

## TOTAL SYNTHESIS OF A NOVEL CYTOTOXIC METABOLITE GYMNASTATIN A

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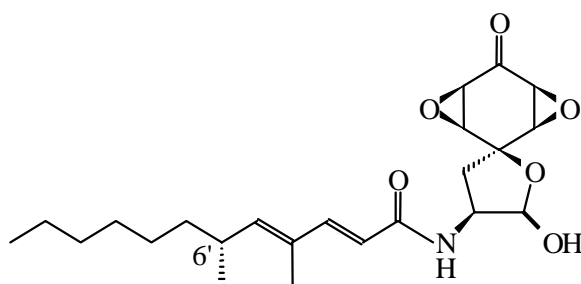
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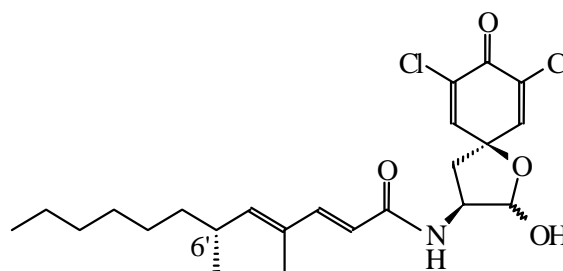
**Abstract** - The first total synthesis of a novel, potent cytotoxic metabolite gymnastatin A is described.

### INTRODUCTION

As a part of our continued interest in natural products belonging to 1-oxaspiro[4.5]decane ring system, we earlier reported studies<sup>1</sup> on the total synthesis of aranorosin (**1**), associated with a potent cytotoxic activity. Recently, five metabolites belonging to the above class and designated as gymnastatin A-E, produced by the strain of *Gymnasella dankaliensis* isolated from the sponge *Halicondria japonica*, were reported.<sup>2</sup> Among the five metabolites, gymnastatin A (**2**) showed the strongest cytotoxicity (ED<sub>50</sub> value 0.018 μg mL<sup>-1</sup>) in the P388 lymphocyte test system in a cell culture.



Aranorosin (**1**)



Gymnastatin A (**2**)

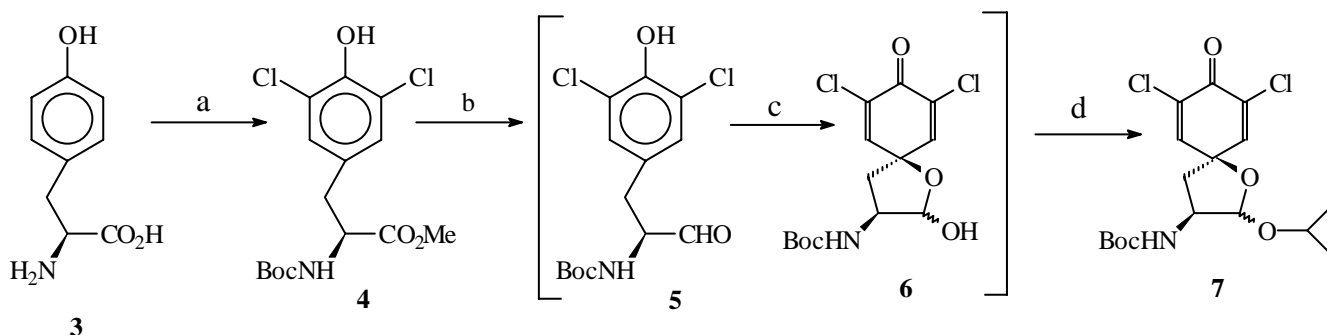
The absolute stereostructure of **2** except that of C-6' was elucidated. However, later studies<sup>3</sup> based on spectroscopic and chemical transformation established the stereochemistry at C-6' to be *R* which correlated with the side chain of aranorosin (**1**). Herein we report the first total synthesis of gymnastatin A (**2**).

### RESULTS AND DISCUSSIONS

The synthetic strategy was based on oxidative cyclisation of 3,5-dichlorotyrosine derivative to obtain 1-oxaspiro[4.5]decane system. The introduction of C-12 side chain on nitrogen mediated by peptide bond

coupling should complete the total synthesis of gymnastatin A.

### Scheme 1



**Reagents and conditions:** a) ref. 4; b) DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h; c)  $\text{PhI}(\text{OCOCF}_3)_2$ ,  $\text{MeCN} : \text{H}_2\text{O}$  (4:1), rt, 30 min; d) isopropanol, cat. CSA, rt, 24 h.

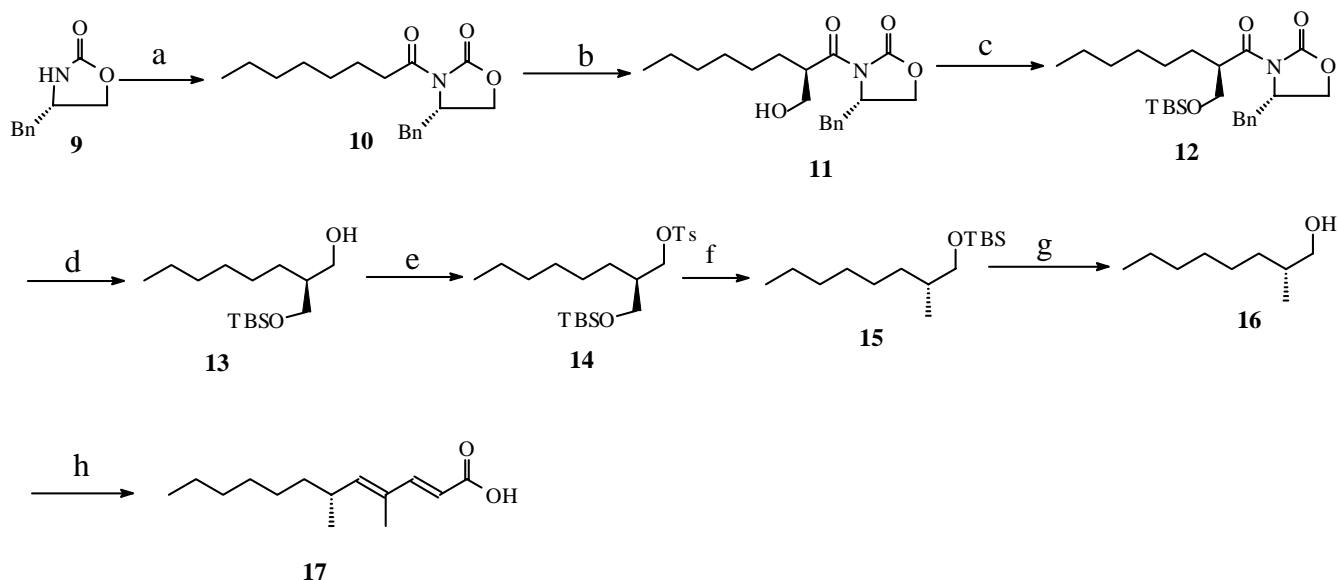
Chlorination of L-tyrosine (**3**) with chlorine in acetic acid at  $0^\circ\text{C}$  furnished 3,5-dichloro-L-tyrosine which was subsequently esterified in the presence of MeOH and acetyl chloride followed by protection of the free amino group with  $(\text{Boc})_2\text{O}$  to give the *N*-Boc protected tyrosine derivative (**4**)<sup>4</sup> (Scheme 1). Conversion of the ester group of **4** into the corresponding aldehyde (**5**) was accomplished with DIBAL-H in toluene- $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ .

Earlier we have reported<sup>1</sup> the oxidative cyclisation of tyrosine derivative<sup>5-7</sup> using bis(trifluoroacetoxy)iodobenzene (PIFA) to afford the spirolactone derivative. A similar approach was sought for the preparation of the spirolactol derivative (**6**). Thus, compound (**5**) was reacted with PIFA in aqueous MeCN to afford the spirolactol derivative (**6**), *albeit in 20%* yield. For convenience it was decided to protect the lactol function in **6** as isopropyl acetal derivative (**7**) using isopropanol and catalytic CSA.

The *N*-octanoyloxazolidinone<sup>8,9</sup> derivative (**10**) was synthesized from Evans oxazolidinone derivative (**9**) and octanoic acid (**8**) by a mixed anhydride method as depicted in Scheme 2. Subsequent condensation<sup>10</sup> of **10** with 1,3,5-trioxane in the presence of titanium tetrachloride and Hunig's base provided the alcohol (**11**). When the present work was undertaken the issue related to the stereochemical configuration at C-6' of **2** was not settled.<sup>2</sup> Therefore we planned to develop a strategy by which both the (6'*R*)- and (6'*S*)- side chains could be synthesized from a common precursor (**11**). Compound (**11**) can form a surrogate for both 6'*R* and 6'*S* chain of gymnastatin A. For example, reduction of hydroxymethyl group at C-2 would lead to 6'*S* derivative (route b) whereas reduction of amide at C-1 (route a) would provide 6'*R* configuration (Figure 1). Since Numata *et al.*<sup>3</sup> conclusively established the stereochemistry of the side chain as *R*, route a should fulfil our requirement. Protection of free hydroxyl with TBS-Cl in the presence of imidazole gave rise to the silyl ether (**12**). Treatment of **12**

with LiBH<sub>4</sub> in ether cleaved the oxazolidinone ring and consequently reduced the carbonyl group to afford the alcohol (**13**). In order to deoxygenate the hydroxymethyl function, compound (**13**) was treated with *p*-toluenesulfonyl chloride and pyridine to afford **14**, which was reduced with LiAlH<sub>4</sub> in THF at 50 °C to give **15**. Removal of the TBS group from **15** with nBu<sub>4</sub>NF in THF gave (2*R*)-2-methyloctanol (**16**) whose optical rotation and <sup>1</sup>H-NMR data were identical with the reported values.<sup>7</sup>

### Scheme 2



**Reagents and conditions:** a) C<sub>7</sub>H<sub>15</sub>CO<sub>2</sub>H (**8**), ref. 8; b) TiCl<sub>4</sub>, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 1,3,5-trioxane, 0°C-rt, 2 h; c) TBSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; d) LiBH<sub>4</sub>, ether, water, rt, 1 h; e) *p*-TsCl, Py, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h; f) LiAlH<sub>4</sub>, THF, 50 °C, 4 h; g) 1M nBu<sub>4</sub>NF, THF, rt, 1 h; h) ref. 1.

Conversion of **16** to (6*R*)-4,6-dimethyldodecadienoic acid (**17**) was carried out by the procedure reported from this laboratory.<sup>1</sup> Having obtained both the moieties *viz.* spirolactol derivative (**7**) and the 6*R*-side chain (**17**), our next concern was to develop a suitable procedure for the coupling reaction. Accordingly, the

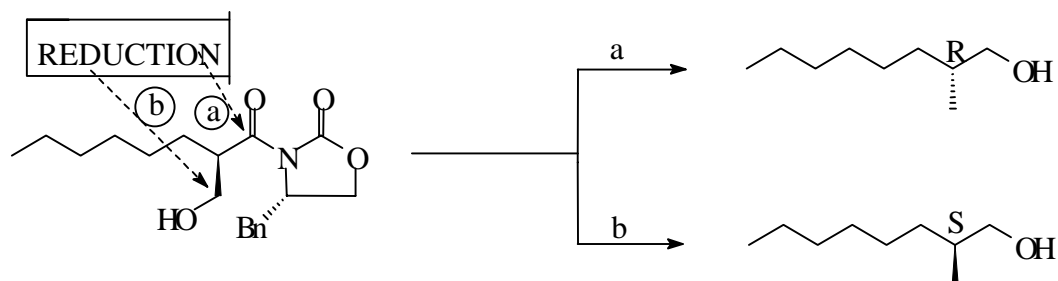
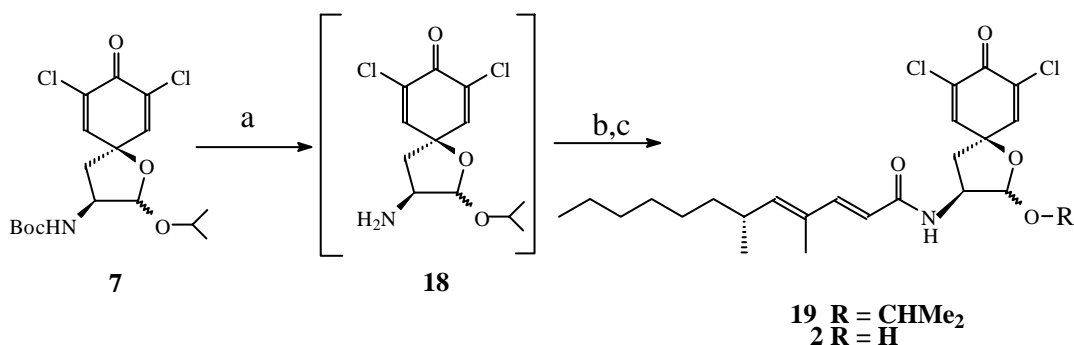


Figure 1

spirolactol derivative (**7**) was treated with CF<sub>3</sub>CO<sub>2</sub>H to cleave the *N*-Boc protecting group and then the free amine (**18**) was coupled with the acid (**17**) in the presence of a promoting agent, EDCI and catalytic DMAP to give **19** (Scheme 3).

### Scheme 3



**Reagents and conditions:** a)  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 30 min; b) EDCI, cat. DMAP, DMF, **17**, rt, 4 h; c) 70%  $\text{CH}_3\text{CO}_2\text{H}$ , cat.  $\text{H}_2\text{SO}_4$ , THF,  $50^\circ\text{C}$ , 12 h.

Finally compound (**19**) was treated with 70%  $\text{CH}_3\text{CO}_2\text{H}$  in the presence of catalytic amount of  $\text{H}_2\text{SO}_4$  in THF to deprotect the isopropyl group and obtain gymnastatin A (**2**). The optical rotation,  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  data for the synthetic product (**2**) were identical with the reported values of the natural product.<sup>2</sup> In the preceding lines we have described the first total synthesis of gymnastatin A by an efficient approach. Based on the strategy adopted it could be possible to obtain analogues of gymnastatin A for undertaking structure-activity relationship.

## EXPERIMENTAL

**(2RS,3S)-3-(N-tert-Butoxycarbonyl)amino-7,9-dichloro-2-isopropoxy-1-oxaspiro[4.5]deca-6,9-dien-8-one (7).**

Compound (**4**)<sup>4</sup> (5.0 g, 13.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was cooled to  $-78^\circ\text{C}$  and 1M solution of DIBAL-H in toluene (42.5 mL, 43.0 mmol) was added slowly maintaining the temperature. After 1 h at  $-78^\circ\text{C}$ , the reaction was quenched by addition of MeOH (1.5 mL) and saturated potassium ammonium tartarate. The organic layer was separated, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford **5** (4.1 g) which was taken further for next reaction.

To the above product (**5**) (4.1 g) in MeCN:  $\text{H}_2\text{O}$  (15 mL, 4:1), PIFA (5.0 g, 11.6 mmol) was added and then stirred at rt for 30 min. MeCN was removed, the residue extracted with  $\text{CH}_2\text{Cl}_2$  and the extract was successively washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The resulting product was chromatographed on silica gel using EtOAc-light petroleum (1:4) to afford **6** (0.96 g, 20%), oil,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz):  $\delta$  1.50 (s, 9H), 2.61 (t, 1H,  $J = 10.6$  Hz), 2.82 (dd, 1H,  $J = 10.6, 12.7$  Hz), 4.45 (m, 1H), 5.25 (br s, 1H), 7.01 (d, 1H,  $J = 2.3$  Hz), 7.17 (br s, 1H), IR (neat): 3392 (NH), 1716 (C=O)  $\text{cm}^{-1}$ , HRFABMS: Found 350.0569 ( $\text{M}^+$ ) calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_5\text{Cl}_2$ : 350.0562.

Compound (**6**) (0.5 g, 1.5 mmol), CSA (25 mg) and isopropanol (5.0 mL) were stirred at rt for 24 h, basified with Et<sub>3</sub>N and concentrated. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub>-water. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue was chromatographed on silica gel using EtOAc-light petroleum (1:9) to give **7** (0.45 g, 80%), oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 1.22 (m, 6H), 1.45 (m, 9H), 2.10 (t, 1H, J= 12.2 Hz), 2.55 (m, 1H), 3.95 (m, 1H), 4.15 (br s, 1/2 H), 4.35 (br s, 1/2 H), 4.87 (d, 1H, J= 8.2 Hz), 5.16 (d, 1/2 H, J= 4.9 Hz), 5.24 (s, 1/2 H), 6.95 (s, 1H), 7.05 (br s, 1H), FABMS m/z M<sup>+</sup>: 392, Anal. Calcd for C<sub>17</sub>H<sub>23</sub>NO<sub>5</sub>Cl<sub>2</sub>. C, 52.04; H, 5.86. Found: C, 52.20; H, 5.71.

**[3(2'S), 4S]-3-(2-Hydroxymethyl-1-oxooctyl)-4-phenylmethyl-2-oxazolidinone (11).**

To a solution of oxazolidinone derivative (**10**) (5.0 g, 16.5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0<sup>o</sup>C, 1M solution of TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (17.3 mL 17.3 mmol) was added followed by, after 15min, with diisopropylethylamine (3.4 mL, 18.6 mmol). The reaction mixture was stirred for 1 h at 0<sup>o</sup>C, 1,3,5-trioxane (3.0 g, 33.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL) was added followed by 1M solution of TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (17.3 mL, 17.3 mmol). The reaction was quenched after 2 h with saturated NH<sub>4</sub>Cl solution and layers separated. The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford a residue which was purified on silica gel using EtOAc-light petroleum (1:3) to give **11** (4.7 g, 85%) as a thick syrup, [α]<sub>D</sub> + 60° (c 1.7, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 0.83 (t, 3H, J= 6.5 Hz), 1.24 (m, 10H), 2.75 (t, 1H, J= 11.3 Hz), 3.24 (d, 1H, J= 11.3 Hz), 3.77 (m, 2H), 3.86 (m, 1H), 4.09 (m, 2H), 4.64 (m, 1H) 7.20 (m, 5H), HRFABMS: Found 333.1923 (M<sup>+</sup>) calcd for C<sub>19</sub>H<sub>27</sub>NO<sub>4</sub>: 333.1940.

**(2R)-2-tert-Butyldimethylsilyloxymethyl-1-octyl-4-methyl-1-benzenesulfonate(14).**

Compound (**11**) (7.0 g, 21.0 mmol), imidazole (3.3 g, 46.0 mmol), and TBSCl (3.8 g, 25.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was stirred for 1 h and worked-up in the usual fashion to afford a residue which was purified on silica gel using EtOAc-light petroleum (1:4) to give **12** (8.2 g, 87%), oil, [α]<sub>D</sub> + 30° (c 1.0, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 0.06 (s, 6H), 0.83 (br s, 12H), 1.38 (br s, OH), 2.66 (dd, 1H, J= 8.5, 12.8 Hz), 3.29 (dd, 1H, J= 3.3, 12.8 Hz), 3.76 (dd, 1H, J= 4.2, 8.5 Hz), 3.87 (t, 1H, J= 8.5 Hz), 4.04 (m, 1H), 4.12 (m, 2H), 4.68 (m, 1H), 7.25 (m, 5H), HRFABMS: Found 448.2870 (M<sup>+</sup>+1) calcd for C<sub>25</sub>H<sub>42</sub>NO<sub>4</sub>Si: 448.2881.

Compound (**12**) (8.2 g, 18.3 mmol), lithium borohydride (0.43 g, 19.7 mmol), ether (30 mL) and water (0.33 mL) were stirred at rt for 1 h, diluted with 1M sodium hydroxide solution and layers separated. The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum (1:9) to afford **13** (3.7 g, 74%), oil, [α]<sub>D</sub> - 12° (c 1.0, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 0.06 (s, 6H), 0.83 (br s, 12H), 1.27 (br s, 10H), 1.68 (br s, 1H), 2.66 (br s, 1H), 3.57 (dd, 1H, J= 8.5, 10.6 Hz), 3.68 (m, 1H), 3.78 (dd, 1H, J= 4.2, 10.6 Hz), FABMS m/z M<sup>+</sup>: 274.

To a solution of **13** (2.0 g, 7.3 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), pyridine (1.0 mL) and PTSCl (1.9 g, 10.0 mmol) were added. The reaction was stirred for 5 h at rt, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated

NaHCO<sub>3</sub> solution, water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum (1:6) to afford **14** (2.8 g, 90%), oil, [ $\alpha$ ]<sub>D</sub> -17° (c 1.2, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  0.06 (s, 6H), 0.84 (br s, 9H), 0.91 (t, 3H, J = 6.5 Hz), 1.25 (br s, 10H), 1.75 (m, 1H), 2.47 (s, 3H), 3.42 (dd, 1H, J = 5.5, 9 Hz), 3.56 (dd, 1H, J = 4.6, 9 Hz), 4.00 (d, 2H, J = 4.55 Hz), 7.34 (d, 2H, J = 8.86 Hz), 7.80 (d, 2H, J = 8.86 Hz), HRFABMS: Found 429.2481 (M<sup>+</sup>+1) calcd for C<sub>22</sub>H<sub>41</sub>O<sub>4</sub>SSi: 429.2494.

**(2R)-2-Methyloctan-1-ol (16).**

A solution of **14** (2.0 g, 4.7 mmol) and LiAlH<sub>4</sub> (0.21 g, 5.60 mmol) in dry THF (12 mL) was heated at 50 °C for 4 h. The reaction mixture was quenched by slow addition of 15 % NaOH solution. The solution was filtered and filtrate concentrated. The residue was chromatographed on silica gel using EtOAc-light petroleum (1:9) to afford **15** (0.98 g, 82%) which was dissolved in THF (5 mL) and then 1M solution of Bu<sub>4</sub>NF in THF (4.2 mL, 4.2 mmol) introduced. After 1 h at rt, saturated NH<sub>4</sub>Cl solution was added, THF removed under reduced pressure and the aqueous layer extracted with ethyl acetate. The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified on silica gel using EtOAc-light petroleum (1:4) to give **16** (0.49 g, 87%), oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  0.88 (m, 6H), 1.25 (m, 10H), 1.64 (m, 1H), 2.50 (br s, 1H), 3.41 (m, 2H); [ $\alpha$ ]<sub>D</sub> + 10° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>), lit.,<sup>7</sup> [ $\alpha$ ]<sub>D</sub> + 10.3° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>).

**(2E,4E,6R)-N-[(2RS,3S)-7,9-Dichloro-2-isopropoxy-8-oxo-1-oxaspiro[4.5]deca-6,9-di-en-3-yl]-4,6-dimethyl-2,4-dodecadienamide (19).**

To a stirred solution of **7** (1.3 g, 3.29 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), cooled at 0 °C, was slowly added CF<sub>3</sub>CO<sub>2</sub>H (5.0 mL). The reaction mixture was brought to rt and stirred for 30 min. The solution was concentrated to give **18** as a salt. This was dissolved in anhydrous DMF (3 mL) and the pH of the solution was adjusted to 8 by adding dry Et<sub>3</sub>N. In a separate flask, compound (**17**) (0.6 g, 2.7 mmol), EDCI (0.51 g, 2.7 mmol) and cat. DMAP were taken in DMF (5 mL) and then the mixture was stirred for 30 min till a clear solution was obtained. To this was added the solution containing compound (**18**). After 4 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. Chromatographic purification on silica gel using EtOAc-light petroleum (1:6) gave **19** (0.78 g, 71 %) as a thick syrup, [ $\alpha$ ]<sub>D</sub> - 6° (c 1.6, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  0.87 (t, 3H, J = 6.5 Hz), 0.99 (d, 3H, J = 6.7 Hz), 1.10-1.26 (m, 10H), 1.30 (d, 6H, J = 6.8 Hz), 1.78 (s, 3H), 2.03-2.30 (m, 1H), 2.37-2.77 (m, 2H), 3.90-4.10 (m, 1H), 4.50 (m, 1/3H), 4.78 (m, 2/3H), 5.20 (d, 2/3H, J = 4.5 Hz), 5.30 (s, 1/3H), 5.65 (d, 1H, J = 11.0 Hz), 5.72 (d, 1H, J = 16 Hz), 5.89 (d, 1H, J = 8.2 Hz), 6.96 (d, 1H, J = 2.3 Hz), 7.03 (d, 1H, J = 2.3 Hz), 7.25 (d, 1H, J = 16 Hz), HRFABMS : Found (M<sup>+</sup>+1) 499.2263 calcd for C<sub>26</sub>H<sub>38</sub>NO<sub>4</sub>Cl<sub>2</sub> : 499.2256; Anal. Calcd for C<sub>26</sub>H<sub>37</sub>NO<sub>4</sub>Cl<sub>2</sub>: C, 62.65; H, 7.42. Found: C, 62.33; H, 7.28.

**Gymnastatin A (2).**

To a solution of **19** (0.70 g, 1.4 mmol) in THF (5 mL) was added 70% acetic acid (3 mL) and catalytic

H<sub>2</sub>SO<sub>4</sub>. After being stirred at 50 °C for 12 h, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with saturated NaHCO<sub>3</sub> solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and the mixture was concentrated. The crude mixture was purified on silica gel using EtOAc-light petroleum (1:3) to obtain **2** (0.32 g, 50 %) as a white solid, mp 70 °C, [α]<sub>D</sub> – 3.9° (c 0.7, CHCl<sub>3</sub>), lit.,<sup>2</sup> [α]<sub>D</sub> -3.8° (c 0.8, CHCl<sub>3</sub>). IR (neat): 3378, 3274, 1698, 1654, 1608 cm<sup>-1</sup>, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 0.87 (t, 3H, J= 6.5 Hz), 0.96 (d, 3H, J= 6.6 Hz), 1.3 (m, 10H), 1.77 (s, 3H), 2.20 (t, 1H, J= 12.8 Hz), 2.50 (m, 1H), 2.60 (dd, 2/3H, J= 8.3, 12.8 Hz), 2.80 (dd, 1/3H, J= 8.3, 12.8 Hz), 4.57 (m, 2/3H), 4.75 (m, 1/3H), 5.54 (m, 1H), 5.75 (d, 1H, J= 15.7 Hz), 5.75 (d, 1H, J= 10 Hz), 6.00 (d, 1H, J= 8.2 Hz), 7.00 (d, 1H, J= 2.9 Hz), 7.08 (d, 1H, J=2.9 Hz), 7.25 (d, 1H, J= 15.7 Hz). <sup>13</sup>C (CDCl<sub>3</sub>, 50 MHz) : δ 172.1, 169.5, 167.7, 149.7, 147.7, 146.3, 144.7, 131.0, 130.5, 130.5, 117.9, 103.1, 96.3, 81.0, 79.7, 58.9, 51.0, 41.0, 38.4, 36.8, 32.7, 31.0, 28.9, 26.8, 22.1, 20.3, 14.7, 13.1, HRFABMS : Found (M<sup>+</sup>) 456.1676 calcd for C<sub>23</sub>H<sub>31</sub>NO<sub>4</sub>Cl<sub>2</sub> : 456.1708.

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