Semisynthetic Macrolide Antibacterials Derived from Tylosin. Synthesis and Structure−Activity Relationships of Novel Desmycosin Analogues[1]

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A series of 20-*O*-substituted and 3,20-di-*O*-substituted derivatives of desmycosin were synthesized and their biological properties were evaluated. In particular, we have synthesized numerous side chain modified analogues of desmycosin as well as some analogues possessing a combination of modified side chain and alternative C-3 substituents. Thus, α,β-unsaturated analogues of desmycosin (**2**), tylosin (**1**), 10,11,12,13-tetrahydrotylosin (**11**), and 2,3-didehydrodesmycosin (**13**) were prepared from the corresponding aldehydes by a Wittig reaction with the stabilized ylides (**a**−**d**), generating a *trans*-double bond, followed by modified Pfitzner−Moffat oxidation of the C-3 hydroxyl group. To evaluate the importance of the C-3 position of desmycosin for biological activity, the C-3 substituted derivatives were synthesized by a standard sequence of protective group chemistry followed by Wittig reaction and esterification as the key steps. For the attachment of the C-3 ester functionality, a mixed anhydride protocol was adopted. Reaction proceeded smoothly to give corresponding esters in yields ranging from 70 to 80%. Base- and acid-catalyzed rearrangement products including desmycosin 8,20-aldols (**24a** and **24b**) and desmycosin 3,19-aldol (**25**) are also described. Parallel array synthesis and purification techniques allowed for the rapid exploration of structure−activity relationships within this class and for the improvement in potency. In vitro evaluation of these derivatives demonstrated good antimicrobial activity against Gram-positive bacteria for most of the compounds. The present derivatives of 16-membered macrolides were active against MLS_B-resistant strains that were inducibly resistant, but not those constitutively resistant to erythromycin.

Introduction

During the past 40 years, the structures of a number of macrolide antibiotics have been elucidated. Of particular interest to us is the group of macrolides containing a 16-membered lactone ring, which include such compounds as tylosin[2] (**1**) and demycarosyltylosine[3] (desmycosin, **2**) (Figure 1). The 16-membered ring macrolide antibiotics[4] are an important series within the macrolide class of antibiotics, since they offer some advantages over 14-membered macrolides. These advantages include better gastrointestinal tolerance, lack of drug−drug interactions, and activity against resistance-expressing strains.[5] Tylosin is an important drug used to treat veterinary Gram-positive and mycoplasma infections as well as to promote livestock growth.[6] This macrolide antibiotic is composed of a polyketide aglycon (tylonolide) and three unusual sugars, D-mycaminose (**3**), L-mycarose (**4**), and D-mycinose (**5**). On the other hand, desmycosin obtained by the mild acidic hydrolysis of tylosin has good antimicrobial activity in vitro against Gram-positive bacteria and mycoplasma but almost no activity in vivo when orally administered. Much of the early efforts on structural modifications within the desmycosin family of compounds have been directed toward modification of the aldehyde group.[7] Derivatives of desmycosin and related macrolides in which the aldehyde function has been modified exhibit enhanced oral bioavailability and higher and more prolonged concentrations of antibiotic activity in vivo. For instance, the introduction of a 3,5-dimethylpiperidine moiety at C-20 of desmycosin (2) via reductive amination has culminated with the synthesis of tilmicosin (**6**), an important drug developed exclusively for veterinary medicine.[8] It has also been shown that derivatives of desmycosin exhibit greater activity against Gram-negative bacteria than do the analogous derivatives of tylosin.[9] Consequently, C-20-modified derivatives of desmycosin represent good starting materials for further chemical modifications in the search for new 16-membered macrolides possessing potentially useful biological activities. Despite the relative maturity of the field, research efforts have continued in order to discover additional new semisynthetic derivatives that may further expand the medicinal application of this class.

Chemistry

As part of a continuing synthetic program focused upon synthesis of desmycosin analogues and related products, we investigated the construction and screening of a small library of compounds with the goal of identifying novel bacterial inhibitors. Access to a library of desmycosin analogues required that we develop a general synthetic strategy that would allow us to explore chemical diversity at sites known to be linked to biological activity. The complexity of the desmycosin scaffold in combination with our desire to investigate multiple structural variations posed a formidable synthetic challenge.

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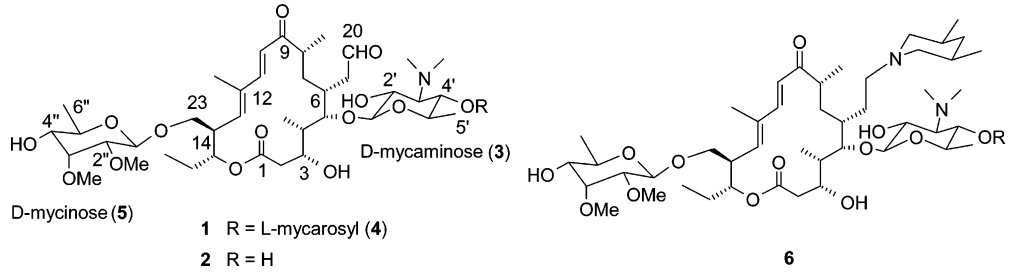


Figure 1. Chemical structures of tylosin (**1**), desmycosin (**2**), and tilmicosin (**6**).

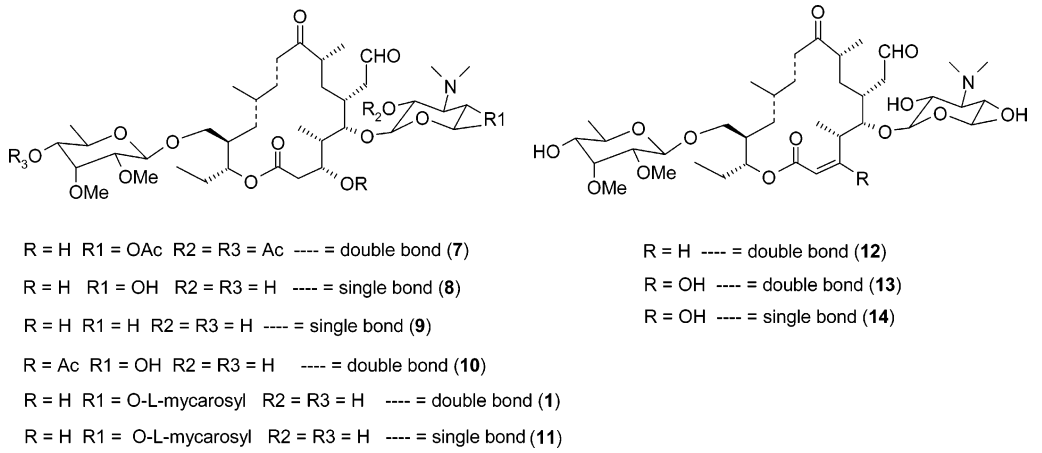
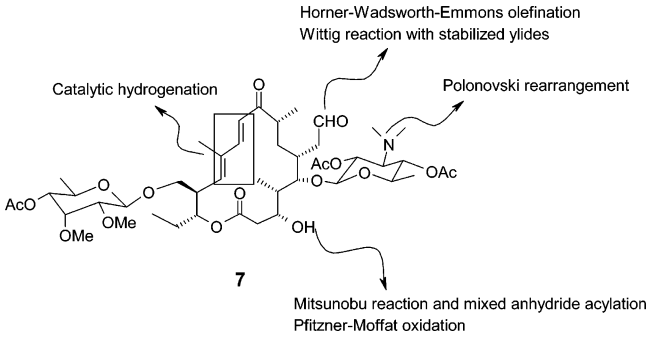


Figure 2. Library building blocks.

Our basic synthetic approach envisioned constructing appropriately functionalized and protected desmycosin that would allow us to explore modifications at C-3, C-20, and explore limited variation in the basic structure of the amino sugar D-mycaminose (**3**). A small focused library was synthesized using various desmycosin and tylosin-related scaffolds (Figure 2) in combination with a wide variety of carboxylic acids and phosphorus ylides as building blocks. The search for new valuable drug candidates not only demands that numerous structural subunits (building blocks) are combined on a particular backbone or template but also that a rich variety of such scaffolds is provided. This takes into account that the core structure of a compound class contributes to the pharmacological profile in addition to the effect it mediates by directing the spatial arrangement of the pharmacophoric substituents. Therefore, the following scaffolds were used for the construction of the library: 2′,4′,4″-tri-*O*-acetyldesmycosin (**7**),[10−11] 10,11,12,13-tetrahydrodesmycosin (**8,** THD),[12] 4′-deoxy-THD (**9**),[13] 3-*O*-acetyldesmycosin (**10**),[10] tylosin (**1**, T), THT (**11**),[14] 2,3-anhydrodesmycosin (**12**),[15] 2,3-didehydrodesmycosin (**13**),[16] and 2,3-didehydro-THD (**14**, Figure 2).[17] A simple straightforward structure such as **7** should allow optimization of potency, by parallel or classical synthesis, for example, by formation of the ester bond or double bond by classical carboxylic acid−alcohol condensation methods or Wittig reaction, respectively. Structural modifications considered for the desmycosin **7** are outlined in Chart 1. Additionally, the wide range of carboxylic acid and stabilized phosphorus ylide libraries that are available to us made this approach particularly attractive and also ensured that a diverse set of compounds was synthesized.

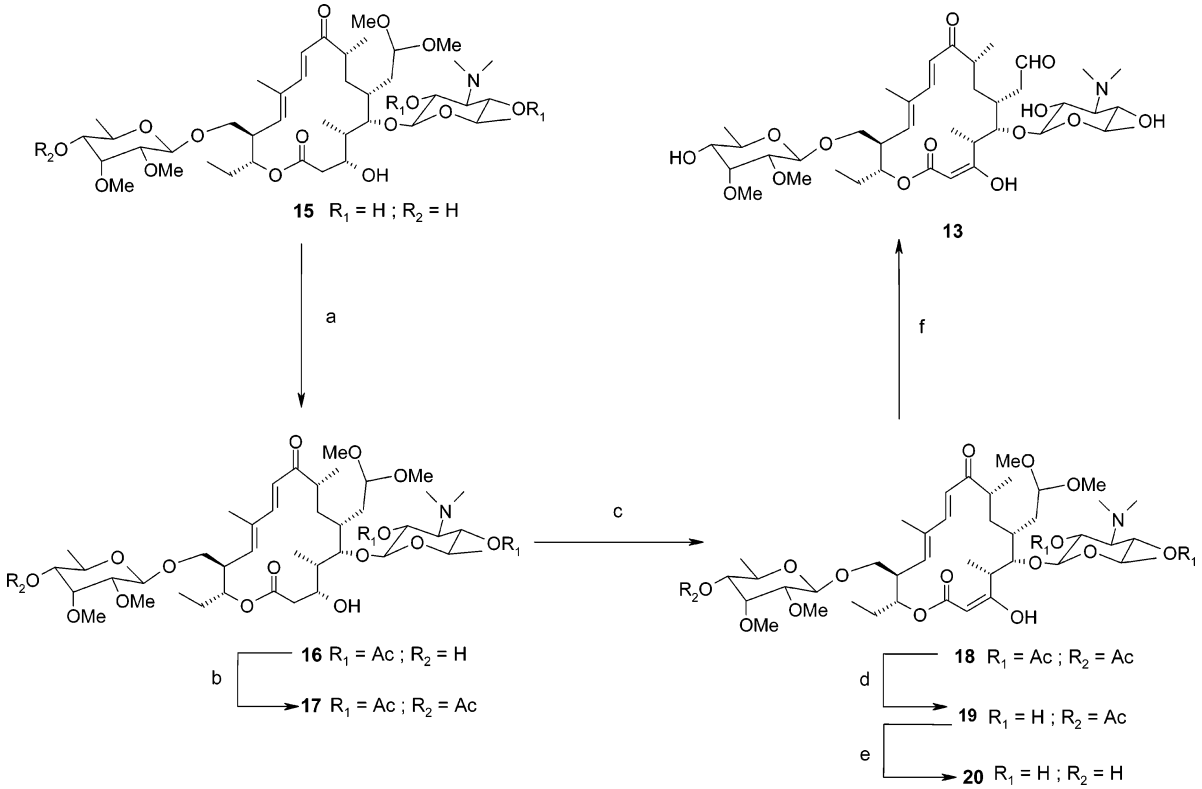
The solution-phase chemistry used to build initial members of our desmycosin library is outlined in

Chart 1



Schemes 1 and 2. The desmycosin library was constructed by using a combination of classical and parallel synthesis methods. Each library member was obtained as a discrete product in ca. 10−50 mg scale and was purified by silica gel chromatography (flash column or thin layer), HPLC, or solid-phase extraction techniques.[18] The synthetic strategy that we chose for the synthesis of C-3 substituted analogues necessitated regioselective protection of hydroxyl groups in the positions C-2′, C-4′, and C-4″ of desmycosin (see Figure 1 for numbering). After extensive experimentation, we established an efficient synthesis of **13** (Scheme 1) by sequentially protecting the various functional groups in desmycosin according to their reactivities, with the aldehyde (**2**) reacted first with trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid followed by acylation of the hydroxyl groups.[10,11] Acetyl-derived protecting groups were selected for all of these hydroxyl groups, because they can be removed cleanly in one step with aqueous ammonia in methanol. This process basically includes selective acetylation of the protected aldehyde (**15**) via two-step sequence and starts with the

Scheme 1. Synthesis of 2,3-Didehydrodesmycosin (**13**)[a]

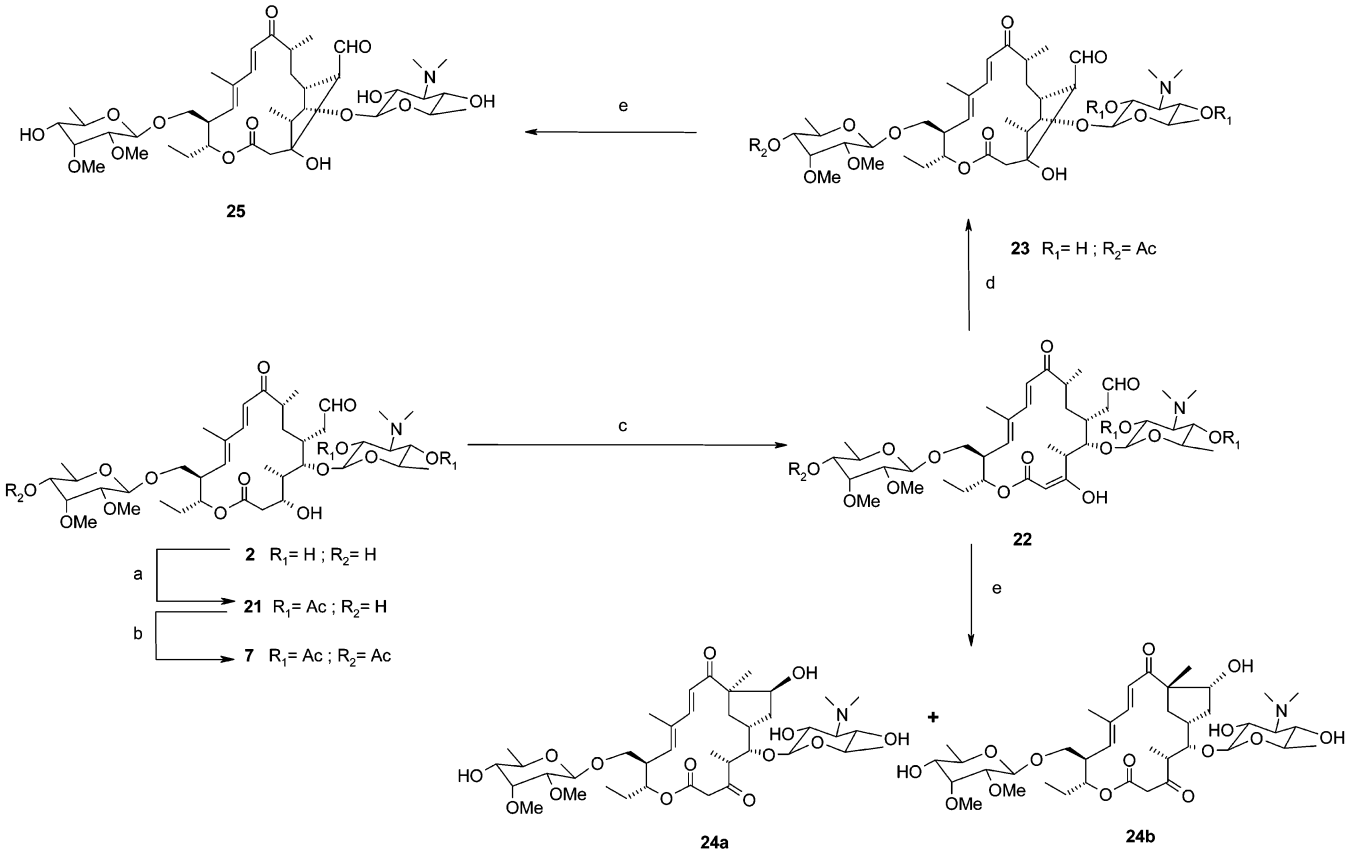


[a] Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, 25 °C, 1 h, 90%; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25 °C, 2 h, 95%; (c) EDC, DMSO, pyridinium trifluoroacetate, CH_2Cl_2, 0−25 °C, 4 h, 85%; (d) MeOH, reflux, 4 h, 85%; (e) aq NH_3, MeOH, 25 °C, 60 h, 74%; (f) 1% TFA, MeCN, 25 °C, 2 h, 80%.

acetylation of the hydroxyl groups on amino sugar D-mycaminose (**3**). Acetylation of the resulting 2′,4′-diacetate (**16**) with acetic anhydride in the presence of a catalytic amount of (dimethylamino)pyridine (DMAP) and triethylamine proceeded selectively at the C-4″ position of D-mycinose (**5**) to yield triacetate (**17**), the substrate for the oxidation. The site of acetylation was unambiguously assigned by one- and two-dimensional ^{1}H NMR and ^{13}C NMR experiments and the usual reactivity found in desmycosin analogues. With the rest of the functionality suitably protected, we were now ready to chemically manipulate the aglycon C-3 alcohol. Oxidation of 2′,4′,4″-tri-*O*-acetyldesmycosin 20-dimethylacetal (**17**) was carried out using modified Pfitzner−Moffat conditions: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl)/DMSO/pyridinium trifluoroacetate in methylene chloride at room temperature (Scheme 1).[19] The reaction proceeded smoothly to give virtually exclusively an enolic form of desmycosin analogue (**18**) according to its ^{13}C NMR spectrum. Deprotection of **18** in methanol gave 4″-monoacetylated desmycosin **19**, which was reacted further with aqueous NH_3 in methanol at room temperature to afford **20** in 90% yield. Further deprotection of **20** under acidic conditions (1% CF_3COOH, CH_3CN) finally resulted in formation of 2,3-didehydrodesmycosin (**13**) in 80% yield. The enol **13** was stable enough to be purified by silica gel column chromatography. Recently, a research group from Eli Lilly reported very similar findings in the synthesis and evaluation of 16-membered ketolide derivatives.[16]

The synthesis summarized in Scheme 2 followed the same route as described for **13**, except that the free aldehyde was used as starting material in the oxidation reaction. Thus, acetylation of desmycosin (**2**) with acetic anhydride and triethylamine led smoothly to diacetate **21**, which was reacted further with acetic anhydride in the presence of a catalytic amount of DMAP to furnish 2′,4′,4″-tri-*O*-acetyldesmycosin (**7**) in 80% overall yield after chromatographic purification.[10,11] The Pfitzner−Moffat oxidation of **7** provided 2′,4′,4″-tri-*O*-acetyl-2,3-didehydrodesmycosin (**22**), whose ^{13}C NMR spectrum in $CDCl_3$ again exhibited a C-3 resonance at ca. 180 ppm, unambiguously indicating that the enol form was present. Deprotection carried out either with triethylamine in methanol or with aqueous methanolic ammonia at 25 °C resulted in a formation of base-catalyzed aldol reaction product as the principal product of the reaction. Initial efforts to remove the protecting groups of enol **22** using triethylamine in methanol yielded the products of intramolecular aldol condensation (**24a** and **24b**) in which cyclization occurred between C-8 and the aldehyde, forming a new five-membered ring. However, hydrolysis of **22** in methanol afforded the product **23** derived from intramolecular cyclization between the carbon alpha to the aldehyde and the C-3 keto group. Removal of the remaining acetyl group of **23** with aqueous ammonia or triethylamine in methanol finally gave bicyclic aldehyde **25**. Therefore, by subtle change of reaction conditions used to deprotect hydroxyl groups on both sugars, it was possible to obtain bicyclic aldehyde **23** substantially free of side products, such as the aldol condensation products (**24a** and **24b**) formed under basic conditions (Scheme 2). According to LC/MS analysis, less than 5% of the side products **24a** and **24b** were actually observed.

Scheme 2. Synthesis of Desmycosines (**24a**, **24b**, and **25**)[a]



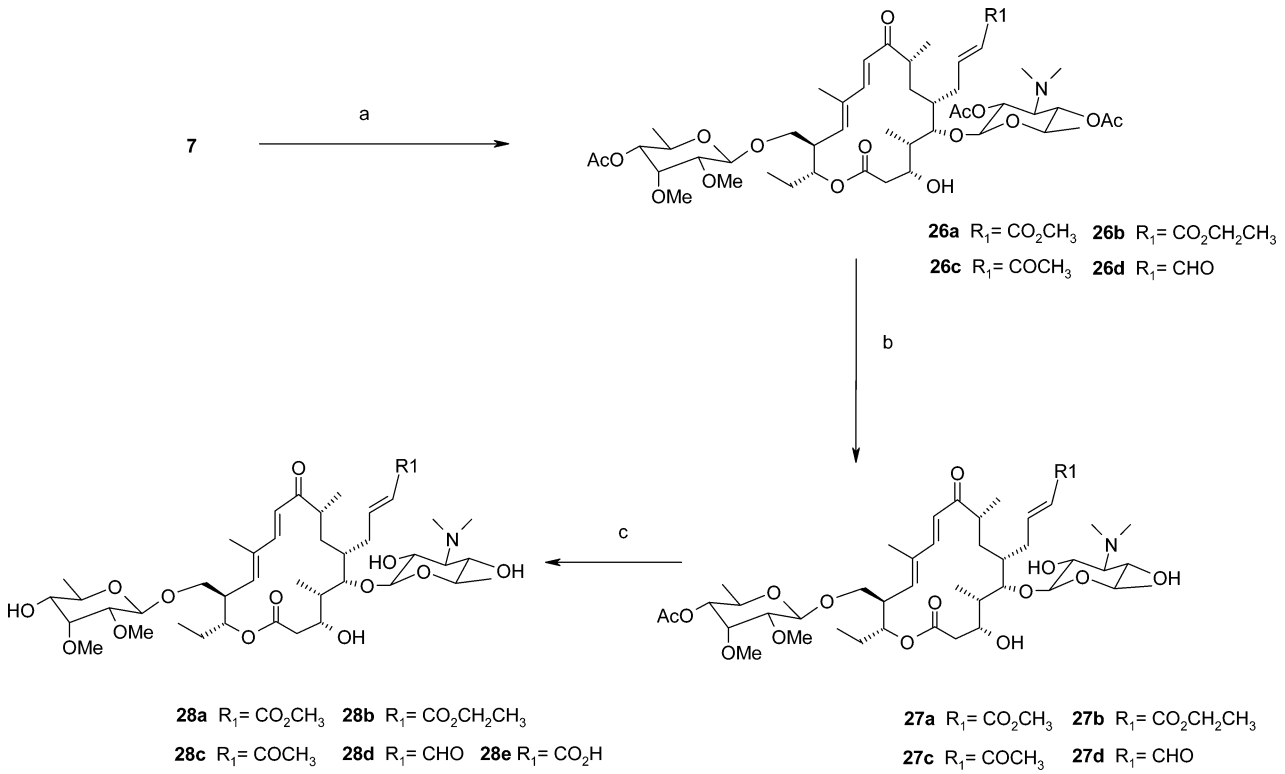
[a] Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, 25 °C, 1 h, 90%; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25 °C, 3 h, ca. 90%; (c) EDC, DMSO, pyridinium trifluoroacetate, CH_2Cl_2, 0−25 °C, 3 h, 85%; (d) MeOH, 25 °, 80%, 6 h; (e) 2% Et_3N or aq NH_3, MeOH, 25 °C, 70%.

This reactivity indicates that the C3-position and the methylene C19 are in close proximity within the lactone ring. The aldehyde proton signal seen as a broad singlet at δ 9.67 in **22** was observed as a doublet ($J_{19,20}$ = 6.0 Hz) at δ 9.72 in **25**. The signal changed to a singlet on irradiation of the C19 methine proton at δ 2.60, indicating that the methine proton must be located at the vicinal position with respect to the aldehyde. An unambiguous NMR assignment of **25** was also made by means of homonuclear $^1H-^1H$ and heteronuclear $^1H-^{13}C$ NMR spectroscopy. Observation of the molecular ion peak at *m*/*z* 770, in addition to the ^1H NMR spectral evidence described above, have led us to propose the structure 3-hydroxybicyclo[12.2.1]desmycosin for **25** (Scheme 2). On the other hand, in the ^1H NMR spectra of **24a** and **24b**, the aldehyde proton signal observed at δ 9.67 in **22** was absent and the signal of the protons attached to a newly formed oxycarbon was observed at δ 4.02 and 3.99 as broad triplets. The other proton signals on the aglycon moiety in **24a** and **24b** showed almost the same chemical shift values as those of **22**. The methyl group substituted at the C8-position, which is observed as a doublet at δ 1.16 in **22**, appeared as a singlet at δ 1.22 and 1.25 in **24a** and **24b**, respectively. The ^{13}C NMR spectra of **24a** and **24b** revealed the conversion of the formyl carbon signal in **22** to the oxycarbon signals at δ 81.1 and 78.6, respectively.

The C-8 methine carbon observed as a doublet in the APT ^{13}C NMR spectrum[20] at δ 40.3 in **22** appeared as a singlet at δ 61.8 and 60.3 in **24a** and **24b**, respectively. Comparison of the chemical shift of the ketone carbonyl at the 9-position in **22**, **24a**, and **24b** revealed a downfield shift of 3.8 ppm in **24a** and 3.5 ppm in **24b** (δ 203.1 in **22**, 206.9 in **24a**, and 206.6 in **24b**) based on the substitution effect at the C-8 methine carbon. The occurrence of C-9 at δ 206.9 and 206.6 suggested that the C-20 hydroxyl group was hydrogen bonded to the 9-oxo group. These data clearly supported the presence of hydrogen bonding between the 20-hydroxy and the 9-oxo group in the aldols **24a** and **24b**. This information again indicated that only isomeric structures *syn*-**24a** and *anti*-**24b**, could accommodate the data. Two-dimensional NMR spectroscopy (DQF COSY, HSQC, and HMBC) at 600 MHz enabled us to assign all of the protons and carbons in **24a** and **24b** unambiguously and to determine the coupling constants. Finally, the structure of **24a** and **24b** was assigned as 8α,20β- and 8β,20α-cyclo-20-hydroxydesmycosin, respectively.

Our next objective was to modify the aldehyde group of desmycosin. Kirst and co-workers have demonstrated that modification of the aldehyde group dramatically enhances the oral efficacy against experimental infections caused by susceptible bacteria in laboratory animals.[21] They also reported that derivatives of desmycosin combine the broadest spectrum of antimicrobial activity with the best efficacy and bioavailability after oral administration. In addition, it has been clearly demonstrated that a C-3 keto group, particularly on the 14-membered ring macrolide erythromycin, can compensate for the lack of α-L-cladinose, and this has given rise to a very active, novel class of compounds, the ketolides.[22] As an extension of this line of thinking, we felt that it would be of interest to study what influence a combination of C-3 and C-20 substituents would have

Scheme 3. Wittig Reaction with Stabilized Phosphorus Ylides[a]



[a] Reagents and conditions: (a) $Ph_3PCHCO_2CH_3$ (**a1**), $Ph_3PCHCO_2CH_2CH_3$ (**a2**), $Ph_3PCHCOCH_3$ (**a3**), or $Ph_3PCHCHO$ (**a4**), benzene, 80 °C, 80−90%; (b) MeOH, 25 °C, 80%; (c) 2% Et_3N or aq NH_3, MeOH, 25 °C, 80%.

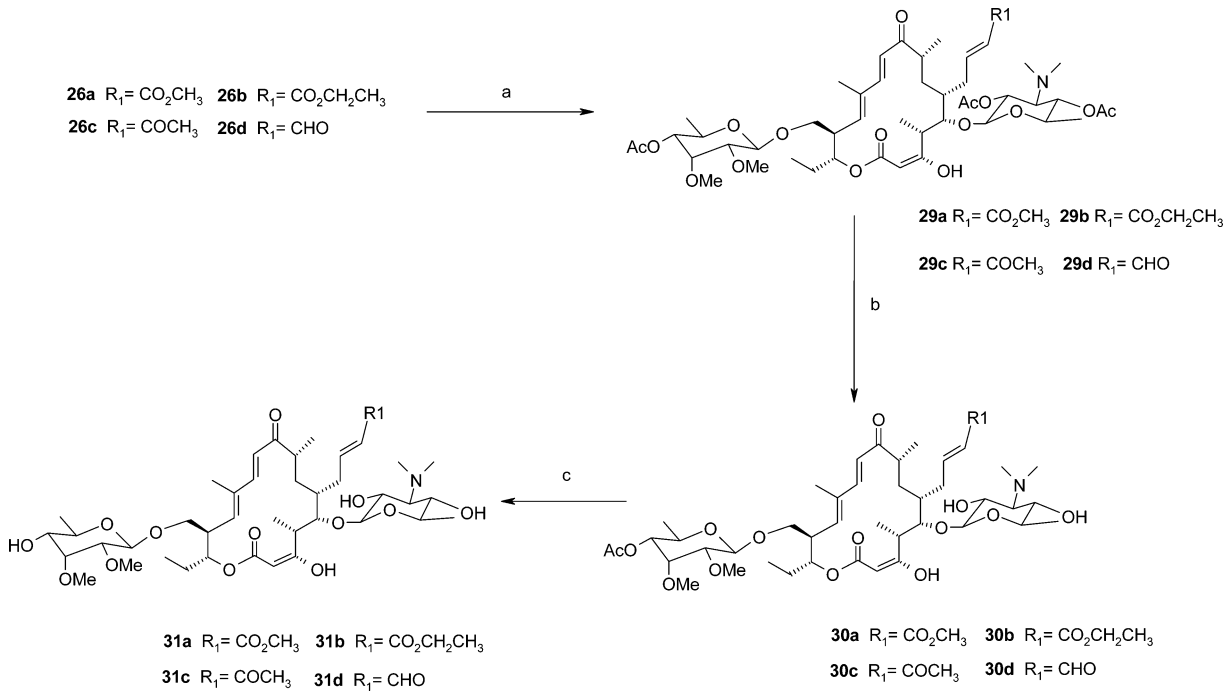
on these properties. However, structural variations at these sites were never explored thoroughly. To expand the structure−activity relationships (SARs) and to more thoroughly define the scope of activity, optimize efficacy, and select the most promising candidates for preclinical development, a range of representative phosphorus ylides (**a1**−**a4**) was reacted with the protected desmycosin **7** in benzene to afford a series of C-20 substituted alkenes (Scheme 3). Further extensions of this series have also been made in which the C3-hydroxyl group has been acylated with aromatic or heteroaromatic carboxylic acids (Scheme 5) rather than oxidized to a C3-ketone (Scheme 4). A stabilized Wittig reaction between the ylides **a1**−**a4** and the aldehyde **7** occurred smoothly and stereoselectively, affording intermediates **26a**−**d** in yields ranging from 80 to 90%. Wittig reactions were both efficient and rapid, typically proceeding to completion within 2 h at 80 °C. Even more encouraging was the fact that products with the trans-geometry of the double bond were formed virtually exclusively using a wide variety of stabilized ylides. This was proven unambiguously from the ^{1}H NMR spectra of the products, which indicated clearly that trans-isomer had formed, as shown by coupling constants for the vinyl protons in the range 12−16 Hz.[23] Deprotection of 2′,4′,4″-tri-*O*-acetyl intermediates (**26a**−**d**) were carried out with methanol followed by either aqueous ammonia or triethylamine in methanol to afford desmycosin analogues **28a**−**d** (Scheme 3). The *E*-α,*β*-unsaturated derivatives (**26a**−**d**) set the stage for further elaboration as summarized in Scheme 4. The Pfitzner−Moffat oxidation of **26a**−**d** provided the corresponding enols **29a**−**d**, which were sequentially hydrolyzed with methanol followed by aqueous ammonia or triethylamine in methanol to give fully deprotected enols **31a**−**d**.

The other members of the library, particularly the acylide family of compounds, were synthesized by the same basic strategy, utilizing Wittig olefination for the attachment of the unsaturated side chains.

Specifically, desmycosins **32**−**39a**−**d** were synthesized as outlined in Scheme 5. Thus, a number of unsaturated side chains were introduced at C-6, and the hydroxyl at C-3 was modified to include aromatic and heteroaromatic acid side chains. Wittig reaction of the ylides **a1**−**a4** and the aldehyde **7** afforded the early intermediates **26a**−**d**. For the attachment of the C-3 ester functionality, a mixed anhydride protocol was adapted. Attachment of the acid side chains (**a1**−**a4**) onto the main framework of desmycosin was accomplished by reaction of alcohols (**26a**−**d**) with mixed anhydride in the presence of Et_3N and DMAP in CH_2Cl_2 at room temperature, leading to esterified products **32**−**35a**−**d**. Finally, exposure of **32**−**35a**−**d** to methanol and then to aqueous ammonia or triethylamine in methanol resulted in the cleavage of the acetyl groups and the liberation of desmycosin esters (**36**−**39a**−**d**).

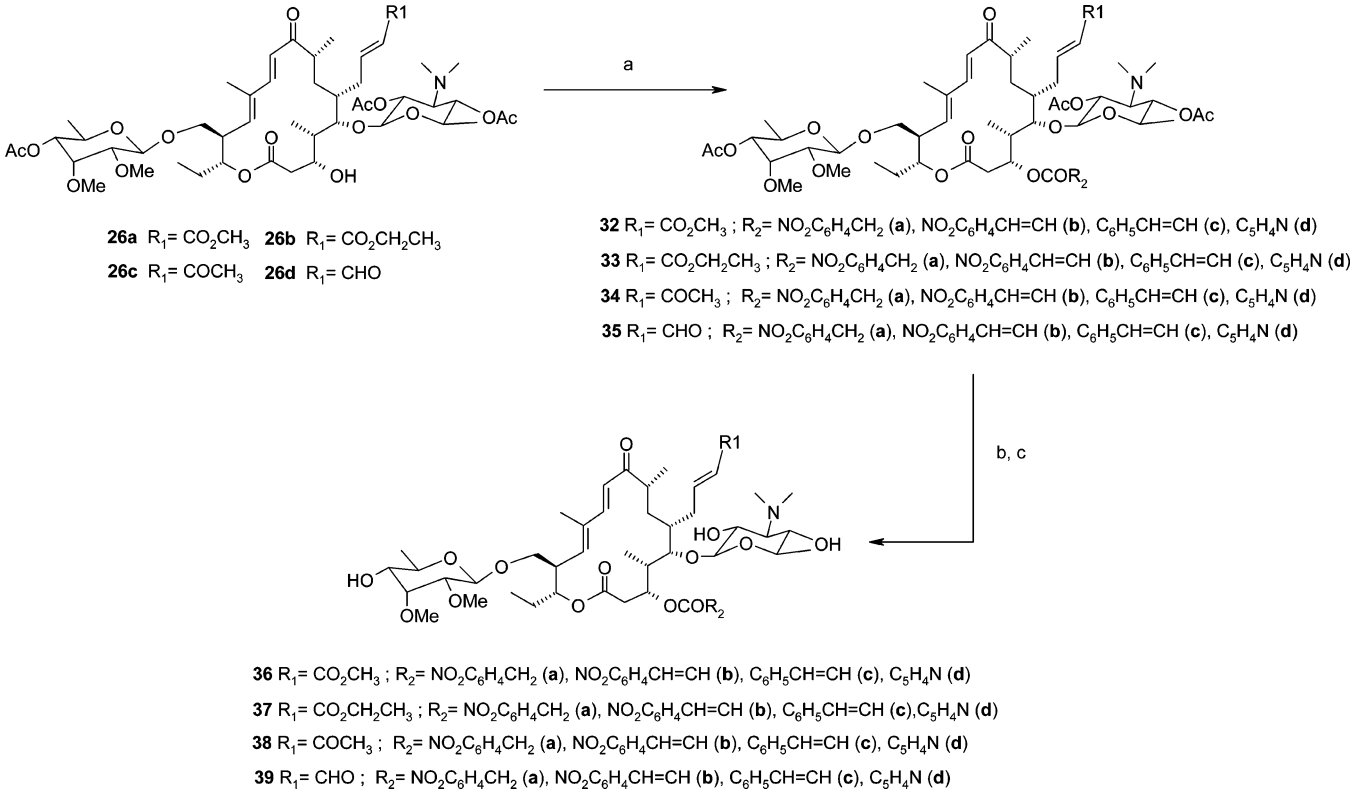
In addition, we realized some inherent flexibility was present at the C-3 position, since the hydroxyl group could be acylated or, alternatively, inverted by a Mitsunobu process to provide both epimers at this position. We examined many variations of the classical Mitsunobu reaction for inverting the C-3 stereogenic center of desmycosin (Scheme 6). Since the C-3 hydroxyl group is in the middle of a large, highly branched aglycon, steric hindrance was expected to impede the reaction. It was decided that modified reaction conditions would have to be applied to achieve the inversion. Therefore, when **26b** was treated successively with diisopropyl azodicarboxylate (DIPAD), Ph_3P, and $ClCH_2CO_2H$[24] in THF and with aqueous ammonia in methanol at room

Scheme 4. Pfitzner–Moffat Oxidation[a]



[a] Reagents and conditions: (a) EDC·HCl, DMSO, pyridinium trifluoroacetate, CH_2Cl_2, 0–25 °C, 80–90%; (b) MeOH, 25 °C, 80%; (c) 2% Et_3N or aq NH_3, MeOH, 25 °C, 80%.

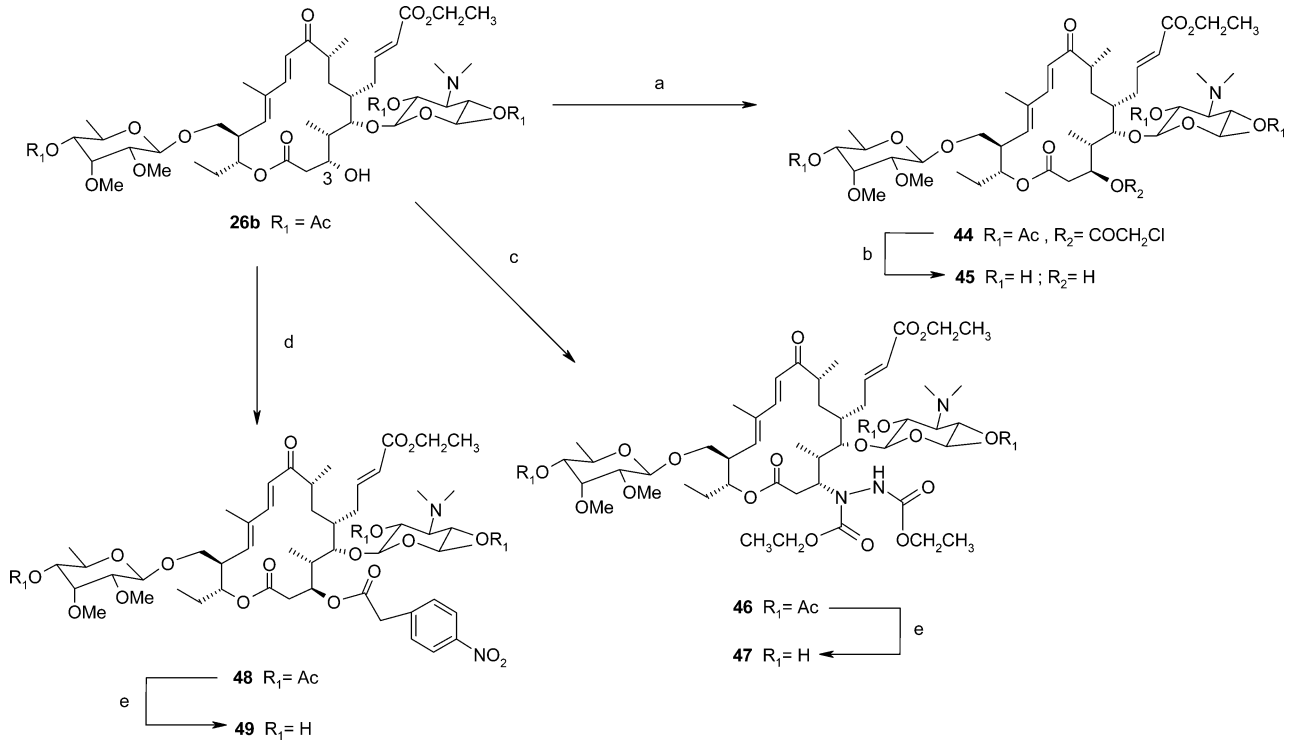
Scheme 5. Synthesis of a Desmycosin Library in Solution Phase[a]



[a] Reagents and conditions: (a) *p*-nitrophenylacetic acid (**a1**), *p*-nitrocinnamic acid (**a2**), cinnamic acid (**a3**), or pyridin-4-carboxylic acid (**a4**), t-BuCOCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 6 h, 60–80%; (b) MeOH, reflux, 3 h, 80%; (c) 2% Et_3N or aq NH_3, MeOH, 25 °C, 10 h, 85%,

temperature, the desired C-3-inverted product **41** was obtained in 90% yield. However, treatment of **26b** with methanol as an acidic component did not give the expected product, but instead, compound **42** formed by addition of diethyl azodicarboxylate on the C-3 position of desmycosin was obtained, as shown in Scheme 6. Subsequent hydrolysis of **42** with aqueous ammonia in methanol at room temperature afforded **43**. Reaction of **26b** with *p*-nitrophenylacetic acid in the presence of 1,1′-azadicarbonylbispiperidine and Bu_3P resulted in formation of inverted acylide **44**, which was hydrolyzed with aqueous ammonia in methanol to give **45**.

Scheme 6. Mitsunobu Reaction−Inversion of Configuration at the C3 Position of Desmycosin[a]



[a] Reagents and conditions: (a) DIPAD, Ph_3P, $ClCH_2CO_2H$, THF, 25 °C, 1 h; (b) NH_3(g), MeOH, 25 °C, overnight, 81% for two steps; (c) DEAD, Ph_3P, MeOH, THF, 25 °C, 3 h, 80%; (d) 1,1′-azadicarbonylbispiperidine, Bu_3P, *p*-nitrophenylacetic acid, THF, 25 °C, 3 h, 85%; (e) aq NH_3, MeOH, 25 °C, 6 h, 70−80%.

Although several modifications of the C-3′-dimethylamino group resulted in diminished antimicrobial activity,[25] there were, to the best of our knowledge, no reports published on the Polonovski reaction within the C-20-substituted desmycosin class of 16-membered macrolides. Therefore, our interest was further focused on chemical transformation of desmycosin derivatives into neutral macrolides having a 3-keto group in order to investigate the effect of this group on their antimicrobial activity. Our synthetic strategy includes conversion of the 3′-dimethylamino compound into the 3′-ketone by utilizing the modified Polonovski rearrangement. Thus, treatment of **15** with *m*-CPBA in CH_2Cl_2 gave the *N*-oxide **46**, which was immediately used for the Polonovski rearrangement. We have found that the reaction of **46** with Ac_2O in CH_2Cl_2 at room temperature overnight yielded the 3′-ketone **47** as the major product. Chromatographic separation allowed the isolation of **47** and the 3′-*N*-acetyl-3′-*N*-demethyl derivative **48** in 50 and 5% yield, respectively.

The two doublet signals for H-2′ (δ 5.20, J = 8.0 Hz) and H-4′ (δ 4.98, J = 10.0 Hz) of **47** supported the absence of H-3′. The two *N*-methyl signals (δ 2.77 and 2.62 in a 1.5:1 ratio) for **48** indicated that it was a mixture of two rotational isomers around the C-3′−N bond in $CDCl_3$. In the phase-sensitive 2D ROESY spectrum,[26,27] the H-3′ signals of the major and minor isomers at δ 4.63 and 3.70, respectively, showed a distinct correlation peak having the same phase with diagonal peaks. Although the respective pairs of the H-1′, H-2′, and *N*-methyl signals of the two isomers appeared close together, their correlation peaks were also observed in the same phase. This type of signal correlation due to saturation transfer occurs via a conformational exchange process. Thus, it was proved that **48** was a mixture of two rotational isomers around the C-3′−N bond. Compounds **47** and **48** were deprotected in methanol to give intermediates **49** and **50**, respectively. Further deprotection of **49** and **50** under acidic conditions finally afforded **51** and **52**, respectively. As shown in Table 1, compounds **51** and **52** showed no antimicrobial activity. Therefore, the dimethylamino group, which is a common structure of basic 16-membered macrolides, is shown to play an important role in their antimicrobial activity.

In continuation of our studies, we have used THD (**8**), 4′-deoxy-THD (**9**), tylosin (**1**), and THT (**11**) as substrates for the Horner−Wadsworth−Emmons reaction (Scheme 8). 4′-Deoxy-THD was prepared in six steps according to literature procedure.[13] For a matter of comparison we have prepared enol **14**, a tetrahydro analogue of **13**, according to a published procedure.[17] For comparisons of antimicrobial activity, we have also prepared desmycosin carboxylic acid **28e**, by base hydrolysis of methyl ester **28a**.

Results and Discussion

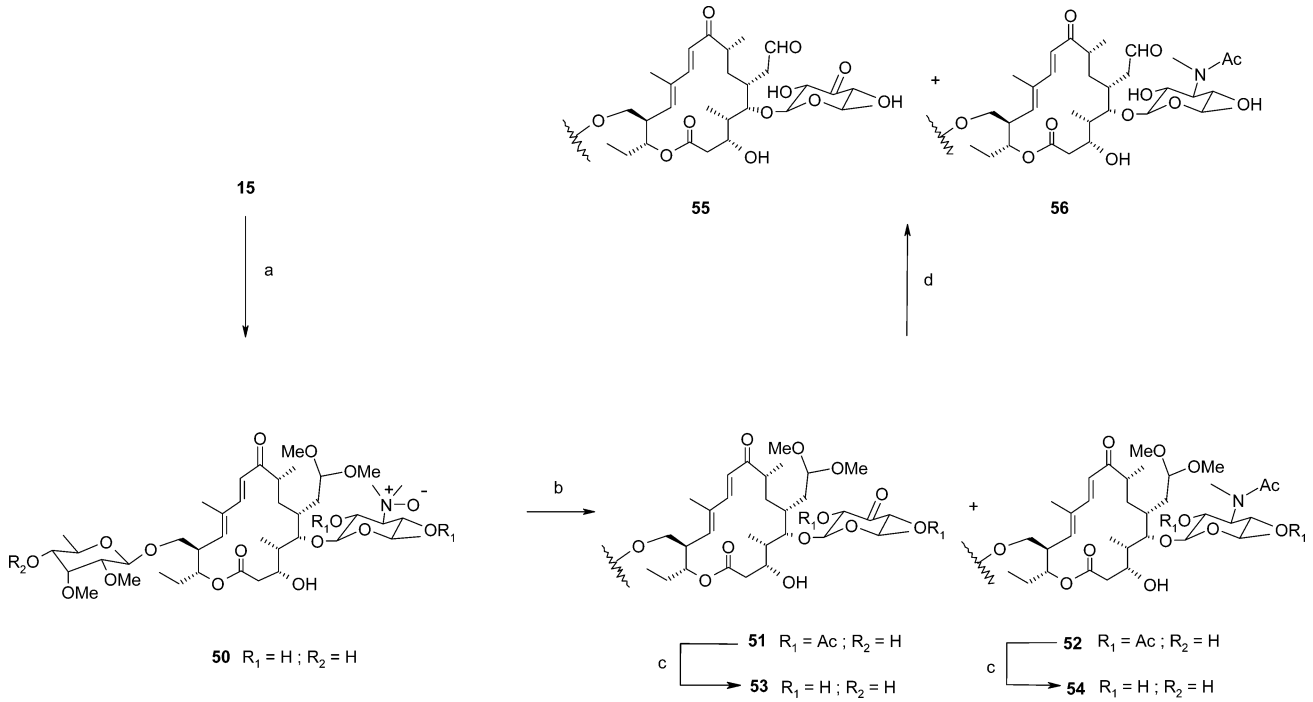
Biological Evaluation of Desmycosin Analogues. All of the compounds were tested in vitro by standard agar dilution method against both erythromycin-susceptible and erythromycin-resistant staphylococci, streptococci, and *Streptococcus pneumoniae*, including constitutive (Ery Rc) and inducible (Ery Ri) phenotype. In addition, one strain each of *Haemophilus influenzae* and *Escherichia coli* was also tested. A preliminary assessment of the relative potency of the synthesized compounds was achieved by rough IC_{50} and MIC determinations. It was readily apparent from these experiments that the conformationally constrained compounds such as **24a**, **24b**, and **25** were significantly less active when

Table 1. Antibacterial Activity of Selected Macrolides in Comparison with Tylosin (**1**) and Desmycosin (**2**)

	MIC (μg/mL)									
	S. aureus				*E. coli*	*H. influenzae*	*E. faecalis*	*S. pneumoniae*	*S. pyogenes*	
compd	ATCC-13709[a]	PSCB-0538[b]	PSCB-0331[c]	PSCB-0330[d]	ATCC-125922	ATCC-49247	ATCC-29212	PSCB-0541[e]	PSCB-0545[f]	PSCB-0543[g]
8	1	2	2	128	128	64	32	2	1	1
9	<0.25	32	0.5	>128	>128	32	8	4	16	2
10	1	8	2	>128	>128	32	8	2	2	2
11	2	4	2	64	64	64	16	8	1	64
12	0.5	4	1	>128	>128	4	8	2	1	2
13	8	16	32	>128	>128	>128	8	8	4	32
14	8	16	8	>128	>128	>128	>128	64	1	8
24a	8	8	32	>128	>128	128	8	4	16	64
24b	8	4	32	>128	>128	128	4	8	16	64
25	32	32	64	>128	>128	64	16	32	32	64
28a	0.5	0.5	0.5	>128	>128	16	0.5	2	0.5	0.5
28b	0.5	0.25	0.25	>128	>128	4	1	2	1	0.5
28c	0.25	0.25	0.5	128	128	4	1	2	0.5	0.5
28e	>128	>128	>128	>128	>128	128	>128	>128	128	>128
31a	2	2	2	>128	>128	128	4	32	4	4
37a	<0.25	0.25	0.5	>128	>128	8	2	4	0.5	2
43	4	64	32	128	128	128	64	32	16	32
45	0.5	16	2	>128	>128	4	8	4	8	32
51	128	128	128	>128	>128	>128	128	128	>128	128
52	128	128	>128	>128	>128	>128	128	128	>128	>128
53	8	128	128	128	128	128	128	64	16	128
54	2	32		128	128	128	128	128	4	128
55	8	4	2	>128	>128	32	32	64	1	64
56	8	>128	32	>128	>128	128	128	128	128	>128
2	1	1	1	>128	128	4	1	1.0	0.5	1
1	1	0.5	1	>128	64	8	1	0.5	0.5	1

[a] *S. aureus* ATCC-13709: erythromycin-susceptible strain. [b] *S. aureus* PSCB-0538: inducibly MLS_B-resistant strain. [c] *S.aureus* PSCB-0331: efflux-resistant strain. [d] *S.aureus* PSCB-0330: constitutively MLS_B-resistant strain encoded by an *ermA* gene. [e] *S. pneumoniae* PSCB-0541: erythromycin-susceptible strain. [f] *S. pyogenes* PSCB-0545: efflux-resistant strain. [g] *S. pyogenes* PSCB-0543: inducibly MLS_B-resistant strain.

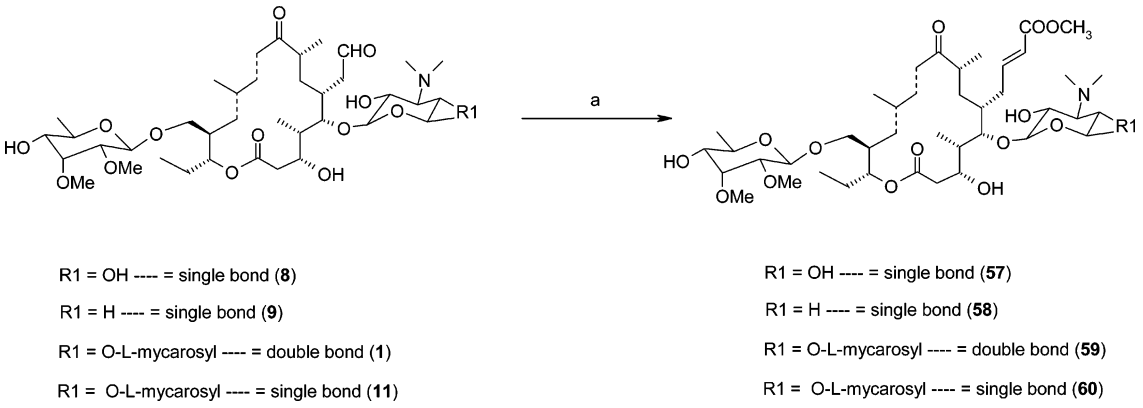
Scheme 7. Polonovski Rearrangement of **16**[a]



[a] Reagents and conditions: (a) mCPBA, $CHCl_3$, 25 °C, 2 h, 90%; (b) Ac_2O, CH_2Cl_2, 25 °C, 18 h, 64%; (c) MeOH, 25 °C, 3 h, 80%; (d) 1 M aq HCl, MeCN, 25 °C, 6 h, 60%.

compared to the unconstrained analogues **28a** and **31a** (Scheme 3, Table 1). It is likely that the reduction of activity caused by forming the bicyclic structure in compounds **24a**, **24b**, and **25** is mainly due to the change of orientation of the aldehyde function in the molecule of **25** or to the change of conformation of the aglycon ring. Compounds (**13** and **14**) displayed relatively poor antibacterial activity compared to their parent macrolides (**2** and **8**). The conversion of the 16-membered ring macrolides to their ketolide analogues (**13** and **14**) led to a decrease in antimicrobial activity against macrolide-susceptible Gram-positive bacteria. No improvement in activity was noted against macrolide-resistant or Gram-negative bacteria. The decrease

Scheme 8. Horner−Wadsworth−Emmons Olefination[a]



[a] Reagents and conditions: (a) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0−25 °C, 5 h.

in activity contrasted with results from the 14-membered ketolides, in which oxidation of the 3-hydroxyl group to a 3-keto moiety resulted in improved activity.[22] In contrast, in vitro activity of desmycosin analogues additionally substituted at the C-20 position (**28a**−**28d**) was enhanced when compared to that of the parent analogue (**2**). Compound **28c** displayed the best activity of all compounds tested from this group and exhibited MIC values around 0.5 μg/mL against most of the strains tested according to this analysis.

The importance of the C-6 unsaturated ester side chain became apparent by a number of substitutions. Thus, replacing the ester functionality (**28a**) with carboxylic acid (**28e**) while maintaing the α,β-unsaturated portion of the side chain resulted in complete loss of activity, thereby suggesting that the ester functionality is a requirement for activity. In contrast, modification at the C-3 hydroxyl group appears much more tolerable for biological activity. Thus, replacement of the OH group of **28a** with a *p*-nitrophenylacetic acid moiety (**37a**) resulted in enhanced biological activity against most of the tested strains, whereas substitution with a dicarbethoxyhydrazine moiety resulted in an overall decrease of activity (**43**, Table 1). Modification of the alcohol component of the C-20 ester group led to negligible modulation of the biological activity of compound **28a** as compared to **28b**. Thus, substitution of the methyl (**28a**) with an ethyl (**28b**) resulted in negligible change of biological activity. Several of the synthesized analogues were identified to be of equal or superior biological activities (e.g. **28a**−**28c** and **37a**) as compared to tylosin (**1**) and desmycosin (**2**), setting the stage for further improvement of antimicrobial activity.

In comparison with unsaturated analogues, the compounds **53**, **54**, and **56** obtained by Horner−Wadsworth−Emmons reaction of parent tetrahydro compounds (**8**, **9**, and **11**, respectively) showed diminished activity against the microorganisms tested.

Structure−Activity Relationships of Desmycosin Analogues. The antibacterial activities in vitro of novel derivatives of desmycosin compared with those of the natural antibiotic tylosin (**1**) and semisynthetic desmycosin (**2**) are shown in Table 1. All the compounds tested were inactive against *E. coli* and erythromycin-resistant (MLS_B constitutive type) strains of *Staphylococcus aureus* (MIC ≥ 128 μg/mL). In contrast, they were very effective against inducibly erythromycin-resistant staphylococci. In our study of desmycosin analogues, we have identified a combination of structural factors that contribute substantially to enhancement of antibacterial activity. Figure 4 summarizes the SARs obtained within the desmycosin family of compounds. These factors are a conformationally restricted unsaturated side chain and an aromatic or heteroaromatic moiety on the C-3 hydroxyl group. Moreover, hydrophilic para substituents such as nitro are preferred for enhancing activity.

Modification of the aldehyde group of tylosin such as in **55** (Table 1) resulted in general loss of activity against all species of bacteria tested. These results are in accord with previous studies reported by Kirst,[7b] which indicate that the exact pattern of substitution with the saccharides mycarose and mycinose is very important for activity and that the broadest spectrum of activity is found with mycinose present and mycarose absent.

Compound **28c** exhibited dramatically improved pharmacokinetics in mice. As a result of Wittig olefination, improvement in both serum and tissue concentrations was achieved. Although compounds **28a**, **28b**, and **28c** displayed similar in vitro activities to desmycosin (**2**), their activities against *S. aureus* were clearly enhanced compared with that of **2**. The activity of **28a**, **28b**, and **28c** against *S. pneumoniae, S. pyogenes, and H. influenzae* was comparable to that **2**. Compound **28c** also exhibited good metabolic stability in rat plasma in vitro. After 24 h of incubation, 85% of initial activity of **28c** was observed against *Micrococcus luteus*, while only 50% activity remained for **2**. Thus, this analogue proved to be more stable than **2** in vitro. Compound **28c**, which was the best compound in terms of potency and stability, was finally examined in vivo. The serum concentration of **28c** following oral administration of 50 mg/kg to Balb/c mice is shown in Figure 3. The serum concentration of **28c** was dramatically higher and longer lasting than that of desmycosin, which gave no detectable blood levels in mice after 50 mg/kg oral dose. Its AUC was also greater than that of desmycosin. The maximum concentration of **28c** in serum was comparable to that of clarithromycin.[28] The peak serum concentration (C_{max}) was 5.01 μg/mL, and the time of peak concentration (T_{max}) was 2 h. The AUC_{0-6} was 0.5075 h μg/mL, and the AUC_{inf} was 0.4495 h μg/mL. The serum concentrations of **28c** after oral administration declined in a monophasic manner, $T_{1/2}$ being 0.28 h.

Following oral administration to mice, **28c** was well-absorbed and extensively distributed into tissues as showed in Table 2.

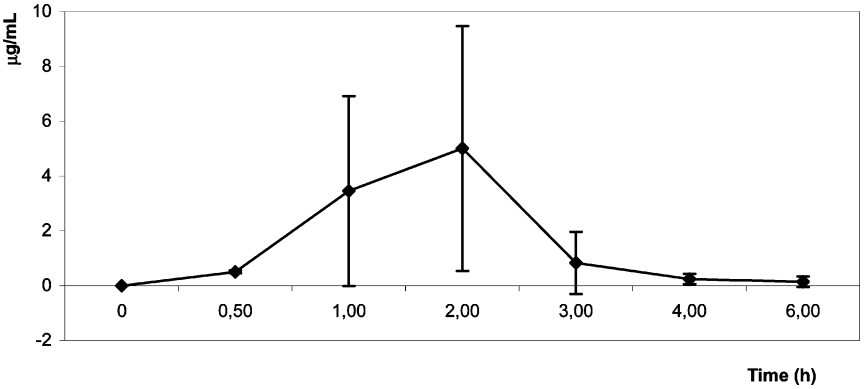


Figure 3. Serum concentration of **28c** in mice after a single oral dose of 50 mg/kg bw ($n = 3$).

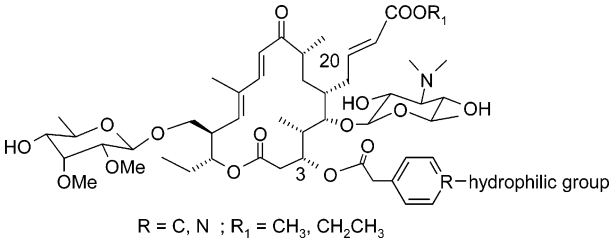


Figure 4. Structure−activity relationship (SARs) of desmycosines: (a) replacement of side chain with carboxylic acid is not tolerated; (b) replacement of the dimethylamino group by a ketone or acetylmethylamino group (Polonovski rearrangement) led to reduced activity; (c) esters at the C-3 position are more active than the corresponding dicarbethoxyhydrazines; (d) hydrophilic para substituents are preferred for enhancement of antibacterial activity.

Table 2. Tissue Pharmacokinetic Parameters for **28c** after a Single Oral 50 mg/kg Dose

tissue	C_{max} (μg/g)	T_{max} (h)	C_2[a] (μg/g)	T_2[b] (h)
liver	33.34	2	24.43	4
kidney	14.28	2	4.58	4
brain	0	0	0	0
spleen	7.97	0.5	7.00	2
lungs	10.41	2	10.24	0.50

[a] C_2, second peak concentration. [b] T_2, time when the second peak was observed.

Peak tissue concentrations of **28c** were reached around 2 h after po application, with the exception of spleen (0.5−1 h). Two peaks were observed in all organs. The first peak in lungs and spleen was observed at 0.5 h, and another at 2 h after administration. For liver, the first peak was observed at 2 h, the second at 4 h; for kidney, the first peak was at 0.5 h and the second at 2 h after administration. This could indicate the formation of an active metabolite, but it can also be explained by the high animal variability, which was observed at each sampling time. C_{max} for liver was 33.34 μg/g, for kidney 14.28 μg/g, for spleen 7.97 μg/g, and for lungs 10.41 μg/g.

The excellent pharmacokinetics of **28c** could be mainly explained by the increased bioavailability of antibiotic after oral administration. These results demonstrate the possibility to design and synthesize 16-membered macrolide derivatives exhibiting similar efficacy to the second-generation 14-membered macrolides, such as clarithromycin. They also point the way for discovery of highly potent and pharmacokinetically excellent derivatives in the 16-membered macrolide series.

Conclusions

In summary, a series of 20-*O*-substituted and 3,20-di-*O*-substituted derivatives of desmycosin and tylosin were prepared and evaluated for in vitro antibacterial activity. The application of high-throughput chemistry and purification techniques facilitated the simultaneous synthesis of arrays of desmycosin analogues and allowed for the rapid elucidation of structure−activity relationships. These compounds were generally better than or equal to desmycosin in potency when tested against macrolide-susceptible organisms. More importantly, these compounds had increased activity against the erythromycin-resistant strains (*S. aureus* PSCB-0538 *and S. pyogenes* PSCB-0543). These compounds, however, were not active against organisms with constitutive MLS resistance. These studies demonstrated a great sensitivity of the side chain domain toward structural changes and thereby reveal a promising potential for further systematic adjustments for fine-tuning the biological properties of future analogues within the same series. Whether the advantages noted here are sufficient to warrant product development can only be ascertained by further studies. We are currently evaluating more compounds from this class in vitro and in vivo, and the results will be reported in due time.

Experimental Section

General. Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectra were recorded on either a Bruker 300 or a Bruker 500 MHz spectrometer and on Varian Inova 600 MHz spectrometer. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane (δ 0.00). Infrared (IR) spectra were recorded on a Perkin-Elmer Infracord 137 or 221 spectrometer or on a Pye Unicam 3-200 spectrometer. UV spectra were run on a Cary 118 spectrometer. Low-resolution electron impact mass spectra (MS) were recorded on a Varian MAT CH5 spectrometer. Fast atom bombardment (FAB) mass spectra were run on a Finnigan MAT 312 double-focusing mass spectrometer, operating at an accelerating voltage of 3 kV. The samples were ionized by bombardment with xenon atoms produced by a saddle-field ion source from Ion Tech operating with a tube current of 2 mA at an energy of 6 keV. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F254 0.2-mm plates. The plates were visualized by using an acid-based stain, prepared from *p*-anisaldehyde (5 mL), concentrated sulfuric acid (5 mL), and glacial acetic acid (0.5 mL) in 95% ethanol (90 mL) and warming on a hot plate. Flash chromatography was carried out using Merck silica gel 60 (230−400 mesh). Solvent systems are reported as volume percent mixtures. Concentration in vacuo refers to the removal of solvent using a Büchi rotary evaporator and an aspirator pump. All chromatography solvents were reagent grade.

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride. All other reagents were purified by literature procedures. All reactions were performed under an inert atmosphere of dry argon. The course of the reaction is followed by chromatography on a thin layer (TLC) of silica gel (Merck 60 F_{254}) in solvent systems methylene chloride−methanol−ammonium hydroxide 25% (90:9:1.5, system A; 90:9:0.5, system A1) or methylene chloride−acetone (8:2, system B; 7:3, system C) unless otherwise stated. The separation of the reaction products and the purification of the products for the purpose of spectral analyses were performed on a silica gel column (Merck 60, 230−400 mesh or 60−230 mesh in solvent system A, B, or C unless otherwise stated.

The structure of all novel compounds was confirmed by IR, MS, and NMR spectroscopic methods. Complete and unambiguous assignments for all ^{1}H and ^{13}C resonances could be achieved on the basis of chemical shift considerations, coupling information (APT[15] and gated decoupled ^{13}C NMR spectra), and COSY-45,[29] HMQC,[30] and 1D-HETCOR[31] spectra as well as on long-range INEPT experiments[32] with selective DANTE excitation.

Determination of Minimum Inhibitory Concentration (MICs). The MICs of all antibiotics were determined by the microdilution broth procedure as recommended by National Committee of Clinical Laboratory Standards (NCCLS) guidelines.[33] Peripheral plasma levels were determined by microbiological assay using *M. luteus* seeded in Difco Antibiotic Media 1. Zone sizes were measured with a Fisher Zone Reader, and antibiotic concentrations were calculated from the standard curve for the appropriate compound.

2,3-Didehydro-2′,4′,4″-tri-*O*-acetyldesmycosin-20-dimethylacetal (18). 2′,4′,4″-Tri-*O*-acetyldesmycosin-20-dimethylacetal (**17**, 10 g, 10 mmol), produced by literature procedures,[10,11] was dissolved in methylene chloride (230 mL), dimethyl sulfoxide (16 mL, 0.22 moL) and, subsequently, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 20 g, 0.1 moL) were added thereto, and the reaction mixture was cooled to 10 °C. A solution of pyridine trifluoroacetate (20.2 g, 0.1 moL) in methylene chloride (115 mL) was added dropwise within 30 min. After 4 h of stirring at room temperature the reaction solution was poured into 850 mL of water and the organic layer was separated and extracted once more with methylene chloride. The combined extracts were washed with a saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The crude product was chromatographed on silica gel eluting with 10% acetone in methylene chloride followed by 30% acetone in methylene chloride (solvent system C) to give **18** (8.0 g, 85%) as pale yellow solid: R_f(A) 0.95, R_f(C) 0.65; FAB-MS *m*/*z* 942 (MH^+, 85%); UV λ_{max} nm (ϵ) 282 (18 900), 258 (17 900); IR (KBr) ν_{max} 2974, 2936, 1746, 1646, 1320, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.04 (1H, s, 3-OH, interchangeable with D_2O), 7.14 (1H, d, H-11), 6.25 (1H, d, H-10), 5.82 (1H, d, H-13), 4.89 (1H, dd, H-2′), 4.74 (1H, dd, H-4′), 4.72 (1H, s, H-2, enol), 4.65 (1H, d, H-1″), 4.44 (1H, dd, H-4″), 4.38 (1H, d, H-1′), 3.53 (3H, s, 3″-OMe), 3.47 (3H, s, 2″-OMe), 3.34 (3H, s, 20-OMe), 3.29 (3H, s, 20-OMe), 2.34 (6H, s, NMe_2), 2.12 (3H, s, COMe), 2.06 (6H, s, 2×COMe), 1.88 (3H, s, H-22); ^{13}C NMR ($CDCl_3$) δ 205.2 (s, C-9), 180.2 (s, C-3, enol), 172.9 (s, C-1), 170.4, 170.1, 169.6 (s, 3×*CO*Me), 147.6 (d, C-11), 140.5 (d, C-13), 137.6 (s, C-12), 124.2 (d, C-10), 88.9 (d, C-2, enol), 20.9, 20.8, 20.6 (q, 3×CO*Me*). Anal. ($C_{47}H_{75}NO_{18}$) C, H, N.

2,3-Didehydro-4″-*O*-acetyldesmycosin-20-dimethylacetal (19). Compound **18** (9 g, 9.6 mmol) was dissolved in methanol (180 mL) and heated at reflux temperature for 4 h, whereupon the reaction solution was evaporated to dryness and the product was dissolved in chloroform (90 mL) and washed with a saturated $NaHCO_3$ solution. The chloroform solution was dried over anhydrous K_2CO_3 and evaporated under vacuum. The crude product was chromatographed on silica gel, eluting with solvent system A, to give the desired product **19** (8.1 g, 98%) as a white solid: R_f(A) 0.45; FAB-MS *m*/*z* 858 (MH^+, 85%); ^{1}H NMR ($CDCl_3$) δ 12.00 (1H, s, 3-OH, interchangeable with D_2O), 6.99 (1H, d, H-11), 6.47 (1H, d, H-10), 5.80, 5.68 (1H, d, H-13), 4.75 (1H, s, H-2, enol), 4.64 (1H, d, H-1″), 4.41 (1H, dd, H-4″), 4.38 (1H, d, H-1′), 3.39 (3H, s, 3″-OMe), 3.34 (3H, s, 2″-OMe), 2.40 (6H, s, NMe_2), 2.08 (3H, s, CO*Me*), 1.81 (3H, s, H-22); ^{13}C NMR ($CDCl_3$) δ 205.4 (s, C-9), 180.1 (s, C-3, enol), 172.5 (s, C-1), 170.4 (s, *CO*Me), 147.6 (d, C-11), 140.5 (d, C-13), 136.8 (s, C-12), 124.3 (d, C-10), 89.0 (d, C-2, enol), 20.5 (q, CO*Me*). Anal. ($C_{43}H_{71}NO_{16}$) C, H, N.

2,3-Didehydrodesmycosin-20-dimethylacetal (20). Compound **19** (3.2 g, 3.73 mmol) was dissolved in methanol (64 mL), 25% NH_4OH (32 mL) was added, and the mixture was left to stand at 5 °C for 60 h. The reaction solution was evaporated to an oily product, which was dissolved in chloroform (60 mL), washed with a saturated $NaHCO_3$ solution, and evaporated in vacuo to a dry residue. Following silica gel chromatography (solvent system A) product **20** (2.25 g, 74%) with the following characteristics was obtained: R_f(A) 0.38; FAB-MS *m*/*z* 816 (MH^+, 89%); ^{1}H NMR ($CDCl_3$) δ 12.05 (1H, s, 3-OH, interchangeable with D_2O), 7.16 (1H, d, H-11), 6.25 (1H, d, H-10), 5.81 (1H, d, H-13), 4.74 (1H, s, enol-H-2), 4.64 (1H, d, H-1″), 4.38 (1H, d, H-1′), 3.53 (3H, s, 3″-OMe), 3.47 (3H, s, 2″-OMe), 3.29 (3H, s, 20-OMe), 3.22 (3H, s, 20-OMe), 2.34 (6H, s, NMe_2), 1.78 (3H, s, H-22). Anal. ($C_{41}H_{69}NO_{15}$) C, H, N.

2,3-Didehydrodesmycosin (13). Compound **20** (1.0 g, 1.22 mmol) was dissolved in acetonitrile (10 mL) and 10% trifluoroacetic acid (12 mL) and stirred for 2 h at room temperature, chloroform (7 mL) was added thereto, and the mixture was alkalized to a pH of 8.5. The organic layer was separated and extracted once more with $CHCl_3$, and the combined extracts were dried and evaporated to a dry residue. By chromatography on a silica gel column (solvent system A), the product **13** (0.79 g, 84%) with the following characteristics was isolated: R_f(A) 0.32; FAB-MS *m*/*z* 770 (MH^+, 80%); ^{1}H NMR ($CDCl_3$) δ 12.10 (1H, s, 3-OH, interchangeable with D_2O), 9.72 (1H, s, H-20), 7.30 (1H, d, H-11), 6.04 (1H, d, H-10), 5.95 (1H, d, H-13), 4.74 (1H, s, enol-H-2), 4.54 (1H, d, H-1″), 4.38 (1H, d, H-1′), 3.53 (3H, s, 3″-OMe), 3.47 (3H, s, 2″-OMe), 2.34 (6H, s, NMe_2), 1.78 (3H, s, H-22). Anal. ($C_{39}H_{63}NO_{14}$) C, H, N.

2,3-Didehydro-2′,4′,4″-tri-*O*-acetyldesmycosin (22). A solution of **7** prepared according to literature procedures[10,11] (1.24 g, 1.38 mmol), EDC·HCl (3.17 g, 16.5 mmol), and DMSO (1.76 mL, 24.8 mmol) in 20 mL of methylene chloride was added dropwise at 0 °C to a solution of pyridinium trifluoroacetate (3.19 g, 16.5 mmol) in 5 mL of methylene chloride. The reaction was stirred for 5 h at room temperature, and 10 mL of water was added. After stirring for 10 min, the mixture was taken up in 50 mL of methylene chloride, followed by washing with water, drying over $MgSO_4$, and evaporation of the solvent. The product was purified by column chromatography eluting with 10% acetone in methylene chloride followed by solvent system C to afford 0.374 g (90%) of enol **22** as pale yellow solid: R_f(A) 0.90, R_f(C) 0.60; FAB-MS *m*/*z* 896 (MH^+, 73%); UV λ_{max} nm (ϵ) 279 (18 200), 256 (17 000); IR (KBr) ν_{max} 2974, 2936, 1747, 1679, 1638, 1595, 1455, 1373, 1231, 1088, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.10 (1H, s, 3-OH, interchangeable with D_2O), 9.70 (1H, s, H-20), 7.30 (1H, d, H-11), 6.05 (1H, d, H-10), 5.92 (1H, d, H-13), 4.85 (1H, dd, H-2′), 4.72 (1H, dd, H-4′), 4.70 (1H, s, H-2 enol), 4.65 (1H, d, H-1″), 4.42 (1H, dd, H-4″), 4.36 (1H, d, H-1′), 3.52 (3H, s, 3″-OMe), 3.45 (3H, s, 2″-OMe), 2.35 (6H, s, NMe_2), 2.12 (3H, s, OCOMe), 2.05 (6H, s, 2×OCOMe), 1.87 (3H, s, Me-22), 1.16 (3H, d, Me-21); ^{13}C NMR ($CDCl_3$) δ 203.1 (s, C-9), 202.9 (d, C-20), 180.0 (s, C-3, enol), 172.7 (s, C-1), 170.2, 170.0, 169.3 (s, 3×*CO*Me), 147.5 (d, C-11), 140.4 (d, C-13), 137.5 (s, C-12), 124.0 (d, C-10), 87.2 (d, C-2 enol), 40.3 (d, C-8), 20.8, 20.7, 20.6 (q, 3×OCO*Me*). Anal. ($C_{45}H_{69}NO_{17}$) C, H, N.

Synthesis of 4″-*O*-Acetyl Bicyclic Aldehyde (23). A solution of **22** (130 mg, 0.15 mmol) in 1 mL of methanol was heated to 60 °C for 6 h. After evaporation of the solvent, the residue was taken up in water, the pH adjusted to 11 with aqueous sodium hydroxide, and the mixture extracted with ethyl acetate. The extracts were washed with water, dried over K_2CO_3, and evaporated to dryness. The product was purified

by column chromatography eluting with 90:10 methylene chloride−methanol to afford 75.5 mg (93%) of **23** as a white foam: FAB-MS *m/z* 812 (MH^+, 78%); ^{1}H NMR ($CDCl_3$) δ 9.72 (1H, d, H-20), 7.30 (1H, d, H-11), 6.02 (1H, d, H-10), 5.95 (1H, d, H-13), 5.11 (1H, dt, H-15, $J_{15,16a} = 9.5$ Hz, $J_{15,16b} = 2.5$ Hz), 4.64 (1H, d, H-1″, $J_{1'',2''} = 7.9$ Hz), 4.46 (1H, dd, H-4″, $J_{3'',4''} = 2.6$ Hz, $J_{4'',5''} = 9.9$ Hz), 4.30 (1H, s, 3-OH, interchangeable with D_2O), 4.29 (1H, d, H-1′, $J_{1',2'} = 9.5$ Hz), 4.01 (1H, dd, H-23b, $J_{23a,23b} = 9.6$ Hz, $J_{14,23b} = 4.2$ Hz), 3.95−3.89 (2H, m, H-5″ and H-3″), 3.88−3.85 (1H, m, H-5), 3.58 (1H, dd, H-23a, $J_{23a,23b} = 9.6$ Hz, $J_{14,23a} = 4.2$ Hz), 3.53 (3H, s, 3″-OMe), 3.51−3.49 (1H, m, H-2′), 3.48 (3H, s, 2″-OMe), 3.30 (1H, dq, H-5′, $J_{4',5'} = 8.8$ Hz, $J_{5',6'} = 6.2$ Hz), 3.21 (1H, br, H-8), 3.09−3.01 (3H, m, H-2″, H-14, and H-4′), 2.80 (1H, dd, H-19, $J_{6,19} = 7.7$ Hz, $J_{19,20} = 6.0$ Hz), 2.61 (1H, d, H-2b, $J_{2a,2b} = 17.2$ Hz), 2.50 (6H, s, NMe_2), 2.37 (1H, t, H-3′, $J_{2',3'} = J_{3',4'ax} = 10.2$ Hz), 2.12 (3H, s, 4″-OCO*CH*$_3$), 2.04 (1H, m, H-7b), 1.97 (1H, d, H-2a, $J_{2a,2b} = 17.2$ Hz), 1.90 (1H, ddq, H-16b, $J_{15,16b} = 3.0$ Hz, $J_{16a,16b} = 14.5$ Hz, $J_{16b,17} = 7.3$ Hz), 1.80 (3H, s, Me-22), 1.65−1.55 (3H, m, H-16a, H-6, and H-4), 1.35 (1H, m, H-7a), 1.31 (3H, d, H-6′ (Me-C-5′), $J_{5',6'} = 6.1$ Hz), 1.18 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''} = 6.2$ Hz), 1.14 (3H, d, Me-18, $J_{4,18} = 6.0$ Hz), 1.02 (3H, d, Me-21, $J_{8,21} = 6.4$ Hz), 0.90 (3H, t, Me-17, $J_{16a,17} = J_{16b,17} = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 206.3 (s, C-9), 201.9 (d, C-20), 173.2 (s, C-1), 170.1 (s, 4″-O*CO*Me), 147.8 (d, C-11), 140.6 (d, C-13), 135.8 (s, C-12), 127.3 (d, C-10), 103.7 (d, C-1′), 101.0 (d, C-1″), 86.9 (d, C-5), 80.6 (d, C-2″), 77.6 (d, C-3″), 75.8 (s, C-3), 75.6 (d, C-15), 74.7 (d, C-4″), 73.3 (d, C-5′), 70.6 (d, C-4′), 70.5 (d, C-3′), 69.9 (d, C-2′), 69.6 (t, C-23), 67.4 (d, C-5″), 61.5 (q, 3″-OMe), 59.4 (q, 2″-OMe), 59.3 (d, C-19), 50.2 (d, C-4), 45.1 (t, C-2), 44.6 (d, C-14), 44.4 (d, C-6), 41.7 (q, NMe_2), 36.1 (d, C-8), 33.9 (t, C-7), 25.9 (t, C-16), 20.9 (q, 4″-OCO*Me*), 17.9 (q, Me-21), 17.4 (q, Me-6′ (Me-C-5′)), 17.3 (q, Me-6″ (Me-C-5″)), 12.5 (q, Me-22), 11.7 (q, Me-18), 9.6 (q, Me-17). Anal. ($C_{41}H_{65}NO_{15}$) C, H, N.

Desmycosin 8α,20*β*- and 8*β*,20α-Aldol (24a and 24b). Compound **22** (800.6 mg, 0.89 mmol) was dissolved in methanol (30 mL), and aqueous ammonia (7.5 mL) was added. The solution was stirred at 25 °C for 30 h, after which evaporation in vacuo gave the title compound as a mixture of epimers at C-8 and C-20. The mixture was chromatographed on a silica gel flash column, using CH_2Cl_2–MeOH−aqueous NH_3 (9:1:0.5) as the eluent, to give 344.0 mg (50%) of the major 8α,20*β*-epimer (**24a**) and 54.8 mg (8%) of the minor 8*β*,20α-epimer (**24b**).

24a (major isomer): FAB-MS *m/z* 770 (MH^+, 52%); UV λ_{max} nm (ϵ) 278 (32 502); IR (KBr) ν_{max} 3444, 2970, 2931, 1741, 1695, 1655, 1456, 1378, 1263, 1166, 1083, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24(1H, d,H-11, $J_{10,11} = 16.5$ Hz), 5.97 (1H, d, H-10, $J_{10,11} = 16.5$ Hz), 5.85 (1H, d, H-13, $J_{13,14} = 10.2$ Hz), 5.05 (1H, dt, H-15, $J_{14,15} = 10.2$ Hz, $J_{15,16b} = 4.3$ Hz), 4.63 (1H, d, H-5, $J_{4,5} = 6.5$ Hz), 4.58 (1H, d, H-1″, $J_{1'',2''} = 7.7$ Hz), 4.49 (1H, d, H-1′, $J_{1',2'} = 7.4$ Hz), 4.05−3.99 (2H, m, H-23b, H-20), 3.88 (1H, d, H-2b, $H_{2a,2b} = 16.4$ Hz), 3.79−3.73 (2H, m, H-4, H-3″), 3.61 (3H, s, 3″-OMe), 3.60−3.50 (4H, m, H-23a, H-5″, H-5′, H-2′), 3.48 (3H, s, 2″-OMe), 3.37 (1H, d, H-2a, $J_{2a,2b} = 16.4$ Hz), 3.19 (1H, dd, H-4″, $J_{3'',4''} = 3.0$ Hz, $J_{4'',5''} = 9.5$ Hz), 3.10−3.04 (1H, dd, H-4′, $J_{3',4'ax} = J_{4',5'} = 10.0$ Hz; 1H, dd, H-2″, $J_{1'',2''} = 7.9$ Hz, $J_{2'',3''} = 3.0$ Hz), 3.03−2.99 (1H, m, H-14), 2.51 (6H, s, NMe_2), 2.42 (1H, t, H-3′, $J_{2',3'} = J_{3',4'ax} = 10.2$ Hz), 2.28 (1H, br, H-6), 2.17 (1H, m, H-7b), 1.97 (1H, m, H-19b), 1.82 (3H, s, H-22), 1.78 (1H, m, H-16b), 1.66−1.57 (2H, m, H-7a, H-16a), 1.52 (1H, m, H-19a), 1.34 (3H, d, H-6′ (Me-C-5′), $J_{5',6'} = 6.1$ Hz), 1.27 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''} = 6.4$ Hz), 1.22 (3H, s, Me-21), 1.10 (3H, d, Me-18, $J_{4,18} = 6.5$ Hz), 0.92 (3H, t, Me-17, $J_{16,17} = 7.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 207.0 (s, C-3), 206.9 (s, C-9), 167.5 (s, C-1), 148.8 (d, C-11), 141.0 (d, C-13), 134.6 (s, C-12), 125.6 (d, C-10), 103.3 (d, C-1′), 100.9 (d, C-1″), 81.8 (d, C-2″), 81.4 (d, C-5), 81.1 (d, C-20), 79.7 (d, C-3″), 76.5 (d, C-15), 73.2 (d, C-4″), 72.7 (d, C-5′), 70.8 (d, C-4′), 70.6 (d, C-3′, C-2′), 70.4 (t, C-23), 70.1 (d, C-5″), 62.9 (q, 3″-OMe), 60.3 (s, C-8), 59.5 (q, 2″-OMe), 44.2 (t, C-2), 43.5 (d, C-14), 41.7 (q, NMe_2), 39.1 (d, C-6), 37.6 (t, C-19), 36.3 (t, C-7), 35.6 (d, C-4), 26.4 (t, C-16), 18.2 (q, Me-C-5′), 17.7 (q, Me-C-5″), 17.0 (q, Me-18), 12.6 (q, Me-22), 10.4 (q, Me-21), 9.4 (q, Me-17). Anal. ($C_{39}H_{63}NO_{14}$) C, H, N.

24b (minor isomer): FAB-MS *m/z* 770 (MH^+, 63%); UV λ_{max} nm (ϵ) 278 (32 492); IR (KBr) ν_{max} 3442, 2973, 2931, 1740, 1692, 1657, 1458, 1374, 1265, 1164, 1086, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44 (1H, d, H-11, $J_{10,11} = 16.5$ Hz), 5.94 (1H, d, H-10, $J_{10,11} = 16.5$ Hz), 5.90 (1H, d, H-13, $J_{13,14} = 10.3$ Hz), 5.10 (1H, dt, H-15, $J_{14,15} = 10.0$ Hz, $J_{15,16b} = 4.0$ Hz), 4.78 (1H, d, H-5, $J_{4,5} = 6.9$ Hz), 4.59 (1H, d, H-1″, $J_{1'',2''} = 7.7$ Hz), 4.47 (1H, d, H-1′, $J_{1',2'} = 7.4$ Hz), 4.05−3.99 (2H, m, H-23b, H-20), 3.79−3.73 (2H, m, H-3″, H-2b), 3.61 (3H, s, 3″-OMe), 3.60−3.50 (5H, m, H-23a, H-5″, H-5′, H-4, H-2′), 3.49 (3H, s, 2″-OMe), 3.42 (1H, d, H-2a, $J_{2a,2b} = 16.5$ Hz), 3.18 (1H, dd, H-4″, $J_{3'',4''} = 3.2$ Hz, $J_{4'',5''} = 9.6$ Hz), 3.10−3.04 (1H, dd, H-4′, $J_{3',4'ax} = J_{4',5'} = 10.0$ Hz; 1H, dd, H-2″, $J_{1'',2''} = 7.9$ Hz, $J_{2'',3''} = 2.9$ Hz), 2.99−2.95 (1H, m, H-14), 2.51 (6H, s, NMe_2), 2.41 (1H, t, H-3′, $J_{2',3'} = J_{3',4'ax} = 10.1$ Hz), 1.99 (1H, br, H-6), 1.86 (1H, m, H-19b), 1.83 (1H, m, H-7b), 1.80 (3H, s, Me-22), 1.76 (1H, m, H-16b), 1.61 (1H, m, H-16a), 1.35 (3H, d, H-6′ (Me-C-5′), $J_{5',6'} = 5.9$ Hz), 1.27 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''} = 6.4$ Hz), 1.25 (3H, s, Me-21), 1.20 (1H, m, H-19a), 1.16 (1H, m, H-7a), 1.09 (3H, d, Me-18, $J_{4,18} = 6.5$ Hz), 0.92 (3H, t, Me-17, $J_{16,17} = 7.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 206.8 (s, C-3), 206.6 (s, C-9), 168.0 (s, C-1), 149.6 (d, C-11), 140.8 (d, C-13), 134.6 (s, C-12), 125.1 (d, C-10), 102.6 (d, C-1′), 100.9 (d, C-1″), 81.8 (d, C-2″), 81.3 (d, C-5), 79.7 (d, C-3″), 78.6 (d, C-20), 76.4 (d, C-15), 73.3 (d, C-5′), 73.1 (d, C-4″), 72.7 (d, C-5′), 70.9 (d, C-4′), 70.7 (d, C-3′), 70.6 (d, C-2′), 70.1 (t, C-23), 70.0 (d, C-5″), 62.9 (q, 3″-OMe), 60.3 (s, C-8), 59.6 (q, 2″-OMe), 46.9 (t, C-2), 43.9 (d, C-14), 41.7 (q, NMe_2), 41.3 (d, C-6), 37.1 (t, C-19), 37.0 (t, C-7), 35.7 (d, C-4), 26.1 (t, C-16), 18.2 (q, Me-C-5′), 17.7 (q, Me-C-5″), 17.5 (q, Me-21), 17.1 (q, Me-18), 12.4 (q, Me-22), 9.7 (q, Me-17). Anal. ($C_{39}H_{63}NO_{14}$) C, H, N.

Bicyclic Aldehyde (25). To a solution of **23** (70.0 mg, 0.09 mmol) in 1 mL of methanol was added 1 mL of aqueous NH_3 (25%). The solution was stirred at room temperature for 16 h. The solvent was removed in vacuo, water was added, and the pH was allowed to reach 11 with concentrated ammonium hydroxide. The solution was extracted with ethyl acetate, and the organic extracts were dried over K_2CO_3 to give 65.0 mg of white foam. The product was purified by column chromatography eluting with solvent system A, to afford 57.0 mg (85.8%) of the bicyclic aldehyde **25** ($R_f = 0.35$) as a white foam: FAB-MS *m/z* 770 (MH^+, 73%); UV λ_{max} nm (ϵ) 278 (32 502); IR (KBr) ν_{max} 3444, 2970, 2929, 1716, 1659, 1628, 1455, 1377, 1199, 1168, 1082, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.72 (1H, d, H-20), 7.32 (1H, d, H-11), 6.03 (1H,d, H-10), 5.96 (1H, d, H-13), 5.11 (1H, dt, H-15, $J_{15,16a} = 9.7$ Hz, $J_{15,16b} = 2.6$ Hz), 4.58 (1H, d, H-1″, $J_{1'',2''} = 8.0$ Hz), 4.31 (1H, s, 3-OH, interchangeable with D_2O), 4.30 (1H, d, H-1′, $J_{1',2'} = 9.5$ Hz), 4.02 (1H, dd, H-23b, $J_{23a,23b} = 9.5$ Hz), 3.86 (1H, t, H-5), 3.79−3.72 (1H, m, H-3″), 3.62 (3H, s, 3″-OMe), 3.60−3.50 (3H, m, H-23a, H-5″, H-2′), 3.48 (3H, s, 2″-OMe), 3.30 (1H, dq, H-5′, $J_{4',5'} = 8.7$ Hz, $J_{5',6'} = 6.3$ Hz), 3.24−3.14 (2H, m, H-8, H-4″), 3.12−2.98 (3H, m, H-14, H-4′, H-2″), 2.78 (1H, dd, H-19, $J_{6,19} = 7.7$ Hz, $J_{19,20} = 6.0$ Hz), 2.62 (1H, d, H-2b, $J_{2a,2b} = 17.1$ Hz), 2.50 (6H, s, NMe_2), 2.37 (1H, dt, H-3′, $J_{2',3'} = 9.0$ Hz, $J_{3',4'ax} = 10.0$ Hz), 2.07 (1H, d, H-7b, $J_{7a,7b} = 15.0$ Hz), 1.97 (1H, d, H-2a, $J_{2a,2b} = 17.1$ Hz), 1.92−1.85 (1H, m, H-16b), 1.80 (3H, s, Me-22), 1.68−1.52 (3H, m, H-16a, H-6, and H-4), 1.31 (3H, d, H-6′ (Me-C-5′), $J_{5',6'} = 6.2$ Hz), 1.28 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''} = 6.1$ Hz), 1.14 (3H, d, Me-18, $J_{4,18} = 6.0$ Hz), 1.02 (3H, d, Me-21, $J_{8,21} = 6.3$ Hz), 0.90 (3H, t, Me-17, $J_{16a,17} = J_{16b,17} = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 206.5 (s, C-9), 202.1 (d, C-20), 173.1 (s, C-1), 147.8 (d, C-11), 140.8 (d, C-13), 135.8 (s, C-12), 127.3 (d, C-10), 103.6 (d, C-1′), 101.0 (d, C-1″), 86.8 (d, C-5), 81.8 (d, C-2″), 79.6 (d, C-3″), 75.7 (s, C-3), 75.4 (d, C-15), 73.1 (d, C-5′), 72.5 (d, C-4″), 70.5 (d, C-2′), 70.4 (d, C-4′), 70.3 (d, C-5″), 69.8 (d, C-3′), 69.4 (t, C-23), 61.6 (q, 3″-OMe), 59.4 (q, 2″-OMe), 59.1 (d, C-19), 50.1 (d, C-4), 45.0 (t, C-2), 44.5 (d, C-14), 44.3 (d, C-6), 41.5 (q, NMe_2), 35.9 (d, C-8), 33.7 (t, C-7), 25.8 (t, C-16), 17.7 (q, Me-6′ (Me-C-5′)), 17.5 (q, Me-6″ (Me-C-5″), 17.2 (q, Me-21), 12.3 (q, Me-22), 11.5 (q, Me-18), 9.4 (q, Me-17). Anal. ($C_{39}H_{63}NO_{14}$) C, H, N.

General Procedure for the Wittig Reaction with Stabilized Ylides. Synthesis of Desmycosin Analogues 26a−d. To a solution of 2′,4′,4″-tri-*O*-acetyldesmycosin **7**[10,11] (898.0 mg, 1.0 mmol) in benzene (5 mL) was added stabilized Wittig ylide **a1**−**a4** (1.5 mmol, 1.5 equiv), and the reaction mixture was heated at reflux temperature for 2 h. After the end of the reaction was established (TLC), the solvent was evaporated under reduced pressure, and the crude product was chromatographed over silica gel to give following compounds.

26a (85%): FAB-MS *m*/*z* 954 (MH^+, 72%); UV λ_{max} nm (ϵ) 278 (30 722); ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, H-11, $J_{10,11}$ = 15.3 Hz), 6.95 (1H, dt, H-20, $J_{20,20'}$ = 15.7 Hz, $J_{19b,20}$ = 2.7 Hz), 6.28 (1H, d, H-10, $J_{10,11}$ = 15.3 Hz), 5.90 (1H, d, H-13, $J_{13,14}$ = 10.9 Hz), 5.86 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 4.97 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16b}$ = 3.8 Hz), 4.90 (1H, dd, H-2′, $J_{1',2'}$ = 9.3 Hz, $J_{2',3'}$ = 10.0 Hz), 4.75 (1H, t, H-4′, $J_{3',4'ax}$ = 9.7 Hz, $J_{4',5'}$ = 9.8 Hz), 4.63 (1H, d, H-1″, $J_{1'',2''}$ = 8.0 Hz), 4.40 (1H, dd, H-4″, $J_{3'',4''}$ = 2.1 Hz, $J_{4'',5''}$ = 9.8 Hz), 4.37 (1H, d, H-1′, $J_{1',2'}$ = 9.3 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 4.3 Hz), 3.96−3.86 (2H, m, H-5″, H-3″), 3.73−3.60 (2H, m, H-5, H-3), 3.70 (3H, s, COO*CH*$_3$), 3.56 (1H, dd, H-23a, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23a}$ = 4.6 Hz), 3.53 (3H, s, 3″-OMe), 3.49 (3H, s, 2″-OMe), 3.39 (1H, dq, H-5′, $J_{4',5'}$ = 9.8 Hz, $J_{5',6'}$ = 6.0 Hz), 3.05 (1H, dd, H-2″, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 2.7 Hz), 2.95 (1H, ddt, H-14, $J_{14,15}$ = 10.0 Hz, $J_{14,23a}$ = 6.5 Hz, $J_{14,23b}$ = 4.0 Hz), 2.73 (1H, t, H-3′, $J_{2',3'}$ = 10.0 Hz), 2.68−2.50 (3H, m, H-19b, H-8, H-7b), 2.44 (1H, dd, H-2b, $J_{2a,2b}$ = 16.7 Hz, $J_{2b,3}$ = 10.8 Hz), 2.34 (6H, s, NMe_2), 2.29−2.16 (1H, m, H-19a), 2.12 (3H, s, OCO*CH*$_3$), 2.06 (6H, s, 2×OCO*CH*$_3$), 2.00 (1H, br, H-6), 1.90 (1H, d, H-2a, $J_{2a,2b}$ = 16.7 Hz), 1.89−1.80 (1H, m, H-16b), 1.78 (3H, s, Me-22), 1.68−1.60 (1H, m, H-16a), 1.58−1.44 (3H, m, H-7a, H-4), 1.21 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.18 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.0 Hz), 1.17 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 0.95 (3H, d, Me-18, $J_{4,18}$ = 6.7 Hz), 0.93 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4 (s, C-9), 174.2 (s, C-1), 170.1 (s, O*CO*CH$_3$), 169.8 (s, O*CO*CH$_3$), 169.3 (s, O*CO*CH$_3$), 167.2 (s, *CO*OCH$_3$), 149.2 (d, C-20), 147.7 (d, C-11), 141.6 (d, C-13), 134.9 (s, C-12), 121.6 (d, C-20′), 118.3 (d, C-10), 101.9 (d, C-1′), 100.9 (d, C-1″), 80.4 (d, C-2″), 80.2 (d, C-5), 77.6 (d, C-3″), 75.1 (d, C-15), 74.6 (d, C-4″), 71.3 (d, C-4′), 70.9 (d, C-5′), 70.5 (d, C-2′), 68.9 (t, C-23), 67.2 (d, C-5″), 67.0 (d, C-3′), 66.7 (d, C-3), 61.4 (q, 3″-OMe), 59.4 (q, 2″-OMe), 51.0 (q, COO*CH3*), 44.8 (d, C-8), 44.7 (d, C-14), 41.0 (q, NMe_2), 40.3 (d, C-4), 39.1 (t, C-2), 35.6 (d, C-6), 32.4 (t, C-7), 30.8 (t, C-19), 25.0 (t, C-16), 21.1 (q, OCO*CH*$_3$), 20.9 (q, OCO*CH*$_3$), 20.7 (q, OCO*CH*$_3$), 17.3 (q, Me-21), 17.1 (q, Me-C-5′), 17.0 (q, Me-C-5″), 12.8 (q, Me-22), 9.4 (q, Me-17), 8.6 (q, Me-18). Anal. ($C_{48}H_{75}NO_{18}$) C, H, N.

26b (90%): FAB-MS *m*/*z* 968 (MH^+, 58%); UV λ_{max} nm (ϵ) 276 (31 894); ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, H-11, $J_{10,11}$ = 15.4 Hz), 6.93 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19,20}$ = 7.8 Hz), 6.28 (1H, d, H-10, $J_{10,11}$ = 15.4 Hz), 5.90 (1H, d, H-13, $J_{13,14}$ = 10.9 Hz), 5.84 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 4.97 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16b}$ = 3.9 Hz), 4.90 (1H, br, H-2′), 4.78 (1H, br, H-4′), 4.63 (1H, d, H-1″, $J_{1'',2''}$ = 8.0 Hz), 4.44 (1H, dd, H-4″, $J_{3'',4''}$ = 2.5 Hz, $J_{4'',5''}$ = 9.9 Hz), 4.20−4.05 (3H, m, $COOCH_2CH_3$, H-1′), 3.99 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 4.4 Hz), 3.94−3.84 (2H, m, H-5″, H-3″), 3.78−3.62 (2H, m, H-5, H-3), 3.55 (1H, dd, H-23a, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23a}$ = 4.7 Hz), 3.52 (3H, s, 3″-OMe), 3.44 (3H, s, 2″-OMe), 3.43−3.28 (2H, m, H-6, H-5′), 3.05 (1H, dd, H-2″, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 2.8 Hz), 2.94 (1H, ddt, H-14, $J_{14,15}$ = 10.0 Hz, $J_{14,23a}$ = 6.5 Hz, $J_{14,23b}$ = 4.1 Hz), 2.85 (1H, br, H-3′), 2.71−2.60 (1H, m, H-8), 2.44 (1H, dd, H-2b, $J_{2a,2b}$ = 16.1 Hz, $J_{2b,3}$ = 9.8 Hz), 2.36 (7H, br, H-19b, NMe_2), 2.11 (9H, s, OCO*CH*$_3$), 1.99−1.83 (3H, m, H-19a, H-16b, H-2a), 1.79 (3H, s, Me-22), 1.63 (1H, ddq, H-16a, $J_{15,16a}$ = 10.5 Hz, $J_{16a,16b}$ = 14.3 Hz, $J_{16a,17}$ = 7.1 Hz), 1.52 (2H, br, H-7b, H-4), 1.27 (3H, t, $COOCH_2CH_3$, $J_{CH3,CH2}$ = 7.1 Hz), 1.21 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.19 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.0 Hz), 1.17 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.2 Hz), 1.10−1.05 (1H, m, H-7a), 0.98 (3H, d, Me-18, $J_{4,18}$ = 6.9 Hz), 0.92 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ203.2 (s, C-9), 174.0 (s, C-1), 170.0 (s, O*CO*CH$_3$), 169.8 (s, O*CO*CH$_3$), 169.2 (s, OCOCH$_3$), 166.7 (s, $COOCH_2CH_3$), 148.5 (d, C-20), 147.5 (d, C-11), 141.6 (d, C-13), 134.9 (s, C-12), 121.9 (d, C-20′), 118.2 (d, C-10), 103.4 (d, C-1′), 100.9 (d, C-1″), 80.4 (d, C-2″), 80.2 (d, C-5), 77.6 (d, C-3″), 75.2 (d, C-3), 75.1 (d, C-15), 74.6 (d, C-4″), 72.0 (d, C-3′), 70.9 (d, C-4′), 70.7 (d, C-2′), 68.9 (t, C-23), 67.2 (d, C-5″), 67.0 (d, C-5′), 61.4 (q, 3″-OMe), 59.8 (t, $COOCH_2CH_3$), 59.5 (q, 2″-OMe), 44.8 (d, C-14, C-8, 2C), 41.2 (q, NMe_2), 40.3 (d, C-4), 39.2 (t, C-2), 35.7 (d, C-6), 32.4 (t, C-7), 30.9 (t, C-19), 25.2 (t, C-16), 21.3 (q, OCO*CH*$_3$), 21.2 (q, OCO*CH*$_3$), 20.9 (q, OCO*CH*$_3$), 17.4 (q, Me-21), 17.3 (q, Me-C-5′), 17.1 (q, Me-C-5″), 14.2 (q, $COOCH_2CH_3$), 13.0 (q, Me-22), 9.5 (q, Me-17), 8.8 (q, Me-18). Anal. ($C_{49}H_{77}NO_{18}$) C, H, N.

26c (88%): FAB-MS *m*/*z* 938 (MH^+, 88%); UV λ_{max} nm (ϵ) 277 (30 569); ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, d, H-11), 6.94 (1H, dt, H-20), 6.25 (1H, d, H-10), 5.99 (1H, d, H-20′), 5.84 (1H, d, H-13), 3.51 (3H, s, 3″-OMe), 3.48 (3H, s, 2″-OMe), 2.35 (6H, s, NMe_2), 2.25 (3H, s, CO*CH*$_3$), 2.11 (3H, s, OCO*CH*$_3$), 2.05 (6H, s, 2×OCO*CH*$_3$), 1.78 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.1 (s, C-9), 199.0 (s, *CO*CH$_3$), 174.1 (s, C-1), 170.2 (s, O*CO*CH$_3$), 169.6 (s, O*CO*CH$_3$), 169.1 (s, O*CO*CH$_3$), 149.2 (d, C-20), 146.8 (d, C-11), 140.8 (d, C-13), 134.5 (s, C-12), 120.8 (d, C-20′), 118.0 (d, C-10), 61.2 (q, 3″-OMe), 59.2 (q, 2″-OMe), 41.2 (q, NMe_2), 26.0 (q, CO*CH*$_3$), 21.0 (q, OCO*CH*$_3$), 20.7 (q, OCO*CH*$_3$), 20.5 (q, OCO*CH*$_3$), 12.7 (q, Me-22). Anal. ($C_{48}H_{75}NO_{17}$) C, H, N.

26d (94%): FAB-MS *m*/*z* 924 (MH^+, 92%); UV λ_{max} nm (ϵ) 279 (28 671); ^{1}H NMR ($CDCl_3$) δ 9.71 (1H, d, CHO), 7.28 (1H, d, H-11), 6.72 (1H, dt, H-20), 6.23 (1H, d, H-10), 5.98 (1H, dd, H-20′), 5.89 (1H, d, H-13), 3.50 (3H, s, 3″-OMe), 3.48 (3H, s, 2″-OMe), 2.40 (6H, s, NMe_2), 2.10 (3H, s, OCO*CH*$_3$), 2.02 (6H, s, 2×OCO*CH*$_3$), 1.77 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.6 (s, C-9), 192.5 (d, CHO), 173.1 (s, C-1), 170.5 (s, O*CO*CH$_3$), 169.1 (s, O*CO*CH$_3$), 169.0 (s, O*CO*CH$_3$), 149.5 (d, C-20), 146.3 (d, C-11), 140.6 (d, C-13), 134.0 (s, C-12), 120.3 (d, C-20′), 117.8 (d, C-10), 61.2 (q, 3″-OMe), 59.1 (q, 2″-OMe), 41.0 (q, NMe_2), 21.1 (q, OCO*CH*$_3$), 20.9 (q, OCO*CH*$_3$), 20.7 (q, OCO*CH*$_3$), 12.8 (q, Me-22). Anal. ($C_{47}H_{73}NO_{17}$) C, H, N.

General Procedure for Deprotection of Desmycosin Analogues 26a−d. Compounds **26a**−**d** (3.0 g, 3.48 mmol) were dissolved in methanol (40 mL) and the reaction mixture was stirred at room temperature. The mixture was than evaporated at room temperature under vacuum to give **27a**−**d**, which were purified by column chromatography (silica gel, E1 solvent system). The following compounds were prepared.

27a (85%): FAB-MS *m*/*z* 870 (MH^+, 58%). Anal. ($C_{44}H_{71}NO_{16}$) C, H, N.

27b (92%): FAB-MS *m*/*z* 884 (MH^+, 73%). Anal. ($C_{45}H_{73}NO_{16}$) C, H, N.

27c (85%): FAB-MS *m*/*z* 854 (MH^+, 91%). Anal. ($C_{44}H_{71}NO_{15}$) C, H, N.

27d (89%): FAB-MS *m*/*z* 840 (MH^+, 62%). Anal. ($C_{43}H_{69}NO_{15}$) C, H, N.

An aqueous solution of NH_3 (25%) was added to **27a**−**d** and the mixture was stirred at 25 °C for 3 h. The crude residue obtained by concentration of the reaction mixture was purified by flash column chromatography (silica gel, E1 solvent system, R_f = 0.30−0.50), furnishing the expected α,β-unsaturated compounds **28a**−**d** (60−90%). By using this procedure, the following compounds were prepared.

28a (90%): FAB-MS *m*/*z* 828 (MH^+, 58%); UV λ_{max} nm (ϵ) 284 (28 634); ^{1}H NMR ($CDCl_3$) δ 7.29 (1H, d, H-11, $J_{10,11}$ = 16.5 Hz), 6.95 (1H, br, H-20), 6.25 (1H, d, H-10, $J_{10,11}$ = 16.5 Hz), 5.90 (1H, d, H-13, $J_{13,14}$ = 10.2 Hz), 5.85 (1H, d, H-20′, $J_{20,20'}$ = 15.7 Hz), 4.99 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16a}$ = 11.1 Hz), 4.56 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.31 (1H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 3.7 Hz), 3.80−3.73 (3H, m, H-5, H-3″, H-3), 3.71 (3H, s, $COOCH_3$), 3.62 (3H, s, 3″-OMe), 3.60−3.51 (3H, m, H-23a, H-5″, H-2′), 3.50 (3H, s, 2″-OMe), 3.33 (1H, br, H-5′), 3.20 (1H, br, H-4″), 3.09 (1H, t, H-4′, $J_{3',4'ax}$ = $J_{4',5'}$ = 10.0 Hz), 3.04 (1H, dd, H-2″, $J_{1'',2''}$ = 7.7 Hz, $J_{2'',3''}$ = 2.7 Hz), 2.98−2.90 (1H, m, H-14), 2.80−2.68 (1H, m, H-8), 2.54 (6H, s, NMe_2), 2.52−2.45 (2H, m, H-19b, H-2b), 2.43 (1H, t, H-3′, $J_{2',3'}$ = $J_{3',4'ax}$ = 10.0 Hz), 2.33 (1H, br, H-19a), 2.05 (1H, br, H-6), 1.95 (1H, d, H-2a, $J_{2a,2b}$ = 16.2 Hz), 1.88 (1H, ddq, H-16b, $J_{15,16b}$ = 3.0 Hz, $J_{16a,16b}$

= 14.5 Hz, $J_{16b,17}$ = 7.3 Hz), 1.79 (3H,s, Me-22), 1.70−1.46 (2H, m, H-16a, H-4), 1.31 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.3 Hz), 1.27 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.0 Hz), 1.25 (1H, br, H-7b), 1.19 (3H, d, Me-21, $J_{8,21}$ = 6.6 Hz), 1.00 (3H, d, Me-18, $J_{4,18}$ = 6.6 Hz), 0.94 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.2 Hz), 0.87 (1H, d, H-7a, $J_{7a,7b}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4 (s, C-9), 174.3 (s, C-1), 167.0 (s, *C*OOCH$_3$), 148.9 (d, C-20), 147.6 (d, C-11), 141.7 (d, C-13), 134.9 (s, C-12), 121.8 (d, C-20′), 118.6 (d, C-10), 104.1 (d, C-1′), 100.9 (d, C-1″), 81.6 (d, C-5, C-2″, 2C), 79.6 (d, C-3″), 75.0 (d, C-15, C-3, 2C), 73.1 (d, C-4″), 72.4 (d, C-4′), 70.7 (d, C-2′), 70.5 (d, C-5″), 70.3 (d, C-3′), 69.9 (d, C-5′), 68.8 (t, C-23), 61.5 (q, 3″-OMe), 59.4 (q, 2″-OMe), 51.0 (q, COOCH$_3$), 44.6 (d, C-14), 43.7 (d, C-8), 42.5 (d, C-4), 41.4 (q, NMe$_2$), 39.1 (t, C-2), 33.1 (d, C-6), 31.2 (t, C-7), 31.1 (t, C-19), 25.1 (t, C-16), 17.6 (q, Me-C-5′), 17.4 (q, Me-C-5″), 17.0 (q, Me-21), 12.6 (q, Me-22), 9.3 (q, Me-17), 8.9 (q, Me-18). Anal. ($C_{42}H_{69}NO_{15}$) C, H, N.

28b (85%): FAB-MS *m*/*z* 842 (MH$^+$, 58%); UV λ_{max} nm (ϵ) 276 (31 894); IR (KBr) ν_{max} 3445, 2971, 2932, 1714, 1681, 1651, 1593, 1455, 1372, 1169, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, d, H-11, $J_{10,11}$ = 16.6 Hz), 6.93 (1H, br, H-20), 6.24 (1H, d, H-10, $J_{10,11}$ = 16.6 Hz), 5.90 (1H, d, H-13, $J_{13,14}$ = 10.3 Hz), 5.85 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 5.00 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16a}$ = 11.1 Hz, $J_{15,16b}$ = 3.8 Hz), 4.56 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.35 (1H, d, H-1′, $J_{1',2'}$ = 7.3 Hz), 4.17 (2H, q, COOCH$_{2b}$CH$_3$, $J_{CH2b,CH3}$ = 7.1 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 3.8 Hz), 3.80−3.70 (3H, m, H-5, H-3″, H-3), 3.62 (3H, s, 3″-OMe), 3.58−3.51 (3H, m, H-23a, H-5″, H-2′), 3.50 (3H, s, 2″-OMe), 3.39 (1H, br, H-5′), 3.27−3.15 (3H, m, H-6, H-4″, H-4′), 3.04 (1H, dd, H-2″, $J_{1'',2''}$ = 7.8 Hz, $J_{2'',3''}$ = 2.9 Hz), 3.00−2.94 (1H, m, H-14), 2.80−2.65 (8H, m, NMe$_2$, H-8, H-3′), 2.63 (1H, br, H-19b), 2.47 (1H, dd, H-2b, $J_{2a,2b}$ = 16.3 Hz, $J_{2b,3}$ = 10.6 Hz), 2.35 (1H, br, H-19a), 1.96 (1H, d, H-2a, $J_{2a,2b}$ = 16.3 Hz), 1.89 (1H, ddq, H-16b, $J_{15,16b}$ = 3.1 Hz, $J_{16a,16b}$ = 14.5 Hz, $J_{16b,17}$ = 7.3 Hz), 1.80 (3H, s, Me-22), 1.70−1.55 (2H, m, H-16a, H-4), 1.53−1.45 (1H, m, H-7b), 1.34 (1H, d, H-7a, $J_{7a,8}$ = 6.0 Hz), 1.29 (2H, q, COOCH$_{2a}$CH$_3$, $J_{CH2a,CH3}$ = 7.1 Hz), 1.28 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 7.1 Hz), 1.27 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.2 Hz), 1.19 (3H, d, Me-21, $J_{8,21}$ = 6.6 Hz), 1.00 (3H, d, Me-18, $J_{4,18}$ = 6.2 Hz), 0.94 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.3 Hz), 0.89 (3H, t, COOCH$_{2a}$*C*H$_3$, $J_{CH3,CH2a}$ = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 203.5 (s, C-9), 174.3 (s, C-1), 166.7 (s, *C*OOCH$_2$CH$_3$), 148.6 (d, C-20), 147.8 (d, C-11), 140.5 (d, C-13), 135.1 (s, C-12), 122.4 (d, C-20′, C-10, 2C), 103.4 (d, C-1′), 101.0 (d, C-1″), 81.9 (d, C-5, C-2″, 2C), 79.8 (d, C-3″), 75.3 (d, C-15, C-3, 2C), 73.3 (d, C-4″), 72.7 (d, C-5′, C-4′, 2C), 70.6 (d, C-5″, C-3′, C-2′, 3C), 69.1 (t, C-23), 61.8 (q, 3″-OMe), 60.1 (t, COO*C*H$_2$CH$_3$), 59.7 (q, 2″-OMe), 44.9 (d, C-14), 43.9 (d, C-8), 42.3 (d, C-4), 41.8 (q, NMe$_2$), 39.5 (t, C-2), 36.5 (d, C-6), 31.6 (t, C-7), 29.0 (t, C-19), 25.5 (t, C-16), 17.9 (q, Me-21), 17.8 (q, Me-C-5″, Me-C-5′, 2C), 14.3 (q, COOCH$_2$*C*H$_3$), 13.0 (q, Me-22), 10.4 (q, Me-18), 9.7 (q, Me-17). Anal. ($C_{43}H_{71}NO_{15}$) C, H, N.

28c (93%): FAB-MS *m*/*z* 812 (MH$^+$, 58%); UV λ_{max} nm (ϵ) 282 (30 184); IR (KBr) ν_{max} 3459, 2970, 2932, 1714, 1673, 1625, 1593, 1375, 1316, 1261, 1168, 1082, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, H-11, $J_{10,11}$ = 16.5 Hz), 6.77 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19b,20}$ = 2.5 Hz), 6.26 (1H, d, H-10, $J_{10,11}$ = 16.5 Hz), 6.08 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 5.91 (1H, d, H-13, $J_{13,14}$ = 10.3 Hz), 4.99 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz), $J_{15,16b}$ = 2.3 Hz), 4.56 (1H, d, H-1″, $J_{1'',2''}$ = 7.7 Hz), 4.30 (1H, d, H-1′, $J_{1',2'}$ = 7.2 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.7 Hz, $J_{14,23b}$ = 3.8 Hz), 3.80−3.68 (3H, m, H-5, H-3″, H-3″), 3.62 (3H, s, 3″-OMe), 3.60−3.52 (3H, m, H-23a, H-5″, H-2′), 3.49 (3H, s, 2″-OMe), 3.32 (1H, br, H-5′), 3.18 (1H, dd, H-4″, $J_{3'',4''}$ = 3.0 Hz, $J_{4'',5'}$ = 9.6 Hz), 3.10 (1H, t, H-4′, $J_{3',4'ax}$ = $J_{4',5'}$ = 10.0 Hz), 3.03 (1H, dd, H-2″, $J_{1'',2''}$ = 7.7 Hz, $J_{2'',3''}$ = 2.6 Hz), 2.99−2.90 (1H, m, H-14), 2.78−2.56 (3H, m, H-19b, H-8, H-7b), 2.51 (6H, s, NMe$_2$), 2.47 (1H, dd, H-2b, $J_{2a,2b}$ = 16.3 Hz, $J_{2b,3}$ = 5.7 Hz), 2.41 (1H, t, H-3′, $J_{2',3'}$ = $J_{3',4'ax}$ = 10.2 Hz), 2.34−2.30 (1H, m, H-19a), 2.25 (3H, s, COCH$_3$), 2.05 (1H, br, H-6), 1.96 (1H, d, H-2a, $J_{2a,2b}$ = 16.3 Hz), 1.86 (1H, ddq, H-16b, $J_{15,16b}$ = 3.0 Hz, $J_{16a,16b}$ = 14.4 Hz, $J_{16b,17}$ = 7.2 Hz), 1.79 (3H, s, Me-22), 1.72−1.48 (4H, m, H-16a, H-7a, H-4), 1.31 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 5.7 Hz), 1.26 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.3 Hz), 1.20 (3H, d, Me-21, $J_{8,21}$ = 6.6 Hz), 1.02 (3H, d, Me-18, $J_{4,18}$ = 6.6 Hz), 0.94 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.6 (s, C-9), 199.2 (s, COCH$_3$), 174.4 (s, C-1), 148.9 (d, C-20), 147.9 (d, C-11), 141.9 (d, C-13), 134.9 (s, C-12), 132.3 (d, C-20′), 118.3 (d, C-10), 104.0 (d, C-1′), 100.9 (d, C-1″), 81.6 (d, C-2″), 80.8 (d, C-3″), 79.6 (d, C-5), 75.1 (d, C-15), 73.1 (d, C-5′), 72.5 (d, C-4″), 70.7 (d, C-4′), 70.6 (d, C-5″), 70.3 (d, C-2′), 70.0 (d, C-3′), 68.7 (t, C-23), 67.1 (d, C-3), 61.5 (q, 3″-OMe), 59.4 (q, 2″-OMe), 44.6 (d, C-14, C-8, 2C), 41.4 (q, NMe$_2$), 39.9 (d, C-4), 39.1 (t, C-2), 36.2 (d, C-6), 33.2 (t, C-7), 31.9 (t, C-19), 26.2 (q, CO*CH$_3$*), 25.1 (t, C-16), 17.7 (q, Me-C-5′), 17.4 (q, Me-C-5″), 17.1 (q, Me-21), 12.6 (q, Me-22), 9.3 (q, Me-17), 8.9 (q, Me-18). Anal. ($C_{42}H_{69}NO_{14}$) C, H, N.

28d (93%): FAB-MS *m*/*z* 798 (MH$^+$, 58%); UV λ_{max} nm (ϵ) 282 (30 184); ^{1}H NMR ($CDCl_3$) δ 9.73 (1H, d, CHO, $J_{CHO,20'}$ = 2.8 Hz), 7.28 (1H, d, H-11, $J_{10,11}$ = 16.4 Hz), 6.70 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19b,20}$ = 2.6 Hz), 6.24 (1H, d, H-10, $J_{10,11}$ = 16.4 Hz), 6.00 (1H, dd, H-20′, $J_{20,20'}$ = 15.8 Hz, $J_{CHO,20'}$ = 2.8 Hz), 5.89 (1H, d, H-13, $J_{13,14}$ = 10.3 Hz), 4.95 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16b}$ = 2.3 Hz), 4.52 (1H, d, H-1″, $J_{1'',2''}$ = 7.5 Hz), 4.25 (1H, d, H-1′, $J_{1',2'}$ = 7.1 Hz), 3.99 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 3.7 Hz), 3.78−3.63 (3H, m, H-23a, H-5″, H-2′), 3.61 (3H, s, 3″-OMe), 3.58−3.49 (3H, m, H-23a, H-5″, H-2′), 3.46 (3H, s, 2″-OMe), 3.27 (1H, br, H-5′), 3.20−3.15 (1H, m, H-4″), 3.10−3.03 (1H, m, H-4′), 3.00 (1H, dd, H-2″, $J_{1'',2''}$ = 7.5 Hz, $J_{2'',3''}$ = 2.5 Hz), 2.96−2.88 (1H, m, H-14), 2.75−2.58 (3H, m, H-19b, H-8, H-7b), 2.50 (6H, s, NMe$_2$), 2.46−2.40 (1H, m, H-2b), 2.38 (1H, t, H-3′, $J_{2',3'}$ = $J_{3',4'ax}$ = 10.1 Hz), 2.35−2.30 (1H, m, H-19a), 2.15 (1H, br, H-6), 2.01−1.85 (2H, m, H-16b, H-2a), 1.78 (3H, s, Me-22), 1.70−1.41 (2H, m, H-16a, H-4), 1.30 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.2 Hz), 1.26 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.0 Hz), 1.24 (1H, br, H-7b), 1.18 (3H, d, Me-21, $J_{8,21}$ = 6.6 Hz), 1.02 (3H, d, Me-18, $J_{4,18}$ = 6.5 Hz), 1.00 (1H, br, H-7a), 0.92 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4 (s, C-9), 192.4 (d, CHO), 173.8 (s, C-1), 148.2 (d, C-20), 147.1 (d, C-11), 140.7 (d, C-13), 133.1 (s, C-12), 132.0 (d, C-20′), 118.1 (d, C-10), 103.5 (d, C-1′), 100.7 (d, C-1″), 82.0 (d, C-2″), 80.5 (d, C-3″), 78.9 (d, C-5), 74.9 (d, C-15), 72.9 (d, C-5′), 72.1 (d, C-4″), 70.5 (d, C-4′), 70.4 (d, C-5″), 70.2 (d, C-2′), 69.8 (d, C-3′), 68.9 (t, C-23), 66.9 (d, C-3), 61.5 (q, 3″-OMe), 59.8 (q, 2″-OMe), 44.6 (d, C-14), 43.9 (d, C-8), 41.0 (q, NMe$_2$), 39.5 (d, C-4), 39.0 (t, C-2), 36.5 (d, C-6), 33.0 (t, C-7), 31.7 (t, C-19), 24.9 (t, C-16), 17.9 (q, Me-C-5′), 17.3 (q, Me-C-5″), 17.0 (q, Me-21), 12.4 (q, Me-22), 9.4 (q, Me-17), 8.8 (q, Me-18). Anal. ($C_{41}H_{67}NO_{14}$) C, H, N.

Preparation of Desmycosin Carboxylic Acid (28e). The methyl ester **28a** (1.0 g, 1.2 mmol) was treated in THF:H_2O (1:1, 30 mL) with LiOH (143.7 mg, 6.0 mmol, 5.0 equiv) at ambient temperature for 3 h, after which time the end of the reaction was established (TLC). The reaction mixture was extracted with saturated aqueous $NaHCO_3$ (3 × 20 mL), and the combined aqueous extracts were acidified with 1 M HCl to pH 4 and further extracted with EtOAc (4 × 20 mL). Concentration of the combined organic solutions furnished, in quantitative yield, essentially pure carboxylic acid **28e** (976.8 mg, 100%): FAB-MS *m*/*z* 814 (MH$^+$, 79%); UV λ_{max} nm (ϵ) 276 (31 543); ^{1}H NMR ($CDCl_3$) δ 12.0 (1H, br, COOH), 7.30 (1H, d, H-11, $J_{10,11}$ = 16.6 Hz), 6.97 (1H, br, H-20), 6.25 (1H, d, H-10, $J_{10,11}$ = 16.6 Hz), 6.97 (1H, br, H-20), 6.25 (1H, d, H-10, $J_{10,11}$ = 16.6 Hz), 5.91 (1H, d, H-13, $J_{13,14}$ = 10.2 Hz), 5.81 (1H, d, H-20′, $J_{20,20'}$ = 15.6 Hz), 4.98 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16a}$ = 11.0 Hz), 4.50 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.29 (1H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 3.7 Hz), 3.85−3.69 (3H, m, H-5, H-3″, H-3), 3.60 (3H, s, 3″-OMe), 3.58−3.50 (3H, m, H-23a, H-5″, H-2′), 3.48 (3H, s, 2″-OMe), 3.31 (1H, br, H-5′), 3.20−3.10 (1H, m, H-4″), 3.08 (1H, t, H-4′, $J_{3',4'ax}$ = $J_{4',5'}$ = 10.0 Hz), 3.04 (1H, dd, H-2″, $J_{1'',2''}$ = 7.8 Hz, $J_{2'',3''}$ = 2.7 Hz), 2.98−2.90 (1H, m, H-14), 2.80−2.66 (1H, m, H-8), 2.53 (6H, s, NMe$_2$), 2.50−2.44 (2H, m, H-19b, H-2b), 2.40 (1H, t, H-3′, $J_{2',3'}$ = $J_{3',4'ax}$ = 10.0 Hz), 2.33 (1H, br, H-19a), 2.10 (1H, br, H-6), 1.94 (1H, d, H-2a, $J_{2a,2b}$ = 16.1 Hz), 1.86 (1H, ddq, H-16b, $J_{15,16b}$ = 3.0 Hz, $J_{16a,16b}$ = 14.5 Hz, $J_{16b,17}$ = 7.2 Hz), 1.80 (3H, s, Me-22), 1.68−1.49 (2H, m, H-16a, H-4),

1.31 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.3 Hz), 1.26 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.0 Hz), 1.25 (1H, br, H-7b), 1.18 (3H, d, Me-21, $J_{8,21}$ = 6.5 Hz), 0.98 (3H, d, Me-18, $J_{4,18}$ = 6.6 Hz), 0.95 (3H,t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.2 Hz), 0.87−0.82 (1H, m, H-7a); ^{13}C NMR ($CDCl_3$) δ 206.9 (s, C-9), 176.2 (s, C-1), 170.3 (s, COOH), 150.2 (d, C-20), 148.3 (d, C-11), 143.1 (d, C-13), 136.1 (s, C-12), 122.5 (d, C-20′), 119.2 (d, C-10), 103.8 (d, C-1′), 100.7 (d, C-1″), 82.0 (d, C-5, C-2″, 2C), 80.9 (d, C-3″), 77.2 (d, C-15, C-3, 2C), 74.5 (d, C-4″), 73.1 (d, C-4′), 71.2 (d, C-2′), 70.8 (d, C-5″), 70.6 (d, C-3′), 69.8 (d, C-5′), 68.9 (t, C-23), 61.5 (q, 3″-OMe), 59.6 (q, 2″-OMe), 44.8 (d, C-14), 43.9 (d, C-8), 43.0 (d, C-4), 41.0 (q, NMe_2), 39.8 (t, C-2), 34.6 (d, C-6), 31.0 (t, C-7), 30.8 (t, C-19), 26.2 (t, C-16), 17.8 (q, Me-C-5′), 17.6 (q, Me-C-5″), 17.0 (q, Me-21), 12.5 (q, Me-22), 9.8 (q, Me-17), 9.4 (q, Me-18). Anal. ($C_{41}H_{67}NO_{15}$) C, H, N.

Pfitzner−Moffat Oxidation of Desmycosin Analogues 26a−d. Compounds **26a−d** (1.4 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). To this solution were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 3.2 g, 16.8 mmol, 12 equiv) and dimethyl sulfoxide (1.8 mL, 25 mmol, 18 equiv) followed by pyridine trifluoroacetate (3.2 g, 16.8 mmol, 12 equiv). After stirring at room temperature for 18 h, CH_2Cl_2 (15 mL) was added and the mixture was filtered. The precipitate was washed with fresh CH_2Cl_2. The filtrates were combined and washed with water and then brine. The organic solution was dried over anhydrous Na_2SO_4 and evaporated at room temperature under vacuum. The residue was chromatographed on silica gel, eluting with system B, to give derivatives **29a−d**.

29a (84%): FAB-MS *m*/*z* 952 (MH^+, 71%); UV λ_{max} nm (ε) 276 (32 413), 255 (17 807); ^{1}H NMR ($CDCl_3$) δ 11.88 (1H, s, H-3 enol), 7.20 (1H, d, H-11, $J_{10,11}$ = 15.5 Hz), 6.85 (1H, dt, H-20, $J_{20,20'}$ = 16.0 Hz, $J_{19b,20}$ = 2.5 Hz), 6.17 (1H, d, H-10, $J_{10,11}$ = 15.5 Hz), 5.75 (1H, d, H-20′, $J_{20,20'}$ = 16.0 Hz), 5.71 (1H, d, H-13, $J_{13,14}$ = 9.5 Hz), 4.88−4.76 (2H, m, H-15, H-2′), 4.68 (1H, t, H-4′, $J_{3',4'ax}$ = $J_{4',5'}$ = 10.0 Hz), 4.64 (1H, s, H-2 enol), 4.56 (1H, d, H-1″, $J_{1'',2''}$ = 8.0 Hz), 4.54 (1H, t, H-3″, $J_{2'',3''}$ = $J_{3'',4''}$ = 3.0 Hz), 4.37 (1H, d, H-4″, $J_{4'',5''}$ = 9.5 Hz), 4.32 (1H, d, H-1′, $J_{1',2'}$ = 7.5 Hz), 3.96−3.88 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 4.5 Hz), 3.87−3.80 (1H, m, H-5″), 3.69 (1H, d, H-5, $J_{4,5}$ = 10.5 Hz), 3.65 (3H, s, COO*CH*$_3$), 3.52 (1H, dd, H-23a, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23a}$ = 4.0 Hz), 3.45 (3H, s, 3″-OMe), 3.42 (3H, s, 2″-OMe), 3.34 (1H, dq, H-5′, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'}$ = 6.3 Hz), 2.99 (1H, dd, H-2″, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 3.0 Hz), 2.93−2.84 (1H, m, H-14), 2.67 (1H, t, H-3′, $J_{2',3'}$ = $J_{3',4'ax}$ = 10.0 Hz), 2.54 (1H, br, H-8), 2.40−2.31 (3H, m, H-19, H-4), 2.27 (6H, s, NMe_2), 2.06 (3H, s, 4″-OCO*CH*$_3$), 2.03 (1H, br, H-6), 1.97 (6H, s, 2′-OCO*CH*$_3$, 4′-OCO*CH*$_3$), 1.82 (1H, ddq, H-16b, $J_{15,15b}$ = 2.7 Hz, $J_{16a,16b}$ = 14.0 Hz, $J_{16b,17}$ = 7.0 Hz), 1.72 (3H, s, Me-22), 1.64−1.48 (2H, m, H-16a, H-7b), 1.43−1.34 (1H, m, H-7a), 1.22 (3H, m, H-16a, H-7b), 1.18 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.13 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.3 Hz), 1.10 (3H, d, H-6″, (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 0.88 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4 (s, C-9), 179.6 (s, C-3 enol), 172.1 (s, C-1), 170.1 (s, O*CO*CH$_3$), 169.7 (s, O*CO*CH$_3$), 169.1 (s, O*CO*CH$_3$), 167.1 (s, *CO*OCH$_3$), 149.2 (d, C-20), 147.2 (d, C-11), 139.5 (d, C-13), 136.8 (s, C-12), 121.9 (d, C-20′), 118.6 (d, C-10), 102.1 (d, C-1′), 100.9 (d, C-1″), 89.1 (d, C-2 enol), 80.4 (d, C-2″), 79.5 (d, C-5), 77.6 (d, C-3″), 74.7 (d, C-15), 74.5 (d, C-4″), 71.2 (d, C-4′), 71.0 (d, C-5′), 70.3 (d, C-2′), 69.3 (t, C-23), 67.2 (d, C-5″), 66.9 (d, C-3′), 61.4 (q, 3″-OMe), 59.4 (q, 2″-OMe), 51.1 (q, COO*CH*$_3$), 44.5 (d, C-14, C-8, 2C), 43.2 (d, C-4), 41.0 (q, NMe_2), 37.9 (d, C-6), 31.6 (t, C-7), 30.4 (t, C-19), 25.6 (t, C-16), 21.0 (q, OCO*CH*$_3$), 20.9 (q, OCO*CH*$_3$), 20.7 (q, OCO*CH*$_3$), 17.7 (q, Me-18), 17.4 (q, Me-21), 17.1 (q, Me-C-5′), 17.0 (q, Me-C-5″), 13.4 (q, Me-22), 9.6 (q, Me-17). Anal. ($C_{48}H_{73}NO_{18}$) C, H, N.

29b (75%): FAB-MS *m*/*z* 966 (MH^+, 71%); UV λ_{max} nm (ε) 278 (29 236), 257 (17 896); IR (KBr) ν_{max} 2971, 2925, 1749, 1716, 1681, 1643, 1596, 1455, 1374, 1232, 1171, 1089, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.70 (1H, s, H-3 enol), 7.31 (1H, d, H-11), 6.83 (1H, dt, H-20), 6.21 (1H, d, H-10), 5.84 (1H, d, H-13), 5.81 (1H, d, H-20′), 4.71 (1H, s, H-2 enol), 4.20 (3H, q, COO*CH*$_2$CH$_3$), 3.64 (3H, s, 3″-OMe), 3.43 (3H, s, 2″-OMe), 2.58 (6H, s, NMe_2), 2.12 (3H, s, 4″-OCO*CH*$_3$), 2.03 (6H, s, 2′-OCO*CH*$_3$, 4′-OCO*CH*$_3$), 1.80 (3H, s, Me-22), 1.29 (3H, t, COOCH$_2$*CH*$_3$); ^{13}C NMR ($CDCl_3$) δ 203.4 (s, C-9), 179.8 (s, C-3 enol), 170.1 (s, O*CO*CH$_3$), 169.6 (s, O*CO*CH$_3$), 169.1 (s, O*CO*CH$_3$), 168.9 (s, C-1), 166.1 (s, *CO*OCH$_2$CH$_3$), 148.3 (d, C-20), 147.5 (d, C-11), 141.7 (d, C-13), 134.3 (s, C-12), 123.7 (d, C-10), 123.1 (d, C-20′), 88.9 (d, C-2 enol), 61.8 (q, 3″-OMe), 59.5 (t, COO*CH*$_2$CH$_3$), 59.1 (q, 2″-OMe), 41.4 (q, NMe_2), 21.4 (q, OCO*CH*$_3$), 20.9 (q, 2×OCO*CH*$_3$), 14.2 (q, COOCH$_2$*CH*$_3$), 12.3 (q, Me-22). Anal. ($C_{49}H_{75}NO_{18}$) C, H, N.

29c (85%): FAB-MS *m*/*z* 936 (MH^+, 86%); UV λ_{max} nm (ε) 277 (28 823), 256 (17 653); ^{1}H NMR ($CDCl_3$) δ 11.90 (1H, s, H-3 enol), 7.30 (1H, d, H-11), 6.90 (1H, dt, H-20), 6.12 (1H, d, H-10), 5.81 (1H, d, H-20′), 5.75 (1H, d, H-13), 4.70 (1H, s, H-2 enol), 3.51 (3H, s, 3″-OMe), 3.45 (3H, s, 2″-OMe), 2.50 (6H, s, NMe_2), 2.27 (3H, s, CO*CH*$_3$), 2.05 (3H, s, 4″-OCO*CH*$_3$), 1.98 (6H, s, 2′-OCO*CH*$_3$, 4′-OCO*CH*$_3$), 1.75 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.5 (s, C-9), 199.2 (s, *CO*CH$_3$), 179.1 (s, C-3 enol), 172.4 (s, C-1), 170.0 (s, O*CO*CH$_3$), 169.8 (s, O*CO*CH$_3$), 169.3 (s, O*CO*CH$_3$), 149.1 (d, C-20), 147.1 (d, C-11), 139.3 (d, C-13), 136.5 (s, C-12), 121.7 (d, C-20′), 118.3 (d, C-10), 89.1 (d, C-2 enol), 61.1 (q, 3″-OMe), 59.3 (q, 2″-OMe), 41.3 (q, NMe_2), 21.0 (q, OCO*CH*$_3$), 20.8 (q, OCO*CH*$_3$), 20.7 (q, OCO*CH*$_3$), 13.3 (q, Me-22). Anal. ($C_{48}H_{73}NO_{17}$) C, H, N.

29d (92%): FAB-MS *m*/*z* 922 (MH^+, 90%); UV λ_{max} nm (ε) 278 (29 128), 258 (16 953); ^{1}H NMR ($CDCl_3$) δ 11.82 (1H, s, H-3 enol), 9.75 (1H, d, CHO), 7.25 (1H, d, H-11), 6.69 (1H, dt, H-20), 6.20 (1H, d, H-10), 5.95 (1H, dd, H-20′), 5.87 (1H, d, H-13), 4.75 (1H, s, H-2 enol), 3.52 (3H, s, 3″-OMe), 3.46 (3H, s, 2″-OMe), 2.37 (6H, s, NMe_2), 2.12 (3H, s, 4″-OCO*CH*$_3$), 2.01 (6H, s, 2′-OCO*CH*$_3$, 4′-OCO*CH*$_3$), 1.78 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.1 (s, C-9), 193.0 (d, CHO), 180.1 (s, C-3 enol), 173.0 (s, C-1), 170.2 (s, O*CO*CH$_3$), 169.7 (s, O*CO*CH$_3$), 169.1 (s, O*CO*CH$_3$), 149.4 (d, C-20), 146.2 (d, C-11), 140.1 (d, C-13), 135.1 (s, C-12), 120.9 (d, C-20′), 118.0 (d, C-10), 89.0 (d, C-2 enol), 61.0 (q, 3″-OMe), 59.4 (q, 2″-OMe), 41.0 (q, NMe_2), 21.3 (q, OCO*CH*$_3$), 21.0 (q, OCO*CH*$_3$), 20.8 (q, OCO*CH*$_3$), 12.9 (q, Me-22). Anal. ($C_{47}H_{71}NO_{17}$) C, H, N.

General Procedure for Deprotection of Desmycosin Analogues 29a−d. Compounds **29a−d** (3.48 mmol) were dissolved in methanol (40 mL) and the solution was heated under reflux for 1 h. The residue obtained after evaporation in vacuo was chromatographed on silica gel (8:2, hexane−acetone) to give **30a−d**. Compounds **30a−d** (2.0 mmol) were dissolved in methanol, then an aqueous solution of NH_3 (25%) was added and the mixture was stirred for 3 h at 25 °C. The crude product obtained by concentration of the reaction mixture was chromatographed on silica gel (E1 solvent system, R_f = 0.30−0.50), furnishing the expected α,β-unsaturated compounds **31a−d** (60−90%). By using these procedures, the following compounds were prepared.

30a (86%): FAB-MS *m*/*z* 868 (MH^+, 79%); UV λ_{max} nm (ε) 276 (31 543), 256 (17 326); ^{1}H NMR ($CDCl_3$) δ 11.67 (1H, br, H-3 enol), 7.22 (1H, d, H-11, $J_{10,11}$ = 15.1 Hz), 6.96 (1H, dt, H-20, $J_{20,20'}$ = 15.5 Hz, $J_{19b,20}$ = 2.3 Hz), 6.24 (1H, d, H-13, $J_{13,14}$ = 10.0 Hz), 5.86 (1H, d, H-20′, $J_{20,20'}$ = 15.5 Hz), 5.80 (1H, d, H-13, $J_{13,14}$ = 10.0 Hz), 4.92 (1H, dt, H-15, $J_{14,15}$ = 9.8 Hz, $J_{15,16b}$ = 2.1 Hz), 4.74 (1H, s, H-2 enol), 4.64 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.44 (1H, dd, H-4″, $J_{3'',4''}$ = 3.0 Hz, $J_{4'',5''}$ = 9.2 Hz), 4.32 (1H, d, H-1′, $J_{1',2'}$ = 7.5 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 4.1 Hz), 3.94−3.92 (1H, m, H-5″), 3.90 (1H, t, H-3″, $J_{2'',3''}$ = $J_{3'',4''}$ = 3.0 Hz), 3.86 (1H, d, H-5, $J_{4,5}$ = 10.0 Hz), 3.73 (3H, s, COOCH$_3$), 3.58 (1H, dd, H-23a, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23a}$ = 4.0 Hz), 3.56−3.51 (1H, m, H-2′), 3.53 (3H, s, 3″-OMe), 3.50 (3H, s, 2″-OMe), 3.32 (1H, dq, H-5′, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'}$ = 6.3 Hz), 3.11 (1H, t, H-4′, $J_{3'4'ax}$ = $J_{4',5'}$ = 9.5 Hz), 3.06 (1H, dd, H-2″, $J_{1'',2''}$ = 7.8 Hz, $J_{2'',3''}$ = 3.0 Hz), 3.00−2.93 (1H, m, H-14), 2.70 (1H, dd, H-19b, $J_{19a,19b}$ = 16.3 Hz, $J_{19b,20}$ = 2.3 Hz), 2.63 (1H, br, H-8), 2.52 (6H, s, NMe_2), 2.44−2.36 (3H, m, H-19a, H-4, H-3′), 2.11 (3H, s, 4″-OCOCH$_3$), 2.02 (1H, br, H-6), 1.90 (1H, ddq, H-16b, $J_{15,15b}$ = 2.8 Hz, $J_{16a,16b}$ = 14.0 Hz, $J_{16b,17}$ = 7.1 Hz), 1.80 (3H, s, Me-22), 1.71−1.57 (2H, m, H-16a, H-7b), 1.56−1.48 (1H, m, H-7a), 1.34 (3H, d, H-6′. (Me-C-5′), J5′,6′ = 6.3 Hz), 1.33 (3H, d, Me-18, $J_{4,18}$ = 6.3 Hz),

1.21 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.18 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 0.95 (3H, t, Me-17, $J_{16a,17} = J_{16b,17}$ = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (s, C-9), 180.8 (s, C-3 enol), 171.3 (s, C-1), 170.1 (s, 4″-O*CO*CH$_3$), 167.1 (s, COOCH$_3$), 149.0 (d, C-20), 147.4 (d, C-11), 139.7 (d, C-13), 136.8 (s, C-12), 122.1 (d, C-20′), 118.5 (d, C-10), 104.1 (d, C-1′), 101.0 (d, C-1″), 89.2 (d, C-2 enol), 80.5 (d, C-2″), 79.3 (d, C-5), 77.7 (d, C-3″), 74.7 (d, C-15, C-4″, 2C), 73.5 (d, C-5′), 71.0 (d, C-2′), 70.7 (d, C-4′), 70.1 (d, C-3′), 69.5 (t, C-23), 67.3 (d, C-5″), 61.5 (q, 3″-OMe), 59.6 (q, 2″-OMe), 51.3 (q, COO*CH$_3$*), 44.8 (d, C-14), 44.0 (d, C-8), 43.7 (d, C-4), 41.7 (q, NMe$_2$), 38.0 (d, C-6), 32.5 (t, C-7), 30.7 (t, C-19), 25.9 (t, C-16), 20.9 (q, 4″-OCO*CH$_3$*), 17.8 (q, Me-18), 17.6 (q, Me-C-5′), 17.4 (q, Me-21), 17.1 (q, Me-C-5″), 13.7 (q, Me-22), 9.9 (q, Me-17). Anal. ($C_{44}H_{69}NO_{16}$) C, H, N.

30b (91%): FAB-MS *m*/*z* 882 (MH$^+$, 79%); UV λ_{max} nm (ϵ) 281 (27 443), 257 (18 108); ^{1}H NMR ($CDCl_3$) δ 11.95 (1H, br, H-3 enol), 7.22 (1H, d, H-11, $J_{10,11}$ = 15.6 Hz), 6.93 (1H, dt, H-20, $J_{20,20'}$ = 15.6 Hz, $J_{19b,20}$ = 2.3 Hz), 6.24 (1H, d, H-10, $J_{10,11}$ = 15.6 Hz), 5.84 (1H, d, H-20′, $J_{20,20'}$ = 15.6 Hz), 5.78 (1H, d, H-13, $J_{13,14}$ = 10.1 Hz), 4.91 (1H, dt, H-15, $J_{14,15}$ = 9.9 Hz, $J_{15,16b}$ = 2.5 Hz), 4.73 (1H, s, H-2 enol), 4.64 (1H, d, H-1″, $J_{1'',2''}$ = 7.7 Hz), 4.44 (1H, dd, H-4″, $J_{3'',4''}$ = 3.0 Hz, $J_{4'',5''}$ = 9.1 Hz), 4.33 (1H, d, H-1′, $J_{1',2'}$ = 7.5 Hz), 4.18 (2H, q, COO*CH$_2$*-CH$_3$, $J_{CH2,CH3}$ = 7.1 Hz), 4.01 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 4.1 Hz), 3.95−3.92 (1H, m, H-5″), 3.90 (1H, t, H-3″, $J_{2'',3''} = J_{3'',4''}$ = 3.0 Hz), 3.86 (1H, d, H-5, $J_{4,5}$ = 10.0 Hz), 3.58 (1H, dd, H-23a, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23a}$ = 4.0 Hz), 3.55−3.50 (1H, m, H-2′), 3.53 (3H, s, 3″-OMe), 3.50 (3H, s, 2″-OMe), 3.37−3.30 (1H, m, H-5′), 3.15 (1H, t, H-4′, $J_{3',4'ax} = J_{4',5'}$ = 9.5 Hz), 3.06 (1H, dd, H-2″, $J_{1'',2''}$ = 7.7 Hz, $J_{2'',3''}$ = 3.0 Hz), 3.01−2.92 (1H, m, H-14), 2.65 (1H, dd, H-19b, $J_{19a,19b}$ = 16.2 Hz, $J_{19b,20}$ = 2.3 Hz), 2.60 (1H, br, H-8), 2.55 (6H, s, NMe$_2$), 2.48−2.37 (3H, m, H-19a, H-4, H-3′), 2.12 (3H, s, 4″-OCO*CH$_3$*), 1.99 (1H, br, H-6), 1.90 (1H, ddq, H-16b, $J_{15,16b}$ = 2.5 Hz, $J_{16a,16b}$ = 14.0 Hz, $J_{16b,17}$ = 7.1 Hz), 1.80 (3H, s, Me-22), 1.72−1.56 (2H, m, H-16a, H-7b), 1.57−1.49 (1H, m, H-7a), 1.36 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.3 Hz), 1.34 (3H, d, Me-18, $J_{4,18}$ = 6.3 Hz), 1.29 (3H, t, COOCH$_2$*CH$_3$*, $J_{CH2,CH3}$ = 7.1 Hz), 1.21 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.18 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 0.95 (3H, t, Me-17, $J_{16a,17} = J_{16b,17}$ = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (s, C-9), 179.8 (s, C-3 enol), 172.3 (s, C-1), 170.2 (s, 4″-O*CO*CH$_3$), 166.4 (s, *CO*OCH$_2$CH$_3$), 148.6 (d, C-20), 147.5 (d, C-11), 139.8 (d, C-13), 136.8 (s, C-12), 123.7 (d, C-20′), 118.6 (d, C-10), 104.1 (d, C-1′), 101.1 (d, C-1″), 89.2 (d, C-2 enol), 80.6 (d, C-2″), 79.4 (d, C-5), 77.7 (d, C-2′), 70.7 (d, C-4′), 70.4 (d,C-3′), 69.5 (t, C-23), 67.4 (d, C-5″), 61.6 (q, 3″-OMe), 60.0 (t, COO*CH$_2$*CH$_3$), 59.6 (q, 2″-OMe), 44.9 (d, C-14), 44.6 (d, C-8), 43.5 (d, C-4), 41.8 (q, NMe$_2$), 38.2 (d, C-6), 32.3 (t, C-7), 30.8 (t, C-19), 26.0 (t, C-16), 21.0 (q, 4″-OCO*CH$_3$*), 18.1 (q, Me-18), 17.9 (q, Me-C-5′), 17.8 (q, Me-21), 17.4 (q, Me-C-5″), 14.3 (q, COOCH$_2$*CH$_3$*), 13.7 (q, Me-22), 9.9 (q, Me-17). Anal. ($C_{45}H_{71}NO_{16}$) C, H, N.

30c (88%): FAB-MS *m*/*z* 852 (MH$^+$, 79%); UV λ_{max} nm (ϵ) 288 (32 135), 255 (17 684); ^{1}H NMR ($CDCl_3$) δ 11.65 (1H, br, H-3 enol), 7.20 (1H, d, H-11), 6.94 (1H, dt, H-20), 6.24 (1H, d, H-10), 5.83 (1H, d, H-20′), 5.78 (1H, d, H-13), 4.76 (1H, s, H-2 enol), 3.51 (3H, s, 3″-OMe), 3.48 (3H, s, 2″-OMe), 2.50 (6H, s, NMe$_2$), 2.25 (3H, s, CO*CH$_3$*), 2.10 (3H, s, 4″-OCO*CH$_3$*), 1.81 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.1 (s, C-9), 199.1 (s, *CO*CH$_3$), 180.5 (s, C-3 enol), 171.3 (s, C-1), 170.0 (s, 4″-OCO*CH$_3$), 149.2 (d, C-20), 147.1 (d, C-11), 139.4 (d, C-13), 136.7 (s, C-12), 122.0 (d, C-20′), 118.1 (d, C-10), 89.4 (d, C-2 enol), 59.8 (q, 3″-OMe), 58.8 (q, 2″-OMe), 41.3 (q, NMe$_2$), 26.2 (q, CO*CH$_3$*), 20.9 (q, 4″-OCO*CH$_3$*), 13.7 (q, Me-22). Anal. ($C_{44}H_{69}NO_{15}$) C, H, N.

30d (94%): FAB-MS *m*/*z* 838 (MH$^+$, 84%); UV λ_{max} nm (ϵ) 286 (29 754), 256 (17 274); ^{1}H NMR ($CDCl_3$) δ11.80 (1H, s, H-3 enol), 9.74 (1H, d, CHO), 7.23 (1H, d, H-11), 6.63 (1H, dt, H-20), 6.25 (1H, d, H-10), 5.91 (1H, dd, H-20′), 5.80 (1H, d, H-13), 4.81 (1H, s, H-2 enol), 3.50 (3H, s, 3″-OMe), 3.45 (3H, s, 2″-OMe), 2.11 (3H, s, 4″-OCO*CH$_3$*), 1.78 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.0 (s, C-9), 193.2 (d, CHO), 180.3 (s, C-3 enol), 173.2 (s, C-1), 170.4 (s, 4″-OCO*CH$_3$*), 149.2 (d, C-20), 146.1 (d, C-11), 140.0 (d, C-13), 135.3 (s, C-12), 121.0 (d, C-20′), 118.3 (d, C-10), 89.2 (d, C-2 enol), 61.0 (q, 3″-OMe), 59.6 (q, 2″-OMe), 41.0 (q, NMe$_2$), 21.6 (q, 4″-OCO*CH$_3$*), 12.8 (q, Me-22). Anal. ($C_{43}H_{67}NO_{15}$) C, H, N.

31a (89%): FAB-MS *m*/*z* 826 (MH$^+$, 57%); UV λ_{max} nm (ϵ) 288 (33 666), 256 (17 345); ^{1}H NMR ($CDCl_3$) δ 11.67 (1H, d, H-11, $J_{10,11}$ = 15.2 Hz), 6.95 (1H, dt, H-20, $J_{20,20'}$ = 15.6 Hz, $J_{19b,20}$ = 2.5 Hz), 6.23 (1H, d, H-10, $J_{10,11}$ = 15.2 Hz), 5.86 (1H, d, H-20′, $J_{20,20'}$ = 15.6 Hz), 5.82 (1H, d, H-13, $J_{13,14}$ = 10.2 Hz), 4.92 (1H, dt, H-15, $J_{14,15}$ = 9.8 Hz, $J_{15,16b}$ = 2.1 Hz), 4.74 (1H, s, H-2 enol), 4.57 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.32 (1H, d, H-1′, $J_{1',2'}$ = 7.5 Hz), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 4.1 Hz), 3.85 (1H, d, H-5, $J_{4,5}$ = 10.1 Hz), 3.76 (1H, t, H-3″, $J_{2'',3''} = J_{3'',4''}$ = 3.1 Hz), 3.73 (3H, s, COO*CH$_3$*), 3.62 (3H, s, 3″-OMe), 3.61−3.52 (3H, m, H-23a, H-5″, H-2′), 3.34−3.30 (1H, m, H-5′), 3.19 (1H, dd, H-4″, $J_{3'',4''}$ = 3.1 Hz, $J_{4'',5''}$ = 9.3 Hz), 3.11 (1H, t, H-4′, $J_{3',4'ax} = J_{4',5'}$ = 9.6 Hz), 3.05 (1H, dd, H-2″, $J_{1'',2''}$ = 7.8 Hz, $J_{2'',3''}$ = 2.8 Hz), 3.05−2.93 (1H, m, H-14), 2.82 (1H, br, H-8), 2.72−2.56 (1H, m, H-19b), 2.52 (6H, s, NMe$_2$), 2.46−2.37 (3H, m, H-19a, H-4, H-3′), 2.03 (1H, br, H-6), 1.89 (1H, ddq, H-16b, $J_{15,16b}$ = 2.1 Hz, $J_{16a,16b}$ = 14.1 Hz, $J_{16b,17}$ = 7.3 Hz), 1.80 (3H, s, Me-22), 1.70−1.57 (2H, m, H-16a, H-7b), 1.55−1.47 (1H, m, H-7a), 1.33 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.3 Hz), 1.27 (3H, d, Me-18, $J_{4,18}$ = 6.3 Hz), 1.26 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 1.21 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 0.96 (3H, t, Me-17, $J_{16a,17} = J_{16b,17}$ = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (s, C-9), 179.8 (s, C-3 enol), 172.2 (s, C-1), 167.1 (s, *CO*OCH$_3$), 149.0 (d, C-20), 147.5 (d, C-11), 139.9 (d, C-13), 136.7 (s, C-12), 122.1 (d, C-20′), 118.6 (d, C-10), 104.2 (d, C-1′), 101.1 (d, C-1″), 89.2 (d, C-2 enol), 81.9 (d, C-2″), 79.8 (d, C-3″), 79.3 (d, C-5), 74.8 (d, C-15), 73.5 (d, C-5′), 72.6 (d, C-4″), 71.0 (d, C-2′), 70.6 (d, C-2″), 70.3 (d, C-4′), 70.1 (d, C-3′), 70.0 (d, C-5″), 69.4 (t, C-23), 61.7 (q, 3″-OMe), 59.8 (q, 2″-OMe), 51.3 (q, COO*CH$_3$*), 44.9 (d, C-14), 44.5 (d, C-8), 43.5 (d, C-4), 41.7 (q, NMe$_2$), 38.3 (d, C-6), 32.5 (t, C-7), 30.7 (t, C-19), 25.9 (t, C-16), 18.1 (q, Me-18), 17.9 (q, Me-C-5′), 17.8 (q, Me-21), 17.6 (q, Me-C-5″), 13.7 (q, Me-22), 9.9 (q, Me-17). Anal. ($C_{42}H_{67}NO_{15}$) C, H, N.

31b (89%): FAB-MS *m*/*z* 840 (MH$^+$, 57%); UV λ_{max} nm (ϵ) 289 (28 696), 256 (17 864); ^{1}H NMR ($CDCl_3$) δ 11.97 (1H, br, H-3 enol), 7.25 (1H, d, H-11, $J_{10,11}$ = 15.5 Hz), 6.93 (1H, dt, H-20, $J_{20,20'}$ = 15.6 Hz, $J_{19b,20}$ = 2.3 Hz), 6.25 (1H, d, H-10, $J_{10,11}$ = 15.5 Hz), 5.87 (1H, d, H-20′, $J_{20,20'}$ = 15.6 Hz), 5.81 (1H, d, H-13, $J_{13,14}$ = 10.1 Hz), 4.94 (1H, dt, H-15, $J_{14,15}$ = 9.8 Hz, $J_{15,16b}$ = 2.5 Hz), 4.76 (1H, s, H-2 enol), 4.61 (1H, d, H-1″, $J_{1'',2''}$ = 7.7 Hz), 4.34 (1H, d, H-1′, $J_{1',2'}$ = 7.5 Hz), 4.20 (2H, q, COO*CH$_2$*CH$_3$, $J_{CH2,CH3}$ = 7.1 Hz), 4.02 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 4.0 Hz), 3.88 (1H, d, H-5, $J_{4,5}$ = 10.1 Hz), 3.77 (1H, t, H-3″, $J_{2'',3''} = J_{3'',4''}$ = 2.9 Hz), 3.64 (3H, s, 3″-OMe), 3.61−3.54 (3H, m, H-23a, H-5″, H-2′), 3.52 (3H, s, 2″-OMe), 3.40−3.33 (1H, m, H-5′), 3.20 (1H, br, H-4″), 3.15 (1H, t, H-4′, $J_{3',4'ax} = J_{4',5'}$ = 9.5 Hz), 3.05 (1H, dd, H-2″, $J_{1'',2''}$ = 7.7 Hz, $J_{2'',3''}$ = 2.8 Hz), 3.03−2.91 (1H, m, H-14), 2.84 (1H, br, H-8), 2.73−2.59 (1H, m, H-19b), 2.57 (6H, s, NMe$_2$), 2.50−2.38 (3H, m, H-19a, H-4, H-3′), 2.00 (1H, br, H-6), 1.88 (1H, ddq, H-16b, $J_{15,16b}$ = 2.5 Hz, $J_{16a,16b}$ = 14.5 Hz, $J_{16b,17}$ = 7.2 Hz), 1.82 (3H, s, Me-22), 1.72−1.60 (2H, m, H-16a, H-7b), 1.58−1.48 (1H, m, H-7a), 1.37 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.3 Hz), 1.35 (3H, d, Me-18, $J_{4,18}$ = 6.3 Hz), 1.32 (3H, t, COOCH$_2$*CH$_3$*, J_{CH2CH3} = 7.1 Hz), 1.29 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 1.23 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 0.97 (3H, t, Me-17, $J_{16a,17} = J_{16b,17}$ = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (s, C-9), 179.8 (s, C-3 enol), 172.3 (s, C-1), 166.7 (s, *CO*OCH$_2$CH$_3$), 149.3 (d, C-20), 147.5 (d, C-11), 140.0 (d, C-13), 136.8 (s, C-12), 122.6 (d, C-20′), 118.6 (d, C-10), 104.0 (d, C-1′), 101.1 (d, C-1″), 89.2 (d, C-2 enol), 81.9 (d, C-2″), 79.9 (d, C-3″), 79.4 (d, C-5), 74.8 (d, C-15), 73.5 (d, C-5′), 72.7 (d, C-4″), 70.9 (d, C-2′), 70.7 (d, C-2″), 70.6 (d, C-4′), 70.3 (d, C-3′), 70.1 (d, C-5″), 69.4 (t, C-23), 61.8 (q, 3″-OMe), 60.0 (t, COO*CH$_2$*CH$_3$), 59.8 (q, 2″-OMe), 44.9 (d, C-14), 44.6 (d, C-8), 43.6 (d, C-4), 41.8 (q, NMe$_2$), 38.2 (d, C-6), 32.9 (t, C-7), 30.8 (t, C-19), 26.0 (t, C-16), 18.7 (q, Me-18), 18.1 (q, Me-C-5′), 17.9 (q, Me-21), 17.8 (q, Me-C-5″), 14.3 (q, COOCH$_2$*CH$_3$*), 13.7 (q, Me-22), 9.9 (q, Me-17). Anal. ($C_{43}H_{69}NO_{15}$) C, H, N.

31c (89%): FAB-MS *m/z* 810 (MH^+, 84%); UV λ_{max} nm (ϵ) 289 (29 476), 256 (17 453); ^{1}H NMR ($CDCl_3$) δ 11.98 (1H, s, H-3 enol), 7.23 (1H, d, H-11), 6.93 (1H, dt, H-20), 6.24 (1H, d, H-10), 5.83 (1H, d, H-20′), 5.75 (1H, d, H-13), 4.78 (1H, s, H-2 enol), 3.68 (3H, s, 3″-OMe), 3.50 (3H, s, 2″-OMe), 2.51 (6H, s, NMe_2), 2.24 (3H, s, COCH_3), 1.81 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.1 (s, C-9), 199.0 (s, COCH$_3$), 179.6 (s, C-3 enol), 172.1 (s, C-1), 149.1 (d, C-20), 147.8 (d, C-11), 140.5 (d, C-13), 136.9 (s, C-12), 122.0 (d, C-20′), 118.1 (d, C-10), 89.0 (d, C-2 enol), 61.8 (q, 3″-OMe), 59.7 (q, 2″-OMe), 41.5 (q, NMe_2), 26.1 (q, COCH_3), 13.6 (q, Me-22). Anal. ($C_{42}H_{67}NO_{14}$) C, H, N.

31d (96%): FAB-MS *m/z* 796 (MH^+, 100%); UV λ_{max} nm (ϵ) 286 (29 864), 256 (17 356); ^{1}H NMR ($CDCl_3$) δ 11.78 (1H, s, H-3 enol), 9.77 (1H, d, CHO), 7.21 (1H, d, H-11), 6.61 (1H, dt, H-20), 6.30 (1H, d, H-10), 5.92 (1H, dd, H-20′), 5.79 (1H, d, H-13), 4.84 (1H, s, H-2 enol), 3.52 (3H, s, 3″-OMe), 3.46 (3H, s, 2″-OMe), 1.79 (3H, s, Me-22); ^{13}C NMR ($CDCl_3$) δ 203.2 (s, C-9), 192.0 (d, CHO), 180.1 (s, C-3 enol), 173.1 (s, C-1), 149.7 (d, C-20), 146.5 (d, C-11), 140.8 (d, C-13), 135.1 (s, C-12), 121.3 (d, C-20′), 118.7 (d, C-10), 89.1 (d, C-2 enol), 59.9 (q, 3″-OMe), 59.3 (q, 2″-OMe), 41.0 (q, NMe_2), 12.7 (q, Me-22). Anal. ($C_{41}H_{65}NO_{14}$) C, H, N.

Synthesis of Mixed Anhydrides of the Carboxylic Acids. To a solution of acids **a1**−**a4** (4.16 mmol, 1.0 equiv) in THF (40 mL) at room temperature (25 °C) was added pivaloyl chloride (0.54 mL, 4.58 mmol, 1.1 equiv), and the reaction mixture was stirred at the same temperature for 12 h. Once complete by TLC, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure and dried under high vacuum to give the corresponding anhydrides. The anhydrides were stored as a 0.2 M solution in CH_2Cl_2 and used in this form for the esterification.

Synthesis of a Desmycosin Library (32−**39a**−**d) in Solution Phase.** A mixture of the corresponding alcohol **26a**−**d** (0.120 mmol, 1.0 equiv), DMAP (14.7 mg, 0.120 mmol, 1.0 equiv), triethylamine (0.3 mL, 2.15 mmol, 17.9 equiv), and the mixed anhydride of the corresponding acid (6.0 mL of 0.2 M solution in methylene chloride, 1.22 mmol, 10.0 equiv) was stirred at room temperature for 22 h. The reaction mixture was then concentrated and purified by flash chromatography (silica gel, 10% acetone in methylene chloride followed by 30% acetone in methylene chloride) to yield esters **32**−**39a**−**d**. By using this procedure, the following compounds were prepared as discrete compounds.

32a (81%): FAB-MS *m/z* 1117 (MH^+, 63%). Anal. ($C_{56}H_{80}N_2O_{21}$) C, H, N.

32b (77%): FAB-MS *m/z* 1129 (MH^+, 74%). Anal. ($C_{57}H_{80}N_2O_{21}$) C, H, N.

32c (59%): FAB-MS *m/z* 1084 (MH^+, 86%). Anal. ($C_{57}H_{81}NO_{19}$) C, H, N.

32d (90%): FAB-MS *m/z* 1059 (MH^+, 43%). Anal. ($C_{54}H_{78}N_2O_{19}$) C, H, N.

33a (78%): FAB-MS *m/z* 1131 (MH^+, 58%); UV λ_{max} nm (ϵ) 276 (31 894), 250 (13 300); ^{1}H NMR ($CDCl_3$) δ 8.17 (2H, d, Ar−C, $J_{B,C}$ = 8.7 Hz), 7.54 (2H, d, Ar−B, $J_{B,C}$ = 8.7 Hz), 7.35 (1H, d, H-11, $J_{10,11}$ = 15.5 Hz), 6.84 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19,20}$ = 7.8 Hz), 6.26 (1H, d, H-10, $J_{10,11}$ = 15.5 Hz), 5.85 (1H, d, H-13, $J_{13,14}$ = 10.3 Hz), 5.83 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 5.12 (1H, br, H-2′), 5.05 (1H, d, H-3, $J_{2b,3}$ = 9.8 Hz), 4.92 (1H, br, H-4′), 4.78 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16b}$ = 3.9 Hz), 4.60 (1H, d, H-1″, $J_{1'',2''}$ = 8.0 Hz), 4.43 (1H, dd, H-4″, $J_{3'',4''}$ = 2.5 Hz, $J_{4'',5''}$ = 9.9 Hz), 4.21−4.09 (3H, m, COOCH$_2$CH$_3$, H-1′), 3.96 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 4.4 Hz), 3.94−3.87 (2H, m, H-5″, H-3″), 3.77−3.66 (2H, m, H-5, H-3b″), 3.52 (3H, s, 3″-OMe), 3.51−3.47 (1H, m, H-23a), 3.43 (3H, s, 2″-OMe), 3.28−3.20 (1H, m, H-5′), 3.13 (1H, br, H-6), 3.02 (1H, dd, H-2″, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 2.8 Hz), 2.96 (1H, ddt, H-14, $J_{14,15}$ = 10.0 Hz, $J_{14,23a}$ = 6.5 Hz, $J_{14,23b}$ = 4.1 Hz), 2.93−2.89 (1H, m, H-3′), 2.70−2.61 (4H, m, H-8, NMea), 2.57 (1H, dd, H-2b, $J_{2a,2b}$ = 16.2 Hz, $J_{2b,3}$ = 9.8 Hz), 2.35 (4H, br, H-19b, NMeb), 2.12 (6H, s, OCOCH_3), 1.93 (1H, d, H-2a, $J_{2a,2b}$ = 16.2 Hz), 1.86 (1H, ddq, H-16b, $J_{15,16a}$ = 10.5 Hz, $J_{16a,16b}$ = 14.4 Hz, $J_{16a,17}$ = 7.3 Hz), 1.78 (3H, s, Me-22), 1.74−1.65 (2H, m, H-19a, H-4), 1.59 (1H, ddq, H-16a, $J_{15,16a}$ = 10.5 Hz, $J_{16a,16b}$ = 14.4 Hz, $J_{16a,17}$ = 7.3 Hz), 1.45 (1H, br, H-7b), 1.28 (3H, t, COOCH$_2$$CH_3$, $J_{CH3,CH2}$ = 7.1 Hz), 1.23 (3H, s, OCOCH_3), 1.19 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.18 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 6.0 Hz), 1.17 (3H, d, H-6″(Me-C-5″), $J_{5'',6''}$ = 6.3 Hz), 1.08−1.01 (1H, m, H-7a), 0.93−0.87 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.3 Hz; 1H, m, H-3a″), 0.85 (3H, d, Me-18, $J_{4,18}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (s, C-9), 183.4 (s, OCOCH$_3$), 170.2 (s, OCOCH$_3$, 2C), 169.9 (s, C-1), 166.8 (s, COOCH$_2$CH$_3$), 166.4 (s, OCOCH$_2$C$_6$H$_4$NO$_2$), 147.9 (d, C-20), 147.7 (d, C-11), 147.1 (s, Ar-D), 142.0 (s, Ar-A), 141.9 (d, C-13), 135.0 (s, C-12), 130.7 (d, Ar−B, 2C), 123.0 (d, C-20′), 103.5 (d, C-1′), 101.0 (d, C-1″), 80.6 (d, C-2″), 79.6 (d, C-5), 77.7 (d, C-3″), 75.6 (d, C-3), 75.3 (d, C-15), 74.7 (d, C-4″), 71.8 (d, C-3′), 71.8 (d, C-3′), 71.2 (d, C-4′), 71.0 (d, C-2′), 69.6 (t, C-23), 67.4 (d, C-5″), 67.1 (d, C-5′), 61. 6 (q, 3″-OMe), 60.1 (t, COOCH_2CH$_3$), 59.4 (q, 2″-OMe), 44.6 (d, C-14, C-8, 2C), 41.2 (q, NMe_2), 40.9 (t, C-3″; d, C-4; 2C), 37.7 (t, C-2), 36.9 (d, C-6), 33.3 (t, C-7), 31.5 (t, C-19), 27.1 (q, OCOCH_3), 21.0 (q, OCOCH_3), 17.4 (q, Me-C-5′, Me-C-5″, 2C), 17.2 (q, Me-21), 14.3 (q, COOCH$_2$$CH_3$), 13.2 (q, Me-22), 10.0 (q, Me-18), 9.5 (q, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.3 Hz). Anal. ($C_{57}H_{82}N_2O_{21}$) C, H, N.

33b (85%): FAB-MS *m/z* 1143 (MH^+, 51%); ^{1}H NMR ($CDCl_3$) δ 8.19 (2H, d, Ar−C), 7.91 (1H, d, H-3″), 7.59 (2H, d, Ar−B), 7.30 (1H, d, H-11), 6.90 (1H, dt, H-20), 6.25 (1H, d, H-2″), 6.22 (1H, d, H-10), 5.89 (1H, d, H-13), 5.81 (1H, d, H-20′), 4.21 (2H, q, COOCH_2CH$_3$), 3.50 (3H, s, 3″-OMe), 3.40 (3H, s, 2″-OMe), 2.15 (3H, s, OCOCH_3), 2.10 (6H, s, OCOCH_3), 1.27 (3H, t, COOCH$_2$$CH_3$); ^{13}C NMR ($CDCl_3$) δ 202.5 (s, C-9), 182.4 (s, C-1″), 173.0 (s, C-1), 171.2 (s, OCOCH3), 169.5 (s, OCOCH3), 169.1 (s, OCOCH3), 165.8 (s, COOCH$_2$CH$_3$), 148.3 (d, C-20), 146.8 (d, C-11), 144.7 (d, C-3″), 144.6 (s, Ar-D), 142.1 (s, Ar-A), 141.3 (d, C-13), 134.3 (s, C-12), 127.5 (d, Ar−B, 2C), 121.5 (d, C-20′), 121.4 (d, Ar−C, 2C), 117.9 (d, C-10), 116.5 (d, C-2″), 75.3 (d, C-3), 61.2 (q, 3″-OMe), 59.4 (t, COOCH_2CH$_3$), 59.2 (q, 2″-OMe), 41.0 (q, NMe_2), 21.1 (q, OCOCH_3), 21.0 (q, OCOCH_3), 20.6 (q, OCOCH_3), 14.0 (q, COOCH$_2$$CH_3$). Anal. ($C_{58}H_{82}N_2O_{21}$) C, H, N.

33c (92%): FAB-MS *m/z* 1098 (MH^+, 74%); ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, d, H-3″), 7.33 (2H, d, Ar−B), 7.32 (1H, d, H-11), 7.24 (2H, d, Ar−C), 7.17 (1H, dd, Ar-D), 6.94 (1H, dt, H-20), 6.25 (1H, d, H-2″), 6.20 (1H, d, H-10), 5.83 (1H, d, H-13), 5.79 (1H, d, H-20′), 4.18 (2H, q, COOCH_2CH$_3$), 3.46 (3H, s, 3″-OMe), 3.27 (3H, s, 2″-OMe), 2.12 (3H, s, OCOCH_3), 2.06 (6H, s, OCOCH_3), 1.22 (3H, t, COOCH$_2$$CH_3$); ^{13}C NMR ($CDCl_3$) δ 201.8 (s, C-9), 181.8 (s, C-1″), 173.6 (s, C-1), 171.9 (s, OCOCH3), 168.7 (s, OCOCH3), 168.9 (s, OCOCH3), 164.3 (s, COOCH$_2$-CH$_3$), 147.6 (d, C-20), 145.3 (d, C-11), 144.0 (d, C-3″), 141.1 (d, C-13) 136.0 (s, Ar-A), 134.8 (s, C-12), 126.5 (d, Ar−B, Ar−C, 4C), 125.5 (d, Ar-D), 121.2 (d, C-20′), 116.8 (d, C-10), 116.2 (d, C-2″), 75.0 (d, C-3), 61.0 (q, 3″-OMe), 59.2 (t, COOCH_2-CH$_3$), 59.1 (q, 2″-OMe), 39.8 (q, NMe_2), 21.4 (q, OCOCH_3), 21.3 (q, OCOCH_3), 20.2 (q, OCOCH_3), 14.1 (q, COOCH$_2$$CH_3$). Anal. ($C_{58}H_{83}NO_{19}$) C, H, N.

33d (90%): FAB-MS *m/z* 1073 (MH^+, 91%); UV λ_{max} nm (ϵ) 275 (32 985), 250 (12 985); ^{1}H NMR ($CDCl_3$) δ 8.76 (2H, s, Ar−C), 7.81 (2H, s, Ar−B), 7.45 (1H, d, H-11, $J_{10,11}$ = 15.5 Hz), 6.85 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19,20}$ = 7.8 Hz), 6.31 (1H, d, H-10, $J_{10,11}$ = 15.5 Hz), 5.90 (1H, d, H-13, $J_{13,14}$ = 10.4 Hz), 5.75 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 5.33 (1H, d, H-3, $J_{2b,3}$ = 9.3 Hz), 4.92 (1H, br, H-2′), 4.81 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16b}$ = 3.8 Hz; 1H, br, H-4′), 4.59 (1H, d, H-1″, $J_{1'',2''}$ = 8.0 Hz), 4.42 (1H, dd, H-4″, $J_{3'',4''}$ = 2.5 Hz, $J_{4'',5''}$ = 9.9 Hz), 4.34 (1H, br, H-1′), 4.08−3.97 (2H, m, COOCH_2CH$_3$), 3.94 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 4.3 Hz), 3.92−3.86 (3H, m, H-5″, H-5, H-3″), 3.51 (3H, s, 3″-OMe), 3.41 (3H, s, 2″-OMe), 3.37 (1H, dd, H-2″, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 2.8 Hz), 2.97−2.93 (1H, m, H-14), 2.76 (1H, dd, H-2b, $J_{2a,2b}$ = 16.1 Hz, $J_{2b,3}$ = 9.3 Hz), 2.70 (5H, br, H-8, H-3′, NMea), 2.37 (4H, br, H-19b, NMeb), 2.11 (6H, s, OCOCH_3), 2.05−1.98 (1H, m, H-2a), 1.87−1.83 (2H, m, H-16b, H-4), 1.82 (3H, s, Me-22), 1.77−1.65 (1H, m, H-19a), 1.60 (1H, ddq, H-16a, $J_{15,16a}$ = 10.5 Hz, $J_{16,16b}$ = 14.4 Hz, $J_{16a,17}$ = 7.3 Hz), 1.51 (3H, br, OCOCH_3), 1.29 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.28−1.21 (3H, t, COOCH$_2$$CH_3$, $J_{CH3,CH2}$ = 7.1 Hz; 1H, m, H-7b), 1.16 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ =

6.2 Hz), 1.10−1.03 (6H, m, Me-18, Me-C-5′), 0.96−0.91 (1H, m, H-7a), 0.88 (3H, t, Me-17, $J_{16a,17} = J_{16b,17} = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (s, C-9), 170.2 (s, O*C*OCH$_3$, 3C), 169.9 (s, C-1), 166.4 (s, OCOPy), 166.3 (s, *C*OOCH$_2$CH$_3$), 150.5 (d, Ar−C, 2C), 147.9 (d, C-20), 147.6 (d, C-11), 141.4 (d, C-13), 137.3 (s, Ar-A), 134.8 (s, C-12), 123.1 (d, C-20′, Ar−B, 3C), 123.0 (d, C-10), 103.5 (d, C-1′), 101.0 (d, C-1″), 80.5 (d, C-2″), 79.4 (d, C-5), 77.6 (d, C-3″), 75.6 (d, C-3), 75.4 (d, C-15), 74.7 (d, C-4″), 71.7 (d, C-3′), 71.2 (d, C-4′), 71.0 (d, C-2′), 69.5 (t, C-23), 67.3 (d, C-5″), 67.0 (d, C-5′), 61.6 (q, 3″-OMe), 59.9 (t, COO*C*H$_2$CH$_3$), 59.4 (q, 2″-OMe), 44.7 (d, C-14, C-8, 2C), 41.2 (q, NMe$_2$; d, C-4), 37.6 (t, C-2), 35.9 (d, C-6), 31.6 (t, C-19, C-7, 2C), 25.6 (t, C-16), 22.0 (q, OCO*C*H$_3$), 21.6 (q, OCO*C*H$_3$), 21.4 (q, OCO*C*H$_3$), 17.4 (q, Me-C-5′, Me-C-5″, 2C), 17.1 (q, Me-21), 14.3 (q, COOCH$_2$*C*H$_3$), 13.1 (q, Me-22), 10.1 (q, Me-18), 9.5 (q, Me-17). Anal. ($C_{55}H_{80}N_2O_{19}$) C, H, N.

34a (65%): FAB-MS *m/z* 1101 (MH$^+$, 64%). Anal. ($C_{56}H_{80}N_2O_{20}$) C, H, N.

34b (75%): FAB-MS *m/z* 1113 (MH$^+$, 58%). Anal. ($C_{57}H_{80}N_2O_{20}$) C, H, N.

34c (84%): FAB-MS *m/z* 1068 (MH$^+$, 92%). Anal. ($C_{57}H_{81}NO_{18}$) C, H, N.

34d (85%): FAB-MS *m/z* 1043 (MH$^+$, 84%). Anal. ($C_{54}H_{78}N_2O_{18}$) C, H, N.

35a (76%): FAB-MS *m/z* 1087 (MH$^+$, 49%). Anal. ($C_{55}H_{78}N_2O_{20}$) C, H, N.

35b (84%): FAB-MS *m/z* 1099 (MH$^+$, 65%). Anal. ($C_{56}H_{78}N_2O_{20}$) C, H, N.

35c (69%): FAB-MS *m/z* 1054 (MH$^+$, 59%). Anal. ($C_{56}H_{79}NO_{18}$) C, H, N.

35d (75%): FAB-MS *m/z* 1029 (MH$^+$, 63%). Anal. ($C_{53}H_{76}N_2O_{18}$) C, H, N.

36a (91%): FAB-MS *m/z* 991 (MH$^+$, 32%). Anal. ($C_{50}H_{74}N_2O_{18}$) C, H, N.

36b (86%): FAB-MS *m/z* 1003 (MH$^+$, 59%). Anal. ($C_{51}H_{74}N_2O_{18}$) C, H, N.

36c (83%): FAB-MS *m/z* 958 (MH$^+$, 53%). Anal. ($C_{51}H_{75}NO_{16}$) C, H, N.

36d (75%): FAB-MS *m/z* 933 (MH$^+$, 39%). Anal. ($C_{48}H_{72}N_2O_{16}$) C, H, N.

37a (88%): FAB-MS *m/z* 1005 (MH$^+$, 79%); UV λ_{max} nm (ϵ) 276 (31 543), 250 (13 336); IR (KBr) ν_{max} 3459, 2972, 2933, 1742, 1594, 1523, 1455, 1347, 1167, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.17 (2H, d, Ar−C, $J_{B,C}$= 8.7 Hz), 7.52 (2H, d, Ar−B, $J_{B,C}$= 8.7 Hz), 7.36 (1H, d, H-11, $J_{10,11}$ = 16.5 Hz), 6.89 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19,20}$ = 7.8 Hz), 6.24 (1H, d, H-10, $J_{10,11}$ = 16.5 Hz), 5.87 (1H, d, H-13, $J_{13,14}$ = 10.4 Hz), 5.86 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 5.13 (1H, d, H-3, $J_{2b,3}$ = 9.8 Hz), 4.81 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16a}$ = 11.0 Hz, $J_{15,16b}$ = 3.7 Hz), 4.55 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.23−4.09 (3H, m, COO*C*H$_2$CH$_3$, H-1′), 3.97 (1H, dd, H-23b, $J_{23a,23b}$ = 9.4 Hz, $J_{14,23b}$ = 4.2 Hz), 3.82−3.71 (3H, m, H-5, H-3b″, H-3″), 3.62 (3H, s, 3″-OMe), 3.57−3.46 (3H, m, H-23a, H-5″, H-2′), 3.44 (3H, s, 2″-OMe), 3.35−3.24 (2H, m, H-6, H-5′), 3.22−3.12 (2H, m, H-4″, H-4′), 3.00 (1H, dd, H-2″, $J_{1'',2''}$ = 7.8 Hz, $J_{2'',3''}$ = 2.9 Hz), 2.97−2.92 (1H, m, H-14), 2.80−2.67 (1H, m, H-8), 2.61 (6H, s, NMe$_2$), 2.54−2.40 (2H, m, H-3′, H-2b), 2.36−2.26 (1H, m, H-19b), 1.98 (1H, d, H-2a, $J_{2a,2b}$ = 16.1 Hz), 1.93−1.87 (1H, m, H-16b), 1.85−1.71 (2H, m, H-19a, H-4), 1.79 (3H, s, Me-22), 1.59 (1H, ddq, H-16a, $J_{15,16a}$ = 10.5 Hz, $J_{16a,16b}$ = 14.4 Hz, $J_{16a,17}$ = 7.3 Hz), 1.51−1.44 (1H, m, H-7b), 1.34 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 5.9 Hz), 1.28 (3H, t, COOCH$_2$*C*H$_3$, $J_{CH3,CH2}$ = 7.2 Hz), 1.27 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.9 Hz), 1.19 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 1.14−1.09 (1H, m, H-7a), 1.02−0.96 (3H, d, Me-18, $J_{4,18}$ = 6.9 Hz; 1H, m, H-3a″), 0.91 (3H, t, Me-17, $J_{16a,17} = J_{16b,17}$ = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (s, C-9), 169.9 (s, C-1), 166.6 (s, *C*OOCH$_2$CH$_3$, O*C*OC$_6$H$_4$NO$_2$; 2C), 148.0 (d, C-20), 147.8 (d, C-11), 146.9 (s, Ar-D), 141.7 (s, Ar-A; d, C-13; 2C), 134.7 (s, C-12), 130.6 (d, Ar−B), 123.5 (d, C-10), 123.3 (d, Ar−C), 122.8 (d, C-20′), 103.5 (d, C-1′), 100.9 (d, C-1″), 81.7 (d, C-2″), 80.4 (d, C-5), 79.6 (d, C-3″), 75.4 (d, C-3), 75.0 (d, C-15), 73.3 (d, C-5′), 72.5 (d, C-4″), 70.7 (d, C-4′, C-3′, 2C), 70.2 (d, C-5″, C-2′, 2C), 69.4 (t, C-23), 61.6 (q, 3″-OMe), 59.9 (t, COO*C*H$_2$CH$_3$), 59.5 (q, 2″-OMe), 44.4 (d, C-14, C-8, 2C), 41.7 (q, NMe$_2$), 40.6 (t, C-3″; d, C-4; 2C), 37.6 (t, C-2), 37.0 (d, C-6), 33.3 (t, C-7), 31.8 (t, C-19), 25.6 (t, C-16), 17.6 (q, Me-C-5′, Me-C-5″, 2C), 17.3 (q, Me-21), 14.2 (q, COOCH$_2$*C*H$_3$), 12.9 (q, Me-22), 10.2 (q, Me-18), 9.4 (q, Me-17). Anal. ($C_{51}H_{76}N_2O_{18}$) C, H, N.

37b (79%): FAB-MS *m/z* 1017 (MH$^+$, 79%); ^{1}H NMR ($CDCl_3$) δ 8.14 (2H, d, Ar−C), 7.87 (1H, d, H-3″), 7.47 (2H, d, Ar−B), 7.25 (1H, d, H-11), 6.73 (1H, dt, H-20), 6.21 (1H, d, H-2″), 6.18 (1H, d, H-10), 5.80 (1H, d, H-13), 5.75 (1H, d, H-20′), 4.20 (2H, q, COO*C*H$_2$CH$_3$), 3.48 (3H, s, 3″-OMe), 3.30 (3H, s, 2″-OMe), 1.22 (3H, t, COOCH$_2$*C*H$_3$); ^{13}C NMR ($CDCl_3$) δ 202.2 (s, C-9), 181.8 (s, C-1″), 173.5 (s, C-1), 165.9 (s, *C*OOCH$_2$CH$_3$), 148.8 (d, C-20), 147.2 (d, C-11), 144.3 (d, C-3″), 144.0 (s, Ar-D), 141.8 (s, Ar-A), 141.1 (d, C-13), 133.8 (s, C-12), 127.9 (d, Ar−B, 2C), 121.2 (d, C-20′), 120.8 (d, Ar−C, 2C), 117.3 (d, C-10), 116.2 (d, C-2″), 75.2 (d, C-3), 61.1 (q, 3″-OMe), 59.6 (t, COO*C*H$_2$CH$_3$), 59.4 (q, 2″-OMe), 41.1 (q, NMe$_2$), 14.0 (q, COOCH$_2$*C*H$_3$). Anal. ($C_{52}H_{76}N_2O_{18}$) C, H, N.

37c (81%): FAB-MS *m/z* 972 (MH$^+$, 64%); ^{1}H NMR ($CDCl_3$) δ 7.87 (1H, d, H-3″), 7.30 (2H, d, Ar−B), 7.24 (1H, d, H-11), 7.20 (2H, d, Ar−C), 7.11 (1H, dd, Ar-D), 6.91 (1H, dt, H-20), 6.15 (1H, d, H-2″), 6.10 (1H, d, H-10), 5.81 (1H, d, H-13), 5.71 (1H, d, H-20′), 4.15 (2H, q, COO*C*H$_2$CH$_3$), 3.43 (3H, s, 3″-OMe), 3.24 (3H, s, 2″-OMe), 1.21 (3H, t, COOCH$_2$*C*H$_3$); ^{13}C NMR ($CDCl_3$) δ 202.5 (s, C-9), 182.1 (s, C-1″), 173.8 (s, C-1), 164.9 (s, *C*OOCH$_2$CH$_3$), 147.4 (d, C-20), 145.0 (d, C-11), 144.6 (d, C-3″), 141.4 (d, C-13) 136.8 (s, Ar-A), 135.4 (s, C-12), 126.9 (d, Ar−B, Ar−C, 4C), 125.3 (d, Ar-D), 121.5 (d, C-20′), 117.6 (d, C-10), 116.6 (d, C-2″), 75.5 (d, C-3), 61.4 (q, 3″-OMe), 59.8 (t, COO*C*H$_2$CH$_3$), 59.6 (q, 2″-OMe), 40.1 (q, NMe$_2$), 14.3 (q, COOCH$_2$*C*H$_3$). Anal. ($C_{52}H_{77}NO_{16}$) C, H, N.

37d (71%): FAB-MS *m/z* 947 (MH$^+$, 48%); ^{1}H NMR ($CDCl_3$) δ 8.69 (2H, s, Ar−C), 7.72 (2H, s, Ar−B), 7.42 (1H, d, H-11), 6.89 (1H, dt, H-20), 6.38 (1H, d, H-10), 5.95 (1H, d, H-13), 5.70 (1H, d, H-20′), 5.31 (1H, d, H-3), 4.87 (1H, br, H-2′), 4.76 (1H, dt, H-15; 1H, br, H-4′), 4.63 (1H, d, H-1″), 4.45 (1H, dd, H-4″), 4.39 (1H, br, H-1′), 4.03−3.95 (2H, m, COO*C*H$_2$CH$_3$), 3.90 (1H, dd, H-23b), 3.88−3.81 (3H, m, H-5″, H-5, H-3″), 3.50 (3H, s, 3″-OMe), 3.44 (3H, s, 2″-OMe), 3.33 (1H, dd, H-2″), 2.96−2.90 (1H, m, H-14), 2.71 (1H, dd, H-2b), 2.67 (5H, br, H-8, H-3′, NMea), 2.30 (4H, br, H-19b, NMeb), 2.05−1.92 (1H, m, H-2a), 1.85−1.81 (2H, m, H-16b, H-4), 1.78 (3H, s, Me-22), 1.75−1.62 (1H, m, H-19a), 1.60 (1H, ddq, H-16a), 1.27 (3H, d, Me-21), 1.25−1.19 (3H, t, COOCH$_2$*C*H$_3$, 1H, m, H-7b), 1.14 (3H, d, H-6″ (Me-C-5″)), 1.11−1.01 (6H, m, Me-18, Me-C-5′), 0.96−0.90 (1H, m, H-7a), 0.85 (3H, t, Me-17); ^{13}C NMR ($CDCl_3$) δ 202.8 (s, C-9), 169.7 (s, C-1), 166.2 (s, OCOPy), 166.0 (s, *C*OOCH$_2$CH$_3$), 150.1 (d, Ar−C, 2C), 147.4 (d, C-20), 147.2 (d, C-11), 141.8 (d, C-13), 137.6 (s, Ar-A), 134.1 (s, C-12), 123.0 (d, C-20′, Ar−B, 3C), 122.7 (d, C-10), 103.9 (d, C-1′), 101.2 (d, C-1″), 80.4 (d, C-2″), 79.8 (d, C-5), 77.4 (d, C-3″), 75.5 (d, C-3), 75.1 (d, C-15), 74.4 (d, C-4″), 71.9 (d, C-3′), 71.4 (d, C-4′), 71.1 (d, C-2′), 69.4 (t, C-23), 67.2 (d, C-5″), 67.5 (d, C-5′), 61.2 (q, 3″-OMe), 59.7 (t, COO*C*H$_2$CH$_3$), 59.2 (q, 2″-OMe), 44.5 (d, C-14, C-8, 2C), 41.7 (q, NMe$_2$; d, C-4), 37.8 (t, C-2), 35.5 (d, C-6), 31.8 (t, C-19, C-7, 2C), 25.0 (t, C-16), 17.2 (q, Me-C-5′, Me-C-5″, 2C), 17.0 (q, Me-21), 14.2 (q, COOCH$_2$*C*H$_3$), 12.8 (q, Me-22), 10.4 (q, Me-18), 9.2 (q, Me-17). Anal. ($C_{55}H_{80}N_2O_{19}$) C, H, N. Anal. ($C_{49}H_{74}N_2O_{16}$) C, H, N.

38a (69%): FAB-MS *m/z* 975 (MH$^+$, 48%). Anal. ($C_{50}H_{74}N_2O_{17}$) C, H, N.

38b (59%): FAB-MS *m/z* 987 (MH$^+$, 64%). Anal. ($C_{51}H_{74}N_2O_{17}$) C, H, N.

38c (68%): FAB-MS *m/z* 942 (MH$^+$, 81%). Anal. ($C_{51}H_{75}NO_{15}$) C, H, N.

38d (72%): FAB-MS *m/z* 917 (MH$^+$, 64%). Anal. ($C_{48}H_{72}N_2O_{15}$) C, H, N.

39a (75%): FAB-MS *m/z* 961 (MH$^+$, 56%). Anal. ($C_{49}H_{72}N_2O_{17}$) C, H, N.

39b (63%): FAB-MS *m/z* 973 (MH$^+$, 64%). Anal. ($C_{50}H_{72}N_2O_{17}$) C, H, N.

39c (85%): FAB-MS *m/z* 928 (MH$^+$, 63%). Anal. ($C_{50}H_{73}NO_{15}$) C, H, N.

39d (59%): FAB-MS *m/z* 903 (MH^+, 69%). Anal. ($C_{47}H_{70}N_2O_{15}$) C, H, N.

Mitsunobu Reaction with Diisopropyl Azodicarboxylate. Preparation of 40 and 41. Diisopropyl azodicarboxylate (514 μL, 2.61 mmol) was added to a mixture of **26b** (842.2 mg, 0.87 mmol), Ph_3P (686 mg, 2.61 mmol), and $ClCH_2CO_2H$ (247 mg, 2.61 mmol) in THF (18 mL) at 0 °C, and the mixture was stirred for 50 min at room temperature. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed on silica gel, eluting with 20% acetone in hexane, to give **40** (816.7 mg, 90%) as a pale yellow solid: FAB-MS *m/z* 1044 (MH^+, 66%). Anal. ($C_{51}H_{78}ClNO_{19}$) C, H, N.

Compound **40** (805.0 mg, 0.77 mmol) was dissolved in NH_3/MeOH (20 mL, saturated at 0 °C) and kept at room temperature overnight. The solvent was removed in vacuo, and the residue was purified on a silica gel column with EtOH in $CHCl_3$ (0−16%) to give **41** (659.3 mg, 90%) as a white solid. An analytical sample was crystallized from AcOEt−hexane to give white crystals: FAB-MS *m/z* 842 (MH^+, 66%); ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, d, H-11), 6.96 (1H, br, H-20), 6.27 (1H, d, H-10), 5.93 (1H, d, H-13), 5.87 (1H, d, H-20′), 4.99 (1H, dt, H-15), 4.43 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.31 (1H, d, H-1′, $J_{1',2'}$ = 7.3 Hz), 4.19 (2H, q, $COOCH_2CH_3$), 4.07 (1H, dd, H-23b, $J_{23a,23b}$ = 9.6 Hz, $J_{14,23b}$ = 3.8 Hz), 3.90−3.80 (2H, m, H-5, H-3″), 3.70 (1H, br, H-3), 3.61 (3H, s, 3″-OMe), 3.58−3.53 (3H, m, H-23a, H-5″, H-2′), 3.46 (3H, s, 2″-OMe), 3.40 (1H, br, H-5′), 3.34−3.10 (3H, m, H-6, H-4″, H-4′), 3.05 (1H, dd, H-2″), 3.00−2.92 (1H, m, H-14), 2.82−2.63 (8H, m, NMe_2, H-8, H-3′), 2.60 (1H, br, H-19b), 2.42 (1H, dd, H-2b), 2.31 (1H, br, H-19a), 2.15 (1H, d, H-2a), 1.85 (1H, ddq, H-16b), 1.82 (3H, s, Me-22), 1.73−1.56 (2H, m, H-16a, H-4), 1.53−1.40 (1H, m, H-7b), 1.35 (1H, d, H-7a), 1.29 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 7.0 Hz), 1.25 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.3 Hz), 1.18 (3H, d, Me-21, $J_{8,21}$ = 6.6 Hz), 1.05 (3H, d, Me-18, $J_{4,18}$ = 6.0 Hz), 0.92 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.1 Hz), 0.88 (3H, t, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 203.6 (s, C-9), 176.8 (s, C-1), 169.1 (s, $COOCH_2CH_3$), 148.0 (d, C-20), 146.4 (d, C-11), 139.8 (d, C-13), 133.5 (s, C-12), 124.1 (d, C-20′), 123.7 (d, C-10), 103.9 (d, C-1′), 101.5 (d, C-1″), 82.1 (d, C-5, C-2″, 2C), 80.5 (d, C-3″), 74.3 (d, C-15), 73.7 (d, C-3), 73.0 (d, C-4″), 72.9 (d, C-5′, C-4′, 2C), 71.3 (d, C-5″, C-3′, 2C), 70.6 (d, C-2′), 66.9 (t, C-23), 61.5 (q, 3″-OMe), 60.6 (t, $COOCH_2CH_3$), 58.1 (q, 2″-OMe), 43.7 (d, C-14), 43.1 (d, C-8), 42.9 (d, C-4), 41.5 (q, NMe_2), 39.3 (t, C-2), 34.9 (d, C-6), 32.8 (t, C-7), 29.9 (t, C-19), 25.7 (t, C-16), 16.6 (q, Me-21), 15.4 (q, Me-C-5″, Me-C-5′, 2C), 14.3 (q, $COOCH_2CH_3$), 13.5 (q, Me-22), 10.8 (q, Me-18), 9.1 (q, Me-17). Anal. ($C_{43}H_{71}NO_{15}$) C, H, N.

Mitsunobu Reaction with Diethyl Azodicarboxylate. Preparation of 42 and 43. Compound **26b** (968.0 mg, 1.0 mmol) in anhydrous THF (10 mL) under argon at 0 °C was sequentialy treated with triphenyl phosphine (525.0 mg, 2.0 mmol) and diethyl azodicarboxylate (330.7 μL, 2.1 mmol) over a 10 min period. After 10 min, the reaction was treated with methanol (405.0 μL, 10.0 mmol) and stirred for an additional 2 h. The solvent was evaporated and the residue was chromatographed on silica gel, eluting with 20% acetone in hexane, to give **42** (1.01 g, 90%) as a white solid: FAB-MS *m/z* 1126 (MH^+, 64%). Anal. ($C_{55}H_{87}N_3O_{21}$) C, H, N.

Compound **42** (1.0 g, 0.88 mmol) was dissolved in NH_3/MeOH (10 mL, saturated at 0 °C) and kept at room-temperature overnight. The solvent was removed in vacuo, and the residue was purified on a silica gel column with EtOH in $CHCl_3$ (0−16%) to give **43** (792 mg, 90%) as a white solid: FAB-MS *m/z* 1000 (MH^+, 47%); ^{1}H NMR ($CDCl_3$) δ 7.28 (1H, d, H-11), 6.87 (1H, br, H-20), 6.59 (1H, br, NH), 6.22 (1H, d, H-10), 5.94 (1H, d, H-13), 5.81 (1H, d, H-20′), 4.95 (1H, dt, H-15), 4.60 (1H, d, H-1″), 4.32 (1H, d, H-1′), 4.22 (2H, q, $NHCOOCH_2CH_3$, $J_{CH2,CH3}$ = 7.2 Hz), 4.15 (1H, q, $COOCH_{2b}CH_3$, $J_{CH2b,CH3}$ = 7.1 Hz), 4.00 (1H, dd, H-23b), 3.80−3.70 (3H, m, H-5, H-3″, H-3), 3.60 (3H, s, 3″-OMe), 3.54−3.51 (3H, m, H-23a, H-5″, H-2′), 3.50 (3H, s, 2″-OMe), 3.36 (1H, br, H-5′), 3.29−3.11 (3H, m, H-6, H-4″, H-4′), 3.07 (1H, dd, H-2″), 3.03−2.93 (1H, m, H-14), 2.83−2.65 (8H, m, NMe_2, H-8, H-3′), 2.60 (1H, br, H-19b), 2.44 (1H, dd, H-2b), 2.35 (1H, br, H-19a), 1.95 (1H, d, H-2a), 1.90 (1H, ddq, H-16b), 1.82 (3H, s, Me-22), 1.75−1.50 (2H, m, H-16a, H-4), 1.52−1.42 (1H, m, H-7b), 1.32 (1H, d, H-7a), 1.31 (1H, q, $COOCH_{2a}CH_3$, $J_{CH2a,CH3}$ = 7.1 Hz), 1.28 (3H, d, H-6′ (Me-C-5′)), 1.27 (3H, d, H-6″ (Me-C-5″)), 1.25 (3H, t, $NHCOOCH_2CH_3$, $J_{CH3,CH2}$ = 7.2 Hz) 1.18 (3H, d, Me-21), 1.00 (3H, d, Me-18), 0.92 (3H, t, Me-17), 0.88 (3H, t, $COOCH_{2a}CH_3$, $J_{CH3,CH2a}$ = 7.1 Hz). δ Anal. ($C_{49}H_{81}N_3O_{18}$) C, H, N.

Mitsunobu Reaction with 1,1′-Azadicarbonylbispiperidine. Preparation of 44 and 45. A solution of 1,1′-(azadicarbonyl)bispiperidine (516 mg, 2.05 mmol) and Bu_3P (85%; 500 μL, 1.73 mmol) in anhydrous THF (15 mL) was added dropwise to a stirred solution of *p*-nitrophenylacetic acid (445.3 mg, 2.46 mmol) in anhydrous THF (15 mL) at room temperature. After stirring at room temperature for 15 min, the mixture was cooled to 0 °C and **26b** (1.98 g, 2.05 mmol) in anhydrous THF (8 mL) was added and the mixture stirred at 0 °C for 3 h and then at room temperature for 3 h. The solvent was evaporated and the residue was chromatographed on silica gel, eluting with 20% acetone in hexane, to give **44** (1.97 g, 85%) as a white solid: FAB-MS *m/z* 1131 (MH^+, 94%). Anal. ($C_{57}H_{82}N_2O_{21}$) C, H, N.

Compound **44** (1.95 g, 1.72 mmol) was dissolved in methanol (5 mL). To this solution was added aqueous ammonia (25%, 2.5 mL) and the mixture was stirred at room temperature for 4 h. The residue obtained after evaporation in vacuo was purified by flash chromatography (silica gel, solvent system A1) to furnish 1.38 g (80%) of inverted acylide **45** as a nearly colorless solid: FAB-MS *m/z* 1005 (MH^+, 52%); UV λ_{max} nm (ε) 275 (30 769), 250 (13 345); IR (KBr) ν_{max} 3448, 2978, 2937, 1748, 1597, 1524, 1373, 1348, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (2H, d, Ar−C), 7.50 (2H, d, Ar−B), 7.30 (1H, d, H-11), 6.85 (1H, dt, H-20), 6.22 (1H, d, H-10), 5.85 (1H, d, H-13), 5.83 (1H, d, H-20′), 5.20−5.10 (1H, m, H-3), 4.80 (1H, dt, H-15), 4.51 (1H, d, H-1″), 4.25−4.12 (3H, m, $COOCH_2CH_3$, H-1′), 3.95 (1H, dd, H-23b), 3.90−3.68 (3H, m, H-5, H-3b″, H-3″), 3.65 (3H, s, 3″-OMe), 3.62−3.49 (3H, m, H-23a, H-5″, H-2′), 3.44 (3H, s, 2″-OMe), 3.35−3.22 (2H, m, H-6, H-5′), 3.20−3.10 (2H, m, H-4″, H-4′), 3.00 (1H, dd, H-2″), 2.96−2.92 (1H, m, H-14), 2.80−2.67 (1H, m, H-8), 2.59 (6H, s, NMe_2), 2.55−2.42 (2H, m, H-3′, H-2b), 2.38 (1H, br, H-19b), 1.99 (1H, d, H-2a), 1.95−1.88 (1H, m, H-16b), 1.84−1.69 (2H, m, H-19a, H-4), 1.80 (3H, s, Me-22), 1.60 (1H, ddq, H-16a), 1.51−1.44 (1H, m, H-7b), 1.35 (3H, d, Me-C-5′), 1.29 (3H, t, $COOCH_2CH_3$), 1.27 (3H, d, Me-C-5″), 1.20 (3H, d, Me-21), 1.15−1.10 (1H, m, H-7a), 1.03−0.98 (3H, d, Me-18; 1H, m, H-3″a), 0.91 (3H, t, Me-17).^{13}C NMR ($CDCl_3$) δ 203.5 (s, C-9), 169.0 (s, C-1), 166.2 (s, $COOCH_2CH_3$), 166.1 (s, $OCOCH_2C_6H_4NO_2$), 148.3 (d, C-20), 147.5 (d, C-11), 146.5 (s, Ar-D), 142.0 (s, Ar-A), 141.8 (d, C-13), 134.5 (s, C-12), 130.8 (d, Ar−B), 123.8 (d, C-10), 123.5 (d, Ar−C), 123.0 (d, C-20′), 103.9 (d, C-1′), 100.9 (d, C-1″), 82.0 (d, C-2″), 80.9 (d, C-5), 79.8 (d, C-3″), 78.0 (d, C-3), 75.3 (d, C-15), 73.1 (d, C-5′), 72.8 (d, C-4″), 70.1 (d, C-4′, C-3′, 2C), 70.0 (d, C-5″), 69.9 (d, C-2′), 69.0 (t, C-23), 61.9 (q, 3″-OMe), 59.4 (t, $COOCH_2CH_3$), 59.2 (q, 2″-OMe), 44.8 (d, C-14), 44.6 (d, C-8), 41.5 (q, NMe_2), 40.9 (t, C-3″), 40.1 (d, C-4), 37.3 (t, C-2), 36.9 (d, C-6), 33.0 (t, C-7), 31.6 (t, C-19), 25.8 (t, C-16), 17.5 (q, Me-C-5′, Me-C-5″, 2C), 17.5 (q, Me-21), 14.3 (q, $COOCH_2CH_3$), 12.5 (q, Me-22), 10.2 (q, Me-18), 9.1 (q, Me-17). Anal. ($C_{51}H_{76}N_2O_{18}$) C, H, N.

3′-De(dimethylamino)-3′-oxodesmycosin (51) and 3′-*N*-Acetyl-3′-*N*-demethyldesmycosin (52). To a solution of bis(methylacetal) **15** (574.0 mg, 0.70 mmol), produced analogously to the literature procedure,[34] in dry $CHCl_3$ (9.2 mL) was added *m*-CPBA (133.3 mg, 0.89 mmol), and the mixture was stirred at room temperature for 2 h, after which TLC (CH_2Cl_2−CH_3OH−aq NH_3 90:9:1.5; R_f = 0.28) indicated that the reaction was complete. The mixture was washed with saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$, dried, and filtered. To the resulting solution of **46** was added Ac_2O (333.5 μL, 3.5 mmol) and the mixture was kept at room temperature overnight. After washing with saturated aqueous $NaHCO_3$, the organic solution was dried and concentrated. The residue

obtained was submitted to column chromatography (8:2 hexane−acetone, then 6:2 hexane−acetone). The fraction having R_f = 0.51 (8:2 hexane−acetone) gave, on concentration, **47** (113.0 mg, 60%) as a colorless solid: FAB-MS *m/z* 873 (MH^+, 89%); IR (KBr)ν_{max} 3459, 2966, 2934, 1746, 1681, 1593, 1455, 1374, 1216, 1168, 1082, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (1H, d, H-11, $J_{10,11}$ = 16.5 Hz), 6.29 (1H, d, H-10, $J_{10,11}$ = 16.5 Hz), 5.91 (1H, d, H-13, $J_{13,14}$ = 10.2 Hz), 5.20 (1H, d, H-2′, $J_{1',2'}$ = 8.0 Hz), 4.98 (1H, d, H-4′, $J_{4',5'}$= 10.0 Hz), 4.95 (1H, dt, H-15, $J_{14,15}$ = 10.1 Hz, $J_{15,16b}$ = 4.3 Hz), 4.66 (1H, d, H-1′, $J_{1',2'}$= 8.0 Hz), 4.55 (1H, d, H-1″, $J_{1'',2''}$ = 7.8 Hz), 4.54−4.51 (1H, m, H-20), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 4.1 Hz), 3.78−3.71 (3H, m, H-5, H-3″, H-3), 3.64 (1H, dq, H-5′, $J_{4',5'}$ = 8.7 Hz, $J_{5',6'}$ = 6.1 Hz), 3.61 (3H, s, 3″-OMe), 3.57−3.49 (2H, m, H-23a, H-5″), 3.48 (3H, s, 2″-OMe), 3.31 (3H, s, MeO−C-20), 3.25 (3H, s, MeO−C-20), 3.22−3.15 (1H, m, H-4″), 3.03 (1H, dd, H-2″, $J_{1'',2''}$ = 7.8 Hz, $J_{2'',3''}$ = 2.7 Hz), 2.98−2.92 (1H, m, H-14), 2.69 (1H, br, H-8), 2.47 (1H, dd, H-2b, $J_{2a,2b}$ = 16.0 Hz, $J_{2b,3}$ = 10.5 Hz), 2.30 (1H, d, 4″-OH, $J_{4'',4''-OH}$ = 10.0 Hz), 2.17 (6H, s, 2′-$OCOCH_3$, 4′-$OCOCH_3$), 2.02−1.92 (2H, m, H-19b, H-7b), 1.93 (1H, d, H-2a, $J_{2a,2b}$ = 16.0 Hz), 1.90−1.82 (2H, m, H-19a, H-16b), 1.79 (3H, s, Me-22), 1.66−1.50 (3H, m, H-16a, H-7a, H-4), 1.39 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$= 6.2 Hz), 1.26 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.1 Hz), 1.22 (3H, d, Me-21, $J_{8,21}$ = 6.7 Hz), 0.94 (3H, d, Me-18, $J_{4,18}$ = 6.3 Hz), 0.91 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 203.7, 194.6, 174.0, 169.5, 169.3, 148.0, 142.6, 135.0, 118.6, 103.0, 102.2, 101.4, 83.3, 82.1, 80.1, 78.3, 78.0, 75.4, 72.9, 70.9, 70.0, 69.3, 67.1, 62.0, 59.9, 53.9, 50.8, 45.4, 41.4, 40.0, 33.6, 33.1, 31.8, 31.6, 25.6, 22.9, 20.7, 20.6, 18.4, 18.0, 14.4, 13.3, 9.9, 8.9. Anal. ($C_{43}H_{68}O_{18}$) C, H.

The fraction having R_f = 0.35 (8:2 hexane−acetone) gave, on concentration, **48** (7.5 mg, 4%) as a colorless solid: FAB-MS *m/z* 930 (MH^+, 63%). Anal. ($C_{46}H_{75}NO_{18}$) C, H, N.

The latter compounds **47** and **48** were sequentially hydrolyzed with methanol to give intermediates **49** and **50**, respectively.

49: FAB-MS *m/z* 789 (MH^+, 63%). Anal. ($C_{39}H_{64}O_{16}$) C, H.

50: FAB-MS *m/z* 846 (MH^+, 58%). Anal. ($C_{42}H_{71}NO_{16}$) C, H, N.

Further deprotection of **49** and **50** by aqueous 1 M HCl in acetonitrile finally afforded **51** and **52**, respectively.

51: FAB-MS *m/z* 743 (MH^+, 75%). Anal. ($C_{37}H_{58}O_{15}$) C, H.

52: FAB-MS *m/z* 800 (MH^+, 91%). Anal. ($C_{40}H_{65}NO_{15}$) C, H, N.

Synthesis of α,β-Unsaturated Esters (53−56) via Horner−Wadsworth−Emmons Reaction. To a THF suspension of sodium hydride (60% w/w in mineral oil, 542 mg, 13.55 mmol, 2.0 equiv) was gradually added a solution of trimethylphosphonoacetate (2.7 mL, 13.55 mmol, 2.0 equiv) in THF (10 mL) via cannula at 0 °C. A solution of the corresponding aldehyde (**8**, **9**, **1**, and **11**; 6.78 mmol, 1.0 equiv) in THF (15 mL) was slowly added to the reaction mixture via cannula at 0 °C, and the reaction mixture was stirred at the same temperature for 1 h and at 25 °C for 4 h. After the end of the reaction was established by TLC, the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL), extracted with EtOAc (2 × 100 mL), dried over Na_2SO_4, and concentrated. The crude product obtained after evaporation of solvent was purified by flash chromatography (silica gel, 2% EtOAc in hexane) to furnish the corresponding α,β-unsaturated esters **53**−**56**. By using this procedure, the following compounds were prepared.

53 (78%): FAB-MS *m/z* 832 (MH^+, 69%); IR (KBr) ν_{max} 3444, 2970, 2932, 1716, 1652, 1439, 1382, 1273, 1169, 1083, 1063 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (1H, dt, H-20, $J_{20,20'}$ = 15.7 Hz, $J_{19b,20}$ = 2.3 Hz), 5.83 (1H, d, H-20′, $J_{20,20'}$ = 15.7 Hz), 5.02 (1H, dt, H-15, $J_{14,15}$ = 9.9 Hz, $J_{15,16b}$ = 3.4 Hz), 4.53 (1H, d, H-1″, $J_{1'',2''}$ = 7.9 Hz), 4.37 (1H, d, H-1′, $J_{1',2'}$= 7.2 Hz), 4.09 (1H, t, H-3, $J_{2b,3}$ = 6.7 Hz), 3.86 (1H, dd, H-23b, $J_{23a,23b}$ = 9.0 Hz, $J_{14,23b}$ = 4.2 Hz), 3.84−3.80 (1H, m, H-5), 3.76 (1H, t, $J_{2'',3''}$ = $J_{3'',4''}$ = 3.0 Hz), 3.71 (3H, s, $COOCH_3$), 3.61 (3H, s, 3″-OMe), 3.56−3.51 (2H, m, H-23a, H-5′), 3.18 (1H, dd, H-4″, $J_{3'',4''}$ = 3.0 Hz, $J_{4'',5''}$ = 9.3 Hz), 3.15 (1H, t, H-4′, $J_{3',4'ax}$= $J_{4',5'}$= 10.0 Hz), 3.02 (1H, dd, H-2″, $J_{1'',2''}$ = 7.9 Hz, $J_{2'',3''}$ = 2.8 Hz), 2.80−2.66 (2H, m, H-19b, H-8), 2.55 (6H, s, NMe_2), 2.53−2.46 (2H, m, H-3′, H-2b), 2.45−2.36 (2H, m, H-12, H-10), 2.10−1.94 (3H, m, H-14, H-6, H-2a), 1.92−1.84 (1H, m, H-19a), 1.82−1.76 (1H, m, H-16b), 1.70−1.62 (2H, m, H-11, H-4), 1.60−1.48 (2H, m, H-16a, H-7b), 1.40−1.33 (2H, m, H-13, H-7a), 1.31 (3H, d, H-6′-(Me-C-5′), J5′,6′ = 5.8 Hz), 1.24 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 5.9 Hz), 1.05 (3H, d, Me-21, $J_{8,21}$ = 6.6 Hz), 0.99 (3H, d, Me-18, $J_{4,18}$ = 7.0 Hz), 0.88 (3H, d, Me-22, $J_{12,22}$ = 7.0 Hz), 0.86 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 214.9 (s, C-9), 172.8 (s, C-1), 167.2 (s, $COOCH_3$), 149.4 (d, C-20), 122.2 (d, C-20′), 105.5 (d, C-1′), 100.9 (d, C-1″), 82.1 8d, C-5, C-2″, 2C), 79.8 (d, C-3″), 76.5 (d, C-15), 73.8 (d, C-4″, C-3, 2C), 72.9 (d, C-4′), 70.8 (d, C-5″, C-5′, 2C), 70.4 (d, C-2′), 69.9 (d, C-3′), 61.9 (q, 3″-OMe), 59.6 (q, 2″-OMe), 51.6 (q, $COOCH_3$), 43.2 (d, C-8), 42.0 (q, NMe_2), 40.7 (d, C-14), 39.7 (t, C-10), 39.3 (t, C-2; d, C-4; 2C), 37.8 (d, C-6), 34.9 (t, C-23), 33.0 (t, C-7), 32.7 (t, C-19), 31.8 (t, C-11), 30.7 (d, C-12), 29.8 (t, C-16), 23.6 (t, C-13), 20.5 (q, Me-22), 18.2 (q, Me-C-5′), 18.0 (q, Me-C-5″), 14.3 (q, Me-21), 10.6 (q, Me-17), 8.3 (q, Me-18). Anal. ($C_{42}H_{73}NO_{15}$) C, H, N.

54 (78%): FAB-MS *m/z* 816 (MH^+, 74%); ^1H NMR ($CDCl_3$) δ 6.89 (1H, dt, H-20, $J_{20,20'}$ = 15.8 Hz, $J_{19b,20}$ = 2.3 Hz), 5.82 (1H, d, H-20′, $J_{20,20'}$ = 15.8 Hz), 4.99 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16b}$ = 3.5 Hz), 4.53 (1H, d, H-1″, $J_{1'',2''}$ = 7.9 Hz), 4.37 (1H, d, H-1′, $J_{1',2'}$ = 7.2 Hz), 4.20 (1H, t, H-3, $J_{2b,3}$ = 6.9 Hz), 3.97 (1H, dd, H-23b, $J_{23a,23b}$ = 9.0 Hz, $J_{14,23b}$ = 4.4 Hz), 3.90−3.80 (1H, m, H-5), 3.76 (1H, t, $J_{2'',3''}$ = $J_{3'',4''}$ = 3.0 Hz), 3.71 (3H, s, $COOCH_3$), 3.61 (3H, s, 3″-OMe), 3.59−3.52 (2H, m, H-5″, H-5′), 3.50 (3H, s, 2″-OMe), 3.34−3.24 (2H, m, H-23a, H-2′), 3.17 (1H, dd, H-4″, $J_{4'',5''}$ = 9.3 Hz, $J_{3'',4''}$ = 3.0 Hz), 3.01 (1H, dd, H-2″, $J_{1'',2''}$ = 7.9 Hz, $J_{2'',3''}$ = 2.8 Hz), 2.91−2.62 (3H, m, H-19b, H-8, H-3′), 2.60−2.52 (1H, m, H-2b), 2.48−2.40 (2H, m, H-12, H-10), 2.17 (1H, br, H-6), 2.05−1.82 (2H, m, H-19a, H-14), 1.80−1.58 (3H, m, H-16b, H-4′b, H-4), 1.56−1.47 (1H, m, H-11), 1.45−1.35 (2H, m, H-16a, H-7b), 1.34−1.27 (4H, m, H-13, H-7a, H-4′a), 1.26 (3H, d, H-6′ (Me-C-5′), $J_{5',6'}$ = 5.8 Hz), 1.24 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.0 Hz), 1.04 (3H, d, Me-21, $J_{8,21}$ = 6.8 Hz), 0.99 (3H, d, Me-18, $J_{4,18}$ = 7.0 Hz), 0.88 (3H, d, Me-22, $J_{12,22}$ = 7.1 Hz), 0.87 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 214.9 (s, C-9), 172.4 (s, C-1), 166.9 (s, $COOCH_3$), 149.6 (d, C-20), 121.6 (d, C-20′), 105.9 (d, C-1′), 100.7 (d, C-1″), 85.4 (d, C-5), 81.9 (d, C-2″), 79.4 (d, C-3″), 75.6 (d, C-15), 72.6 (d, C-4″, C-3, 2C), 70.4 (d, C-5″, C-5′, 2C), 69.5 (d, C-2′), 65.4 (d, C-3′), 61.6 (q, 3″-OMe), 59.3 (q, 2″-OMe), 51.2 (q, $COOCH_3$), 41.8 (d, C-8), 40.2 (q, NMe_2), 39.9 (d, C-14), 39.6 (t, C-2), 39.4 (t, C-10), 39.3 (d, C-4), 37.5 (d, C-6), 35.4 (t, C-23), 32.9 (t, C-7), 32.5 (t, C-19), 30.2 (t, C-11), 29.5 (d, C-12), 28.9 (t, C-16), 22.1 (t, C-13), 21.1 (q, Me-C-5′), 20.6 (q, Me-22), 17.6 (q, Me-C-5″), 16.2 (q, Me-21), 10.6 (q, Me-17), 7.6 (q, Me-18). Anal. ($C_{42}H_{73}NO_{14}$) C, H, N.

55 (92%): FAB-MS *m/z* 972 (MH^+, 71%); ^1H NMR ($CDCl_3$) δ 7.30 (1H, d, H-11, $J_{10,11}$ = 16.6 Hz), 6.93 (1H, br, H-20), 6.25 (1H, d, H-10, $J_{10,11}$ = 16.6 Hz), 5.90 (1H, d, H-13, $J_{13,14}$ = 10.1 Hz), 5.86 (1H, d, H-20′, $J_{20,20'}$ = 15.7 Hz), 5.12 (1H, br, H-1″), 4.99 (1H, dt, H-15, $J_{14,15}$ = 10.0 Hz, $J_{15,16a}$ = 11.1 Hz), 4.56 (1H, d, H-1″, $J_{1'',2''}$ = 7.7 Hz), 4.39 (1H, br, H-1′), 4.00 (1H, dd, H-23b, $J_{23a,23b}$ = 9.5 Hz, $J_{14,23b}$ = 3.7 Hz), 3.82−3.72 (3H, m, H-5, H-3″, H-3), 3.71 (3H, s, $COOCH_3$), 3.62 (3H, s, 3″-OMe), 3.60−3.51 (3H, m, H-23a, H-5″, H-2′), 3.50 (3H, s, 2″-OMe), 3.35 (1H, br, H-5′), 3.23−3.12 (2H, m, H-4″, H-4′), 3.03 (1H, dd, H-2″, $J_{1'',2''}$ = 7.7 Hz, $J_{2'',3''}$ = 2.6 Hz), 2.99−2.89 (2H, m, H-14, H-4″), 2.75−2.60 (2H, m, H-19b,H-8), 2.57−2.49 (1H, m, H-19a; 6H, s, NMe_2), 2.46 (1H, dd, H-2b, $J_{2a,2b}$ = 16.7 Hz, $J_{2b,3}$ = 10.8 Hz), 2.33 (1H, d, H-3′, $J_{3',4'}$ = 11.1 Hz), 2.05 (1H, br, H-6), 2.03 (1H, d, H-2″b, $J_{2''a,2''b}$ = 14.2 Hz), 1.95 (1H, d, H-2a, $J_{2a,2b}$ = 16.7 Hz), 1.91−1.80 (1H, m, H-16b), 1.79 (3H, s, Me-22), 1.75 (1H, dd, H-2″a, $J_{2''a,2''b}$ = 14.2 Hz, $J_{1'',2''a}$ = 4.0 Hz), 1.70−1.54 (2H, m, H-16a, H-4), 1.53−1.45 (1H, m, H-7b), 1.40−1.28 (9H, m, Me-C-5″, Me-C-5′, Me-C-3″), 1.26 (3H, d, H-6″ (Me-C-5″), $J_{5'',6''}$ = 6.2 Hz), 1.23 (1H, br, H-7a), 1.19 (3H, d, Me-21, $J_{8,21}$ = 6.4 Hz), 1.00 (3H, d, Me-18, $J_{4,18}$ = 6.2 Hz), 0.94 (3H, t, Me-17, $J_{16a,17}$ = $J_{16b,17}$ = 7.3 Hz). Anal. ($C_{49}H_{81}NO_{18}$) C, H, N.

56 (74%): FAB-MS *m*/*z* 976 (MH^+, 86%). Anal. ($C_{49}H_{85}NO_{18}$) C, H, N.

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Supporting Information Available: Pharmacokinetics of **28c** and desmycosin after po administration. This material is available free of charge via the Internet at http://pubs.acs.org.

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