_2CO_3 (0.1 g, 0.72 mmol) and methyl iodide (0.03 mL, 0.44 mmol) and stirred for 3 h. The reaction mixture was filtered through a Celite pad and washed with EtOAc; the filtrate was concentrated under vacuum, the residue was dissolved in (50 mL) of EtOAc, washed with water, brine and dried over Na_2SO_4. The solvent was removed on a rotary evaporator; the crude ester **24** was purified by column chromatography using EtOAc/hexane (2:3) to give ester **24** (0.04 g) as a syrup in an 80% yield (over 2 steps). $[\alpha]_D^{24} = +45.6$ (*c* 0.8, $CHCl_3$); IR (neat) ν_{max}: 2921, 2363, 1693, 1516, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.42 (s, 3H), 1.43 (s, 3H), 3.43 (s, 3H), 3.54 (s, 3H), 3.82 (s, 3H), 4.04 (dd, 1H, *J* = 3.3, 6.04 Hz), 4.4 (d, 1H, *J* = 6.04 Hz), 4.57 (dd, 1H, *J* = 3.02, 5.6 Hz), 4.72 (m, 1H), 4.78 (d, 1H, *J* = 6.79 Hz), 4.86 (d, 1H, *J* = 6.79 Hz), 6.82 (d, 1H, *J* = 3.02); ^{13}C NMR (75 MHz, $CDCl_3$); 25.7, 26.9, 52.0, 55.6, 59.6, 71.5, 74.0, 74.0, 75.0, 97.0, 110.2, 132.2, 136.0, 166.6; ESI/MS (*m*/*z*): 325 $(M+Na)^+$; HRMS Calcd for $C_{15}H_{24}O_7Na$ $(M+Na)^+$ 325.1263, found 325.1257.

4.14. (+)-Pericosine C 3

To a solution of compound **24** (0.04 g, 0.13 mmol) in methanol (1 mL) TFA (0.5 mL) was added and the reaction mixture stirred at room temperature for 3 h. Then the solvent was removed under vacuum to afford crude (+)-pericosine C, which was subjected to column chromatography and eluted using MeOH/$CHCl_3$ (1:24) to give (+)-pericosine C **3** as an oil (0.018 g) in a 65% yield. $[\alpha]_D^{24} = +72.1$ (*c* 0.9, EtOH); (lit.[6e] $[\alpha]_D^{20} = +69.9$ (*c* 0.17, EtOH)); IR (neat) ν_{max}: 3620, 2924, 2362, 1740, 1462, 1080 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz): 3.49 (s, 3H), 3.77 (s, 3H), 3.87–3.93 (m, 2H), 3.94–4.02 (m, 2H, 1 -*OH*), 4.20 (d, 1H, *J* = 4.5 Hz), 4.27 (m, 1H), 4.43 (d, 1H *J* = 6.0 Hz, *OH*), 6.75 (1H, d, *J* = 3.7 Hz); ^{13}C NMR (acetone-d_6, 75 MHz): 52.00, 59.4, 67.4, 70.1, 73.3, 79.1,131.5, 140.4, 166.7; ESI/MS (*m*/*z*): 241 $(M+Na)^+$; HRMS Calcd for $C_9H_{14}O_6Na$ $(M+Na)^+$ 241.0688, found 241.0678.

4.15. (3a*S*,4*R*,5*S*,7a*S*)-4-(Methoxymethoxy)-2,2-dimethyl-6-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol 25

To a solution of **13** (0.2 g, 0.7 mmol) in toluene (44 mL), Grubbs second generation catalyst (0.062 g, 0.07 mmol) was added at room temperature and refluxed for 12 h. Toluene was removed under vacuo and purified by column chromatography using EtOAc/hexane (1:4) to provide cyclohexenol **25** as an oily compound (0.14 g, 80%). $[\alpha]_D^{24} = +76.31$ (*c* 0.56, $CHCl_3$): IR (neat) ν_{max}: 2933, 2355, 1201, 1119, 1030, 908, 762 cm^{-1}; ^1H NMR (300 MHz); 1.39 (s, 6H), 1.42–1.67 (m, 6H), 3.43–3.56 (m, 4H), 3.64–3.94 (m, 2H), 4.15 (m, 1H), 4.31–4.70 (m, 5H), 4.78–4.99 (m, 2H), 5.66 (d, 1H, *J* = 9.0 Hz); ^{13}C ($CDCl_3$, 75 MHz); (19.3, 19.9)*, (25.2, 25.3)*, 26.6, 27.7, 30.4, 30.7, 55.8, 62.2, 63.1 66.9, 67.2, 67.5, 68.2, 73.6, (75.4, 75.5)*, 80.7, 81.5, (97.6, 97.6)*, 98.3, 98.5, 109.84, 116.2, 122.6, 123.3, (136.9, 137.1); ESI/MS (*m*/*z*): 367 $(M+Na)^+$.

4.16. (3a*S*,4*R*,5*S*,7a*S*)-5-Methoxy-4-(methoxymethoxy)-2,2-dimethyl-6-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole 26(a)

To an ice-cooled, stirred solution of NaH (0.03 g, 60% w/v dispersion in mineral oil, 0.88 mmol) in THF (5 mL) were added compound **25** (0.14 g, 0.41 mmol) in THF (5 mL) and methyl iodide (0.03 mL, 0.6 mmol). The mixture was stirred at room temperature for 3 h and then quenched with saturated NH_4Cl solution and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on silica gel by using EtOAc/hexane (1:9) to give compound **26(a)** (0.1 g, 70%) as a syrup. $[\alpha]_D^{24} = -7.3$ (*c* 1.17, $CHCl_3$); IR (neat) ν_{max}: 2933, 2355, 1201, 1119, 1030, 908 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.39 (s, 3H), 1.40 (s, 3H), 1.44–1.90 (m, 6H), 3.46 (s, 3H), 3.57 (2s, 3H), 3.80–3.90 (m, 2H), 3.95–4.13 (m, 3H), 4.30 (m, 1H), 4.51 (br s, 1H), 4.58–4.69 (m, 3H), 4.82–4.91 (m, 2H), 5.69 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): (19.1, 19.3)*, 25.4, (26.5, 26.6)*, (27.6, 27.7)*, (30.5, 30.6)*, 55.5, 60.5, 60.7, 61.8, 62.1, 66.0, 66.6, 73.1, (75.3, 75.4)*, 77.09, (77.7, 77.8)*, (96.7, 96.8)*, 97.1, 98.3, 109.6, 109.7, 122.5, 123.4, 137.0, 137.4; ESI/MS (*m*/*z*); 381 $(M+Na)^+$.

4.17. ((3a*S*,6*S*,7*R*,7a*S*)-6-Methoxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetra-hydrobenzo[*d*][1,3]dioxol-5-yl)methanol 26(b)

To compound **26(a)** (0.1 g, 0.36 mmol) in methanol (5 mL) at 0 °C, a catalytic amount of PPTS was added. The mixture was stirred for 1 h at 0 °C, the methanol was removed under vacuo and purified by column chromatography using EtOAc/hexane (3:2) to give compound **26(b)** (0.05 g, 65%) as a syrup. $[\alpha]_D^{24} = +22.5$ (*c* 0.17, $CHCl_3$): IR (neat) ν_{max}: 3470, 2926, 1376, 1123, 1031, 975, 907, 863 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz); 1.37 (s, 6H), 3.46 (s, 3H), 3.64 (s, 3H), 3.86 (dd, 1H, *J* = 2.4, 8.3 Hz), 4.04–4.28 (m, 4H), 4.51–4.64 (m, 2H), 4.86 (s, 2H), 5.63 (br s, 1H); ^{13}C ($CDCl_3$, 75 MHz): 26.4, 27.7, 55.6, 61.1, 64.4, 73.1, 75.1, 78.4, 78.7, 96.7, 109.6 124.0, 138.9; ESI/MS (*m*/*z*): 297 $(M+Na)^+$.

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