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Stereoselective total synthesis of synparvolide B and *epi*-synparvolide A

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ABSTRACT

Stereoselective total synthesis of synparvolide B and *epi*-synparvolide A has been achieved following a convergent approach. Noyori asymmetric Transfer Hydrogenation of ketone and Wadsworth–Emmons olefination reaction are the key steps involved.

α,β-Unsaturated δ-lactone-motif containing molecules continue to attract medicinal chemists due to their wide occurrence in large number of plants displaying potent biological activities.[1] Very often these molecules are isolated in low quantities and thus becomes the limit for further evaluation towards biological activity. A few examples include Fostriecin **1**,[2] tarchoanthuslactone **2**,[3] anamarine **3**,[4] spicigerolide **4**,[5] and synrotolide **5**[6]. (Fig. 1). In 1996, Davies-Coleman and Rivett have isolated three new poly hydroxy δ-pyrones namely synparvolide A **6**, synparvolide B **7** and synparvolide-C **8** from the leaves of *Syncolostemon parviflorus*, a medicinal plant which is used as an emetic to treat loss of appetite. The structures of synparvolide A–C were established based on spectral, chiroptical and chemical evidences.[7] A thorough search for the literature showed no synthetic reports for these compounds. And also as these compounds are not available abundantly, total synthesis was the only attractive solution for their ready accessibility towards biological screening. This feature also allows synthesizing and identifying the analogs with better therapeutic properties.

Our own interest in the synthesis of the naturally occurring biologically active lactone containing molecules has inspired us to take up the total synthesis of these less abundant α,β-unsaturated δ-lactone containing molecules. Towards this direction, we have recently reported the total synthesis of dodoneine[8] and synrotolide diacetate.[9] In the present communication, we describe the first stereoselective total synthesis of synparvolide B.

Our approach relies on a convergent strategy wherein the two fragments **11** and **12** are coupled and then proceeds further for the total synthesis. The alkyl halide **11** is readily synthesized starting from L(+)-DET in five steps and Weinreb amide **12** can be obtained from **13** which is synthesized starting from homo propargyl alcohol **14** (Scheme 1).

Initially, the synthesis began with masking of L(+)-DET as cyclohexylidine acetal with cyclohexanone and pTSA followed by reduction of the ester functionalities with $LiAlH_4$ to yield diol **15**.[10] The primary alcohol was selectively mono protected as tosylate[11] **16** and treated with $NaBH_4$ to result in a terminal methyl compound **17**.[12] The primary hydroxyl group was converted to iodide **11** upon treatment with I_2, triphenyl phosphine, and imidazole (Scheme 2). The synthesis of the other fragment **12** is shown in Scheme 3 which departs from the prior work at the readily available alkyne **13**.[9] Thus alkyne **13** was lithiated with *n*-BuLi and then treated with ethylchloroformate to get substituted propargylic ester **14**. The ester **14** was treated with *N*-methyl methoxy aminohydrochloride salt to get Weinreb amide **12**[13] in 90% yield.

With the two intermediates **11** and **12** in hand, the rest was to couple them and proceed further for the target synthesis. The alkyl lithium derived from iodide **11** was coupled with Weinreb amide **12** to get the ketone **10**.[14] Stereoselective reduction of the ketone with (*S,S*)-Noyori catalyst[15] afforded required 1,3-*anti*-isomer **18** in 86% yield (Scheme 4).

As the yield for the coupling reaction was not satisfactory to our expectations, alternatively, the compound **18** was also synthesized starting from alcohol **17** following the Scheme 5.

The alcohol **17** was oxidized to aldehyde **21** and treated with (methoxymethyl)triphenylphosphonium chloride in presence of *n*-BuLi to get enol ether **22**. The enol ether was hydrolyzed[16] to get the homologated aldehyde **23**, and was further treated with lithiated alkyne (prepared in situ by treatment of alkyne **13** with *n*-BuLi to get the mixture of easily separable diastereomers **18** and **18a** (7.5:2.5) containing the desired isomer **18** as the major product. The formation of the major 1,3-*anti* diastereomer can be explained based on the prechelation of the lithium bromide with alkoxy aldehyde favoring the nucleophilic attack from less hindered side.[17]

The generated free secondary alcohol **18** was protected as benzyl ether **19** and the triple bond was reduced partially to *cis* double bond **20** under Lindlar's conditions. Thus the geometry of all the carbons with required asymmetric centers was set and the remaining was to complete the total synthesis by converting 1,3-diol to lactone ring. Selective PMB deprotection followed by Swern oxidation of the compound **20** yielded aldehyde **24**. The aldehyde was subjected to modified Wadsworth–Emmons reaction to yield α,β-unsaturated ester **9** exclusively.[18] One-pot ketal deprotection,

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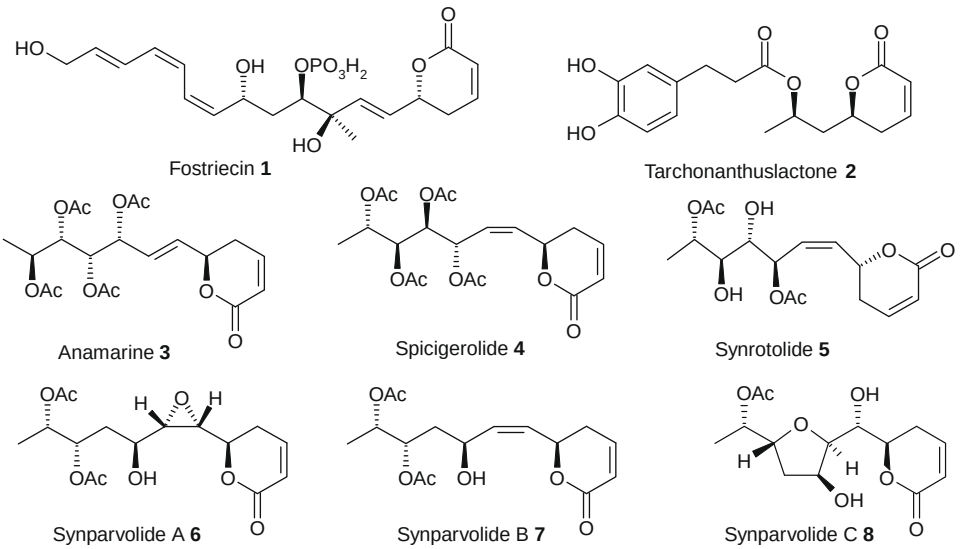
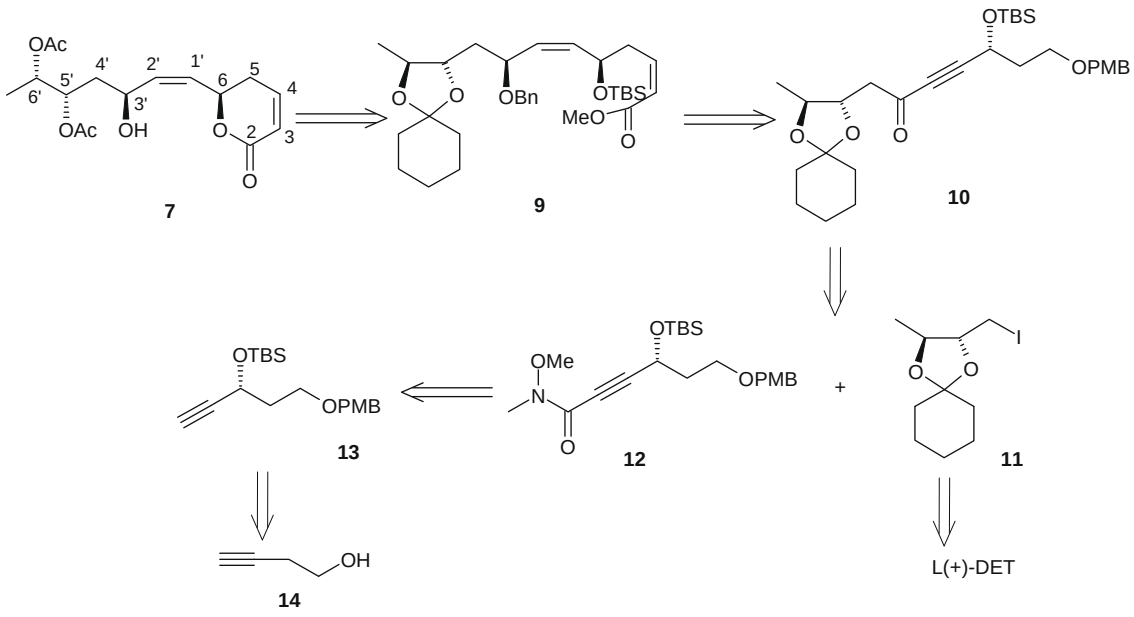
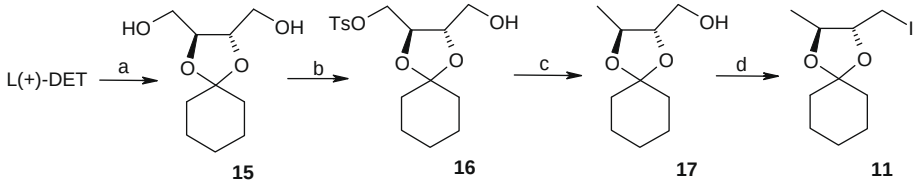


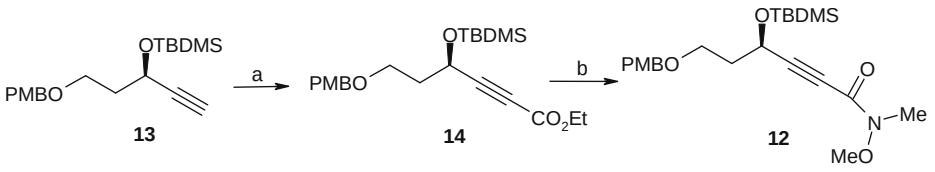
Figure 1.



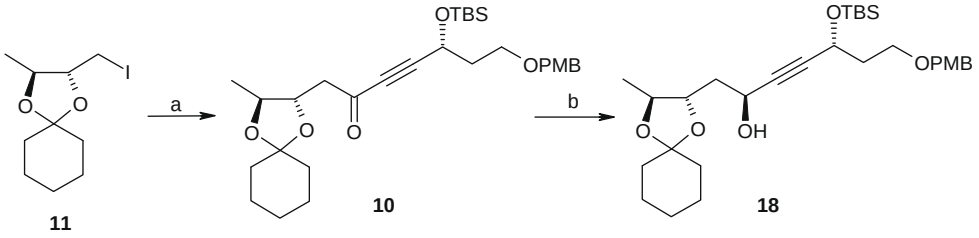
Scheme 1. Retrosynthesis.



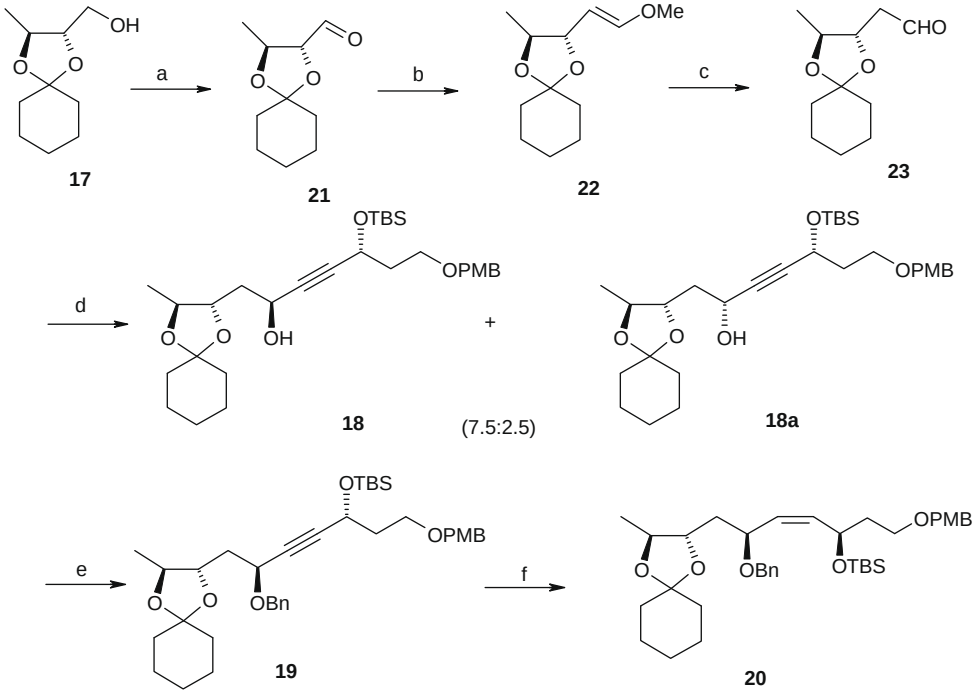
Scheme 2. Reagents and conditions: (a) (i) cyclohexanone, TsOH, benzene, reflux, 6 h; (ii) $LiAlH_4$, THF, reflux, 3 h, 78% for two steps; (b) *n*-BuLi, TsCl, THF–DMSO, −15 to 0 °C to rt, 2 h, 86%; (c) $NaBH_4$, DMSO, 80 °C, 2 h, 88%; (d) I_2, TPP, imidazole, benzene, 0 °C to rt, 30 min 84%.



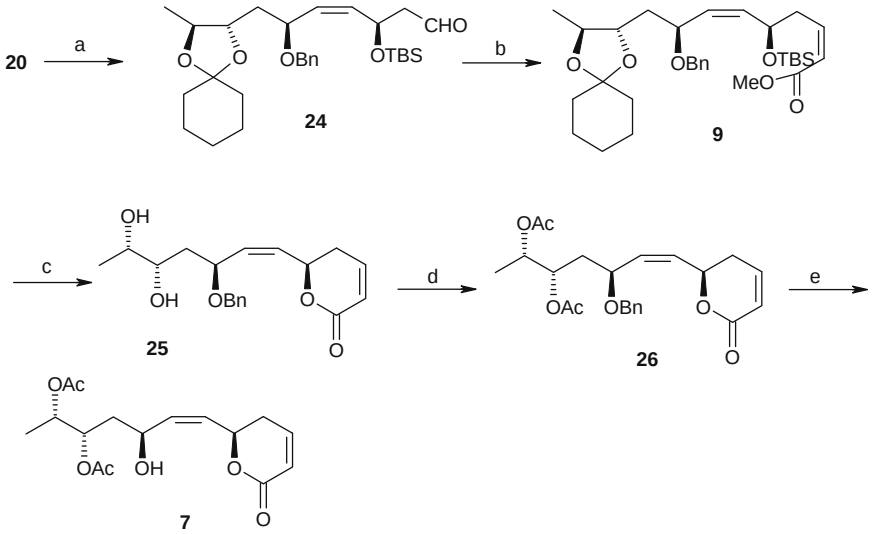
Scheme 3. Reagents and conditions: (a) (i) *n*-BuLi, $ClCO_2Et$, THF, −78 °C to 0 °C, 1 h, 86%; (b) $(Me(OMe)NH_2)Cl$, $^{i}PrMgCl$, THF, −20 °C, 1 h, 90%.



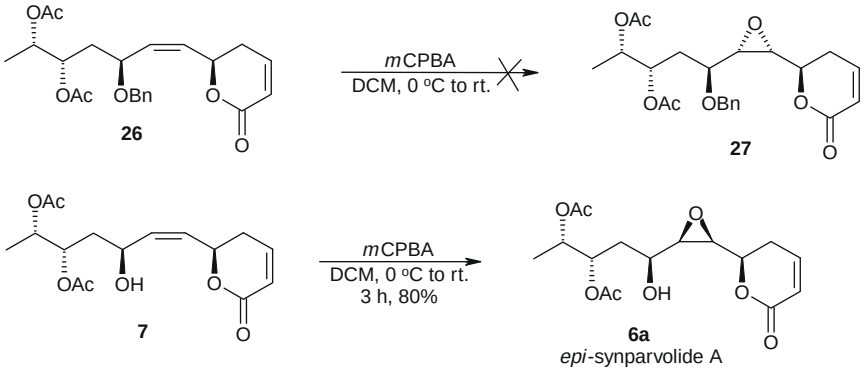
Scheme 4. Reagents and conditions: (a) *t*-BuLi, Et_2O, 12, −78 °C, 30 min 33%; (b) (*S,S*)-Noyori catalyst (20 mol %), *i*-PrOH, 86%.



Scheme 5. Reagents and conditions: (a) DMSO, $(COCl)_2$, TEA, DCM, −78 °C, 3 h, 87%; (b) $ClPPh_3CH_2OCH_3$, *n*-BuLi, THF, −20 to 0 °C to rt, 2 h, 84%; (c) $Hg(OAc)_2$, $NaBH_4$, THF, 0 °C, 30 min 72%; (d) 13, *n*-BuLi, LiBr, 4 A mol. sieves. THF, −78 °C to −50 °C, 1.5 h, 90%; (e) NaH, BnBr, THF, 0 °C to rt, 3 h, 92%; (f) $Pd/BaSO_4$, quinoline, H_2 atm. toluene, rt, 20 min 93%.



Scheme 6. Reagents and conditions: (a) (i) DDQ, DCM:H_2O (8:1), 2 h, 80%; (ii) PCC, NaOAc, DCM, 0 °C to rt, 2 h, 90%; (b) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, 0 °C to −78 °C, 1 h, 83%; (c) AcOH:1 N HCl:THF (1:1:1), 65 °C, 4 h, 65%; (d) Ac_2O, pyridine, DCM, 0 °C to rt, 2 h, 84%; (e) $TiCl_4$, DCM, 0 °C to rt, 2 h, 78%.



Scheme 7. Synthesis of *epi*-synparvolide A.

TBS deprotection, and lactonization of compound **9** were achieved by treating with a mixture of AcOH:1 N HCl:THF (1:1:1) solution to yield **25**[19] in 65% yield. With the required skeleton in hand the rest was to manipulate the protective groups. Thus the precursor for the target synthesis was achieved by diacetylation of the two secondary alcohols in **25** to give the diacetate **26**. $TiCl_4$ mediated debenzylation[20] without affecting acetate moieties or double bond gave the desired target compound **7** in 78% yield (Scheme 6). The product **7** obtained was characterized and its rotation was found to be similar with a small variation to that of the natural product $[\alpha]_D$ −12.2 (*c* 1.2, $CHCl_3$) {lit.[7] $[\alpha]_D$ −11 (*c* 1.0, $CHCl_3$). Also the ^1H NMR and ^{13}C NMR were comparable with the data of the natural product.[21] Thus the structure of the natural product synparvolide B has been confirmed with 6*R*, 3′*S*, 5′*S* and 6′*S*, 1*Z* configuration and is in agreement as established by Rivette et al.

Attempts to synthesize the synparvolide A by epoxidation of compound **26** with *m*CPBA were unsuccessful which may be attributed to steric hindrance by benzyl moiety and lactone ring. However, when epoxidation was attempted on compound **7**, we ended up with the other isomer which is attributed to the chelation of *m*CPBA with hydroxyl group. Thus, we have also accomplished the synthesis of *epi*-synparvolide A **6a** (Scheme 7).

In conclusion, we have accomplished the first total synthesis of synparvolide B and re-confirmed its structure. Also an analog of synparvolide A, *epi*-synparvolide A has been synthesized. Stereocontrolled reduction using Noyori catalyst, coupling of alkyl iodide with Weinreb amide, Wadsworth–Emmons olefination, and one-pot ketal and TBS deprotection followed by lactonization are the key steps involved in this synthesis. Investigations for the biological activity of the presently synthesized compounds and synthesis of other analogs are currently underway.

Acknowledgment

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21. *Analytical data for selected intermediates and synparvolide B: Spectral data for compound* **10**: Colorless oil; $[\alpha]_D^{25}$ +0.5 (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$); IR (neat) ν_{max}: 2955(s), 2932(s), 2234(w), 1648(s), 1613(m), 1513(s), 1465(m), 1250(s), 1099(s), 1036(m), 839(s), 779(s), 580(w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.73 (t, *J* = 6.6 Hz, 1H), 4.46 (m, 2H), 4.04 (dt, *J* = 12.6, 4.7 Hz, 1H), 3.80 (s, 3H), 3.84–3.73 (m, 1H), 3.64–3.50 (m, 1H), 2.28–2.64 (m, 2H), 2.05–1.96 (m, 2H), 1.68–1.51 (m, 9H), 1.42–1.32 (m, 2H), 1.28 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.11 (3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.0, 159.1, 130.2, 129.2, 113.7, 109.1, 94.1, 83.0, 77.2, 76.2, 72.7, 65.2, 59.6, 55.2, 48.4, 38.0, 36.8, 36.5, 25.6, 25.0, 23.8, 23.7, 18.0, 17.5, −4.6, −5.1; mass (ESI-MS) *m*/*z*: 548 (M^++NH_4); HRMS(ESI) calcd for $C_{30}H_{46}O_6NaSi$ (M+Na)$^+$, 530.3063; found 530.3056. *Compound* **18**: Colorless oil; $[\alpha]_D^{25}$ −10.7 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max}: 3450 (br m), 2933 (s), 2857 (m), 1613 (w), 1513 (s), 1363 (w), 1249 (s), 1099 (s), 838 (s), 779 (m)cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 4.62–4.54 (m, 2H), 4.38 (dd, *J* = 14.3, 11.3 Hz, 2H), 3.93–3.45 (m, 2H), 3.78 (s, 3H), 3.77–3.68 (m, 1H), 3.58–3.45 (m, 2H), 2.99 (d,–OH, *J* = 6.0 Hz, 2H), 1.91 (q, *J* = 6.0 Hz, 2H), 1.84–1.77 (m, 2H), 1.66–1.34 (m, 10H), 1.24 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 130.4, 129.1, 113.6, 109.1, 86.4, 84.1, 78.9, 76.3, 72.6, 65.9, 60.5, 59.8, 55.1, 39.8, 38.7, 36.7, 36.6, 25.7, 25.0, 23.9, 23.8, 18.1, 17.1, −4.5, −5.1; mass (ESI-MS) *m*/*z*: 550 (M^++NH_4); HRMS (ESI) calcd for $C_{30}H_{52}NO_6Si$ (M+NH_4)$^+$, 532.3220; found 532.3211. *Compound* **18a**: Colorless oil; $[\alpha]_D^{25}$ −2.5 (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.66–4.56 (m, 2H), 4.40 (dd, *J* = 14.7, 11.3 Hz, 2H), 3.78 (s, 3H), 3.83–3.73 (m, 1H), 3.69–3.48 (m, 3H), 3.05 (br s, OH, 1H), 1.94 (q, *J* = 6.2 Hz, 2H), 1.90–1.82 (m, 2H), 1.66–1.50 (m, 8H), 1.43–1.32 (m, 2H), 1.26 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.0, 130.3, 129.1, 113.6,109.0, 86.3, 84.3, 80.1, 76.3, 72.5, 65.7, 61.0, 59.7, 55.0, 40.1, 38.6, 36.7,

36.5, 25.7, 25.0, 23.8, 23.7, 18.1, 17.2, −4.4, −5.1. *Synparvolide B* **7**: Colorless viscous oil; $[\alpha]_D^{25}$ −12.2 (c 1.2, $CHCl_3$); lit. $[\alpha]_D^{25}$ −11 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 3442 (br m, OH), 2926 (m), 1733 (s), 1710 (sh, α,β unsaturated-δ-lactone), 1377 (m), 1236 (s), 1034 (s), 950 (w), 759 (m) cm^{-1}; ^1H NMR (400, MHz, $CDCl_3$): δ 6.86 (ddd, *J* = 9.9, 5.1, 3.0 Hz, 1H), 6.01 (ddd, *J* = 9.9, 1.8, 1.5 Hz, 1H), 5.61 (dd, *J* = 11.0, 6.7 Hz, 1H), 5.55 (dd, *J* = 11.0, 6.9 Hz, 1H), 5.36 (ddd, *J* = 9.0, 6.6, 2.6 Hz, 1H), 5.11–5.05 (m, 1H), 4.98 (dq, *J* = 6.5, 4.8 Hz, 1H), 4.40–4.34 (m, 1H), 2.91 (br, OH, 1H), 2.43–2.37 (m, 2H), 2.09 (s, 3H), 2.04 (s, 3H), 1.80–1.60 (m, 2H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 170.2, 163.7, 144.9, 135.8, 127.6, 121.4, 73.9, 72.0, 70.8, 64.6, 38.4, 29.8, 21.0, 20.9, 16.2; mass (ESI-MS) *m/z*: 349 (M^++Na); HRMS (ESI) calcd for $C_{16}H_{22}NaO_7$ $(M+Na)^+$, 326.1365; found 326.1362. Epi synparvolide A **6a**: Colorless viscous oil; $[\alpha]_D^{25}$ −4 (c 0.2, $CHCl_3$); IR (neat) ν_{max}: 3447 (br m, OH), 2925 (w), 1732 (s), 1710 (sh, α,β unsaturated-δ-lactone), 1377 (m), 1236 (s), 1035 (s), 856 (w), 768 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (ddd, *J* = 9.8 Hz, 5.4 Hz, 3.0 Hz, 1H), 6.05 (ddd, *J* = 9.8, 2.2, 1.1 Hz, 1H), 5.17–5.01 (m, 2H), 4.81–4.72 (m, 1H), 3.84–3.76 (m, 1H), 3.27 (dd, *J* = 6.4, 4.3 Hz, 1H), 3.08–3.04 (m, 1H), 2.94 (br s, OH, 1H), 2.57–2.40 (m, 2H), 2.14 (s, 3H), 2.08 (s, 3H), 1.94–1.70 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 171.8, 170.2, 162.7, 143.8, 121.6, 75.8, 71.9, 70.8, 64.8, 59.0, 58.1, 36.0, 26.3, 21.1, 20.8, 16.3; mass (ESI-MS), *m/z*: 343 (M^++H); HRMS (ESI) calcd for $C_{16}H_{26}NO_8$ $(M+NH_4)^+$, 342.1314; found 342.1319.