# Two New *N*-(*O*-Carbamoylglucopyranosyl)-*N*-dimethylansamitocins from *Actinosynnema pretiosum*

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Two new and a known *N*-(*O*-carbamoylglucopyranosyl)ansamitocins were isolated from *Actinosynnema pretiosum* ssp. *auranticum* ATCC 31565. The known *N*-(4-*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocin P 2 (= ACGP-2; **1**) was assigned according to 1D- and 2D-NMR data, and the two new compounds were identified as *N*-(6-*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocin P 2 (= ACGP-2′; **2**) and *N*-(4-*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocin P 1 (= ACGP-1; **3**) on the basis of spectroscopic data interpretation including 2D-NMR and tandem MS analysis.

**Introduction.** – Maytansinoids are a family of 19-membered macrocyclic lactams having extraordinary cytotoxic and antineoplastic activities [1][2], and are products of a bacterium (*Actinosynnema pretiosum*) [3], mosses, and three closely related plant families [4], *i.e.*, Celastraceae, Rhamnaceae, and Euphorbiaceae [5]. They are structurally related to ansamycin antibiotics of microbial origin. *Floss* and co-workers have reported the maytansinoid (ansamitocin) biosynthetic gene cluster of *Actinosynnema pretiosum* ssp. *auranticum* ATCC 31565 [6], and recently, our group characterized the glycosyltransferase (*asm25*) functions in the ansamitocin biosynthesis pathway [7].

To explore the potential of *A. pretiosum* to generate glycosides, this strain was cultivated on solid-state YMG medium in our previous work, and two new *N*-demethyl-*N*-(*β*-D-glucopyranosyl)ansamitocins were reported [8][9]. In the present work, two new *N*-(*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocins were isolated and characterized. Here, we report the isolation and structure elucidation of the new ansamitocins.

**Results and Discussion.** – In the present work, we applied an improved TLC method. By using preparative TLC as the vital isolation procedure, three *N*-(*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocins, named ACGP 2 (**1**; 20 mg), ACGP 2′ (**2**; 3 mg), and ACGP 1 (**3**; 12 mg) were obtained from the AcOEt extract of the strain of *A. pretiosum* ATCC 31565 cultivated on solid-state YMG medium (6 l) (*Fig. 1*).

Compound **1** was obtained as straw yellow solid. The positive-ion-mode HR-ESI-MS suggested the molecular formula to be $C_{37}H_{50}ClN_3O_{15}$ ($[M+Na]^+$ at $m/z$ 834.2833). The structure of compound **1** was reported in a patent [10], and its full

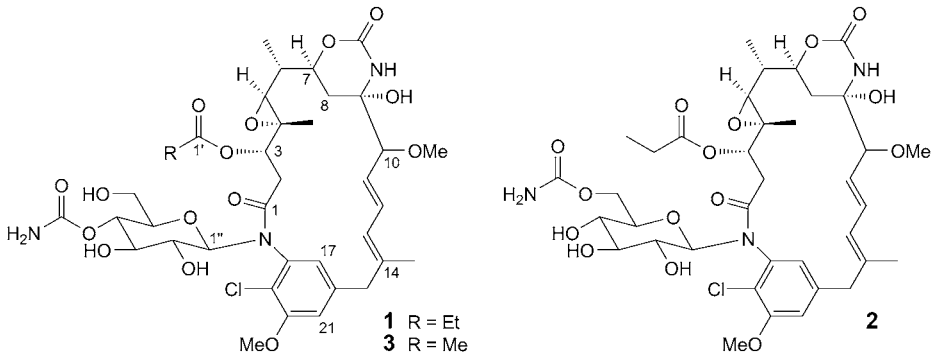


Fig. 1. *Compounds* **1**–**3***, isolated from the strain of* A. pretiosum *ATCC 31565*

NMR data are now provided (*Tables 1* and *2*). Compound **1** was analyzed by tandem MS (*Fig. 2*). The quasimolecular-ion peak of compound **1** at *m*/*z* 834 ($[M+Na]^+$) lost a fragment derived from the 3-ester group to produce the product-ion peak at *m*/*z* 760 ($[M+Na]^+$) in the MS (*Fig. 2*,*a*), and in the MS/MS experiment, the parent-ion peak at *m*/*z* 760 lost a neutral fragment (derived from 4-*O*-carbamoylglucopyranosyl) to produce the MS/MS product-ion peak at *m*/*z* 555 ($[M+Na]^+$) (*Fig. 2*,*b*). Therefore, compound **1** was determined to be *N*-(4-*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocin P 2 and named ACGP 2 (ansamitocin P 2 = 2′-de(acetylmethylamino)maytansine).

Compound **2** was obtained as straw yellow solid. The positive-ion-mode HR-ESI-MS suggested the molecular formula to be $C_{37}H_{50}ClN_3O_{15}$ ($[M+Na]^+$ at *m*/*z* 834.2846). The $^{13}$C-NMR spectrum of **2** (*Table 1*) showed 37 C-atom signals, including 6 Me, 5 $CH_2$, and 15 CH groups and 11 quaternary C-atoms. The NMR data (*Tables 1* and *2*) of **2** was very close to those of **1**, and the same molecular formula and $^{13}$C-NMR data of **2** and **1** suggested their isomeric relationship. According to the NMR data, two chemical shifts had obvious dissimilarity: the H–C(4″) appeared at $\delta$(H) 3.04–3.10 ($\delta$(C) 71.5) in **2** instead of $\delta$(H) 4.24 ($\delta$(C) 73.0) in **1**, and the chemical shifts of $CH_2$(6″) at $\delta$(H) 4.38–4.46 and 4.01–4.20 ($\delta$(C) 65.4) of **2** replaced the signals at $\delta$(H) 3.57–3.62 and 3.46–3.50 ($\delta$(C) 62.9) of **1**. The $^{13}$C,$^1$H long-range HMBC data showed that one H–C(6″) was correlated with the C-atom at $\delta$(C) 159.3 ($NH_2CO$–C(6″)). So, **2** was determined to be *N*-(6-*O*-carbamoyl-*β*-D-glucopyranosyl)-*N*-demethylansamitocin P 2 and named ACGP 2′ [8][9][11].

Compound **3** was obtained as straw yellow solid. The positive-ion-mode HR-ESI-MS suggested the molecular formula to be $C_{36}H_{48}ClN_3O_{15}$ ($[M+Na]^+$ at *m*/*z* 820.2659). The NMR data of **3** (*Tables 1* and *2*) showed signals for 36 C-atoms including 6 Me, 4 $CH_2$, and 15 CH groups and 11 quaternary C-atoms. According to the relative molecular masses of compounds **3** and AGP 1 [8], the presence of a carbamoyl ($CONH_2$) group in **3** accounted for the increase of its molecular mass by 43 mass units as compared to AGP 1. Compound **3** was also analyzed by tandem MS (*Fig. 2*). The quasimolecular-ion peak of **3** (*m*/*z* 820 ($[M+Na]^+$)) lost a fragment derived from the 3-ester group to produce the product-ion peak at *m*/*z* 760 ($[M+Na]^+$) in the MS (*Fig. 2*,*c*), and in the MS/MS experiment, the parent-ion peak at *m*/*z* 760 had lost a

Table 1. *$^{13}$C-NMR Data of Compounds* **1**–**3** *and AGP-2.* $\delta$ in ppm.

| C-Atom | **1** | **2** | **3** | AGP 2 |
|---|---|---|---|---|
| C(1) | 172.9 | 172.8 | 172.9 | 172.9 |
| $CH_2$(2) | 34.7 | 34.7 | 34.7 | 34.7 |
| H–C(3) | 77.8 | 77.9 | 78.8 | 77.8 |
| C(4) | 62.0 | 62.0 | 62.0 | 62.0 |
| H–C(5) | 68.0 | 68.0 | 68.0 | 68.0 |
| H–C(6) | 39.2 | 39.2 | 39.1 | 39.2 |
| H–C(7) | 75.9 | 75.9 | 75.9 | 75.9 |
| $CH_2$(8) | 37.5 | 37.5 | 37.5 | 37.4 |
| C(9) | 81.9 | 81.9 | 82.0 | 81.9 |
| H–C(10) | 89.7 | 89.8 | 89.8 | 89.8 |
| H–C(11) | 129.3 | 129.3 | 129.5 | 129.3 |
| H–C(12) | 134.0 | 134.1 | 134.0 | 134.1 |
| H–C(13) | 125.5 | 125.5 | 125.6 | 125.5 |
| C(14) | 141.5 | 141.5 | 141.45 | 141.5 |
| $CH_2$(15) | 47.5 | 47.5 | 47.5 | 47.5 |
| C(16) | 141.4 | 141.2 | 141.49 | 141.4 |
| H–C(17) | 126.3 | 126.3 | 126.2 | 126.3 |
| C(18) | 137.3 | 137.6 | 137.4 | 137.6 |
| C(19) | 123.4 | 123.4 | 123.5 | 123.4 |
| C(20) | 157.1 | 157.1 | 157.2 | 157.1 |
| H–C(21) | 115.2 | 115.2 | 115.3 | 115.1 |
| C(1′) | 175.3 | 175.2 | 171.8 | 175.3 |
| $CH_2$(2′) or Me(2′) | 27.7 | 27.7 | 21.6 | 27.7 |
| Me(3′) | 8.5 | 8.5 | – | 8.5 |
| H–C(1″) | 84.5 | 84.6 | 84.5 | 84.7 |
| H–C(2″) | 71.9 | 71.7 | 72.0 | 71.8 |
| H–C(3″) | 77.0 | 79.2 | 78.8 | 79.3 |
| H–C(4″) | 73.0 | 71.5 | 73.1 | 71.8 |
| H–C(5″) | 78.7 | 78.0 | 77.1 | 80.2 |
| $CH_2$ (6″) | 62.9 | 65.4 | 62.9 | 63.3 |
| *C*ONH–C(9) | 155.3 | 155.3 | 155.3 | 155.3 |
| *Me*O–C(10) | 56.9 | 56.9 | 56.9 | 56.9 |
| *Me*O–C(20) | 57.1 | 57.1 | 57.2 | 57.1 |
| *Me*–C(4) | 12.1 | 12.1 | 12.1 | 12.1 |
| *Me*–C(6) | 14.7 | 14.7 | 14.6 | 14.7 |
| *Me*–C(14) | 15.8 | 15.8 | 15.8 | 15.8 |
| $NH_2$*C*OO–C(4″) or –C(6″) | 159.3 | 159.3 | 159.3 | – |

neutral fragment ($NH_2COOH$) to produce an MS/MS product-ion peak at *m*/*z* 699 ($[M+Na]^+$) (*Fig. 2*, *d*). Comparing the NMR data of **3** and AGP 1 [8], revealed differences in the signals of H–C(4″), *i.e.*, $\delta$(H) 4.19–4.23 and $\delta$(C) 73.1 for **3** and $\delta$(C) 3.04 and $\delta$(C) 71.9 for AGP 1 [8], thus establishing the position of the $NH_2COO$ group at C(4″) of **3**. Therefore, **3** was determined to be *N*-(4-*O*-carbamoyl-$\beta$-D-glucopyranosyl)-*N*-demethylansamitocin P 1 and named ACGP 1 (ansamitocin P 1 = 2′-de-(acetylmethylamino)-2′-demethylmaytansine).

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Table 2. *$^1$H-NMR and HMBC Data of Compounds* **1**–**3**. $\delta$ in ppm, $J$ in Hz.

| H-Atom | **1** | | **2** | | **3** |
|---|---|---|---|---|---|
| | $\delta$(H) | HMBC | $\delta$(H) | HMBC | $\delta$(H) |
| $CH_2$(2) | 2.47 (*dd*, $J$ = 13.2, 11.9), | C(1), C(3), C(4) | 2.59–2.61 (*m*), | C(3), C(4) | 2.47 (*dd*, $J$ = 12.1, 13.2), |
| | 2.20 (*dd*, $J$ = 2.8, 13.2) | – | 2.17–2.19 (*m*) | – | 2.18 (*dd*, 4.5, 13.7) |
| H–C(3) | 4.76 (*dd*, $J$ = 2.9, 11.9) | C(1′) | 4.76 (*d*, $J$ = 11.8) | C(4), *Me*–C(4), C(1′) | 4.74 (*dd*, $J$ = 3.1, 12.0) |
| H–C(5) | 2.72 (*d*, $J$ = 9.7) | C(3), C(6), *Me*–C(4) | 2.71–2.73 (*m*) | C(3), C(4), C(6), C(7), *Me*–C(4) | 2.66–2.70 (*m*) |
| H–C(6) | 1.49–1.58 (*m*) | – | 1.49–1.52 (*m*) | – | 1.54–1.58 (*m*) |
| H–C(7) | 4.17 (*dd*, $J$ = 3.3, 10.6) | – | 4.25 (*t*, $J$ = 3.0) | – | 4.20 (*dd*, $J$ = 2.8, 10.4) |
| $CH_2$(8) | 1.49–1.58 (*m*) | – | 1.52–1.54 (*m*) | C(7), C(9) | 1.54–1.58 (*m*) |
| H–C(10) | 3.53–3.58 (*m*) | C(9), C(12), *Me*–C(10) | 3.55–3.59 (*m*) | C(9), C(11), C(12), *MeO*–C(10) | 3.55–3.63 (*m*) |
| H–C(11) | 5.53 (*dd*, $J$ = 9.0, 15.4) | C(13) | 5.51–5.54 (*m*) | C(13) | 5.57 (*dd*, $J$ = 8.8, 15.2) |
| H–C(12) | 6.60 (*dd*, $J$ = 11.1, 15.5) | C(10), C(13), C(14) | 6.63 (*dd*, $J$ = 11.2, 15.0) | C(10), C(13), C(14) | 6.63 (*dd*, 10.8, 15.6) |
| H–C(13) | 6.25 (*d*, $J$ = 11.1) | C(11), C(12), C(15), *Me*–C(14) | 6.26 (*d*, $J$ = 10.8) | C(11), C(12), C(15), *Me*–C(14) | 6.26 (*d*, $J$ = 11.6) |
| $CH_2$(15) | 3.53–3.58 (*m*), | C(13), C(14), C(21), *Me*–C(14) | 3.55–3.59 (*m*), | C(13), C(14), C(17), C(21), *Me*–C(14) | 3.55–3.63 (*m*), |
| | 3.29–3.31 (*m*) | | 3.32–3.35 (*m*) | – | 3.28–3.30 (*m*) |
| H–C(17) | 7.20 (*d*, $J$ = 1.6) | C(15), C(16), C(18), C(21) | 7.20 (*s*) | C(15), C(16), C(18), C(21) | 7.21 (*d*, $J$ = 2.0) |
| H–C(21) | 7.16 (*d*, $J$ = 1.5) | C(14), C(15), C(16), C(20), *Me*–C(14) | 7.16 (*s*) | C(15), C(16), C(17), C(20) | 7.16 (*d*, $J$ = 2.0) |
| $CH_2$(2′) or | 2.72–2.77 (*m*) | C(1′), C(3′) | 2.73–2.75 (*m*) | C(1′), C(3′) | 1.24 (*s*) |
| Me(2′) | 2.50–2.56 (*m*) | – | 2.62–2.64 (*m*) | – | |
| Me(3′) | 1.08 (*t*, $J$ = 7.4) | C(1′), C(2′) | 1.13 (*t*, $J$ = 7.3) | C(1′), C(3′) | – |
| H–C(1″) | 5.73 (*d*, $J$ = 9.4) | C(1), C(18), C(2″), C(3″) | 5.71 (*d*, $J$ = 9.5) | C(18), C(1), C(3″) | 5.74 (*d*, $J$ = 9.6) |
| H–C(2″) | 3.12 (*t*, $J$ = 9.2) | C(1″) | 3.04–3.10 (*m*) | C(1″) | 3.08–3.13 (*m*) |
| H–C(3″) | 3.46–3.50 (*m*) | C(5″) | 3.53–3.56 (*m*) | C(2″), C(4″) | 3.43–3.46 (*m*) |
| H–C(4″) | 4.24 (*t*(*dd*), $J$ = 9.6) | C(3″), C(6″), $NH_2$*C*OO–C(4″) | 3.04–3.10 (*m*) | C(3″), C(6″) | 4.19–4.23 (*m*) |
| H–C(5″) | 3.46–3.50 (*m*) | C(4″) | 3.56–3.59 (*m*) | – | 3.28–3.30 (*m*) |
| $CH_2$(6″) | 3.57–3.62 (*m*) | – | 4.38–4.46 (*m*) | C(5″), $NH_2$*C*OO–C(6″) | 3.55–3.64 (*m*) |
| | 3.46–3.50 (*m*) | – | 4.01–4.20 (*m*) | – | 3.43–3.46 (*m*) |
| MeO–C(10) | 3.34 (*d*, $J$ = 2.0) | C(10) | 3.37 (*d*, $J$ = 2.0) | C(10) | 3.35 (*s*) |
| MeO–C(20) | 3.98 (*s*) | C(20) | 3.98 (*s*) | C(20) | 3.96 (*s*) |
| Me–C(4) | 0.79 (*s*) | C(4), C(5) | 0.80 (*s*) | C(4), C(5) | 0.80 (*s*) |
| Me–C(6) | 1.21 (*d*, $J$ = 6.4) | C(5), C(6), C(7) | 1.24 (*d*, $J$ = 6.3) | C(5), C(6), C(7) | 1.24 (*d*, $J$ = 6.4) |
| Me–C(14) | 1.74 (*s*) | C(13), C(14), C(15) | 1.75 (*s*) | C(13), C(14), C(15) | 1.74 (*s*) |

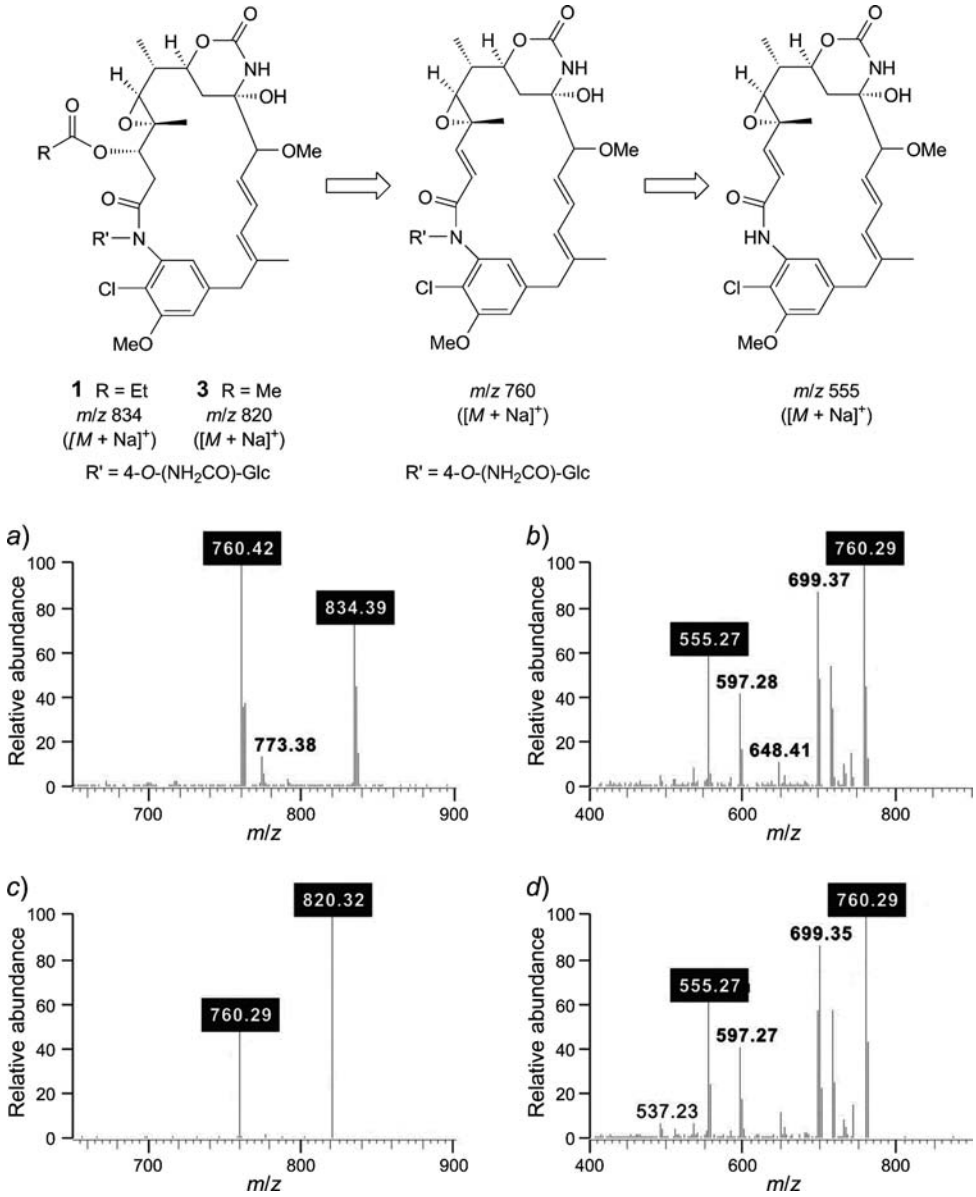


Fig. 2. *Tandem MS of* a) b) *ACGP 2* (**1**) *and* c) d) *ACGP 1* (**3**)

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## Experimental Part

*General*. TLC: Silica gel $GF_{254}$ for separating plates and silica gel *G* for precoated TLC plates from *Qingdao Marine Chemical Factory*, Qingdao, P. R. China. Column chromatography (CC): *Sephadex LH-20* (*Amersham Biosciences*) reversed-phase $C_{18}$ silica gel (*Merck*), and silica gel *G* (200–300 mesh; *Qingdao Marine Chemical Factory*). Optical rotation: *Jasco-DIP-370* digital polarimeter. UV Spectra: *Shimadzu UV-2401PC*; $\lambda_{max}$ (log $\varepsilon$) in nm. IR Spectra: *Paragon-1000pc* spectrometer; KBr pellets; in $cm^{-1}$. NMR-Experiments: *Bruker-AM-400* or *-DRX-500* spectrometer; chemical shifts $\delta$ in ppm rel. to $Me_4Si$, coupling constants *J* in Hz. HR-ESI- and ESI-MS: *VG-Auto-Spec-3000* mass spectrometer and *Finnigan Trace DSQ*; values in *m*/*z*.

*Microbial Material*. The strain *A. pretiosum* ssp. *aurantium* ATCC31565 was obtained from Dr. *T.-W. Yu* and *H. G. Floss* of the University of Washington (Seattle, Washington State, U.S.A.), and was conserved in 20% glycerol at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences (Kunming, Yunnan Province, P. R. China). *A. pretiosum* was used to inoculate a plate on YMG medium (glucose (4.0 g), malt extract (10.0 g), and yeast extract (4.0 g) in 1 liter of $H_2O$; pH 7.2.) at 28° for 5–8 days to afford a working seed culture. Solid fermentation was performed with solid YMG medium (6 l) at 28° for 7 days.

*Extraction and Isolation.* The culture agar was chopped, diced, and extracted with AcOEt/MeOH/AcOH 80:15:5 at r.t. (4 × 20 l, each three days) to afford the extract (21 g). The extract (21 g) was subjected to medium-pressure CC (reversed-phase $C_{18}$ silica gel (145 g), $H_2O$/MeOH containing increasing amounts of MeOH); *Fractions 1–4*. *Fr. 2* (864 mg) was subjected to CC (*Sephadex LH-20* (130 g), MeOH) and then medium-pressure CC (reversed-phase $C_{18}$ silica gel (45 g), $H_2O$/MeOH containing increasing amounts of MeOH): *Frs. 2.1–2.3*. Fraction *Fr. 2.2* (240 mg) was dissolved in MeOH and then repeated subjected to prep. TLC (separating plates ($GF_{254}$), particular developing agent (AcOEt/MeOH 5:1 (100 ml) and 0.5 ml of 25% $NH_3/H_2O$ per plate). The prep. TLCs were run once or twice for best separation; densitometric analyses of the chromatogram were carried out with a ternary wavelength TLC scanner *ZF-I* at 254 nm. The products were removed from the plates by elution of the scratched zones with the particular developing agent. All the compounds were purified by CC (*Sephadex LH-20* (30 g), acetone): ACGP 2 (**1**; 20 mg), ACGP 2′ (**2**; 3 mg), and ACGP 1 (**3**; 6 mg).

*ACGP 2* (= N-*(4*-O-*Carbamoyl-β*-D-*glucopyranosyl)*-N-*demethylansamitocin P 2* = *22-[4*-O-*(Aminocarbonyl)-β*-D-*glucopyranosyl]-2′-de(acetylmethylamino)-22-demethylmaytansine*; **1**): Straw yellow solid. $[\alpha]_D^{15} = -37$ ($c = 0.8$, MeOH). UV (MeOH): 201.8 (4.58), 232.0 (4.37), 253.4 (4.34), 282.8 (3.73) IR (KBr): 3443, 1694, 1659, 1429, 1362, 1161, 1082. NMR: *Tables 1* and *2*. ESI-MS: 834 ($[M+Na]^+$). HR-ESI-MS: 834.2833 ($[M+Na]^+$, $C_{37}H_{50}ClN_3NaO_{15}^+$; calc. 834.2828).

*ACGP 2′* (= N-*(6*-O-*Carbamoyl-β*-D-*glucopyranosyl*-N-*demethylansamitocin P 2* = *22-[6*-O-*(Aminocarbonyl)-β*-D-*glucopyranosyl]-2′-de(acetylmethylamino)-22-demethylmaytansine*; **2**): Straw yellow solid. $[\alpha]_D^{19} = -52$ ($c = 0.56$, MeOH). UV (MeOH): 202.6 (4.54), 231.0 (4.34), 253.4 (4.28), 282.8 (3.69), 290.6 (3.68). IR (KBr): 3431, 1699, 1634, 1428, 1162, 1082. NMR: *Tables 1* and *2*. ESI-MS: 834 ($[M+Na]^+$). HR-ESI-MS: 834.2846 ($[M+Na]^+$, $C_{37}H_{50}ClN_3NaO_{15}^+$; calc. 834.2828).

*ACGP 1* (= N-*(4*-O-*Carbamoyl-β*-D-*glucopyranosyl)*-N-*demethylansamitocin P 1* = *22-[4*-O-*(Aminocarbonyl)-β*-D-*glucopyranosyl]-2′-de(acetylmethylamino)-2′,22-didemethylmaytansine*; **3**): Straw yellow solid. $[\alpha]_D^{19} = -22$ ($c = 0.58$, MeOH). UV (MeOH): 201.8 (4.63), 231.6 (4.43), 253.2 (4.39), 282.4 (3.79). IR (KBr): 3440, 1703, 1657, 1386, 1111, 1042. NMR: *Tables 1* and *2*. ESI-MS: 820 ($[M+Na]^+$). HR-ESI-MS: 820.2659 ($[M+Na]^+$, $C_{36}H_{48}ClN_3NaO_{15}^+$; calc. 820.2671).

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