

## SYNTHESIS OF MYCALAMIDE ANALOGS

Shunya Takahashi,<sup>a</sup> Akihiro Okada,<sup>a</sup> and Tadashi Nakata<sup>b\*</sup>

<sup>a</sup>RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama  
351-0198, Japan

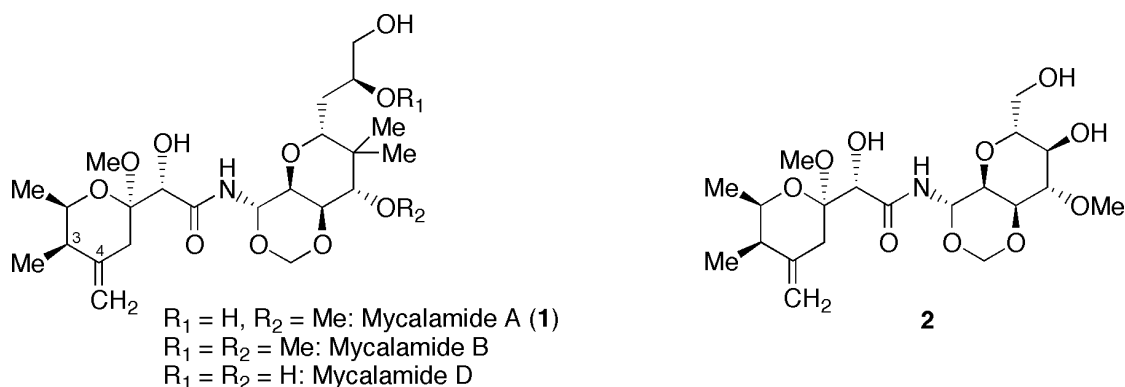
<sup>b</sup>Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3,  
Kagurazaka, Shinjuku-Ku, Tokyo 162-8601, Japan

E-mail: nakata@rs.kagu.tus.ac.jp

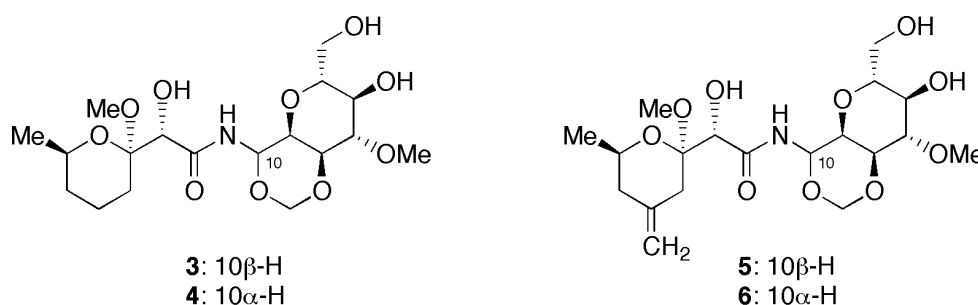
**Abstract** – Several new artificial analogs (**3-6**) of mycalamide A (**1**), a potent antiviral and antitumor agent, were synthesized through a coupling reaction of a bicyclic amine (**19**) with two tetrahydropyran carboxylic acids (**15**) and (**18**), and their cytotoxicity and antiviral activity were tested.

## INTRODUCTION

The mycalamides were isolated from a marine sponge of the *Mycale* genus found in New Zealand.<sup>1,2</sup> Structurally related compounds, onnamides<sup>3</sup> and theopederins,<sup>4</sup> have also been isolated from a Japanese marine sponge of the genus *Theonella*. Interestingly, the structure of these compounds is strikingly similar to that of pederin, a strong insect poison isolated from *Paederus fuscipes*.<sup>5</sup> The mycalamides exhibit potent *in vitro* cytotoxicity and *in vivo* antitumor activity as well as potent antiviral activity.<sup>1,6</sup> In addition, mycalamide A (**1**) is reported to have immunosuppressive activity *via* inhibition of T-cell activation and to be 10-fold more potent than FK-506.<sup>7</sup> As a result, the mycalamides have attracted much attention of synthetic organic chemists.<sup>8</sup> The structure-activity relationship studies of simple derivatives



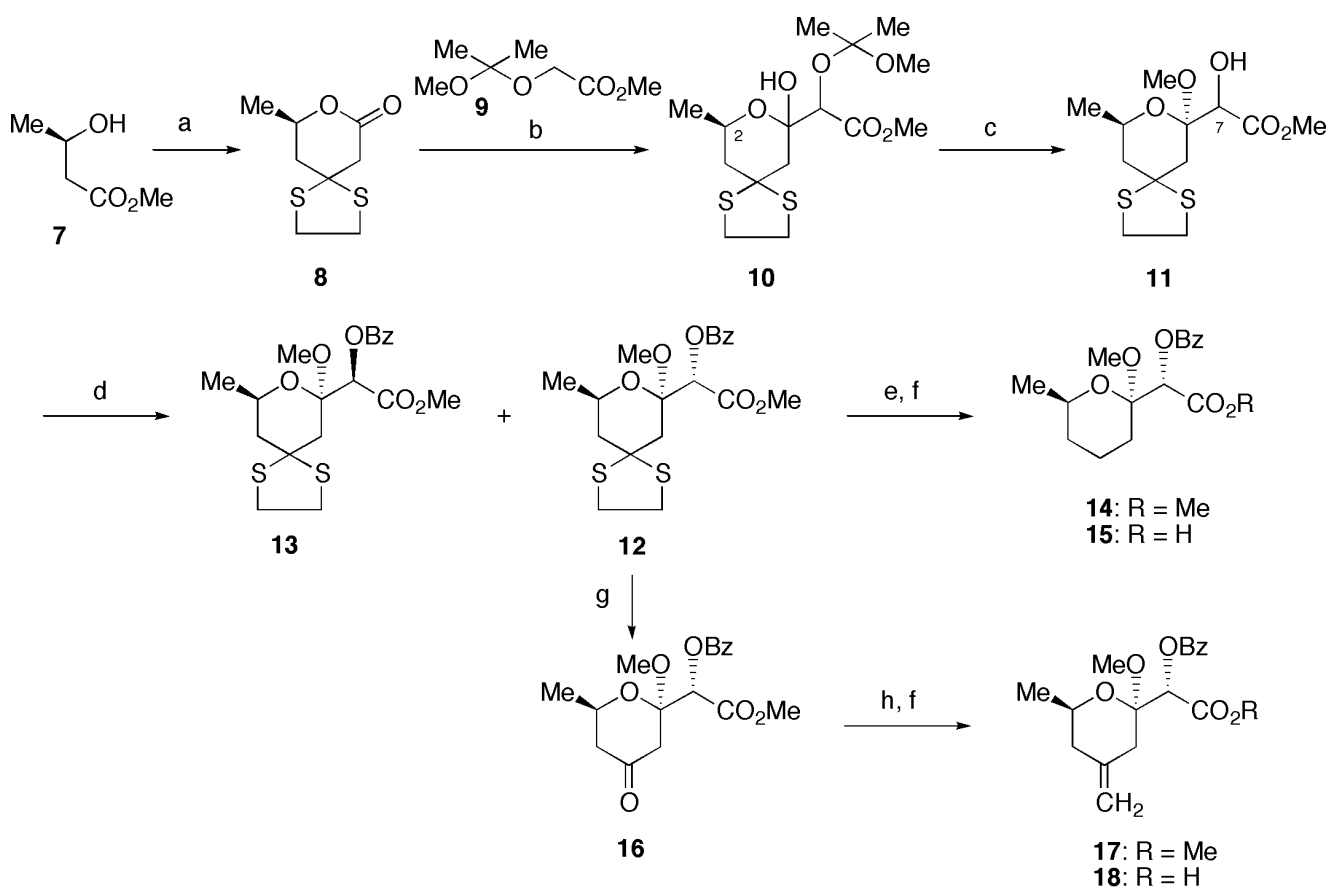
prepared from naturally occurring mycalamides and their model compounds have been also reported.<sup>9</sup> In preceding papers,<sup>10</sup> we reported stereoselective total syntheses of mycalamide A (**1**). We also prepared its simplified analogs, and revealed their cytotoxicity and antiviral activity did not decrease by removing the C-3 methyl and/or C-4-exomethylene group on the left half segment of **1**.<sup>11</sup> Furthermore, analog (**2**) that replaced the right half by glucose derivative showed almost the same cytotoxicity against HeLa cells as that of 5-fluorouracil and good antiviral activity (MIC 3.125  $\mu\text{g/mL}$ , IC<sub>50</sub> >50  $\mu\text{g/mL}$ ) against VZV. These interesting results prompted us to investigate the effect of the methylene and/or methyl group in **2** on the inhibitory activities. Here, we describe synthesis of several new analogs (**3-6**).



## RESULTS AND DISCUSSION

For the syntheses of **3-6**, 3-desmethyl-4-desmethylenepederic acid (**15**) and 3-desmethylpederic acid (**18**) were needed. In previous work,<sup>11</sup> syntheses of **15** and **18** required 13 (6% overall yield) and 20 steps (2% overall yield) from methyl (*R*)-3-hydroxybutyrate (**7**), respectively. In order to shorten the synthetic route, we developed a highly efficient synthesis of these compounds. Our new process involves Claisen condensation of a  $\delta$ -lactone (**8**)<sup>12</sup> with a methyl glycolate derivative (**9**) as a key step (Scheme 1). The usefulness of this procedure was demonstrated in our synthesis of methyl pederate.<sup>10c</sup> Generation of a lithium enolate of **9** at  $-78$  °C followed by addition of  $\text{ZnCl}_2$  gave the corresponding zinc enolate,<sup>13</sup> which reacted with **8** to afford a mixture of coupling products (**10**). Upon treatment with methyl orthoformate in the presence of CSA in methanol- $\text{CH}_2\text{Cl}_2$ , **10** afforded a *ca.* 23:1 of diastereomeric mixture (**11**) in 76% yield. As described previously,<sup>10c</sup> both yield and stereoselectivity were reduced as a result of no  $\text{ZnCl}_2$  being added. After benzylation { $\text{BzCl}$ , *N,N*-dimethylaminopyridine (DMAP), pyridine} of **11**, the resulting compounds were separated into a (*7S*)-benzoate (**12**) (88%) and the corresponding (*R*)-isomer (**13**) (4%) by chromatography on silica gel. The newly created stereochemistry was confirmed by the transformation of **12** into the known compounds (**15**) and (**18**) (*vide infra*). The ethylenedithio moiety in **12** was removed by radical reaction using tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile in toluene at 90 °C to give an ester (**14**) in 76% yield. This was subjected to demethylation with lithium propanethiolate in HMPA<sup>14</sup> to give the corresponding carboxylic acid (**15**) quantitatively. On the other

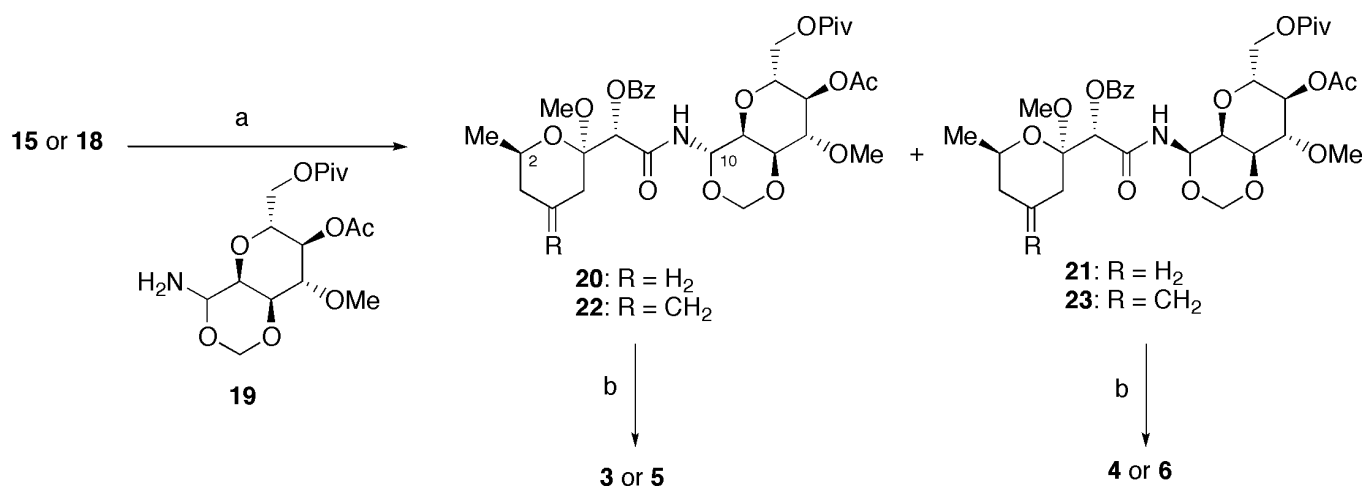
hand, the thioacetal moiety in **12** was hydrolyzed by treatment with HgO-HgCl<sub>2</sub> in aqueous acetonitrile to afford a ketone (**16**) in 83% yield. Methylenation of **16** was performed by Takai-Nozaki's method<sup>15</sup> to afford an olefin (**17**) in 73% yield. Treatment of **17** as described for preparation of **15** from **14** gave the corresponding carboxylic acid (**18**) quantitatively. The overall yields of **15** and **18** from **7** attained 37% (7 steps) and 30% (8 steps), respectively.



Scheme 1. Reagents and conditions: a) ref. 12b, 76%; b) LDA, ZnCl<sub>2</sub>, THF-Et<sub>2</sub>O, -78~40 °C; c) HC(OMe)<sub>3</sub>, CSA, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, rt, 76% from **8** in 2 steps; d) BzCl, DMAP, pyridine, 0 °C~rt, 88% for **12**, 4% for **13**; e) *n*-Bu<sub>3</sub>SnH, AIBN, toluene, 90 °C, 76%; f) *n*-PrSLi, HMPA, rt, quant.; g) HgO, HgCl<sub>2</sub>, MeCN, H<sub>2</sub>O, rt, 83%; h) Zn, TiCl<sub>4</sub>, CH<sub>2</sub>I<sub>2</sub>, THF, 0 °C~rt, 73%.

After obtaining the key intermediates, we turned our attention to the coupling reaction with a bicyclic amine (**19**) (Scheme 2).<sup>11</sup> Activation of the carboxylic acid (**15**) was performed by treatment with *p*-TsCl and DMAP in CH<sub>2</sub>Cl<sub>2</sub> followed by addition of the amine (**19**) to afford a 10 $\alpha$ -amide (**20**) and the corresponding 10 $\beta$ -isomer (**21**) in 14 and 46% yields, respectively. The newly created stereochemistry was determined by the coupling constant value of C-10 proton.<sup>8a</sup> Thus, the proton derived from C-10 of **20** was observed at 5.73 ppm as triplet with  $J = 8.5$  Hz, while that of **21** at 5.38 ppm as a doublet of doublets ( $J_{10,11} = 2.0$  Hz,  $J_{10,NH} = 9.8$  Hz). Each compound was hydrolyzed by LiOH in H<sub>2</sub>O-methanol to

provide the new analogs (**3**) and (**4**) in good yield. In a similar way, the carboxylic acid (**18**) was coupled with the amine (**19**) and the resulting amides (**22** and **23**) were transformed into the analogs (**5** and **6**), respectively.



Scheme 2. Reagents and conditions: a) *p*-TsCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C~rt, 16% for **20**, 52% for **21**, 6% for **22**, 55% for **23**; b) LiOH, MeOH-H<sub>2</sub>O, 0 °C~rt, 86% for **3**, 70% for **4**, 65% for **5**, 98% for **6**.

The cytotoxicity and antiviral activity of the analogs (**3-6**) were tested according to a method previously reported.<sup>11</sup> In a cytotoxicity test, compound (**5**) was found to have a weak antitumor activity against HeLa cell (IC<sub>50</sub> = 51.4 µg/mL), while no compound showed the antiviral activity against HSV-1 and VZV at less than 50 µg/mL. These results suggest that the presence of the C-3 methyl and/or C-4-exomethylene group on the left half segment of **2** is important for such biological activities.

In summary, we developed a new synthesis of the left half analogs of **1** and synthesized several new analogs (**3-6**) therefrom. The design and synthesis of the artificial analogs of **1** are under further investigation.

## EXPERIMENTAL

**Preparation of methyl acetal (11).** To a stirred solution of LDA prepared from diisopropylamine (1.6 mL, 12.2 mmol) and *n*-BuLi (7.7 mL, 1.59 M in hexane, 11.8 mmol) in THF (25 mL) was added dropwise **9** (1.9 mL, 12.2 mmol) at -78 °C. After 0.5 h, a 1.0 M ether solution of ZnCl<sub>2</sub> (11.8 mL, 11.8 mmol) was added and the solution was stirred for 0.5 h. Then, a solution of **8** (804 mg, 3.94 mmol) in THF (5 mL) was added at -78 °C, and the mixture was stirred at -78 °C for 2 h and -78~-40 °C for 3 h. After quenching with addition of sat. NH<sub>4</sub>Cl solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. The residual

syrup was passed through a short column of silica gel {CHCl<sub>3</sub>→ CHCl<sub>3</sub>-EtOAc (10:1)} to afford **10** (1.87 g), which was dissolved in CH<sub>2</sub>Cl<sub>2</sub>-methanol (1:1, 50 mL). To this solution were added methyl orthoformate (5.5 mL, 50.3 mmol) and CSA (377 mg, 1.62 mmol) at rt, and the mixture was stirred at rt for 4.5 h. After addition of sat. NaHCO<sub>3</sub> solution, the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. Chromatography on silica gel with hexane-ether (3:1→ 1:1) as the eluent yielded **11** (929 mg, 76%) as a diastereomeric mixture (7*S*/7*R* = ca. 23/1 by <sup>1</sup>H-NMR spectrometry).

**11**; colorless oil; IR (neat): 3483, 1740, 1278, 1219, 1127 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) of major isomer: δ 1.23 (3H, d, *J* = 6.3 Hz, 2-Me), 1.66 (1H, dd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2,3a</sub> = 11 Hz, H-3a), 2.03 (1H, ddd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2,3b</sub> = *J*<sub>3b,5b</sub> = 2.0 Hz, H-3b), 2.16 (1H, d, *J*<sub>5a,5b</sub> = 14 Hz, H-5a), 2.47 (1H, dd, *J*<sub>5a,5b</sub> = 14 Hz, *J*<sub>3b,5b</sub> = 2.0 Hz, H-5b), 2.88 (1H, d, *J* = 5.3 Hz, OH), 3.15-3.39 (4H, m, SCH<sub>2</sub>), 3.34 (3H, s, OMe), 3.82 (3H, s, OMe), 3.85-4.02 (1H, m, H-2), 4.29 (1H, s, H-7). HRFABMS (*m/z*): Calcd for C<sub>12</sub>H<sub>20</sub>O<sub>5</sub>NaS<sub>2</sub> (M+Na<sup>+</sup>) 331.0650, Found 331.0654. *Anal.* Calcd for C<sub>12</sub>H<sub>20</sub>O<sub>5</sub>S<sub>2</sub>: C, 46.73; H, 6.54. Found: C, 46.64; H, 6.46.

**Preparation of 7*S*- and 7*R*-benzoates (**12**) and (**13**).** To a stirred solution of **11** (929 mg, 3.0 mmol) and *N,N*-dimethylaminopyridine (403 mg, 3.3 mmol) in pyridine (11 mL) was added benzoyl chloride (0.5 mL, 4.5 mmol) at 0 °C, and the mixture was stirred at 0 °C~rt for 1.5 h. After addition of water, the resulting mixture was vigorously stirred and then extracted with ether. The extracts were washed with cold 10% HCl solution, water, sat. NaHCO<sub>3</sub> solution, water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. Chromatography on silica gel with hexane-ether (3:1→ 1:1) as the eluent yielded **12** (1.09 g, 88%) and **13** (45 mg, 4%).

**12**; colorless oil; [α]<sub>D</sub><sup>22</sup> +68.9° (*c* 0.29, CHCl<sub>3</sub>); IR (neat): 1750, 1728, 1275, 1221, 1116 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.21 (3H, d, *J* = 6.3 Hz, 2-Me), 1.70 (1H, dd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2,3a</sub> = 11 Hz, H-3a), 2.04 (1H, ddd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>3b,5a</sub> = 2.0 Hz, *J*<sub>2,3b</sub> = 1.7 Hz, H-3b), 2.59 (1H, dd, *J*<sub>5a,5b</sub> = 14 Hz, *J*<sub>3b,5a</sub> = 2.0 Hz, H-5a), 2.64 (1H, d, *J*<sub>5a,5b</sub> = 14 Hz, H-5b), 3.16-3.38 (4H, m, SCH<sub>2</sub>), 3.32 (3H, s, OMe), 3.79 (3H, s, OMe), 3.96-4.03 (1H, m, H-2), 5.40 (1H, s, H-7), 7.42-7.48 (2H, m, Ph), 7.55-7.62 (1H, m, Ph), 8.06-8.10 (2H, m, Ph); HRFABMS (*m/z*): Calcd for C<sub>19</sub>H<sub>24</sub>O<sub>6</sub>NaS<sub>2</sub> (M+Na<sup>+</sup>) 435.0912, Found 435.0909. *Anal.* Calcd for C<sub>19</sub>H<sub>24</sub>O<sub>6</sub>S<sub>2</sub>: C, 55.32; H, 5.86. Found: C, 55.62; H, 5.88.

**13**; colorless oil; [α]<sub>D</sub><sup>22</sup> -28.5° (*c* 0.24, CHCl<sub>3</sub>); IR (neat): 1754, 1727, 1275, 1223, 1136, 1115 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.20 (3H, d, *J* = 6.3 Hz, 2-Me), 1.78 (1H, dd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2,3a</sub> = 11 Hz, H-3a), 2.06 (1H, ddd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2,3b</sub> = 2.3 Hz, *J*<sub>3b,5a</sub> = 2.0 Hz, H-3b), 2.31 (1H, dd, *J*<sub>5a,5b</sub> = 14 Hz, *J*<sub>3b,5a</sub> = 2.0 Hz, H-5a), 2.72 (1H, d, *J*<sub>5a,5b</sub> = 14 Hz, H-5b), 3.19-3.35 (4H, m, SCH<sub>2</sub>), 3.45 (3H, s, OMe), 3.80 (3H, s, OMe), 3.98-4.07 (1H, m, H-2), 5.32 (1H, s, H-7), 7.43-7.51 (2H, m, Ph), 7.57-7.65 (1H, m, Ph), 8.03-8.12 (2H, m, Ph); HRFABMS (*m/z*): Calcd for C<sub>19</sub>H<sub>24</sub>O<sub>6</sub>NaS<sub>2</sub> (M+Na<sup>+</sup>) 435.0912, Found 435.0919.

**Methyl Benzoyl-3-desmethyl-4-desmethylenepederate (14).** To a stirred solution of **12** (15.0 mg, 0.04 mmol) and a trace amount of 2,2'-azobisisobutyronitrile in toluene (1 mL) was added tributyltin hydride (0.04 mL, 0.15 mmol). The mixture was stirred at 90 °C for 3 h and then concentrated. Chromatography on silica gel with hexane-ether (4:1) as the eluent yielded **14** (8.8 mg, 76%) as a crystalline solid. mp 129-130 °C (hexane-ether);  $[\alpha]_D^{29} +104.4^\circ$  (*c* 0.55, CHCl<sub>3</sub>); IR (KBr): 1750, 1720, 1600 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.16 (3H, d, *J* = 6.3 Hz, 2-Me), 1.19-2.17 (6H, m, H-3,4,5), 3.30 (3H, s, OMe), 3.74 (1H, m, H-2), 3.79 (3H, s, OMe), 5.36 (1H, s, H-7), 7.45 (2H, dd, *J* = 8.1 Hz, *J* = 7.8 Hz, Ph), 7.58 (1H, t, *J* = 7.7 Hz, Ph), 8.09 (2H, d, *J* = 8.3 Hz, Ph); FABMS (*m/z*): 291 (M+H<sup>+</sup>-MeOH).

**Benzoyl-3-desmethyl-4-desmethylenepederic acid (15).** To a stirred solution of **14** (55.1 mg, 0.17 mmol) in HMPA (1 mL) was added a 0.55 M HMPA solution of *n*-PrSLi (0.47 mL, 0.26 mmol) at rt, and the mixture was stirred at rt for 3.5 h. After addition of ice-water, the resulting mixture was vigorously stirred for 0.5 h, and washed with ether. The aqueous layer was acidified with cold 10% HCl solution, and then extracted with ether. The extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated to give a syrup (74.4 mg), which was revealed to be an almost pure **15**<sup>11</sup> by the <sup>1</sup>H-NMR spectral analysis although a slight amount of HMPA was included. Therefore, this compound was employed to the next step without further purification. IR (neat): 3600-2500, 1728, 1602 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.30 (3H, d, *J* = 6.1 Hz, 2-Me), 1.30-2.11 (6H, m, H-3,4,5), 3.28 (3H, s, OMe), 3.94 (1H, m, H-2), 5.67 (1H, s, H-7), 7.45 (2H, dd, *J* = 8.1 Hz, *J* = 7.8 Hz, Ph), 7.58 (1H, t, *J* = 7.7 Hz, Ph), 8.09 (2H, d, *J* = 8.3 Hz, Ph); FABMS (*m/z*): 277 (M+H<sup>+</sup>-MeOH).

**Preparation of oxoester (16).** To a stirred solution of **12** (570 mg, 1.38 mmol) in acetonitrile-water (4:1, 17.5 mL) were added sequentially HgO (449 mg, 2.07 mmol) and HgCl<sub>2</sub> (750 mg, 2.76 mmol) at rt. The mixture was stirred at rt for 1 day, diluted with ether, and then filtered through a pad of Celite. The filtrate was washed with sat. NH<sub>4</sub>Cl solution, sat. NaHCO<sub>3</sub> solution, water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. Chromatography on silica gel with toluene-ether (10:1→5:1) as the eluent yielded **16** (387 mg, 83%) as a crystalline solid. mp 122-124 °C (hexane-ether);  $[\alpha]_D^{22} +87.0^\circ$  (*c* 0.35, CHCl<sub>3</sub>); IR (KBr): 1749, 1720, 1268, 1243, 1119 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.35 (3H, d, *J* = 6.3 Hz, 2-Me), 2.25 (1H, dd, *J*<sub>3a,3b</sub> = 15 Hz, *J*<sub>2,3a</sub> = 12 Hz, H-3a), 2.43 (1H, ddd, *J*<sub>3a,3b</sub> = 15 Hz, *J*<sub>2,3b</sub> = 3.0 Hz, *J*<sub>3b,5a</sub> = 1.7 Hz, H-3b), 2.79 (1H, dd, *J*<sub>5a,5b</sub> = 15 Hz, *J*<sub>3b,5a</sub> = 1.7 Hz, H-5a), 3.02 (1H, d, *J*<sub>5a,5b</sub> = 15 Hz, H-5b), 3.30 (3H, s, OMe), 3.83 (3H, s, OMe), 4.05-4.13 (1H, m, H-2), 5.50 (1H, s, H-7), 7.44-7.50 (2H, m, Ph), 7.58-7.64 (1H, m, Ph), 8.04-8.07 (2H, m, Ph). HRFABMS (*m/z*): Calcd for C<sub>17</sub>H<sub>20</sub>O<sub>7</sub>Na (M+Na<sup>+</sup>) 359.1107, Found 359.1110. *Anal.* Calcd for C<sub>17</sub>H<sub>20</sub>O<sub>7</sub>: C, 60.71; H, 5.99. Found: C, 60.70; H, 5.97.

**Methyl Benzoyl-3-desmethylpederate (17).** To a stirred suspension of powdered Zn (130 mg, 1.98 mmol) in THF (1 mL) were added sequentially a 1.0 M CH<sub>2</sub>Cl<sub>2</sub> solution of TiCl<sub>4</sub> (0.22 mL, 0.22 mmol) and diiodomethane (90 μL, 1.10 mmol) at 0 °C, and the mixture was stirred at 0 °C~rt for 0.5 h. To this

suspension was added a solution of **16** (74.3 mg, 0.22 mmol) in THF (1.5 mL) and the mixture was stirred at rt for 2 h. After addition of sat. NaHCO<sub>3</sub> solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. Chromatography on silica gel with hexane-ether (5:1) as the eluent yielded **17** (53.3 mg, 73%) as a colorless oil. [ $\alpha$ ]<sub>D</sub><sup>28</sup> +76.4° (*c* 1.88, CHCl<sub>3</sub>); IR (neat): 3073, 1753, 1728, 1659, 1602 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  1.22 (3H, d, *J* = 6.0 Hz, 2-Me), 1.93 (1H, dd, *J*<sub>3a,3b</sub> = 13 Hz, *J*<sub>2,3a</sub> = 12 Hz, H-3a), 2.26 (1H, dd, *J*<sub>3a,3b</sub> = 13 Hz, *J*<sub>2,3b</sub> = 2.1 Hz, H-3b), 2.64 (2H, m, H-5), 3.29 (3H, s, OMe), 3.74-3.78 (1H, m, H-2), 3.80 (3H, s, OMe), 4.86 (1H, m, 4=CH<sub>2</sub>), 4.88 (1H, m, 4=CH<sub>2</sub>), 5.43 (1H, s, H-7), 7.46 (2H, dd, *J* = 7.8 Hz, *J* = 7.3 Hz, Ph), 7.59 (1H, t, *J* = 7.3 Hz, Ph), 8.09 (2H, d, *J* = 8.3 Hz, Ph); FABMS (*m/z*): 335 (M+H<sup>+</sup>).

**Benzoyl-3-desmethylpederic acid (18).** Treatment of **17** (56.5 mg, 0.17 mmol) as described for preparation of **15** from **14** afforded **18**<sup>11</sup> (66.7 mg) quantitatively. IR (neat): 3600-2500, 1728, 1659, 1602 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  1.32 (3H, d, *J* = 6.1 Hz, 2-Me), 2.05 (1H, br dd, *J*<sub>3a,3b</sub> = 13 Hz, *J*<sub>2,3a</sub> = 12 Hz, H-3a), 2.34 (1H, br d, *J*<sub>3a,3b</sub> = 13 Hz, H-3b), 2.46 (1H, br d, *J*<sub>5a,5b</sub> = 14 Hz, H-5a), 2.70 (1H, dd, *J*<sub>5a,5b</sub> = 14 Hz, *J* = 1.2 Hz, H-5b), 3.28 (3H, s, OMe), 3.90 (1H, m, H-2), 4.91 (2H, m, 4=CH<sub>2</sub>), 5.64 (1H, s, H-7), 7.47 (2H, dd, *J* = 7.8 Hz, *J* = 7.3 Hz, Ph), 7.60 (1H, t, *J* = 7.6 Hz, Ph), 8.11 (2H, d, *J* = 8.3 Hz, Ph); FABMS (*m/z*): 321 (M+H<sup>+</sup>).

**Preparation of amides (20) and (21).** To a stirred solution of **15** (74.4 mg, 0.15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added *p*-TsCl (45.6 mg, 0.24 mmol) and DMAP (58.5 mg, 0.48 mmol) at 0 °C and the mixture was stirred at 0 °C for 15 min and rt for 30 min. To this solution was added a solution of **19** (51.0 mg), prepared by hydrogenolysis of the corresponding azide (52.9 mg, 0.14 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and the mixture was stirred at rt for 7 h. After quenching with methanol followed by addition of sat. NaHCO<sub>3</sub> solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. Chromatography on silica gel with hexane-EtOAc (2:1 → 1:1) as the eluent followed by preparative TLC {hexane-EtOAc (1:1)} yielded **20** (12.8 mg, 14%) and **21** (41.0 mg, 46%).

**20**; amorphous solid; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +79.8° (*c* 0.18, CHCl<sub>3</sub>); IR (KBr): 1732, 1710, 1231, 1144, 1125 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.18 (9H, s, *t*-Bu), 1.24-2.04 (6H, m, H-3, 4, 5), 1.26 (3H, d, *J* = 6.4 Hz, 2-Me), 2.08 (3H, s, Ac), 3.22 (3H, s, 6-OMe), 3.52 (3H, s, 13-OMe), 3.78 (1H, dd, *J*<sub>10,11</sub> = 7.6 Hz, *J*<sub>11,12</sub> = 5.2 Hz, H-11), 3.86 (1H, dd, *J*<sub>12,13</sub> = 8.1 Hz, *J*<sub>13,14</sub> = 7.6 Hz, H-13), 3.87 (1H, m, H-2), 3.97-4.01 (2H, m, H-15, 16a), 4.16 (1H, dd, *J*<sub>12,13</sub> = 8.1 Hz, *J*<sub>11,12</sub> = 5.2 Hz, H-12), 4.22 (1H, dd, *J*<sub>16a,16b</sub> = 13 Hz, *J*<sub>15,16b</sub> = 4.9 Hz, H-16b), 4.96, 5.06 (2H, each d, *J* = 7.0 Hz, 10-OCH<sub>2</sub>), 4.99 (1H, dd, *J*<sub>13,14</sub> = 7.6 Hz, *J*<sub>14,15</sub> = 7.3 Hz, H-14), 5.53 (1H, s, H-7), 5.73 (1H, t, *J* = 8.5 Hz, H-10), 7.42-7.46 (3H, m, NH, Ph), 7.55-7.59 (1H, m, Ph), 8.10 (2H, m, Ph). HRFABMS (*m/z*): Calcd for C<sub>31</sub>H<sub>42</sub>NO<sub>12</sub> (M+H<sup>+</sup>-MeOH) 620.2707, Found 620.2711.

**21**; amorphous solid;  $[\alpha]_D^{27} +70.2^\circ$  (*c* 0.52, CHCl<sub>3</sub>); IR (KBr): 1734, 1717, 1150, 1034 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.27 (9H, s, *t*-Bu), 1.28 (3H, s, 2-Me), 1.30-2.00 (6H, m, H-3, 4, 5), 2.12 (3H, s, Ac), 3.20 (3H, s, 6-OMe), 3.47 (3H, s, 13-OMe), 3.49 (1H, t, *J* = 3.4 Hz, H-13), 3.74 (1H, br s, H-11), 3.77 (1H, br s, H-12), 3.85 (1H, m, H-2), 4.14 (1H, dd, *J*<sub>16a,16b</sub> = 12 Hz, *J*<sub>15,16a</sub> = 4.4 Hz, H-16a), 4.28 (1H, m, H-15), 4.48 (1H, dd, *J*<sub>16a,16b</sub> = 12 Hz, *J*<sub>15,16b</sub> = 7.8 Hz, H-16b), 4.80, 5.07 (2H, each d, *J* = 6.8 Hz, 10-OCH<sub>2</sub>), 4.91 (1H, t, *J* = 3.4 Hz, H-14), 5.38 (1H, dd, *J*<sub>10,NH</sub> = 9.8 Hz, *J*<sub>10,11</sub> = 2.0 Hz, H-11), 5.44 (1H, s, H-7), 7.43 (2H, t, *J* = 7.8 Hz, Ph), 7.56 (1H, t, *J* = 7.3 Hz, Ph), 8.05 (1H, d, *J*<sub>10,NH</sub> = 9.8 Hz, NH), 8.09 (2H, d, *J* = 7.8 Hz, Ph); HRFABMS (*m/z*): Calcd for C<sub>31</sub>H<sub>42</sub>NO<sub>12</sub> (M+H<sup>+</sup>-MeOH) 620.2707, Found 620.2714.

**Preparation of 3-desmethyl-4-desmethylenemycalamide analog (3).** To a stirred solution of **20** (9.9 mg, 15.2  $\mu$ mol) in methanol (0.4 mL) was added a 1.0 M LiOH solution (0.2 mL) at 0 °C, and the mixture was stirred at 0 °C~rt for 2 h. After addition of brine, the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried over anhydrous MgSO<sub>4</sub> and concentrated. Chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (1:0 → 50:1) as the eluent yielded **3** (5.5 mg, 86%) as an amorphous solid.  $[\alpha]_D^{28} +86.0^\circ$  (*c* 0.17, CHCl<sub>3</sub>); IR (KBr): 3450, 1688, 1541, 1086, 1034 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.10-1.22 (2H, m, H-3a, 5a), 1.20 (3H, d, *J* = 6.3 Hz, 2-Me), 1.54-1.64 (2H, m, H-3b, 4a), 1.71-1.83 (2H, m, H-4b, 5b), 1.94 (1H, br s, 16-OH), 2.90 (1H, br s, 14-OH), 3.30 (3H, s, 6-OMe), 3.58-3.66 (3H, m, H-14, 15, 16a), 3.61 (3H, s, 13-OMe), 3.72-3.79 (3H, m, H-11, 16b, 7-OH), 3.79-3.85 (1H, m, H-2), 3.88 (1H, dd, *J*<sub>12,13</sub> = 8.8 Hz, *J*<sub>13,14</sub> = 7.8 Hz, H-13), 4.14 (1H, dd, *J*<sub>12,13</sub> = 8.8 Hz, *J*<sub>11,12</sub> = 5.9 Hz, H-12), 4.19 (1H, s, H-7), 4.89, 5.14 (2H, each d, *J* = 7.0 Hz, 10-OCH<sub>2</sub>), 5.78 (1H, dd, *J*<sub>10,NH</sub> = 9.3 Hz, *J*<sub>10,11</sub> = 8.8 Hz, H-10), 7.63 (1H, d, *J* = 9.3 Hz, NH); <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  18.5 (C-4), 22.1 (2-Me), 27.7 (C-5), 32.9 (C-3), 48.0 (6-OMe), 60.6 (13-OMe), 62.2 (C-16), 68.1 (C-2), 70.2 (C-14), 71.0 (C-11), 71.3 (C-7), 74.8 (C-10), 75.4 (C-15), 75.7 (C-12), 77.6 (C-13), 87.1 (10-OC), 99.5 (C-6), 172.8 (C-8); HRFABMS (*m/z*): Calcd for C<sub>17</sub>H<sub>28</sub>NO<sub>9</sub> (M+H<sup>+</sup>-MeOH) 390.1764, Found 390.1777.

**Preparation of 3-desmethyl-4-desmethylenemycalamide analog (4).** Treatment of **21** (20.6 mg, 31.6  $\mu$ mol) as described for preparation of **3** from **20** afforded **4** (9.3 mg, 70%) as an amorphous solid.  $[\alpha]_D^{25} +39.2^\circ$  (*c* 0.23, CHCl<sub>3</sub>); IR (KBr): 3425, 1684, 1539, 1086, 1034 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.08-1.30 (2H, m, H-3a, 5a), 1.23 (3H, d, *J* = 6.3 Hz, 2-Me), 1.54-1.77 (4H, m, H-3b, 4, 5b), 1.96 (1H, m, 16-OH), 3.30 (3H, s, 6-OMe), 3.39 (1H, d, *J* = 11 Hz, 14-OH), 3.45 (3H, s, 13-OMe), 3.53 (1H, t, *J* = 2.5 Hz, H-13), 3.63-3.73 (2H, m, H-14, 16a), 3.72 (1H, d, *J* = 3.9 Hz, 7-OH), 3.77-3.85 (1H, m, H-2), 3.83 (1H, br s, H-11), 3.88 (1H, br t, *J* = 1.5 Hz, H-12), 3.96-4.01 (1H, m, H-16b), 4.07-4.10 (1H, m, H-15), 4.16 (1H, d, *J* = 3.9 Hz, H-7), 4.84, 5.09 (2H, each d, *J* = 6.8 Hz, 10-OCH<sub>2</sub>), 5.36 (1H, dd, *J*<sub>10,NH</sub> = 9.3 Hz, *J*<sub>10,11</sub> = 2.0 Hz, H-10), 8.30 (1H, d, *J*<sub>10,NH</sub> = 9.3 Hz, NH); <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  18.6 (C-4), 21.8 (2-Me), 27.7 (C-5), 32.9 (C-3), 48.0 (6-OMe), 58.5 (13-OMe), 60.9 (C-16), 63.5 (C-11), 66.3 (C-14), 68.2 (C-2), 71.2 (C-7),



73.7 (C-12), 77.3 (C-13), 77.8 (C-10), 80.2 (C-15), 92.2 (10-OC), 99.4 (C-6), 173.2 (C-8); HRFABMS (m/z): Calcd for C<sub>17</sub>H<sub>28</sub>NO<sub>9</sub> (M+H<sup>+</sup>-MeOH) 390.1764, Found 390.1798 .

**Preparation of amides (22) and (23).** Treatment of **18** (49.0 mg, 0.15 mmol) as described for preparation of **20** and **21** from **15** afforded **22** (4.3 mg, 6%) and **23** (34.0 mg, 55%).

**22**; amorphous solid;  $[\alpha]_D^{26} +45.8^\circ$  (*c* 0.10, CHCl<sub>3</sub>); IR (KBr): 1732, 1705, 1541, 1277, 1231, 1136, 1100 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.16 (9H, s, *t*-Bu), 1.32 (3H, d, *J* = 6.3 Hz, 2-Me), 2.07 (3H, s, Ac), 2.10, 2.27 (2H, each br d, *J* = 13 Hz, H-3), 2.35, 2.65 (2H, each br d, *J* = 14 Hz, H-5), 3.22 (3H, s, 6-OMe), 3.52 (3H, s, 13-OMe), 3.78-3.86 (3H, m, H-11, 13, 16a), 3.90 (1H, m, H-2), 3.97 (1H, m, H-15), 4.16 (1H, dd, *J* = 8.3 Hz, *J* = 5.4 Hz, H-12), 4.30 (1H, dd, *J*<sub>16a,16b</sub> = 12 Hz, *J*<sub>15,16b</sub> = 3.9 Hz, H-16b), 4.86, 4.89 (2H, each br s, 4=CH<sub>2</sub>), 4.95 (1H, t, *J* = 7.8 Hz, H-14), 4.97, 5.06 (2H, each d, *J* = 6.8 Hz, 10-OCH<sub>2</sub>), 5.58 (1H, s, H-7), 5.72 (1H, dd, *J*<sub>10,NH</sub> = 9.2 Hz, *J*<sub>10,11</sub> = 8.3 Hz, H-10), 7.35 (1H, d, *J*<sub>10,NH</sub> = 9.2 Hz, NH), 7.46 (2H, t, *J* = 7.8 Hz, Ph), 7.59 (1H, t, *J* = 7.3 Hz, Ph), 8.12 (2H, d, *J* = 7.3 Hz, Ph). HRFABMS (m/z): Calcd for C<sub>32</sub>H<sub>42</sub>NO<sub>12</sub> (M+H<sup>+</sup>-MeOH) 632.2707, Found 632.2710.

**23**; amorphous solid;  $[\alpha]_D^{27} +50.2^\circ$  (*c* 0.45, CHCl<sub>3</sub>); IR (KBr): 1734, 1522, 1275, 1152, 1100, 1032 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.28 (9H, s, *t*-Bu), 1.34 (3H, d, *J* = 6.3 Hz, 2-Me), 2.12 (3H, s, Ac), 2.15, 2.27 (2H, each br d, *J* = 13 Hz, H-3), 2.38, 2.61 (2H, each br d, *J* = 14 Hz, H-5), 3.19 (3H, s, 6-OMe), 3.47 (3H, s, 13-OMe), 3.49 (1H, dd, *J*<sub>12,13</sub> = *J*<sub>13,14</sub> = 2.9 Hz, H-13), 3.76 (1H, br s, H-11), 3.77 (1H, br s, H-12), 3.87 (1H, m, H-2), 4.15 (1H, dd, *J*<sub>16a,16b</sub> = 12 Hz, *J*<sub>15,16a</sub> = 4.9 Hz, H-16a), 4.29 (1H, ddd, *J*<sub>15,16b</sub> = 7.8 Hz, *J*<sub>15,16a</sub> = 4.9 Hz, *J*<sub>14,15</sub> = 3.4 Hz, H-15), 4.49 (1H, dd, *J*<sub>16a,16b</sub> = 12 Hz, *J*<sub>15,16b</sub> = 7.8 Hz, H-16b), 4.79, 5.04 (2H, each d, *J* = 6.8 Hz, 4=CH<sub>2</sub>), 4.86 (2H, br s, H-9), 4.91 (1H, dd, *J*<sub>14,15</sub> = 3.4 Hz, *J*<sub>13,14</sub> = 2.9 Hz, H-14), 5.38 (1H, dd, *J*<sub>10,NH</sub> = 9.8 Hz, *J*<sub>10,11</sub> = 1.5 Hz, H-10), 5.50 (1H, s, H-7), 7.44 (2H, t, *J* = 7.3 Hz, Ph), 7.57 (1H, t, *J* = 7.3 Hz, Ph), 8.01 (1H, d, *J*<sub>10,NH</sub> = 9.8 Hz, NH), 8.10 (2H, d, *J* = 8.3 Hz, Ph); HRFABMS (m/z): Calcd for C<sub>32</sub>H<sub>42</sub>NO<sub>12</sub> (M+H<sup>+</sup>-MeOH) 632.2707, Found 632.2705.

**Preparation of 3-desmethylmycalamide analog (5).** Treatment of **22** (3.8 mg, 5.7  $\mu$ mol) as described for preparation of **3** from **20** afforded **5** (1.6 mg, 65%) as an amorphous solid.  $[\alpha]_D^{22} +94.9^\circ$  (*c* 0.04, CHCl<sub>3</sub>); IR (KBr): 3450, 1686, 1541, 1132, 1096, 1017 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.27 (3H, d, *J* = 5.9 Hz, 2-Me), 1.79 (1H, br s, 16-OH), 1.92-1.97 (2H, m, H-3a, 5a), 2.28 (1H, ddd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2a,3b</sub> = 1.5 Hz, *J*<sub>3b,5b</sub> = 1.0 Hz, H-3b), 2.38 (1H, dd, *J*<sub>5a,5b</sub> = 14 Hz, *J*<sub>3b,5b</sub> = 1.0 Hz, H-5b), 2.79 (1H, br s, 14-OH), 3.28 (3H, s, 6-OMe), 3.55-3.62 (3H, m, H-14, 15, 16a), 3.62 (3H, s, 13-OMe), 3.67-3.71 (1H, m, H-16b), 3.75 (1H, d, *J* = 3.4 Hz, 7-OH), 3.76-3.79 (1H, m, H-11), 3.81-3.90 (2H, m, H-2, 13), 4.15 (1H, dd, *J* = 9.8 Hz, *J* = 6.0 Hz, H-12), 4.26 (1H, d, *J* = 3.4 Hz, H-7), 4.78, 4.83 (2H, each br dd, *J* = 4.0 Hz, *J* = 2.0 Hz, 4=CH<sub>2</sub>), 4.90, 5.15 (2H, each d, *J* = 7.3 Hz, 10-OCH<sub>2</sub>), 5.79 (1H, dd, *J*<sub>10,11</sub> = *J*<sub>10,NH</sub> = 9.3 Hz, H-10), 7.59 (1H, d, *J*<sub>10,NH</sub> = 9.3 Hz, NH); <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  21.8 (2-Me), 37.0 (C-5), 41.6 (C-3), 48.5 (6-OMe), 60.6 (13-OMe), 62.2 (C-16), 68.7 (C-2), 70.2 (C-14), 71.0 (C-7), 71.2 (C-11), 74.8 (C-10), 75.4 (C-15),

75.8 (C-12), 77.6 (C-13), 87.2 (10-OC), 100.4 (C-6), 111.6 (C-9), 140.3 (C-4), 172.6(C-8); HRFABMS (m/z): Calcd for C<sub>18</sub>H<sub>28</sub>NO<sub>9</sub> (M+H<sup>+</sup>-MeOH) 402.1764, Found 402.1775 .

**Preparation of 3-desmethylnycalamide analog (6).** Treatment of **23** (22.9 mg, 34.5 μmol) as described for preparation of **3** from **20** afforded **6** (14.8 mg, 98%) as an amorphous solid.  $[\alpha]_D^{27} +25.7^\circ$  (c 0.27, CHCl<sub>3</sub>); IR (KBr): 3444, 1689, 1684, 1539, 1100, 1030 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>): δ 1.30 (3H, d, *J* = 6.3 Hz, 2-Me), 1.92 (1H, d, *J*<sub>5a,5b</sub> = 14 Hz, H-5a), 1.96-2.03 (2H, m, H-3a, 16-OH), 2.26 (1H, ddd, *J*<sub>3a,3b</sub> = 14 Hz, *J*<sub>2,3b</sub> = 2.0 Hz, *J*<sub>3b,5b</sub> = 1.5 Hz, H-3b), 2.34 (1H, dd, *J*<sub>5a,5b</sub> = 14 Hz, *J*<sub>3b,5b</sub> = 1.5 Hz, H-5b), 3.28 (3H, s, 6-OMe), 3.40 (1H, d, *J* = 11 Hz, 14-OH), 3.45 (3H, s, 13-OMe), 3.53 (1H, br t, *J* = 2.9 Hz, H-13), 3.64-3.74 (2H, m, H-14, 16a), 3.75-3.86 (1H, m, H-2), 3.79 (1H, d, *J* = 3.9 Hz, 7-OH), 3.84 (1H, br t, H-11), 3.88 (1H, dd, *J*<sub>12,13</sub> = 2.9 Hz, *J*<sub>11,12</sub> = 1.5 Hz, H-12), 3.96-4.02 (1H, m, H-16b), 4.08-4.11 (1H, m, H-6), 4.24 (1H, d, *J* = 3.9 Hz, H-7), 4.74, 4.81 (2H, each m, 4=CH<sub>2</sub>), 4.83, 5.07 (2H, each d, *J* = 6.8 Hz, 10-OCH<sub>2</sub>), 5.37 (1H, dd, *J*<sub>10,NH</sub> = 9.3 Hz, *J*<sub>10,11</sub> = 2.0 Hz, H-10), 8.30 (1H, d, *J*<sub>10,NH</sub> = 9.3 Hz, NH); <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>): δ 21.4 (2-Me), 37.0 (C-5), 41.6 (C-3), 48.5 (6-OMe), 58.5 (13-OMe), 60.9 (C-16), 63.5 (C-11), 66.2 (C-14), 68.9 (C-2), 70.8 (C-7), 73.7 (C-12), 77.4 (C-13), 77.8 (C-10), 80.2 (C-15), 92.2 (10-OC), 100.3 (C-6), 111.0 (C-9), 140.8 (C-4), 172.9 (C-8); HRFABMS (m/z): Calcd for C<sub>18</sub>H<sub>28</sub>NO<sub>9</sub> (M+H<sup>+</sup>-MeOH) 402.1764, Found 402.1763.

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