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Chemical Modification of Ansamitocins. I. Synthesis and Properties of 4,5-Deoxymaytansinoids

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4,5-Deoxymaytansinoids, *e.g.*, 4,5-deoxyansamitocin P-3 (VI) and 4,5-deoxymaytansine (VII), were synthesized a) by conversion of maytansinol into 4,5-deoxymaytansinol (V), followed by acylation using active esters of appropriate carboxylic acids, and b) by direct deoxygenation of the parent maytansinoids. Chromatographic and spectral analyses proved that conformational isomerism exists among these 4,5-deoxymaytansinoids. Compounds VI and VII showed biological activities characteristic of maytansine; thus, the epoxide function in maytansinoids is not essential for their biological properties.

Keywords——maytansinoid; 4,5-deoxymaytansinoid; deoxygenation; 4,5-deoxymaytansine; 4,5-deoxyansamitocin P-3; 4,5-deoxymaytansinol; *N*-methylmaysenine; conformational isomerism; CD; antitumor activity

Maytansine has attracted much attention because of its unique structure and high antitumor activity.[1,2] However, its extremely low isolation yields from plant sources prevented detailed analog studies until the discovery of ansamitocins,[3] a novel class of maytansinoids produced in the fermentation broth of *Nocardia* species. Total syntheses of maytansine have recently been achieved.[4,5] Although maytansine had to be withdrawn from clinical studies due to its toxicity, studies on its chemical modification with the aim of finding a better therapeutic agent continue to be of great interest.

Maytansinoids possess a macrocyclic ring with a number of functional groups, many of which are considered to have roles in its biological activity. Earlier studies suggested that the epoxy and cyclic carbinolamide groups are essential for activity of maytansine.[6-8] The requirement for the cyclic carbinolamide for activity is clear, since blocking[7] or ring opening[9] of this function led to a marked decrease or loss of the biological properties characteristic of maytansine. As for the epoxy group, experimental evidence is still insufficient to establish whether or not it plays an essential role in the activity.

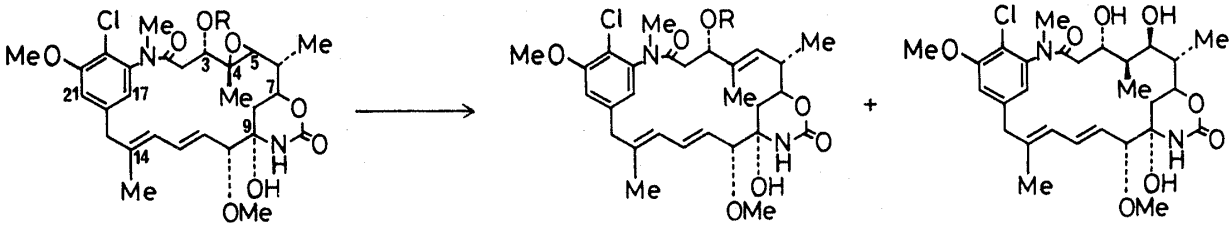
In order to clarify the biological significance of the 4,5-epoxy group on the maytansinoid skeleton, we synthesized 4,5-deoxymaytansinoids and examined their biological activities, such as microtubulin polymerization inhibition, and antiprotozoal and antitumor activities.

In general, an epoxide can be deoxygenated to the corresponding olefin by a variety of reagents which involve metals and metal salts.[10-18] With maytansinoids, deoxygenation of normaysine (XI)[19] and maysine (IX)[4,20] has been reported, but these studies dealt exclusively with the reaction using chromous chloride. This reagent was not suitable for our purpose since the isolated epoxide group in maytansinol is much less reactive than the corresponding epoxide adjacent to a conjugated double bond, *e.g.*, in IX. After several attempts to improve the deoxygenation process, we found that the use of low-valent titanium, prepared from titanium chloride and lithium aluminum hydride (LAH),[10] was effective especially for the reaction of maytansinoids with a C_3-substituent. On treatment of maytansinol (I) with the

low-valent titanium, the epoxide was deoxygenated smoothly to give 4,5-deoxymaytansinol (V) in good yield (Chart 1). Compound V turned out to be a key intermediate for the synthesis of the desired 4,5-deoxymaytansinoids. In fact, treatment of V with isobutyric acid, dicyclohexylcarbodiimide (DCCD) and 4-dimethylaminopyridine (DMAP) gave the desired 4,5-deoxyansamitocin P-3 (VI) in good yield. The reaction of V with L-*N*-acetyl-*N*-methylalanine, DCCD and DMAP gave an epimeric mixture of the 3-(*N*-acetyl-*N*-methyl)alanyl-4,5-deoxy compounds due to racemization of the alanine moiety. The desired 4,5-deoxymaytansine (VII) was separated chromatographically from 4,5-deoxy-D-maytansine (VIII) (Chart 2).

By use of the low-valent titanium in the deoxygenation of maytansinoids with a C_3-ester group, *e.g.*, ansamitocin P-3 (II) and maytansine (III), the corresponding 4,5-deoxymaytansinoids (VI and VII) were obtained, but the yields were poor. Deacylation progressed concurrently with deoxygenation of the maytansinoids to afford, besides the desired product, 4,5-deoxymaytansinol (V) and the epoxide-ring-opened diol, IV, with the former (V) predominating (Chart 1).

The structure of 4,5-deoxymaytansinol (V) was confirmed by conversion to *N*-methylmaysenine (4,5-deoxymaysine, X) by the dehydration of V with DCCD and $ZnCl_2$. In a similar way, maytansinol (I) gave maysine[25] (IX) in good yield (Chart 3). Spectral data and

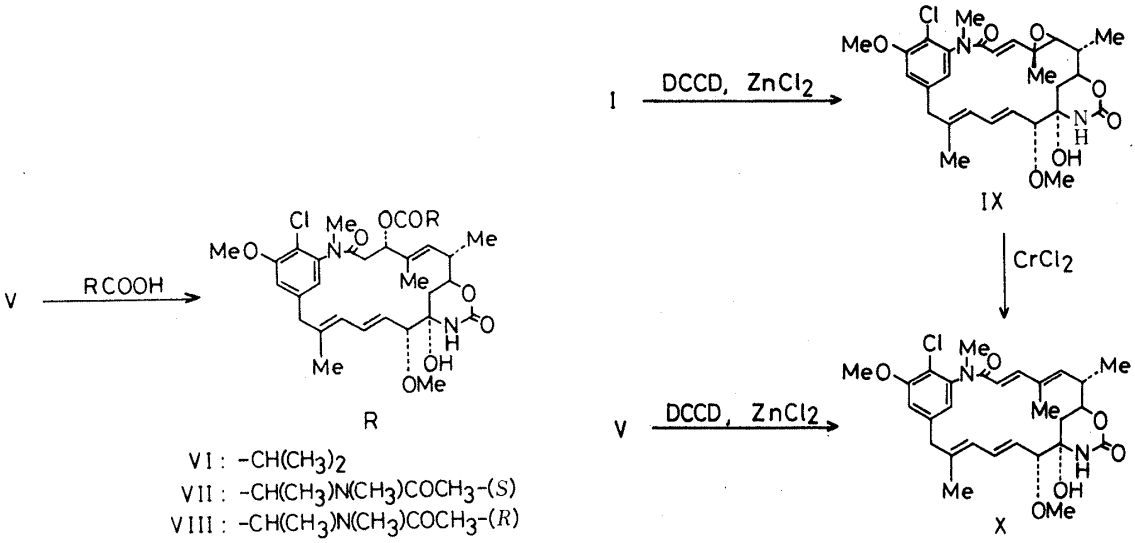


maytansinol
I: R=H V: R=H IV

ansamitocin P-3
II: R=$COCH(CH_3)_2$ V: R=H, VI: R=$COCH(CH_3)_2$ IV

maytansine
III: R=$COCH(CH_3)NCH_3$ V: R=H, VII: R=$COCH(CH_3)NCH_3$ IV
$COCH_3$ $CHCO_3$

Chart 1



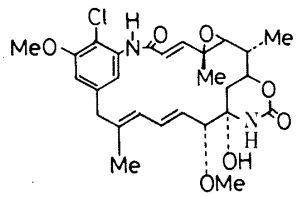
VI: $-CH(CH_3)_2$
VII: $-CH(CH_3)N(CH_3)COCH_3$-(*S*)
VIII: $-CH(CH_3)N(CH_3)COCH_3$-(*R*)

Chart 2 Chart 3

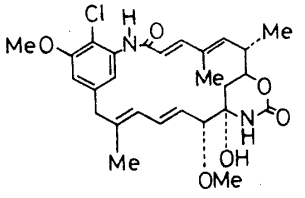
chromatographic properties of X derived from 4,5-deoxymaytansinol (V) were identical with those of the reference sample which was derived from maysine (IX) by the established method, mentioned above.[4,20] Careful comparison of the 4,5-deoxymaytansinoids (VI and VII) derived from maytansinoids (II and III) direclty with those obtained by acylation of 4,5-deoxymaytansinol (V) with active esters of the corresponding carboxylic acids confirmed that the respective products are identical on the basis of the spectral data and chromatographic properties.

Compound VI was shown to exist in the presence of the solvent as an equilibrium mixture (approximately 1 : 1 ratio) of two isomers, VIa and VIb, which could be isolated only at low temperatures (−5 °C or below). Each isolate remained unchanged only at low temperature and readily isomerized to the original equilibrium mixture on standing at 20 °C for approximately 2 h. Similar properties were found for 4,5-deoxymaytansine (VII). On circular dichroism (CD) analysis at low temperature, a marked difference between the spectra of VIa and VIb, and a striking similarity between those of VIb and II were observed. The results suggest that there exists a great difference in conformation between the two isomers (VIa and VIb) and a good conformational similarity between VIb and its parent compound, II.[21] These observations can be explained in terms of conformational isomerism. As is supported by molecular model considerations, 4,5-deoxygenation of maytansinoids is considered to increase the conformational flexibility of the macrocyclic ring system. In contrast to the case of the deoxymaytansinoids, VI and VII, no such isomerism was observed with natural maytansinoids having the 4,5-epoxy function or with 4,5-deoxy compounds which lack the bulky substituent at the C_3-position, *e.g.*, 4,5-deoxymaytansinol (V), *N*-methylmaysenine (X) and maysenine (XII). In view of these facts, the coexistence of the 4,5-deoxy ring system and a relatively bulky substituent at the C_3-position in the molecule are considered to permit the existence of this conformational isomerism. A recent report that the synthetic precursors for maytansine, XIII and XIV, exist as mixtures of two rotamers[4b] is in good accord with the present results. In contrast to that of 4,5-deoxymaytansinoids, VI and VII, the conformation of the macrocyclic ring of the parent maytansinoids, II and III, appears to be highly restricted due to the presence of the 4,5-epoxy function and the sterically hindered substituent at the C_3 position, and this molecular rigidity appears to preclude the conformational isomerism.

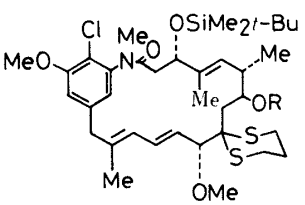
4,5-Deoxymaytansinoids, VI and VII, showed potent growth-inhibitory activities against



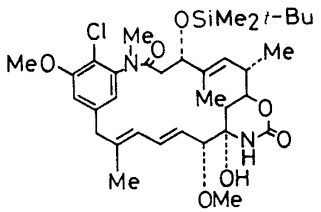
XI
normaysine



XII
maysenine



R=MEM, H, $CONH_2$
XIII



XIV

Chart 4

Tetrahymena pyriformis and inhibited the cilia regeneration of the deciliated cells of *Tetrahymena*. The latter criterion has been used to evaluate the antitubulinic activity of maytansinoids.[22,23] The activities of VI and VII were essentially the same in potency as those of the corresponding maytansinoids, II and III, respectively. Antitumor activities of ansamitocin P-3 and its congeners have been reported previously.[24] Similarly, 4,5-deoxyansamitocin P-3 (VI) showed strong therapeutic activity against B16 melanoma in mice. The potency of VI appears to be comparable to that of the parent ansamitocin P-3 (II). Details of these results will be reported elsewhere. Thus, the results show that, in contrast to previous reports,[6,7] the presence of the epoxide function is not essential for the biological properties characteristic of maytansine.

Experimental

All melting points were measured on a Yanagimoto hot plate apparatus, and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer. Mass spectra (MS) were determined with a JMS-01SC spectrometer equipped with a direct inlet system. Ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on Varian XL-100-12 and Varian EM-360 instruments. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane (TMS). High-performance liquid chromatography (HPLC) was performed using a Waters ALC/GPC 204 instrument. For analytical thin-layer chromatography (TLC), silica gel HPTLC (Kieselgel 60 F_{254} Art. 5642, E. Merck) was used.

4,5-Deoxymaytansinol (V)——Maytansinol (I, 50 mg) was added to a solution of the low-valent titanium reagent [prepared from $LiAlH_4$ (20 mg) and $TiCl_3$ (321 mg) according to the literature[10]] in dry THF, (6 ml). After being stirred at room temperature for 30 min, the reaction mixture was cooled on a ice bath and quenched by addition of water (15 ml). This mixture was extracted with $CHCl_3$ (20 ml × 2) and the extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using 1.5% MeOH in $CHCl_3$ as an eluent. The elution, monitored by TLC analysis, gave one fraction which contained a minor product and a second fraction which contained V. From the second fraction, the desired product was obtained as colorless needles. Yield 22 mg (45.3%). mp 147—149 °C (AcOEt–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1700, 1640, 1580, 1460, 1430, 1080. MS *m/e*: 548 (M^+), 530 (M^+-18), 487 (M^+-61). UV λ_{max}^{MeOH} nm (ε): 231 (23000), 243 (21000), 252 (21000), 280 (4400), 288 (4400). NMR ($CDCl_3$) δ: 1.15 (3H, d, C_6–CH_3), 1.31 (3H, br s, C_4–CH_3), 1.80 (3H, br s, C_{14}–CH_3), 3.20 (3H, s, C_1–NCH_3), 3.35 (3H, s, C_{10}–OCH_3), 3.98 (3H, s, C_5–H), 5.47 (1H, m, C_5–H), 6.71 (1H, d, C_{17}–H), 6.82 (1H, d, C_{21}–H).

(1*S*,2*S*,3*R*,4*S*,5*S*,15*E*,17*E*,19*R*,20*S*)-10-Chloro-11,19-dimethoxy-2,4,8,15-tetramethyl-7,22-dioxo-23-oxa-8,21-diazatricyclo[18,3,1,$1^{9,13}$]pentacosa-9,11,13(25),15,17-pentaene-3,5,20-triol (IV)——From the first fraction in the above chromatography, IV (2.5 mg, 5.0%) was obtained as colorless needles. mp 135—137 °C (AcOEt–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1710, 1650, 1580, 1460, 1430, 1110. MS *m/e*: 566 (M^+), 548 (M^+-18), 505 (M^+-61). UV λ_{max}^{MeOH} nm (ε): 231 (23000), 243 (22000), 252 (21700), 280 (5200), 288 (5000). NMR ($CDCl_3$) δ: 0.49 (3H, d, C_4–CH_3), 1.07 (3H, d, C_6–CH_3), 1.86 (3H, br s, C_{14}–CH_3), 3.15 (3H, s, C_1–NCH_3), 3.37 (3H, s, C_{10}–OCH_3), 3.97 (3H, s, C_{20}–OCH_3), 6.71 (1H, d, C_{17}–H), 6.82 (1H, d, C_{20}–H).

4,5-Deoxyansamitocin P-3 (VI)——A mixed solution of V (200 mg), DCCD (451 mg), DMAP (92.7 mg) and isobutyric acid (192.7 mg) in CH_2Cl_2 (15 ml) was stirred at room temperature for 10 h. A colorless precipitate was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on a silica gel column with 1% MeOH in $CHCl_3$ as an eluent. After work-up, the desired product was obtained as a colorless powder. Yield 112 mg (49.7%). IR ν_{max}^{KBr} cm^{-1}: 1720, 1700, 1660, 1580, 1460, 1430, 1080. MS *m/e*: 618 (M^+), 600 (M^+-18), 577 (M^+-61). UV λ_{max}^{MeOH} nm (ε): 232 (26500), 243 (22900), 252 (22300), 281 (5600), 288 (5400). NMR ($CDCl_3$) δ: 1.08, 1.12 (3H, s, ratio 51 : 49, C_6–CH_3), 1.18, 1.23 (6H, s, ratio 51 : 49, $C_{2'}$–CH_3), 1.53 (3H, br s, C_4–CH_3), 1.77 (3H, br s, C_{14}–CH_3), 3.12, 3.15 (3H, s, ratio 51 : 49, C_1–NCH_3), 3.28, 3.33 (3H, s, ratio 51 : 49, C_{10}–OCH_3), 3.93 (3H, s, C_{20}–OCH_3), 6.30 (1H, dd, C_{13}–H), 6.53 (1H, br d, C_{12}–H), 6.80 (2H, s, C_{17}–H, C_{21}–H).

Conformers of 4,5-Deoxyansamitocin P-3 (VIa and VIb)——Preparative thin layer chromatography (PTLC) of VI, obtained as described above, was performed at −5 °C on Silica gel 60F_{254} (Art. 5642, E. Merck) using 5% MeOH in $CHCl_3$ as the eluent, and gave to UV-absorbing bands corresponding to VIa (*Rf* 0.41) and VIb (*Rf* 0.34). Isolation of each band at −5 °C gave VIa and VIb, respectively. The products showed the following circular dichroism (CD) properties. VIa, CD (c = 0.002, EtOH) $\Delta\varepsilon^{-10}$: −8.4 (214), −7.0 (225), −11.7 (245), 0 (275), +1.4 (285). VIb, CD (c = 0.002, EtOH) $\Delta\varepsilon^{-10}$: +5.2 (211), 0 (218), −18.3 (233), −7.7 (250), −6.1 (281), −6.1 (289). VIa and VIb each showed a single band on TLC analysis at low temperature, but on storage at room temperature for 2 h, they isomerized to the equilibrium mixture which showed exactly the same physical properties as the starting compound (VI).

4,5-Deoxymaytansine (VII)——A solution of V (55 mg), L-*N*-acetyl-*N*-methylalanine (96 mg), DCCD (135 mg) and DMAP (30 mg) in CH_2Cl_2 (6 ml) was stirred at room temperature for 1.5 h. The solution was filtered to remove a

white precipitate, and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel with aqueous ethyl acetate as an eluent.

The eluate fractions containing the desired product were collected and after work-up, VII was obtained as colorless prisms. Yield 17 mg (25.1%). IR ν_{max}^{KBr} cm^{-1}: 1740, 1710, 1650, 1580, 1450, 1430, 1080. MS *m/e*: 675 (M^+), 657 (M^+-18), 614 (M^+-61), 599. UV λ_{max}^{MeOH} nm (ε): 232 (23000), 243 (21000), 253 (20000), 281 (4400), 288 (4400). NMR ($CDCl_3$) δ: 1.06 (3H, d, C_6–CH_3), 1.28 (3H, br s, C_4–CH_3), 1.48 (3H, d, $C_{2'}$–CH_3), 1.75 (3H, br s, C_{14}–CH_3), 2.08, 2.16 (3H, ratio 2:8, $C_{2'}$–$NCOCH_3$), 2.96, 3.06 (3H, s, ratio 2:8, $C_{2'}$–NCH_3), 3.14, 3.17 (3H, s, ratio 2:8, C_1–NCH_3), 3.32, 3.35 (3H, s, ratio 2:8, C_{10}–OCH_3), 3.99 (3H, s, C_{20}–OCH_3), 4.90 (1H, dd, C_3–H), 6.22 (1H, s, C_9–NH), 6.88 (2H, s, C_{17}–H, C_{21}–H).

4,5-Deoxy-D-maytansine (VIII)——Further elution in the above chromatography with the same solvent gave VIII (22 mg, 32.5%) as a colorless powder. IR ν_{max}^{KBr} cm^{-1}: 1740, 1710, 1650, 1580, 1450, 1430, 1080. MS *m/e*: 675 (M^+), 657 (M^+-18), 614 (M^+-61), 599. UV λ_{max}^{MeOH} nm (ε): 232 (22500), 243 (20000), 253 (20000), 281 (4300), 288 (4300). NMR ($CDCl_3$) δ: 1.10 (3H, d, C_6–CH_3), 1.26 (3H, br s, C_4–CH_3), 1.36 (3H, d, $C_{2'}$–CH_3), 1.71 (3H, br s, C_{14}–CH_3), 2.10 (3H, s, $C_{2'}$–$NCOCH_3$), 2.84 and 2.90 (3H, s, ratio 3:7, $C_{2'}$–NCH_3), 3.13 (3H, s, C_1–NCH_3), 3.27 and 3.33 (3H, s, ratio 3:7, C_{10}–OCH_3), 3.93 (3H, s, C_{20}–OCH_3), 5.30 (1H, dd, $C_{2'}$–H), 6.23 (1H, s, C_9–NH), 6.76 (2H, s, C_{17}–H, C_{21}–H).

Reaction of Maytansine (III) with the Low-Valent Titanium Reagent——Maytansine (100 mg) was added to a THF solution of the low-valent titanium reagent [prepared from $LiAlH_4$ (35.3 mg) and $TiCl_3$ (573 mg)], and the mixture was allowed to react at room temperature for 30 min. The reaction mixture was worked up and chromatographed on silica gel using 1% MeOH in $CHCl_3$ as an eluent to yield V (17.9 mg), IV (3.04 mg), and VII (1.08 mg), all in pure form. The physicochemical properties of these products were identical with those of corresponding authentic samples.

Reaction of Ansamitocin P-3 (II) with the Low-Valent Titanium Reagent——Ansamitocin P-3 (II, 50 mg) was treated with the low-valent titanium reagent in a way similar to that described above. As the reaction products, 4,5-deoxymaytansinol (7.9 mg), the triol IV (2.0 mg) and 4,5-deoxyansamitocin P-3 (VI, 2.6 mg) were isolated in pure forms. The physicochemical properties of these products were identical with those of the corresponding authentic samples.

Maysine (IX)[25]——A solution of I (100 mg), DCCD (400 mg), and $ZnCl_2$ (200 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h. The solution was washed with water, then the organic layer was separated and concentrated to dryness *in vacuo*. The pale yellow residue was dissolved in MeOH (40 ml) and the solution was refluxed for 40 min, then evaporated to dryness. The residue was chromatographed on a silica gel column using 1% MeOH–$CHCl_3$ as an eluent and, after work-up, was obtained as a colorless powder. Yield 68 mg (70.0%). IR ν_{max}^{KBr} cm^{-1}: 1710, 1660, 1580, 1080. MS *m/e*: 485 (M^+-61). NMR ($CDCl_3$) δ: 1.03 (3H, s, C_4–CH_3), 1.29 (3H, d, C_6–CH_3), 1.68 (3H, s, C_{14}–CH_3), 2.63 (1H, d, C_5–H), 3.03 (1H, d, C_{15}–H), 3.23 (3H, s, C_1–NCH_3), 3.32 (3H, s, C_{10}–OCH_3), 3.95 (3H, s, C_{20}–OCH_3), 4.20 (1H, m, C_7–H), 5.43 (1H, dd, C_{11}–H), 5.66 (1H, d, C_2–H), 6.05 (1H, d, C_{13}–H), 6.28 (1H, d, C_{12}–H), 6.30 (1H, br s, C_9–NH), 6.66 (1H, d, C_{17}–H), 6.76 (1H, d, C_{21}–H).

***N*-Methylmaysenine (X)**——A solution of V (54.8 mg) in $CHCl_2$ (5 ml) was treated with $ZnCl_2$ (100 mg) and DCCD (200 mg) at room temperature for 2 h and the reaction mixture was worked up in a manner similar to that described above. The desired product was obtained as a colorless powder. Yield 38 mg (71.7%). IR ν_{max}^{KBr} cm^{-1}: 1710, 1660, 1580, 1090. MS *m/e*: 530 (M^+), 512 (M^+-18), 469 (M^+-61). UV λ_{max}^{EtOH} nm (ε): 232 (43000), 242 (45000), 252 (42000), 271 (22000). NMR ($CDCl_3$) δ: 1.23 (3H, d, C_6–CH_3), 1.40 (3H, br s, C_4–CH_3), 1.67 (3H, br s, C_{14}–CH_3), 3.25 (3H, s, C_1–NCH_3), 3.30 (3H, s, C_{10}–OCH_3), 3.97 (3H, s, C_{20}–OCH_3), 4.13 (1H, m, C_7–H), 5.44 (1H, d, C_{11}–H), 6.33 (1H, br s, C_9–NH), 6.60 (1H, d, C_{17}–H), 6.77 (1H, d, C_{21}–H), 7.26 (1H, d, C_3–H).

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