New Derivatives of Ascomycin with Modifications in the Amino Acid Region – Synthesis and Biological Activities, and X-Ray Crystal Structure of 5,6-Dehydroascomycin

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Dedicated to Professor Dr. *Andrea Vasella* on the occasion of his 65th birthday

The immunomodulatory macrolide ascomycin (**1a**) inhibits T-cell activation *via* binding to macrophilin-12 and inhibition of the phosphatase calcineurin. Its structural analogs pimecrolimus and tacrolimus have recently become available as the first novel topical treatments of atopic dermatitis since the introduction of topical corticosteroids in the 1950s. This stimulated the search for novel derivatives with an improved biological profile. Though several derivatives of **1a** are known, only a few derivatives with modifications on the amino acid moiety are available because of the chemical inaccessibility of this region. To this end, we present here a new approach using a photochemical reaction as the key step. Thus, irradiation of ascomycin (**1a**) led to mixtures of the methoxy products **2a** and **8**, the cleavage product **4a**, the but-1-enyl derivative **7**, and the oxazolidinone **9** depending on the solvent. The selectivity of the reaction was improved to furnish **2a** or **9** in preparatively useful yields. The mechanism and scope of the reaction were investigated. Starting from **2a**, several analogs featuring novel modifications on the amino acid moiety, which are not easily accessible through routine methods, were synthesized in a few steps. Further, using the photoreaction key intermediates with potential for broader modifications on the amino acid moiety were synthesized, and their utility was exemplified by the synthesis of vinylpipecolic acid and vinylproline analogs. An interesting photochemical cleavage of the amide bond in the derivatives of ascomycin (**1a**) is presented. The structural and conformational features of the new analogs together with the X-ray crystal structure of 5,6-dehydroascomycin (**6a**) are presented, and their biological activities are discussed. Of all the derivatives, **6a** showed the best activities in *in vitro* and *in vivo* models of allergic contact dermatitis whilst showing a lower risk of immunosuppression.

1. Introduction. – Inflammatory skin diseases such as atopic dermatitis (AD) and psoriasis are chronic and genetically predisposed conditions that impair patients' quality of life [1][2]. AD is the most common skin disease of young children, with a prevalence of up to 20%, and psoriasis is mostly a disease of adulthood, affecting 2–3% of the Western population. The macrolactam ascomycin (**1a**) is a fermentation product

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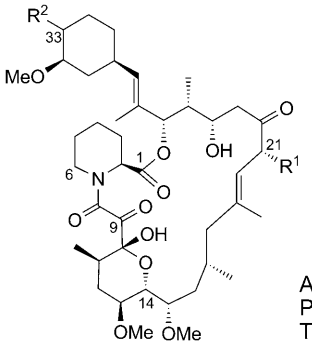
from *Streptomyces hygroscopicus* var. *ascomyceticus*, originally isolated due to its antifungal activities [3]. Recently, pimecrolimus (*Elidel*®, SDZ ASM 981; **1b**), which is a Cl analog of **1a**, and tacrolimus (*Protopic*®, FK 506; **1c**), both possessing a common core structure, have become available as the first novel topical treatments of AD since the introduction of the corticosteroids more than 40 years ago [4]. The clinical results with **1b** stimulated the search for novel derivatives and their biological evaluation [4][5].



Ascomycin (**1a**) R^1 = Et, R^2 = (*R*)-OH
Pimecrolimus (**1b**) R^1 = Et, R^2 = (*S*)-Cl
Tacrolimus (**1c**) R^1 = allyl, R^2 = (*R*)-OH

Although the pathophysiologies of AD and psoriasis are different, and are still a matter of ongoing intensive research, there is general agreement that T cells play a key role in both diseases. The initial step in the immunomodulatory activity of the macrolides **1a**–**1c** is binding of the macrolide to macrophilin-12 (FKBP 12), which is then followed by binding to calcineurin A and B, thus inhibiting the activity of the phosphatase [6], an enzyme required for the dephosphorylation of the cytosolic form of the nuclear factor of activated T cells (NF-AT). This leads to the inhibition of the release of cytokines such as IFN-γ, and IL-2, -4, -5, -10, and TNF-α, thus targeting T-cell activation and proliferation. The region C(1)-C(14) comprising the pipecolic acid (= piperidine-2-carboxylic acid) and the three carbonyl moieties is involved in binding to macrophilin and hence is called the *binding domain*. The region C(14)-C(22) is involved in the subsequent steps of the mechanism of action and hence termed the *effector domain*. The analogs studied so far are limited with respect to the structural variations in the binding and effector domains because of the inaccessibility, in particular, of the pipecolic acid and C(14)-C(22) regions, for derivatization through routine organic methods. Some of our efforts leading to new derivatives of **1a**–**1c** with modifications primarily in the binding and also in effector domains have been communicated earlier [7]. Here, we give the full details including further work and the biological activities.

2. Results and Discussion. – 2.1. *Photochemistry of Ascomycin* (**1a**) *and Its Analogs, and Synthesis of New Analogs.* α-Keto amides upon irradiation lead to several types of products arising primarily through intramolecular abstraction of γ-H-atom by the C=O group. Allylic C=O compounds undergo a variety of reactions such as oxadi-π-methane rearrangement, 1,3-sigmatropic shifts, and *Norrish* type-I cleavage [8]. The macrolide ascomycin (**1a**) features a novel tricarbonyl system, connected through an

amide bond at one end and masked as a hemiketal at the other end, in the binding domain, and an allylic C=O moiety in the effector domain. Furthermore, because of the cyclic structure, the molecule possesses a relatively rigid conformation. These features prompted us to study the photochemistry of **1a** with a view to discovering new pathways to novel synthetic derivatives, with modifications in the amino acid and effector domains, which are less accessible for routine derivatization.

Irradiation of **1a** in MeOH for 2 h at room temperature using *Pyrex*-filtered UV light (>280 nm) led to 6-β-methoxy-9-dihydroascomycin (**2a**; 22%), the lactone **4a** (10%), and the but-1-enyl derivatives **7** (40%) and **8** (4%); in addition, unchanged **1a** (19%) was recovered (*Scheme 1* and *Table 1*). The reaction is stereoselective giving only the 6-β-MeO isomer **2a** and only one of the two possible C(19)-diastereoisomers of each of **7** and **8** with the but-1-enyl chain exclusively with (*E*)-configuration. On the other hand, irradiation of **1a** in MeCN/H_2O 4:1 for 2 h at room temperature led to the lactone **4a** (10%), the but-1-enyl compound **7** (30%), and the oxazolidinone **9** (11%); in addition, unchanged **1a** (26%) was recovered.

The formation of **2a** could be rationalized through the intermediacy of the zwitterion $\mathbf{Z_1}$ formed by electron transfer from the amide N-atom to the C(9)=O group, followed by H-transfer [8]. The alternative conformer $\mathbf{Z_2}$ is expected to be of higher energy than $\mathbf{Z_1}$ because of the 1,2-steric repulsions between the C(1)(O)–O and the *N*-acyl groups. Attack of MeOH from the β-face of $\mathbf{Z_1}$ (*via* a chair-like transition state, resulting in **2a**) is favored over that from the α-face (boat-like transition state). The transformation of **1a** to **7** could be rationalized as a photochemically allowed [1,3]-sigmatropic shift. Molecular models and X-ray crystal structure [6c–f] of **1a** indicate an ideal alignment of the bonds involved for a $\sigma_S^2 + \pi_S^2$ mode of interaction, which is expected to result in C(19)-β-Me and (*E*)-but-1-enyl configurations. The formation of only one isomer **7** with (*E*)-but-1-enyl chain led us to tentatively assign the configuration of the Me group at C(19) as β. No epimerization at C(21) in the recovered starting material could be detected, thus indicating a concerted migration pathway for the formation of **7**. The acyclic derivative **4a** could be arising through decarbonylative fragmentation. The formation of the oxazolidinone **9** in the non-nucleophilic solvent MeCN involves intramolecular α-attack of the O-atom at C(9) (*i.e.*, $\mathbf{Z_1}$) through the higher-energy boat-like transition state. That no oxazolidinone **9** is formed upon irradiation of **1a** in MeOH would imply that β-attack by MeOH on $\mathbf{Z_1}$ (through chair-like transition state) is more favored than intramolecular α-attack (through boat-like transition state). Finally, the derivative **8**, featuring modifications both in the binding and effector regions, could be formed *via* a consecutive photoreaction of **2a** or **7**.

The photoproduct **2a** features a versatile MeO group in the amino acid moiety and was of interest for further synthetic modifications. Hence, we focused on improving the selectivity of the photoreaction. Interestingly, selective excitation of the tricarbonyl chromophore of **1a** in MeOH using filtered UV light (>360 nm, aq. NaBr-$Pb(NO_3)_2$ filter) at 5° for 9 h resulted in total consumption of the starting material leading to **2a** (75%) and **4a** (15%) as the only products isolated (*Table 1*). Analysis of the crude reaction mixture by HPLC also gave similar yields, and no other products could be detected. The reaction could be scaled up conveniently (40 g), and the required **2a** could be freed of **4a** by a short chromatographic filtration, followed by crystallization.

Scheme 1. *Irradiation of the Ascomycin Analogs* **1a**–**1d**

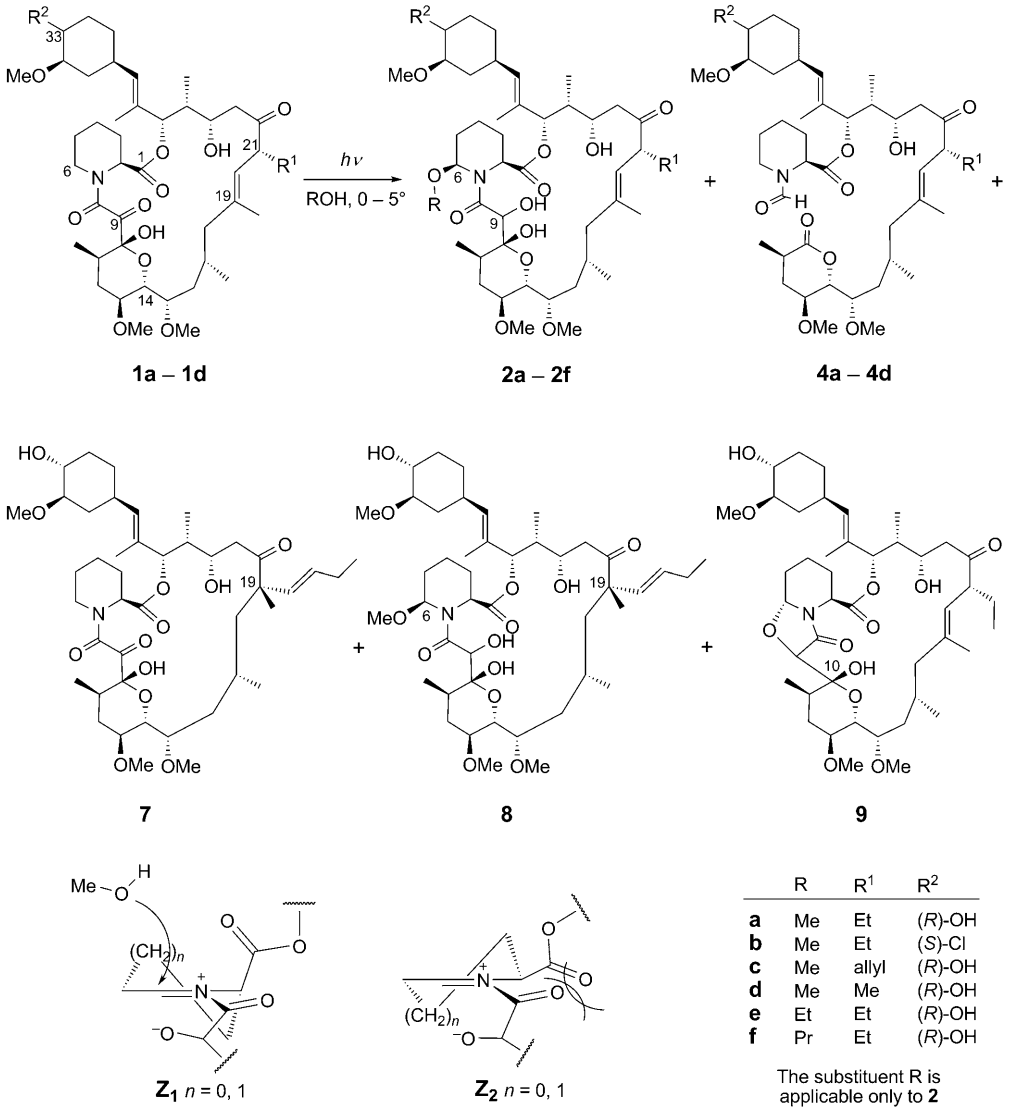


Table 1. *Yields of the Isolated Products* [%] *upon Irradiation of* **1a** *under Different Conditions*

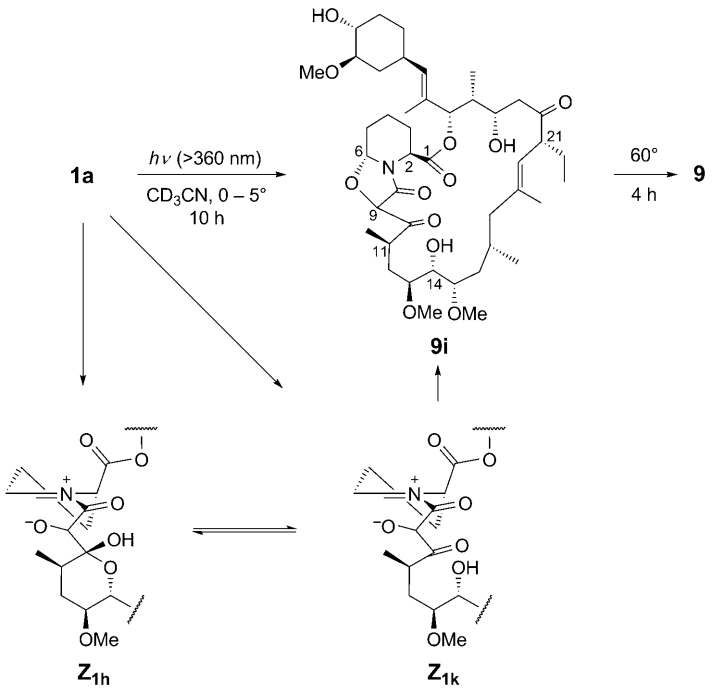
Reaction conditions	**2a**	**4a**	**7**	**8**	**9**	**1a**[a])
> 280 nm, MeOH, r.t., 2 h	22	10	40	4	–	19
> 280 nm, MeCN/H_2O 4 : 1, r.t., 2 h	–	10	30	–	11	26
> 360 nm, MeOH, 5°, 9 h	75	15	–	–	–	–

[a]) Unchanged recovered starting material.

It should be mentioned here that, in a semiquantitative study, O_2 did not show any effect on the reaction, thus indicating that the triplet state is not involved.

The reaction of **1a** in CD_3CN using light of $\lambda > 360$ nm was investigated by NMR methods. Thus, irradiation of **1a** in CD_3CN at 0° for 5 h led to a 3:2 mixture consisting of **9i**, which is the C(10)=O isomer of **9**, and **1a**, in addition to small amounts of **4a** (*Scheme 2*). Irradiation for 10 h led to a mixture consisting mainly of **9i**, and only minor amounts of **1a** and **4a**. Heating this sample at 60° for 4 h led to the disappearance of **9i** and formation of the oxazolidinone **9**. This confirms that the initial photoproduct is **9i** which is converted to **9** slowly upon warming. In a preparative experiment, 2 g of **1a** in MeCN (1 l) was irradiated for 16 h at 0°, and an aliquot was purified by semipreparative HPLC (cyclohexane/i-PrOH 85:15, all operations carried out at 0°) to give an enriched sample of **9i** for spectral analysis (^1H, ^{13}C, and C,H correlation). Characteristic of **9i** are the ^{13}C-NMR signals at δ 212.5 (C(22)), 210.6 (C(10)), 168.4 (C(1)), 165.4 (C(8)), 85.8 (C(6) and cross-peak for H–C(6) at δ 4.97 (*ddd*, $J = 9.7, 3.7, 1.9$ Hz)), 81.7 (C(9) and cross-peak for H–C(9) at δ 5.17 (*d*, $J = 1.9$ Hz)), 51.9 (C(2) and cross-peak for H–C(2) at δ 4.67 (*d*, $J = 6.0$ Hz)), 38.6 (C(11)).

Scheme 2. *Irradiation of* **1a** *in* CD_3CN



The primary photoproduct **9i** could be formed through $\mathbf{Z_{1k}}$, which is formed either directly through excitation of the trioxo form of **1a**, or indirectly through excitation of **1a** in the hemiketal form leading to $\mathbf{Z_{1h}}$, followed by its equilibration to $\mathbf{Z_{1k}}$. The macrolide **1a** does exist as a mixture of the interconvertible C(10)-hemiketal and trioxo forms [5b]. The trioxo chromophore imparts bright yellow color to the compounds and

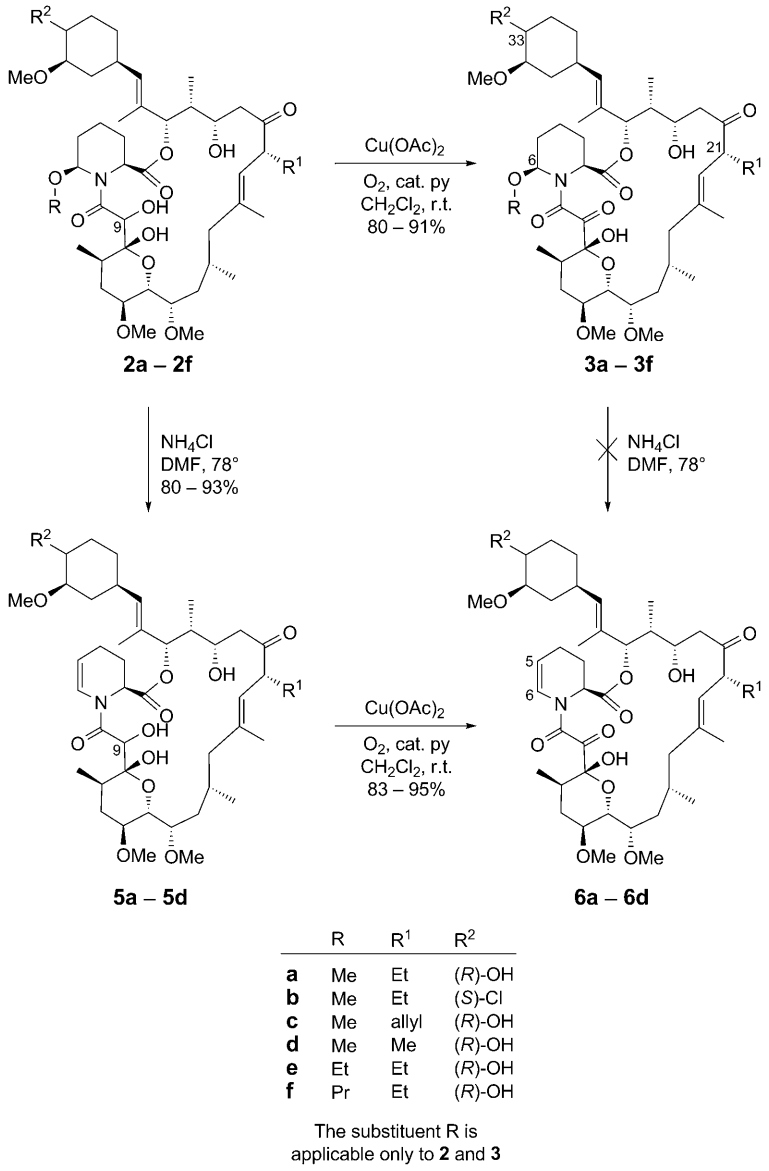
is expected to absorb more strongly in the $\lambda > 360$-nm region, and, therefore, it could be the chromophore being excited leading to the $\mathbf{Z_{1k}}$. However, our photochemical amide cleavage reactions with a locked hemiketal structure at C(10) demonstrated that the dicarbonyl (hemiketal) forms also show photoreactivity under the irradiation conditions [7d]. Therefore, no conclusion could be drawn as to whether the dioxo or trioxo forms alone, or both, are actually involved in these photoreactions. However, the more flexible $\mathbf{Z_{1k}}$ form appears to be necessary for attaining the required higher energy boat-like transition state involved in the cyclization leading to **9i**. Similar intermediates could be involved in the irradiation of **1a** in MeOH; this was not investigated in detail.

Larger alkoxy groups could also be introduced at C(6) using the photochemical method. Thus, irradiation of **1a** in EtOH and PrOH led to the (6*S*)-ethoxy derivative **2e** (59%) and the (6*S*)-propoxy derivative **2f** (10%), respectively. Irradiations in higher alcohols such as BuOH and i-BuOH led to complex mixtures which were not pursued further. The lower yields of the alkoxy products with higher alcohols is probably due to their lower nucleophilicity which allows unspecific side reactions to predominate.

The intact tricarbonyl moiety is crucial for the biological activity of **1a**–**1c** [5a]. Thus, **2a** was oxidized [9] selectively employing 5 mol-% $Cu(OAc)_2$ or cupric 2-ethylhexanoate and 5 mol-% pyridine/O_2 /4-Å molecular sieves/CH_2Cl_2 /16 h at room temperature to give 6-β-methoxyascomycin (**3a**) in 96% yield (*Scheme 3*). A control run employing 5 mol-% cupric 2-ethylhexanoate and omitting pyridine resulted in *ca.* 30% yield after 20 d, thus indicating the role of pyridine in the high catalytic turnover, possibly through its ligation or depolymerization of the catalyst. To our knowledge, this represents a very mild and efficient variation compared to the reported methods for the oxidation of α-hydroxy ketones using copper salts [9]. The analogs **3b**–**3f**, comprising modifications at C(21), C(33), and C(6), were prepared analogously through irradiation of **1a**–**1d** in appropriate alcohol to give the photoproducts **2b**–**2f** (in addition to **4b**–**4d**), followed by their oxidation.

The pipecolic acid ring in ascomycin **1a** possesses a $^2C_5$ conformation in solution, solid state, and in its binding complex with macrophilin [6]. This feature, combined with the tricarbonyl moiety, is expected to play a pivotal role in deciding the conformation of the cyclic structure which is important for its biological action. We, therefore, envisaged transforming the photoproducts **2a**–**2d** to the corresponding enamides **5a**–**5d**, incorporating dehydropipecolic acid unit as a close bioisoster of pipecolic acid, with potential for a good macrophilin-12 affinity. Thus, heating the derivatives **2a**–**2d** with NH_4Cl in DMF at 78° under reduced pressure in a rotary evaporator, to ensure removal of the MeOH formed in the reaction, afforded the enamides **5a**–**5d** (80–93%) [10]. Again, oxidation of the OH group at C(9) of **5a**–**5d**, as described above using $Cu(OAc)_2$, afforded the analogs **6a**–**6d** (83–95%) featuring the 5,6-dehydropipecolic acid unit. It is noteworthy that, in contrast to the facile elimination of MeOH from **2a**–**2d** featuring C(9)–OH, **3a**, featuring C(9)=O, was recovered (95%) unchanged under identical reaction conditions. It appears that the highly electronegative C(9)=O in **3a** disfavors the formation of a cationic site adjacent to the amide N-atom, hence disfavoring the acid-catalyzed elimination reaction. It is also likely that stereoelectronic effects resulting from a change in the conformation (**2a** *vs.* **3a**), or the conformational flexibility, also play a role in this reaction. The three-step strategy for the synthesis of 5,6-dehydroascomycin (**6a**) features high yields, inexpensive reagents, simple oper-

Scheme 3. *Transformation of the Photoproducts* **2a**–**2f** *to Derivatives with Modifications on the Pipecolic Acid Moiety of* **1a**–**1d**



	R	R^1	R^2
a	Me	Et	(*R*)-OH
b	Me	Et	(*S*)-Cl
c	Me	allyl	(*R*)-OH
d	Me	Me	(*R*)-OH
e	Et	Et	(*R*)-OH
f	Pr	Et	(*R*)-OH

The substituent R is applicable only to **2** and **3**

ations, and is devoid of protecting groups on a highly functionalized and sensitive molecule. It could successfully be employed for preparing **6a** on a 100-g scale in the laboratory and multi-kg scale in a pilot plant.

We further studied the applicability of the above chemistry to the proline analog **10** which is available as a side-product in the fermentation of ascomycin (*Scheme 4*).

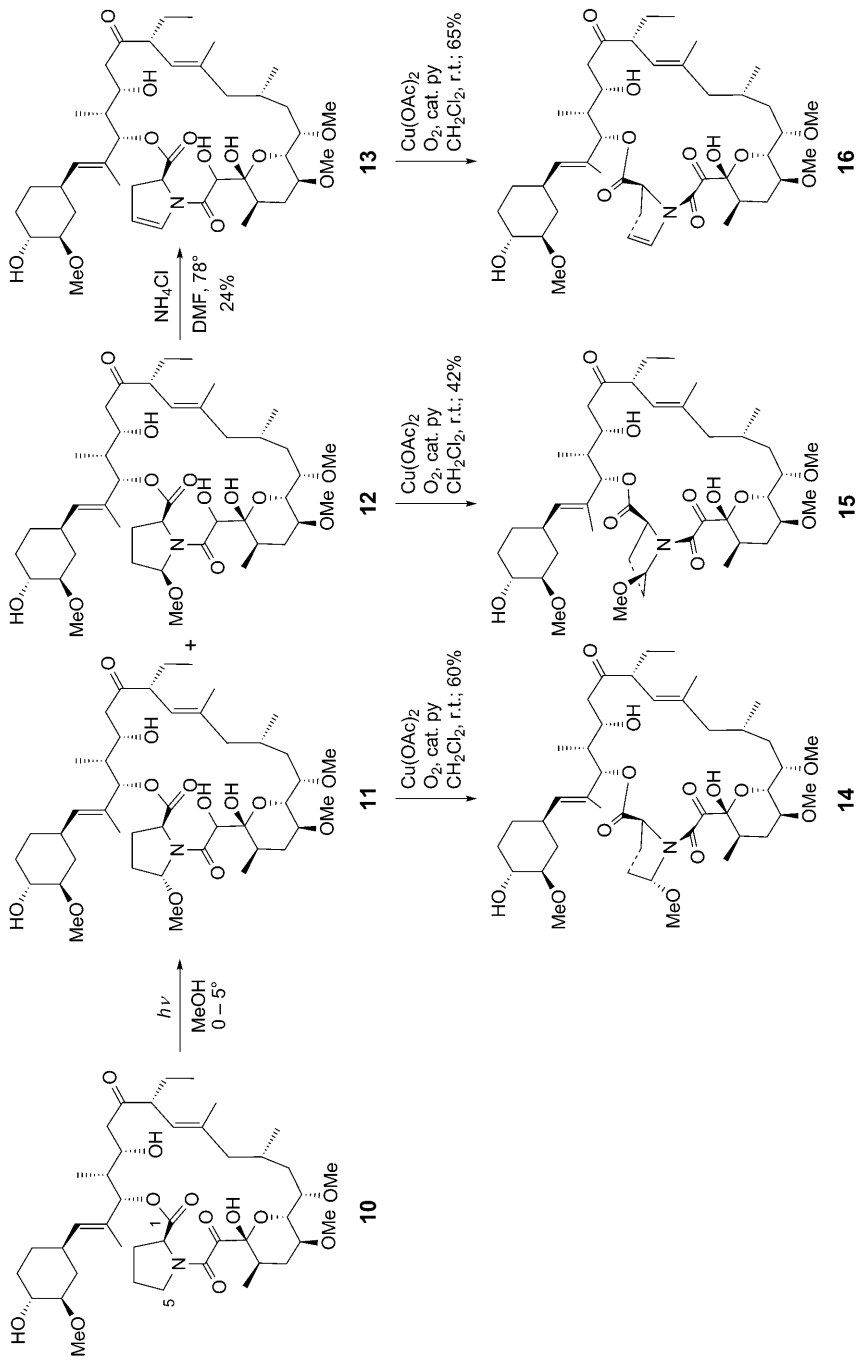
Irradiation of **10** in MeOH gave rise to both the (5*R*)- and (5*S*)-MeO derivatives **11** (8%) and **12** (24%), respectively. The lower stereoselectivity observed in the photoreaction of **10**, as opposed to the formation of a single isomer with the pipecolic acid analogs **1a**–**1d**, is probably due to the higher flexibility of the five-membered enaminium intermediate $\mathbf{Z_1}$ ($n=0$; *Scheme 1*). It may be noted that β-attack by MeOH leading to **12** is still the more favored pathway. The photoproducts **11** and **12** could be transformed to the methoxy-proline and dehydroproline analogs **14**, **15**, and **16** as described previously. The yields in this series were not optimized because of the limited availability of **10**.

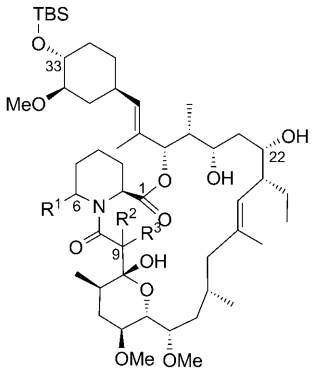
Irradiation of 22-dihydro-33-TBS-ascomycin (**17**) in MeOH at 0–5° for 10 h using *Pyrex*-filtered light resulted in the 6-MeO derivatives **17a** (37%) and **17b** (9%) as the only products; the lower yields are due to losses during repeated chromatographic purification. Clearly, the transformation of the trigonal C(22) to a tetrahedral center made the macrolactam ring more flexible, thus reducing the stereoselectivity of the attack by MeOH. Nevertheless, β-attack is still predominant over α-attack. Furthermore, due to the lack of allylic carbonyl chromophore, the photoreaction is selective even with *Pyrex*-filtered light. Selective oxidation of **17a** and **17b** as before, followed by desilylation with aqueous HCl/MeCN, afforded the analogs **18a** and **18b**, respectively, in good yields. Selective hydrogenation ($Pd/C/H_2$/AcOEt) of the but-1-enyl double bond in **7** gave **19** (75%). Cu^{II} xidation of the OH at C(9) of **8** afforded the analog **20** (35%).

2.2. *Transformation of the Photoproduct* **2a** *to New Analogs.* The photoproduct **2a** features a versatile hetero-acetal functionality which, as expected, could be hydrolyzed under mild acidic conditions affording the aldehyde **21** in a 89% yield (*Scheme 5*). In **21**, which is easily available in multigram quantities in two simple steps staring from **1a**, the original reactive C(9)=O group is now formally protected as C(9)–OH, and C(22)=O being a keto group, the high reactivity of the aldehyde group could be used for selective modifications on the amino acid side chain without employing protecting groups. To this end, **21** was oxidized selectively with aqueous $NaClO_2$ to the acid **22** in a good yield [11]. Selective oxidation of the OH group at C(9) of **22** with $Cu(OAc)_2$ led to the homoglutamic acid analog **24a** in a 64% yield. Attempted esterification of **24a** with CH_2N_2 resulted in a complex mixture because of the competing reaction of the reactive C(9)=O with CH_2N_2 [12]. This problem, however, could be overcome by reversing the reaction sequence. Thus, esterification of **22** with CH_2N_2 gave **23** (85%), which, after oxidation with $Cu(OAc)_2$, led to the homoglutamic acid ester analog **24b** (72%). *Wittig* olefination of the aldehyde **21** with 1.4 equiv. Ph_3PCHCO_2Bn gave the unsaturated benzyl ester **27a** (49%), which, after $Cu(OAc)_2$ oxidation of the OH group at C(9), afforded **28a** in a 75% yield. Catalytic hydrogenation of **28a** resulted in saturation of the enone C=C bond and cleavage of the Bn group affording the acid analog **29a**. The methyl ester analog **29b** was prepared similarly *via* **27b** and **28b**. The analogs **24a, 24b, 28b**, and **29a** exist as a mixture of their six-membered and seven-membered ring hemiketals (see *Structural and Conformational Aspects*).

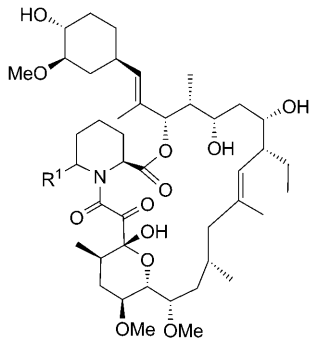
The aldehyde **21** is also a good intermediate for the synthesis of bridged derivatives with rigid conformations in the binding region. Thus, oxidation of **21** with $Cu(OAc)_2$, followed by careful neutral workup, afforded the analog **25** (90%; crude product). The keto-aldehyde **25** exists as the free aldehyde as evidenced by ^{1}H-NMR ($CDCl_3$), and not as aminal. However, **25** upon standing in $CDCl_3$ for a few days, or on FC (SiO_2), is transformed to an isomer mixture **26a**/**26b**. Alternatively, **3a**, upon mild acidic

Scheme 4. *Synthesis of Derivatives with Modifications on the Proline Moiety of* **10**

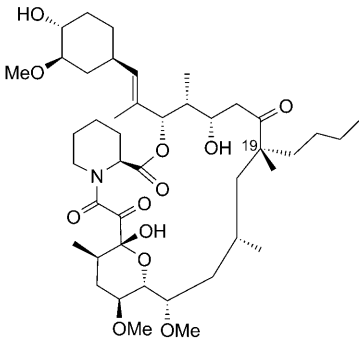




17 R^1 = H, R^2,R^3: =O
17a R^1 = β-MeO, R^2 = H, R^3 = OH
17b R^1 = α-MeO, R^2 = H, R^3 = OH



18a R^1 = β-MeO
18b R^1 = α-MeO



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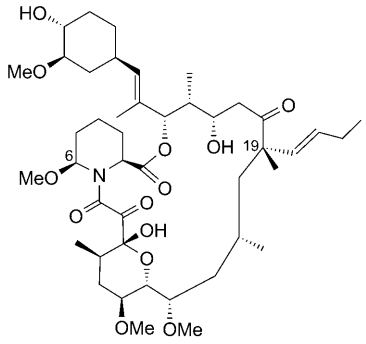

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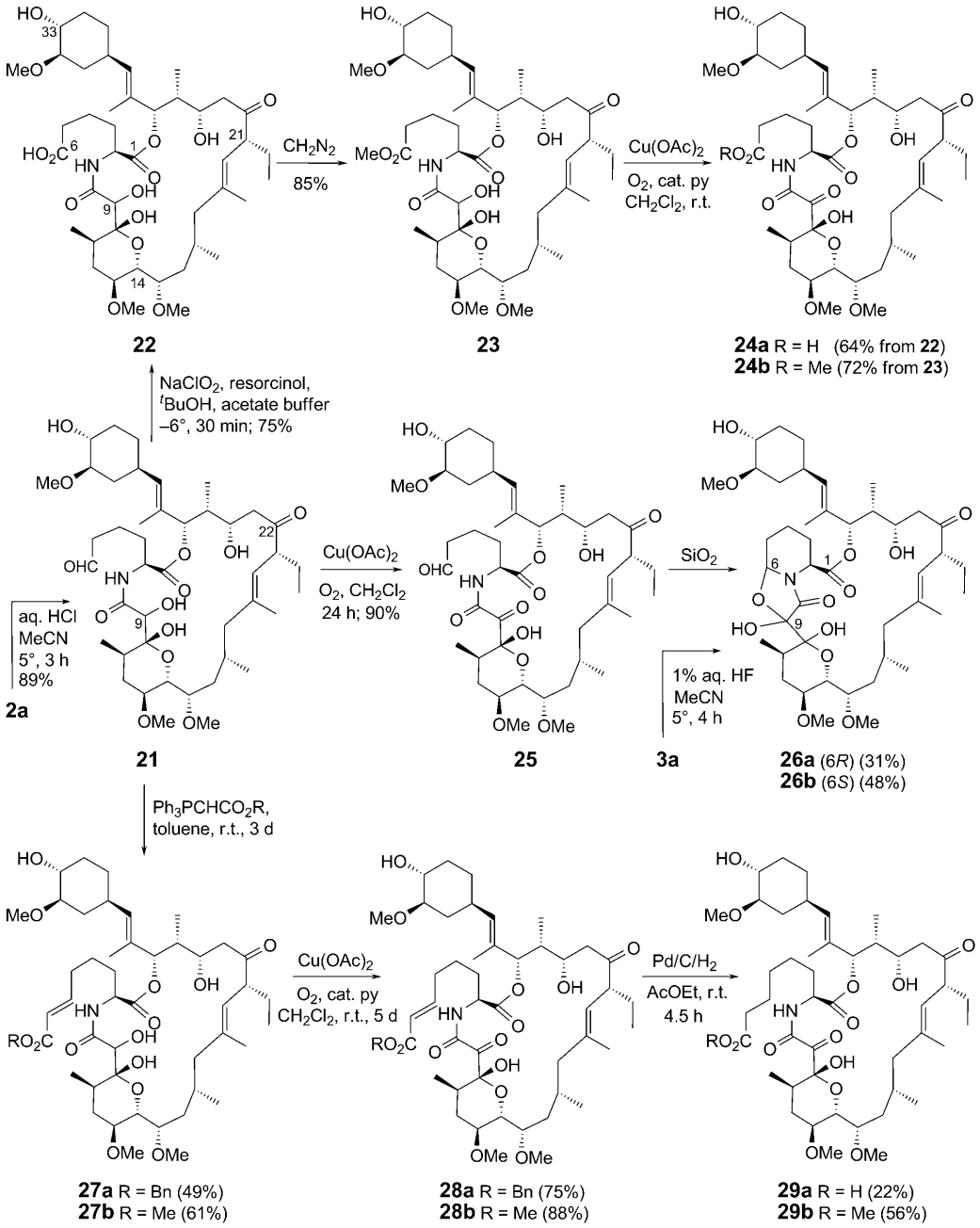
hydrolysis, followed by FC, afforded **26a** (16%), **26b** (25%), and unchanged **3a** (48%). The ^{1}H-NMR spectrum of **26a** (2:1 mixture of C(9)-isomers) showed signals at δ 4.90 (*d*, *J*(2,3a) = 6.3 Hz, H–C(2)) for the major component and at δ 4.58 (*d*, *J*(2,3a) = 7.5, H–C(2)) for the minor one; at δ 5.09 (*dd*, *J*(5,6) = 3.5, 10, H–C(6)) for the major component, and δ 5.37 (*dd*, *J*(5,6) = 4, 10, H–C(6)) for the minor one. These data indicate the (6*R*)-configuration with chair conformation for the amino acid ring with C(1) in the axial and C(6)–O in the equatorial position for both components of **26a**. On the other hand, the ^{1}H-NMR spectrum of **26b** (one major isomer) showed signals at δ 3.82 (*dd*, *J*(2,3) = 4.5, 10, H–C(2)) and δ 4.85 (*dd*, *J*(5,6) = 3.5, 10, H–C(6)), indicating (6*S*)-configuration with the flipped chair with C(1) and C(6)–O placed equatorially.

2.3. *Transformation of the Enamide* **6a** *to New Rigid Analogs.* We further explored the transformation of the enamide **6a** to further rigid analogs through cyclopropanation (*Scheme 6*). However, the enamide C=C bond was much less reactive than C(9)=O. Thus, **6a**, upon treatment with CH_2N_2, gave a mixture of the spiro-oxiranes **33** (C(9)-

Scheme 5. *Transformation of the Photoproduct* **2a** *to New Noncyclic Amino Acid Analogs*



isomers) in excellent yield, from which the individual isomers could be isolated in 19 and 41% yields [12]. On the other hand, treatment of **6a** with a large excess of CH_2N_2 in the presence of [Cu(acac)$_2$], followed by partial purification by HPLC, led to a 1:4:3 mixture **30a**/**31a**/unreacted **6a** in a 48% yield. After repeated FC, pure samples of **30a** and **31a** could be obtained and characterized. On the other hand, selective reduction of the C(9)=O of **6a** with H_2S led to the deoxo derivative **32** in good yield [13]. Cyclopropanation of **32** with CH_2N_2 as described above afforded the 9-deoxo-derivatives **30b** (9%) and **31b** (15%) in low yields.

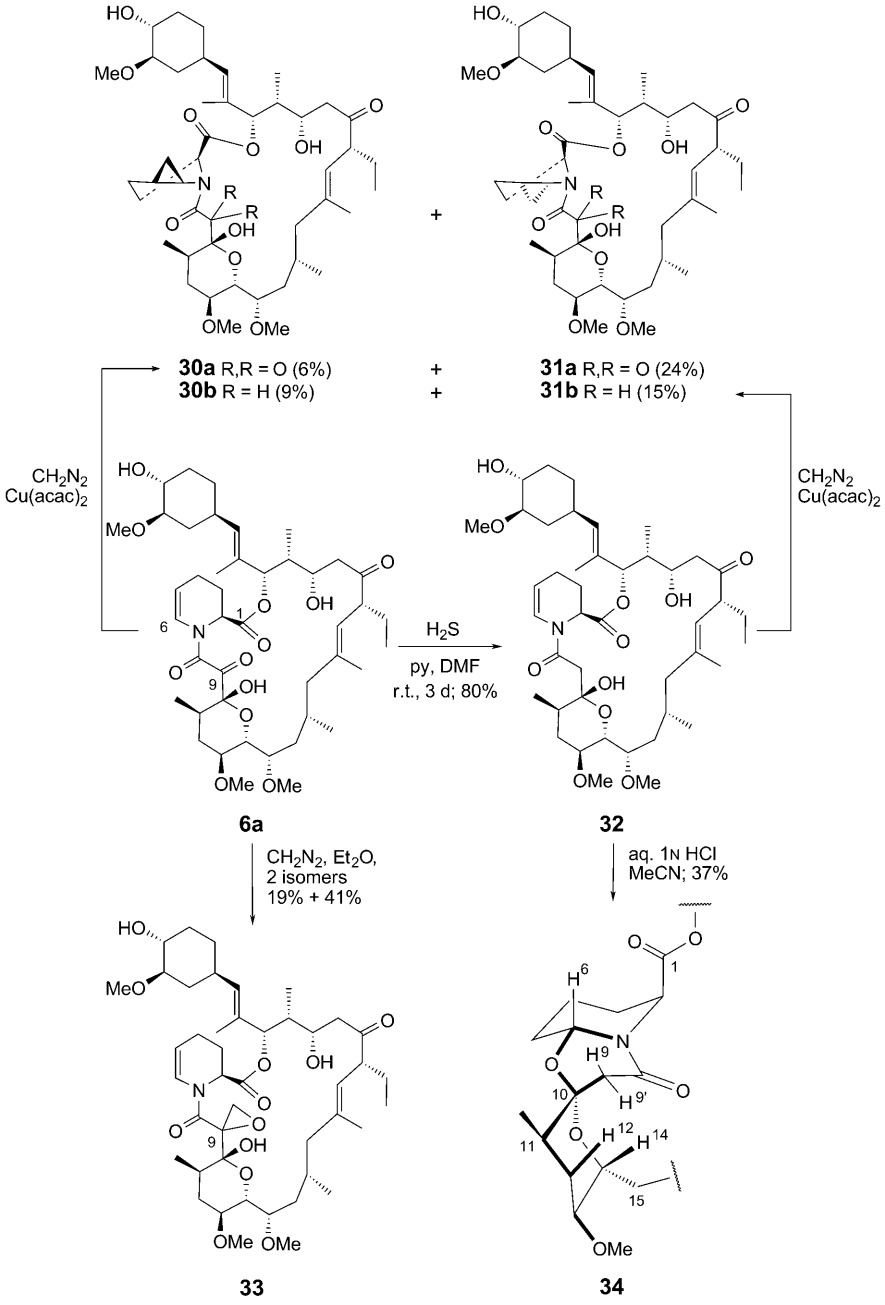
The derivatives **30a** and **30b** showed ^{1}H-NMR signals at δ 4.36 (*dd*, $J = 6.1, 2.7$) and 4.34 (*dd*, $J = 6.5, 1.6$), respectively, which were assigned to H–C(2). In the derivatives **31a** and **31b**, H–C(2) appeared at δ 4.41 (*dd*, $J = 8.6, 6.2$) and δ 4.47 (*t*, $J = 6.5$), respectively. We believe that **30a** and **30b** contain the cyclopropane ring on the β-face of the pipecolic acid ring, and the resulting 1,3-diaxial interactions distort the half-chair, thus leading to a small and a large coupling constant between H–C(2) and H–C(3), respectively, as observed above. In support of this, for **30b** a weak NOESY cross-peak was observed between H–C(2) and H–C(6). On the other hand, **31a** and **31b** possess the cyclopropane ring on the α-face of the pipecolic acid ring, hence, the ring can adopt an undistorted half-chair conformation leading to two coupling constants of the same order between H–C(2) and H–C(3). Because of the overlapping signals, it was not possible to further confirm the configurations of C(5) and C(6).

The rigid derivative **34** featuring C(6), C(10) bridging was obtained through hydrolysis of the enamide **32** with aqueous HCl in a 37% yield (*Scheme 6*). The ^{1}H-NMR spectrum of **34** indicated a single isomer and showed signals at δ 4.65 (*dd*, $J = 7.1, 1.8$, H–C(2)), 5.19 (*dd*, $J = 9.0, 5.3$, H–C(6)), 2.95 (*d*, $J = 15.9$, H′–C(9)), 2.50 (*d*, $J = 16.2$, H–C(9)). In addition, NOEs were observed from H–C(6) to H–C(9); H–C(9) to Me–C(11); H′–C(9) to H–C(12), and, H′–C(9) to H–C(14). These data suggest a structure featuring a chair conformation for the amino acid ring with C(1) in the axial position and C(6)–O in the equatorial position, a chair conformation for the pyran ring with the substituents on C(11), C(13), and C(14) placed equatorially, a boat conformation for the lactam ring, and an inversion of configuration at C(10) as depicted by formula **34**.

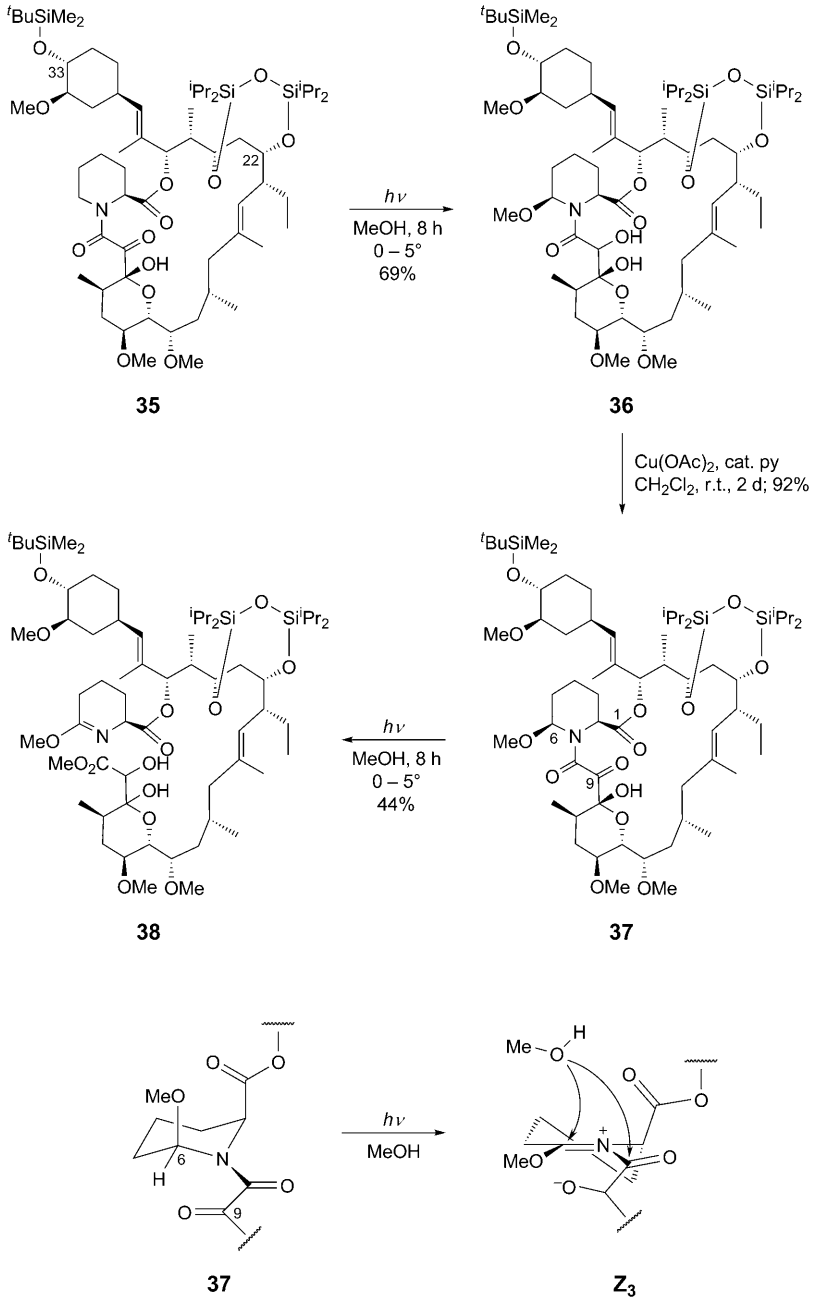
2.4. *Synthesis of the Protected Derivatives* **36** *and* **38** *as Key Intermediates through Photoreactions.* The amino acid analogs described so far were synthesized in a few steps from ascomycin (**1a**) without using any protecting groups and hence were also limited in the extent of modification on the amino acid moiety. To establish new synthetic strategies for synthesizing analogs with broader modifications on the amino acid, appropriate protecting groups are required. Hence, we studied the photochemistry of the ^{i}Pr$_2$Si-protected derivative **35** [14] (*Scheme 7*), which was prepared from **1a** through monosilylation of the OH group at C(33), *Evans*' reduction of C(22)=O (1.1 equiv. $Me_4N^+(OAc)_3HB^-$, MeCN/AcOH 100:35, -5 to 3°, 12 h, 70%), followed by silylation (3.0 equiv. (Cl^{i}Pr$_2$Si)$_2$O, 3.0 equiv. 1*H*-imidazole, DMF, r.t., 3 d, 70%).

Irradiation of **35** in MeOH for 8 h afforded the (6*S*)-9-hydroxy-6-methoxy derivative **36** in good yield, which, after oxidation with Cu(OAc)$_2$, gave the (6*S*)-6-methoxy-9-oxo derivative **37** in excellent yield. The derivative **37** still possesses a H-atom at C(6) in the equatorial position and can, in principle, undergo a similar photoreaction which would initially lead to the intermediate $\mathbf{Z_3}$, the fate of which would be interesting. In fact, irradiation of **37** in MeOH for 6 h, followed by chromatography,

Scheme 6. *Transformation of the Enamide* **6a** *to New Rigid Analogs*



Scheme 7. *Synthesis of the Key Intermediates* **36** *and* **38** *through Photoreactions*



led to the amide-leavage product **38** in a 44% yield. It appears that attack of MeOH at C(6), or intramolecular nucleophilic attack by C(9)–O at C(6), which have been the observed pathways so far, are indeed not favored for $\mathbf{Z_3}$ because of the resulting steric congestion. Instead, $\mathbf{Z_3}$ undergoes attack by MeOH on the activated electrophilic amide C=O group, leading to the amide cleavage product **38** [8]. Alternatively, the zwitterion $\mathbf{Z_3}$ could undergo cleavage leading to a hydroxy ketene which is then trapped by MeOH to give **38**. Other derivatives of ascomycin (**1a**), especially the unprotected **3a**, underwent a similar cleavage reaction [7d]. This represents a simple and mild method of cleaving a strong amide bond in a highly sensitive molecule such as **3a** not containing any protecting groups.

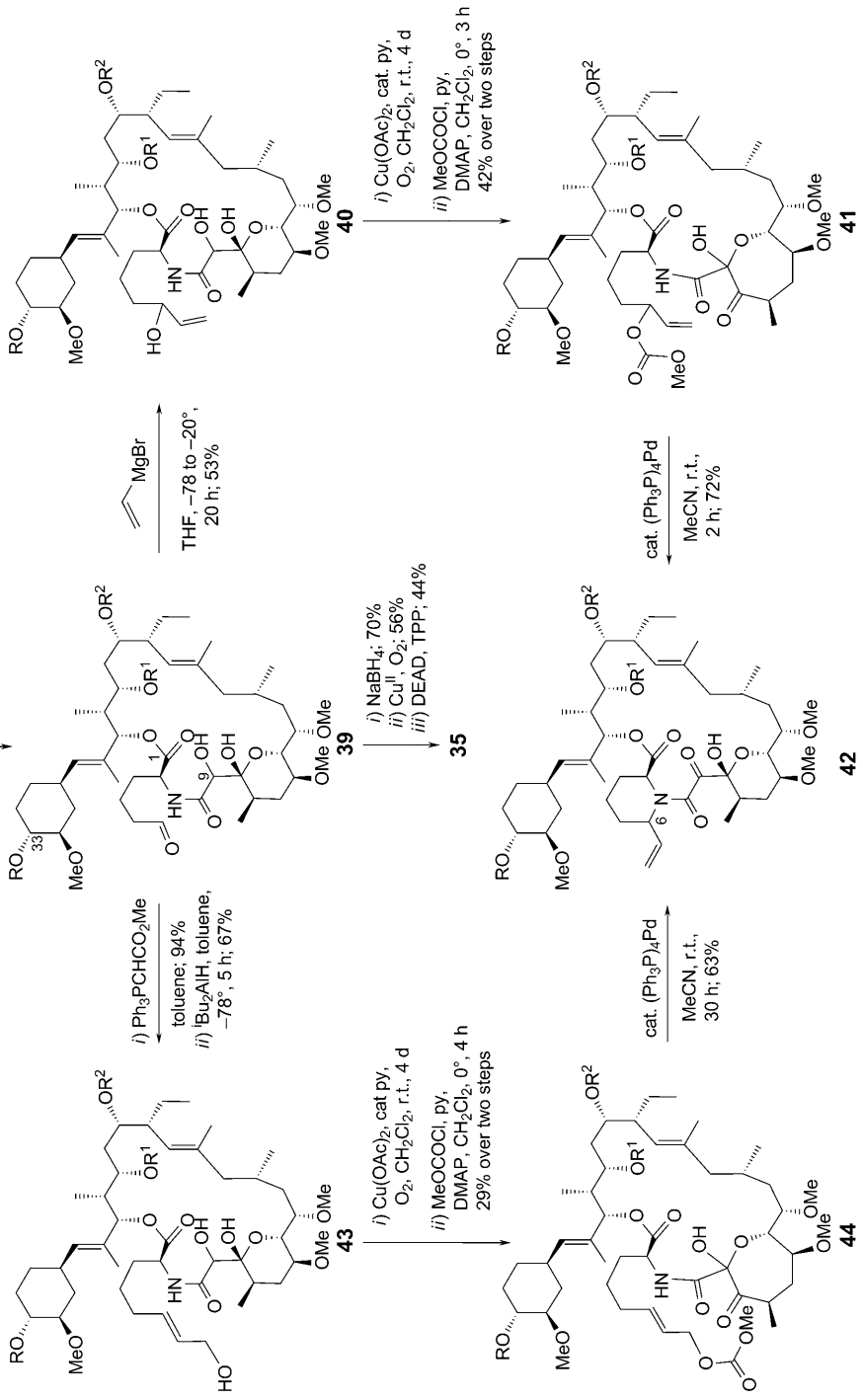
2.5. *Synthesis of 6-Vinyl- and 5-Vinylproline Analogs of Ascomycin* (**1a**) *from* **36**. The two photoproducts **36** and **38**, bearing the appropriate protecting groups, are available in multigram scale. We studied the scope of **36** for synthesizing the 6-vinyl analog **46** (*Scheme 8*) as well as the 5-vinylproline analogs **52** and **53** (*cf. Scheme 9*).

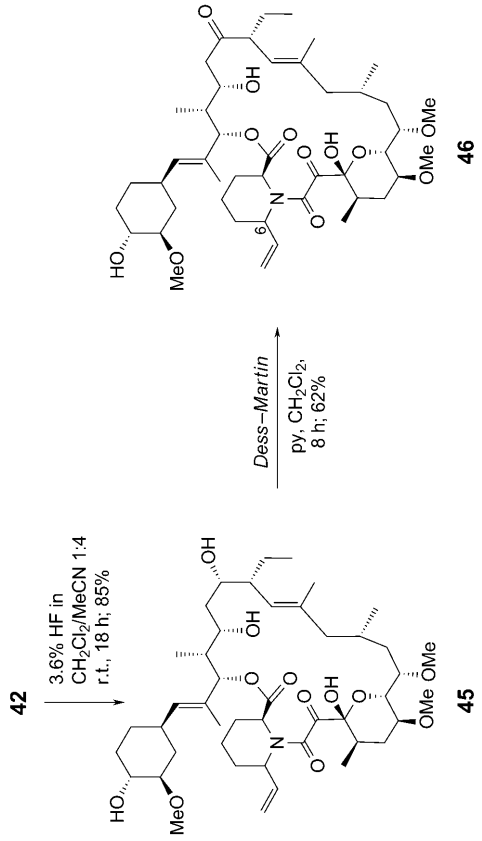
Acidic hydrolysis of the hemiacetal **36**, followed by reintroduction of ^{t}BuMe$_2$Si (TBS) on C(33)–OH afforded the aldehyde **39**. Addition of vinylmagnesium bromide to **39** gave the allyl alcohol **40**. Selective oxidation of the OH group at C(9) of **40** with Cu(OAc)$_2$, followed by selective activation of the secondary allylic alcohol as methyl carbonate, afforded the secondary carbonate **41** in 42% yield over two steps. The key step, namely the reinstallation of the C(ε)–N bond, was achieved through Pd-catalyzed cyclization of **41** leading to the protected vinyl analog **42** in good yield [15]. An alternative route was also explored for the transformation of **39** to **42**. Thus, *Wittig* olefination of **39** with Ph$_3$PCHCO$_2$Me afforded the corresponding unsaturated ester, which, upon reduction with ^{i}Bu$_2$AlH (DIBAH), led to the primary allylic alcohol **43**. Transformation of **43** to **44** was effected as described above through Cu(OAc)$_2$-catalyzed selective oxidation of the OH group at C(9), followed by selective activation of the primary allylic alcohol as methyl carbonate derivative. Again, similar to the transformation of **41** to **42**, Pd-catalyzed cyclization of **44** afforded **42** in 63% yield. The ^{1}H-NMR spectra of the samples of **42**, obtained from either **44** or **41**, are identical to each other, and indicated the presence of three inseparable components (C(6)-epimers or conformers in 0.7:1:1.9 ratio). Desilylation of **42**, followed by selective oxidation of the OH group at C(22), afforded 6-vinylascomycin (**46**) in good yield. The ^{1}H- and ^{13}C-NMR spectra of **46** showed it to consist of two major (*ca.* 1:1 ratio) and two minor components. No coalescence of the signals was observed in the ^{1}H-NMR in (D$_6$)DMSO at 80°, indicating it to be a mixture of C(6)-epimers, each as a pair of rotamers. Because of overlapping of the signals, no information could be obtained on the configuration of C(6) or conformation of the C(6)-epimers. The basic structure of **46**, however, was established using C,H correlation spectra.

It should be mentioned here that the derivative **39** could be transformed to **35** through reduction of the H–C(6)=O with NaBH$_4$, followed by oxidation of OH at C(9) with Cu(OAc)$_2$, and subsequently by ring-closure according to the *Mitsumobu* method. This offers yet another route for synthesizing derivatives which was not explored further.

The transformation of the aldehyde **39** to the 5-vinylproline analogs **52** and **53** is depicted in *Scheme 9*. Addition of a C$_1$-unit to **39** through a *Grignard* reaction gave the vinyl ether **47**, which was first converted to the α,β-unsaturated aldehyde and then

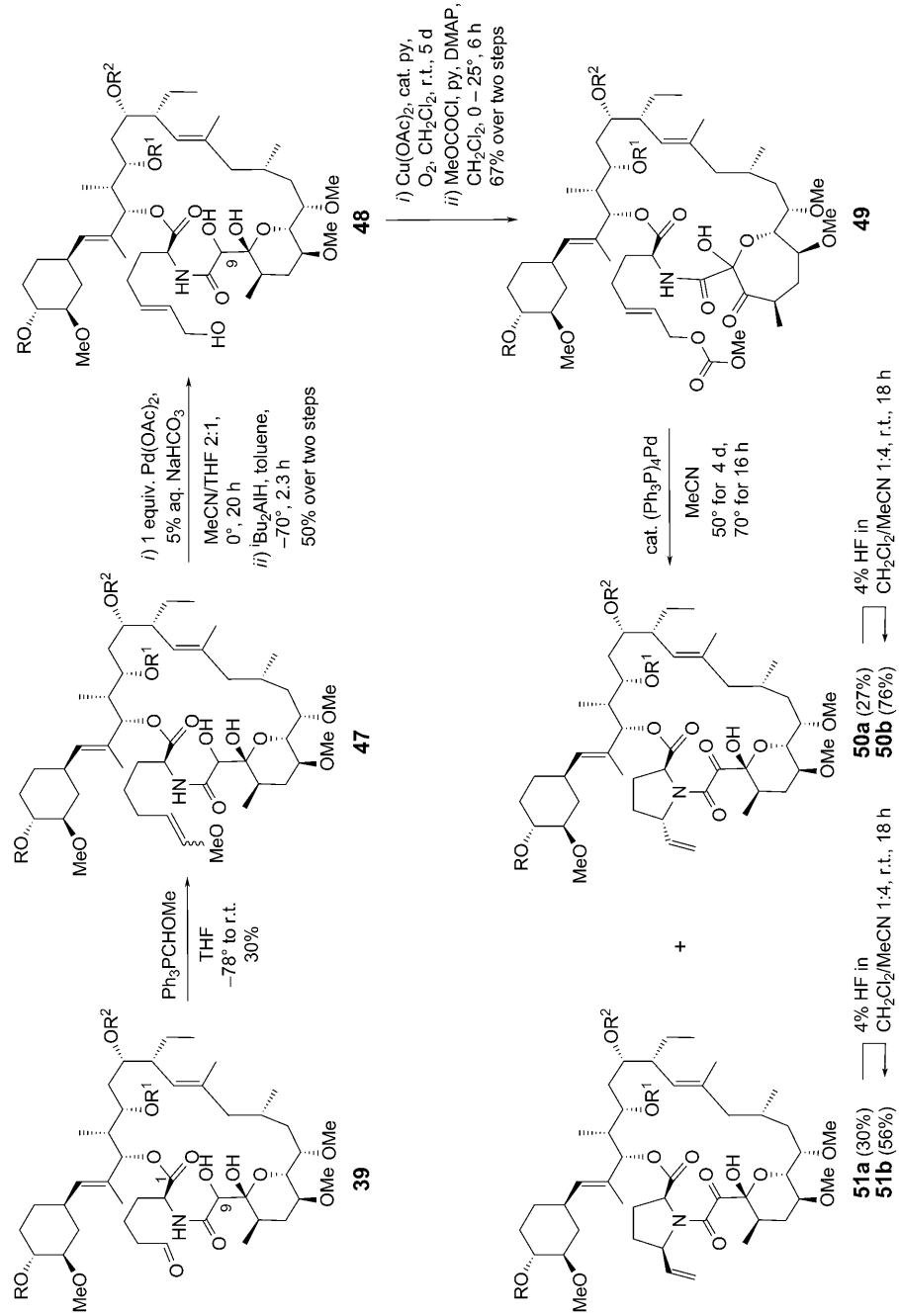
Scheme 8. *Synthesis of the 6-Vinyl Analog* **46** *from* **36**



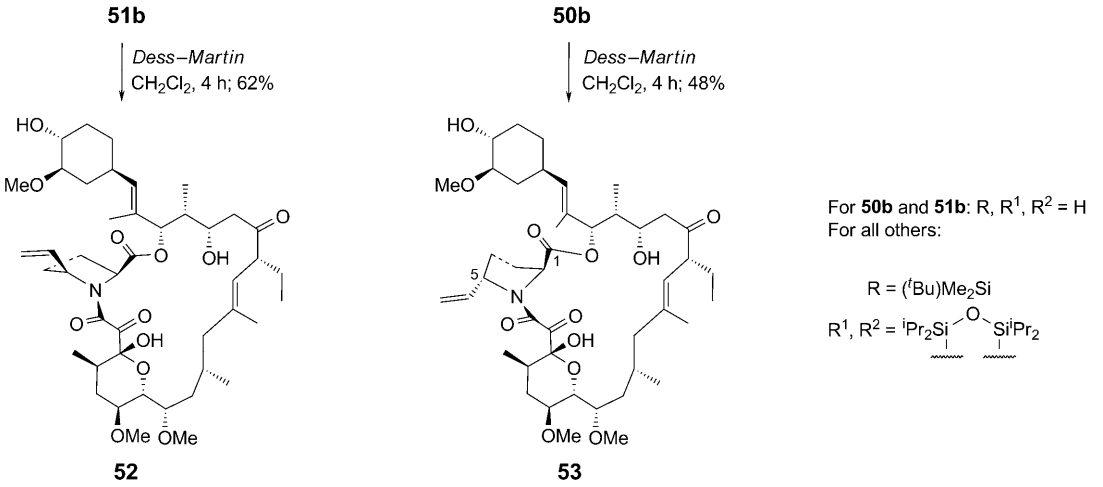


Scheme 8 (cont.)

Scheme 9. *Synthesis of the 5-Vinylproline Analogs* **52** *and* **53** *from* **39**



Scheme 9 (cont.)



reduced with DIBAH to the primary allylic alcohol **48**. $Cu(OAc)_2$ Oxidation of the OH group at C(9), followed by methoxycarbonylation, afforded the primary allyl carbonate **49**. Pd-Catalyzed cyclization of **49**, followed by chromatographic separation of the epimers, led to the protected (5*S*)-vinylproline analog **50a** (27%) and the (5*R*)-proline analog **51a** (30%). Noteworthy here are the longer reaction time and the higher temperature required for the cyclization of **49**, compared to those for **41** and **44**. Desilylation of **50a** and **51a** gave **50b** and **51b**, which, after *Dess–Martin* oxidation, afforded **53** and **52**, respectively.

The ^{1}H-NMR spectra of the series of proline derivatives **50a**, **50b**, and **53** showed signals at δ 4.51 (*dd*, $J = 8.5, 2.1$), 4.70 (*dd*, $J = 8.5, 2.3$), and 4.46 (*dd*, $J = 8.6, 2.1$), respectively, which are assigned to H–C(2) based on C,H correlation spectra. These splittings are similar to those in (5*R*)-methoxyproline analog **14**, and indicate (5*S*)-configuration for **50a**, **50b**, and **53**, with C(1) placed pseudoaxially as shown in **53** (*Scheme 9*). On the other hand, the ^{1}H-NMR spectra of the other series **51a**, **51b**, and **52** displayed signals at δ 4.49 (*t*, $J = 8.6$), 4.55 (*t*, $J = 8.3$), and 4.41 (*t*, $J = 8.4$), respectively, which are assigned to H–C(2). Again, these splittings are analogous to those in (5*S*)-methoxyproline analog **15**, indicating (5*R*)-configuration for **51a**, **51b**, and **52**, with C(1) oriented pseudoequatorially as shown in **52** (*Scheme 9*).

2.6. *Structural and Conformational Aspects.* The conformation of the macrolides **1a**–**1c** in the binding domain containing the pipecolic acid moiety is expected to play a crucial role in its binding to macrophilin (FKBP 12), and hence in its further downstream activities. Here, we summarize some of the structural and likely conformational features of the new derivatives deduced from the ^{1}H-NMR coupling constants in $CDCl_3$.

2.6.1. *Derivatives Containing Modified Pipecolic Acids.* The macrolide **1c** exists as a 2:1 mixture of s-*cis* and s-*trans* amide-bond rotamers; both rotamers possess chair conformation for the pipecolic acid with the ester group containing C(1) placed axially [6]. 6-β-Methoxyascomycin (**3a**) consisted of two isomers in a 2:1 ratio; the major isomer showed coupling constants representative of a chair conformation ($J(2,3) = 1.8, 5.3$; $J(5,6) = 2.7, 2.7$), whereas the minor isomer that of a boat-like conformation ($J(2,3) = 6.5, 7.1$; $J(5,6) = 1.4, 4.0$). Coalescence of the signals was observed upon heating in DMSO at 380 K, indicating their interconvertibility. The 6β-EtO and the 6β-PrO analogs, **3e** and **3f**, respectively, consisted of similar conformers, but the distribution was slightly shifted towards the boat conformation (chair/boat 3:2). This deviation is most probably due to the 1,3-diaxial interactions between the ester group containing C(1) and the RO groups at C(6).

The X-ray crystal structure[3]) of **6a** is given in *Fig. 1*, and the side-on view of the amino acid region in *Fig. 2*. Due to the presence of the C=C bond, the conformation of the piperidine ring differs significantly from the chair found in ascomycin (**1a**) [6e]. It is best described by a least-squares plane through the atoms C(2), C(4), N(5), C(6), and N(7) (maximum deviation from the plane 0.0777(9) Å for N(7), and the distance

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[3]) CCDC 710864 contains the supplementary crystallographic data for this work. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

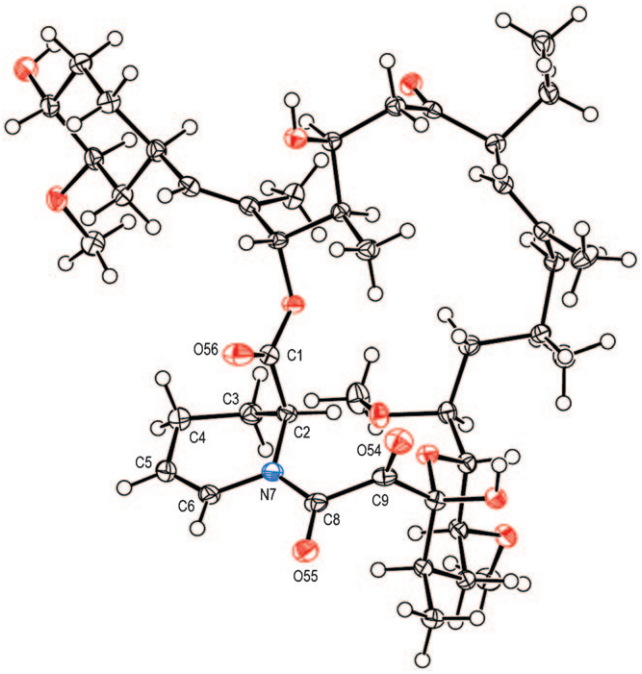

Fig. 1. *Structure of* **6a** *in the crystal* [16a]. Atomic displacement ellipsoids are drawn at the 50% probability level, and H-atoms are drawn as spheres of arbitrary radius. For clarity, only atoms discussed in the text are labeled. For the enantiomer shown the *Flack* × parameter refined to 0.00(8) [16d].

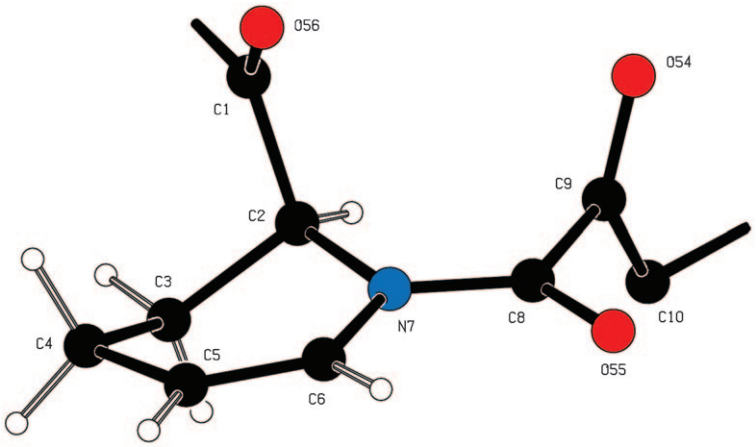

Fig. 2. *Side-on view of the amino acid region of* **6a** [16a]. All atomic radii are arbitrary.

between this plane and C(3), which is 0.634(2) Å). The geometry at the ring atom N(7) is planar, the bond angles around this atom sum up to 359.97(19)°. The entire amide moiety is also planar which is reflected in a torsion angle C(6)–N(7)–C(8)–O(55) of

0.4(2)°. The angle between the planes of the C(8)=O(55) and C(9)=O(54) group is 89.90(1)°. The overall conformation of **6a**, however, is close to that of ascomycin (**1a**).

The derivatives **30a** and **30b** bearing the cyclopropane ring on the β-face of the ring adopt a half-chair conformation similar to **6a**, but probably slightly distorted to accommodate the 1,3-diaxial interaction. On the other hand, **31a** and **31b** featuring the cyclopropane ring on the α-face of the ring adopt an undistorted half-chair conformation with the ester group placed axially.

The ester group containing C(1) is oriented pseudoaxially in the α-methoxyproline analog **14** and the α-vinyl-proline analog **53** (thus coming closer to the conformation of **1a**), and pseudoequatorially in the β-methoxyproline analog **15** and the β-vinylproline analog **52** (thus deviating considerably from the conformation of **1a**). Both of the C(9)-isomers of the oxazolidinone **9** showed a small (*ca.* 4 Hz) and a large (*ca.* 10 Hz) J between H–C(6) and H–C(5); H–C(2) appeared as a *doublet* ($J \approx 6$). This points to a $^2C_5$-conformation for the pyrrolidine ring with the ester group placed axially and the C(6)–O placed equatorially.

2.6.2. *Derivatives Containing Noncyclic Amino Acids.* The tricarbonyl moiety of ascomycin derivatives is known to exist predominantly as six-membered-ring hemiketal; the amount of seven-membered-ring hemiketal is low and is dependent on the structure and the solvent [6]. The derivatives **41** and **44** existed exclusively as the seven-membered-ring hemiketals, and **49** existed as 95:5 mixture of the seven-membered- and six-membered-ring hemiketals. Freshly prepared $CDCl_3$ solutions of the derivatives **24a**, **24b**, **28b**, and **29a** contained the isomers in varying proportions, which equilibrated (24 h) to mixtures containing the six-membered-ring as the major component as well as a considerable amount of the seven-membered-ring hemiketal as the minor component; other derivatives in this series were not investigated. All the derivatives featuring cyclic amino acids discussed before existed mainly as six-membered-ring hemiketals. The six- and seven-membered-ring structures are distinguished by ^{1}H,^{13}C-long range-correlation spectroscopy (HMBC), generally optimized for three-bond couplings. In the seven-membered-ring hemiketal, the Me–C(11) H-atoms showed, as expected, a cross-peak to the ketone C-atom (C(10), at *ca.* 210 ppm), whereas, in the case of the six-membered-ring hemiketal Me–C(11) H-atoms showed a cross-peak to a ketal C-atom (C(10), at *ca.* 100 ppm). Moreover, due to the spatial vicinity to the ketone C=O group, the Me–C(11) H-atoms of the seven-membered-ring hemiketal are shifted to lower field (*ca.* 1.2 ppm) compared to those of the six-membered-ring isomer (*ca.* 1.0 ppm), allowing the deduction of the ^{1}H chemical shifts of Me–C(11) from these spectra. Hence, the only Me group resonating at *ca.* 1.2 ppm is the Me–C(11) of the seven-membered-ring isomer, and all other Me groups of these derivatives, except those located on the C=C bonds, resonate in the region 1.0–0.8 ppm.

3. Biological Activities. – Selected derivatives are grouped into structural types, and their *in vitro* and *in vivo* activities along with those of the reference compounds **1c** and **1a** are collected in *Table 2*. For easy understanding of the SARs, the structural modifications are mnemonically abbreviated.

3.1. In vitro *Activities* (MBA, RGA, and MLR). The first step in the mode of action of these compounds is binding to the cytosolic receptor macrophilin-12 [6]; this is

measured by macrophilin binding assay (MBA). The binary complex then inhibits the Ca-dependent phosphatase calcineurin, an enzyme required for the dephosphorylation of the cytosolic form of the nuclear factor of activated T cells (NF-AT), thus inhibiting the release of cytokines such as IFN-γ, IL-2, -4, -5, -10, and TNF-α, thus targeting T-cell activation and proliferation. These events are assayed by IL-2 reporter gene assay (RGA) and mixed lymphocyte reaction (MLR). It should be noted that binding (MBA) is necessary but not sufficient for the elicitation of the T-cell modulatory activities (RGA and MLR). Whereas the 6-MeO derivative **3a** showed weak binding, and correspondingly weak RGA and MLR activities, the 6-EtO and 6-PrO, **3e** and **3f**, respectively, showed negligible activities. This is probably due to the change in the conformation of these molecules as discussed above, or a misfit of the alkoxy groups at C(6) into the binding pocket. It is known that the pipecolinyl ring of **1c** is deeply embedded in its complex with FKBP 12, and, hence, binding is sensitive to modifications in this region [6g]. The 5,6-dehydroascomycin (**6a**) is very close to **1c** both in conformation and space-filling (X-ray structure) and, as expected, showed very good activities; the corresponding 9-deoxo analog **32** showed somewhat weaker activities, reflecting the importance of the C(9)=O group for the activity. Interestingly, the α-cyclopropano derivatives **31a** and **31b**, which are conformationally very close to **6a** but with the α-face of the ring filled with CH_2 group, showed reasonably good activities. On the other hand, their β-counterparts **30a** and **30b** were significantly less active; the reason for this could lie in their deviation from the chair conformation and filling of the space on the β-face of the ring (as in **3a**, **3e**, and **3f**). Note that the 9-deoxo analogs **32**, **31b**, and **30b** are weaker in their activities than their corresponding C(9)=O analogs **6a**, **31a**, and **30a**. The 6-vinyl derivative **46** is much less active, similar to **3e**. Neither of the isomers of the epoxide **33** showed any appreciable activity, pointing to the importance of the C(9)=O group for binding.

Among the proline derivatives, neither of the vinyl analogs **52** and **53** showed any useful activity. Interestingly, the 5α-MeO analog **14**, in spite of its apparent closeness in space-filling to the biologically inactive 5α-vinyl analog **53**, showed useful activities (analogous to 5α-cyclopropano analog **31a**). This is probably due to the higher rotational freedom of the MeO group allowing it to orient itself better in the binding pocket, compared to the spacially more rigid vinyl group. Unfortunately, no data are available on the 5β-MeO analog **15**. The dehydroproline **16** showed good activity, analogously to the dehydropipecolic **6a**.

The analogs **24a** and **24b**, featuring the noncyclic amino acid, were not active. Because of the lack of the rigid cyclic amino acid, these molecules adopt a totally different inactive conformation.

The rigid bicyclic structures **9** and **26a**, in spite of their ideal piperidine chair conformation with the ester group at C(2) in the axial position, and **26b**, featuring the piperidine ring in the chair conformation with the ester group at C(2) in the equatorial position, are inactive. Apparently, some flexibility in this region is needed for good binding.

The ring-contracted derivatives **7** and **19**, which feature unaltered binding domains, showed excellent binding to macrophilin. However, their weak activities in the RGA and MLR indicate that these modifications in the effector domain do not favor further interactions of the initially formed FKBP-binding complex with calcineurin A and

Table 2. *Biological Activities of the Derivatives of Ascomycin*

{PRIVATE}	Abbreviated structural feature	MBA[a]) rIC_{50}	RGA[b]) rIC_{50}	MLR[c])[d]) rIC_{50}	ACD mouse[e])[f])[g])	ACD pig[g])[h])
Reference compounds						
1c	Tacrolimus (FK 506)	1.0	1.0	1.0	57*	68*
1a	Ascomycin	0.6	1.8	2.1	44*	58*
Derivatives containing modified pipecolic acid						
3a	6β-MeO-**1a**	70	240	470	9 ns	
3e	6β-EtO-**1a**	14500	> 2600	n.a.	36*	27*
3f	6β-OPr-**1a**		> 15305		19 ns	
6a	5,6-Dehydro-**1a**	2.0	2.0	24.0	53*	51*
32	9-Deoxo-**6a**	15	47	170	26 ns	
31a	5,6-α-Cyclopropyl-**1a**	8.2	15.0	22.0	41*	34*
31b	9-Deoxo-**31a**		40		22*	
30a	5,6-β-Cyclopropyl-**1a**		41.0			
30b	9-Deoxo-**30a**		535		49*	31*
46	6-Vinyl-**1a**			4600		
33	Minor epoxide-**1a**	2000			24*	
33	Major epoxide-**1a**	250			21*	
Derivatives containing modified proline						
14	5α-OMe-**10**	14	19.4		3 ns	
16	4,5-Dehydro-**10**	1.7	4.0			
52	5β-Vinyl-**10**			5300		
53	5α-Vinyl-**10**			n.a.		
Derivatives containing noncyclic amino acid						
24a	C-6-Acid-**1a**			n.a.		
24b	C-6-Acid Me ester-**1a**			n.a.		
Derivatives containing bicyclic structures in the binding domain						
9	Oxazolidinone-**1a**	290	3150	> 1000	26 ns	
26a	6β-*O*-Ketal-**1a**	6000	> 3300	n.a.	3*	
26b	6α-O-Ketal-**1a**	1900	> 3300	n.a	26*	
Derivatives with modifications in the effector domain						
7	But-1-enyl-**1a**	1.7	425	> 1000	24 ns	
19	Butyl-**1a**	0.7	2200	> 1000	23 ns	
20	6β-MeO-**7**	1700	2700	n.a.	8 ns	

[a]) Macrophilin binding assay: IC_{50} value relative to **1c**; IC_{50}(**1c**) 1.1 nM (S. D. 0.4, $n = 35$). Test method: **1c** coupled to BSA is used to coat microtiter plate wells. Biotinylated recombinant human macrophilin-12 is allowed to bind to the immobilized **1c** in the absence (as a control) and presence of a test sample. Bound biotinylated macrophilin-12 is assessed by incubation with a streptavidin-alkaline phosphatase conjugate, followed by incubation with *p*-nitrophenyl phosphate as a substrate. Readout is the OD at 405 nm. Binding of a test sample to the biotinylated macrophilin-12 results in a decrease in the amount of macrophilin available for binding to the immobilized **1c** and, thus, in a decrease in the OD 405 compared to the control. A dilution series of the test sample (in duplicate) allows the calculation of the concentration which results in 50% inhibition of the macrophilin/immobilized **1c**-binding (IC_{50}). The inhibitory ability of the test sample is expressed as relative IC_{50} (rIC_{50}), *i.e.*, the ratio IC_{50}(test sample) to IC_{50}(free **1c**). [b]) Inhibition of production of IL2 reporter gene assay: IC_{50} value relative to **1c**. IC_{50}(**1c**) 0.27 nM (S.D. 0.09, $n = 3$). Test method: the *E. coli* gene *lacZ* (reporter gene), which encodes the enzyme β-galactosidase, has been placed under transcriptional control of the human IL-2 promoter and stably transfected into the human T cell JURKAT. The IL-2 promoter-driven β-galactosidase expression, which

calcineurin B, thus not resulting in any T-cell modulatory activities. The derivative **20** featuring modifications both in the binding and effector domains showed very weak binding, and hence also very weak RGA and MLR activities.

3.2. In vivo *Activities*. Selected derivatives were tested topically in ACD (allergic contact dermatitis) mouse model as well as a few selected ones in ACD pig model. Of the two ACD models, the mouse model is less stringent than the pig model. Since the murine skin is more permeable than the human skin, the activities in mice are only indicative and not predictive for the human situation. The data marked as 'ns' (not statistically significant) can be considered as no activity. The pig model is more predictive, because pig skin and human skin are closely related in their drug

Table 2 (cont.)

is quantified by measuring the fluorescence of its cleaved substrate, correlates with IL-2 expression and is thus a direct readout for IL-2 gene transcription. The results are expressed as relative IC_{50} (rIC_{50}), *i.e.*, the ratio of the IC_{50} (nM) of the test compound to the IC_{50} (nM) of **1c**. [c]) Inhibition of mixed lymphocyte reaction: IC_{50} value relative to **1c**. IC_{50}(**1c**) 0.15 nM (S.D. 0.04, $n = 6$). Test method: 1×10^5 spleen cells of each BALB/c and CBA mice are cultivated in flat-bottom microtiter plates for 4 d in serum-free tissue culture medium. [^{3}H]Thymidine (1 μCi/well) is then added. The cells are harvested after another 16-h cultivation period and the [^{3}H]thymidine incorporation into the DNA is subsequently measured. The extent of [^{3}H]thymidine incorporation reflects the number of cells which were dividing during the last 16 h of cultivation and is thus representative for cell proliferation. The MLR is performed in the absence or presence of a serially diluted compound and **1c** as a standard. The concentration required for 50% inhibition of cell proliferation (IC_{50}) is calculated; results are expressed as relative IC_{50} (rIC_{50}), *i.e.*, the ratio of the IC_{50}(test sample) to IC_{50}(**1c**). [d]) n.a.: Not active (> 8000). [e]) Inhibition [%] of allergic contact dermatitis in mouse after topical application of 0.01% drug soln. Test method: female NMRI mice were sensitized on the abdomen with oxazolone (2% in acetone) and, after 7 d, challenged with 2% oxazolone (for topical testing) or 0.5% oxazolone (for systemic testing) on the inner surface of the right ears (8 animals per group in each experiment). The unchallenged left ears served as internal controls, and evaluation was made from the difference in auricular weights as a measure of inflammatory swelling 24 h after the challenge. Topical treatment with ethanolic solns. (10 μl) of the test compound or the reference compound **1c**, and dexamethasone was performed once, 30 min after elicitation of ACD. Groups of controls were treated similarly with the vehicle topically. Auricular weight differences in test and control groups were evaluated with one way ANOVA followed by *Dunnet* test (parametric) or by *Kruskal–Wallis* and *Dunn*'s test (non-parametric) using the *SigmaStat*® program. Significance was taken as $p < 0.05$. The activity was calculated as the % inhibition of inflammatory swelling (weight increase) relative to vehicle treated animals. [f]) ns: Not statistically significant. [g]) *: Statistically significant ($p < 0.05$). [h]) Inhibition [%] of allergic contact dermatitis in domestic pig after topical application of 0.13% drug soln. Test method: young domestic hybrid pigs (*Landrasse* × *Deutsches Edelschwein*) were sensitized with 400 μl 2,4-dinitrofluorobenzene (10% in DMSO/acetone/olive oil) applied to four areas at both pinnae and groins. Challenge reactions were elicited 12 d later with 15 μl DNFB (1%) at test sites arranged at craniocaudal lines on the dorsolateral back. The test sites were treated twice with 20 μl soln. of test compounds or vehicle, 30 min and 6 h post challenge. For testing formulated compounds, *ca.* 100 mg of creames (in doses) were applied. One day after challenge, each test site was visually evaluated for intensity, and expanse of erythema and induration (gross lesion). Each sign was scored on a scale from 0 (normal) to 4 (severe) allowing a combined maximal score of 12 per designated site. The percentage inhibition was calculated using the equation: % Inhibition = $\{(M_{VS} - M_{DS}) \times 100\}/M_{VS}$; M: mean; VS: vehicle-treated sites; DS: drug-treated sites. For statistical analysis of the differences between scores of contralateral test sites, *Student*'s *t*-test (two tailed paired) was applied. The significance level was set at $p < 0.05$.

penetration properties. The derivatives **6a** and **31a** which showed good *in vitro* activities also showed good activities in these two animal models.

The derivative **6a** with its established practical synthesis and good biological activities was evaluated further, and the data are summarized here. In the murine ACD model after subcutaneous or oral applications, **6a** showed good activity. In the pig model, upon topical application, **6a** was comparable to the ultrapotent corticosteroid clobetasol-17-propionate and fluticasone propionate. Furthermore, **6a** was less potent by a factor of ≥ 10 than FK 506 in the localized graft *vs.* host model in rats when given subcutaneously. Compound **6a** was also by a factor of ≥ 15 less potent than FK 506 in preventing the allogeneic kidney transplant rejection in rats after oral application. These results indicate a good potential for **6a** in treating ACD and other T cell-mediated dermatitis disorders with substantially lower risk of systemic immunosuppression.

4. Conclusions. – A novel photoreaction on ascomycin (**1a**) leading to methoxylation in the ε-position of the pipecolic acid moiety was described. Starting from this methoxy photoproduct, several derivatives featuring novel modifications on the amino acid, which are not easily accessible through routine methods, could be synthesized in fewer steps. Using the photoreaction, key intermediates with potential for broader modifications in the binding domain were synthesized, and their utility was exemplified through synthesis of vinylpipecolic acid and vinylproline analogs. An interesting photochemical cleavage of the amide bond in the derivatives of ascomycin (**1a**) was discussed. The structural and conformational features of the derivatives together with the X-ray crystal structure of the biologically most active 5,6-dehydroascomycin (**6a**) were presented, and their biological activities were discussed.

Experimental Part

General. Solvents (THF, DMF, CH_2Cl_2, toluene) were dried over 4-Å molecular sieves. MeOH was distilled over Na. Flash chromatography (FC): silica gel *60* (40–63 μm). SiO_2-2.5% $NaHCO_3$ was prepared by mixing 400 g of SiO_2 with 1 l of aq. 1% $NaHCO_3$, evaporating to dryness on a rotary evaporator under vacuum, followed by drying under vacuum at 80° for 3 h. M.p.: uncorrected. NMR Spectra: either on a *Bruker AMX 500* or a *Bruker DRX-500* spectrometer (500.13 MHz for ^1H and 125.77 MHz for ^{13}C); unless stated otherwise, the solvent was $CDCl_3$; chemical shifts in ppm, referenced to residual solvent signals (7.26 for ^1H, 77.0 for ^{13}C in $CDCl_3$, 3.31 and 49.0 in CD_3OD). The assignments were based on diagnostically relevant NMR experiments such as homonuclear ^1H,^1H-COSY, TOCSY, NOESY, heteronuclear ^1H,^{13}C-correlation, HSQC, and long-range HMBC spectra, or, comparison with analogous compounds and are highly reliable. In case of isomers/rotamers, where possible, the data of the minor isomer are marked with an asterisk (*). The system as indicated in the atom-numbering scheme (*Fig. 3*) with slight adaptation for other derivatives is used for all the compounds for assigning the signals. HR-MS: *9.4T APEX-III FT-MS* (*Bruker Daltonics*).

CA *Index Name of* **1a**: *15,19-Epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone, 8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-*; other names: *ascomycin; changchuanmycin*; *FK 520*; *FR 520*; *FR 900520*; *immunomycin*; *L 683590*.

General Procedure A (*GP A*): A soln. of the compound (5–10 g) in a dry solvent (1 l) in a *Pyrex* tube was degassed with He and irradiated externally using a medium-pressure Hg lamp (*Hanovia*, TQ-150)

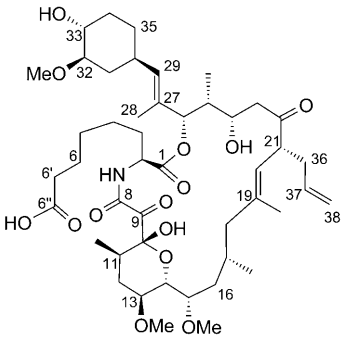

Fig. 3. *Atom-numbering scheme*

fitted with a *Pyrex* filter. The jacket containing the light source was placed in a large H_2O bath (5° or r.t.), and the reaction vessels were placed all around in the same bath.

The reaction was monitored using TLC or anal. HPLC (*Polygosyl 10 CN* column, cyclohexane/i-PrOH 9:1 or 85:15, isocratic). After completion of the reaction (2–9 h), the solvent was removed, and the residue was purified by FC on SiO_2 or prep HPLC (*Polygosyl CN* column, cyclohexane/i-PrOH 9:1 or 85:15; isocratic).

General Procedure B (*GP B*). Similar to *GP A*, but employing a *TQ 718* lamp fitted with a *Duran* filter in a well-type reactor. The well (which usually contains the reactant) was filled with an aq. filter soln. (transparent to $\lambda > 360$ nm) prepared by dissolving 650 g of $NaBr \cdot 2\,H_2O$ and 3.0 g of $Pb(NO_3)_2$ in doubly distilled H_2O and made up to 1 l. The well-reactor containing the light source and the filter soln. was placed in a large H_2O bath, and the reaction vessels were placed all around in the same bath.

General Procedure C (*GP C*). A mixture of the sample (0.2 g) and 1–2 equiv. of $Cu(OAc)_2$ or cupric-2-ethylhexanoate in CH_2Cl_2 or THF (10 ml) was stirred under O_2 balloon at r.t. or reflux temp. until the reaction was complete (1–3 d; TLC or anal. HPLC). The solvent was removed, and the residue was partitioned between aq. $NaHCO_3$ and AcOEt. The org. phase was separated and washed repeatedly with aq. $NaHCO_3$, until the washings were colorless, and finally with brine. The org. extract was dried, concentrated, and the residue was purified by FC or prep. HPLC.

General Procedure D (*GP D*). A mixture of the sample (10 g), $Cu(OAc)_2$, or cupric 2-ethylhexanoate (5–100 mol-%), py (10–20 mol-%), and 4-Å mol. sieves was stirred in CH_2Cl_2 under O_2 balloon at r.t. until completion (1–2 d). The mixture was passed through a bed of *Celite*, and the filtrate was concentrated. The residue was processed as in *GP C*.

General Procedure E (*GP E*). A mixture of the sample (1 g) and dry NH_4Cl (0.5–1.0 equiv.) in DMF (100 ml) was reacted in a rotary evaporator under reduced pressure at 78° such that the DMF slowly distilled off. After completion of the reaction (4 h), the remaining DMF was removed under high vacuum, and the residue was dried and partitioned between aq. $NaHCO_3$ and AcOEt. The org. layer was separated, and the aq. layer was re-extracted with AcOEt. The combined org. extracts were washed with brine, dried, and concentrated. The residue was purified by FC or prep. HPLC.

Compounds **2a**, **4a**, **7**, *and* **8**. According to *GP A*, **1a** (0.2 g, 0.252 mmol) in MeOH (50 ml) was irradiated at r.t. for 2 h. 25 Such batches (total 5 g, 6.31 mmol) were combined and purified by prep. HPLC to give **2a** (1.09 g, 22%), **7** (1.983 g, 40%), **8** (0.206 g, 4%), **4a** (0.482 g, 10%), and unchanged starting material **1a** (0.955 g, 19%). Alternatively, according to *GP B*, **1a** (10 g, 12.63 mmol) in MeOH (1 l) was irradiated at 5° for 9 h, and 1/10 of the resulting residue was purified as described above to give **2a** (0.78 g, 75%) and **4a** (0.145 g, 15%); the crude photolysate from this step could also be taken without purification to the next step.

Data of **2a**. Crystallized from AcOEt. White solid. M.p. 130–137°; ^{1}H-NMR (*ca.* 3:1 mixture isomers/rotamers): major isomer: 5.84 (br. *s*, H–C(6)); 5.45 (*d*, $J = 5.5$, H–C(2)); 5.22 (*d*, $J = 8.9$, H–C(20/29)); 5.07 (br. *s*, H–C(26)); 4.88 (*d*, $J = 10.4$, H–C(20/29)); 4.49 (*s*, HO–C(10)); 4.42 (*s*, H–C(9), HO–C(9)); 3.78 (*dd*, $J = 9.6$, 1.2, H–C(14)); 3.60 (*m*, H–C(15), H–C(24)); 3.40 (*s*,

MeO–C(32)); 3.40 (*m*, H–C(13/33)); 3.38 (*s*, MeO–C(13)); 3.28 (*s*, MeO–C(15)); 3.37 (*m*, H–C(13), H–C(33)); 3.20 (*m*, H–C(21)); 3.10 (*s*, MeO–C(6)); 3.00 (*ddd*, *J* = 11.2, 7.8, 4.2, H–C(32)); 2.84 (br. *s*, OH); 2.81 (*dd*, *J* = 18.1, 3.5, 1 H–C(23)); 2.39 (*dd*, *J* = 18.1, 5.8, H_b–C(23)); 2.4–0.8 (overl. *m*s); minor isomer: 6.14 (*s*, HO–C(10)); 5.55 (br. *s*, H–C(6)); 5.04 (*d*, *J* = 9.1, H–C(20/29)); 5.02 (br. *s*, H–C(26)); 4.82 (*d*, *J* = 9.7, H–C(20/29)); 4.68 (*dd*, *J* = 6.6, 4.4, H–C(2)); 4.47 (br. *d*, H–C(9)/HO–C(9)); 4.37 (br. *d*, *J* = 8.6, H–C(9)/HO–C(9)); 3.90 (*m*, H–C(24)); 3.85 (*dd*, *J* = 9.5, 2.1, H–C(14)); 3.75 (*d*, *J* = 2.3, OH)); 3.60 (*m*, H–C(15)); 3.40 (*s*, MeO–C(32)); 3.35 (*s*, MeO–C(13)); 3.27 (*s*, MeO–C(15)); 3.45–3.25 (*m*, H–C(13), H–C(33), H–C(21)); 3.00 (*ddd*, *J* = 11.2, 7.8, 4.2, H–C(32)); 2.59 (*dd*, *J* = 16.6, 2.0, H_a–C(23)); 2.4–0.7 (overl. *m*s). ^{13}C-NMR: major isomer: 214.0 (C(22)); 173.3 (C(8)); 170.7 (C(1)); 139.7 (C(19)); 131.1 (C(27)); 129.7 (C(29)); 123.9 (C(20)); 97.0 (C(10)); 84.2 (C(32)); 80.5 (C(6)); 77.8; 75.2; 74.8; 73.5; 73.4; 72.6; 71.8; 57.1; 56.5; 56.3; 54.2; 52.1; 49.3; 43.7; 40.4; 36.1; 35.0; 34.8; 33.9; 33.5; 31.3; 30.5; 30.2; 26.1; 25.7; 22.6; 20.8; 16.0; 15.4; 15.0; 13.9; 11.3; 11.1; minor isomer: 213.2 (C(22)); 174.3 (C(8)); 168.4 (C(1)); 140.6 (C(19)); 129.0 (C(29)); 122.7 (C(20)); 99.8 (C(10)); 84.3 (C(6)); 76.9; 73.8; 70.8; 70.1; 69.5; 57.6; 56.0; 55.8; 55.0; 52.3; 48.7; 44.1; 41.1; 36.6; 34.93; 34.87; 32.9; 32.2; 30.3; 29.9; 25.4; 25.0; 23.4; 18.0; 16.21; 16.16; 15.4; 14.2; 11.5; 9.9. Anal calc. for $C_{44}H_{73}N_1O_{13}$: C 64.13, H 8.93, N 1.70; found: C 63.75, H 8.47, N 1.53. HR-MS: 846.4977 ($[M+Na]^+$; calc. 846.4980).

Data of **4a**. White foam, ^{1}H-NMR (*ca.* 12:5 mixture of rotamers): major rotamer: 8.08 (*s*, HC=O); 5.35 (*d*, *J* = 9.0, H–C(20/29)); 5.21 (*d*, *J* = 8.4, H–C(26)); 5.13 (*d*, *J* = 5.2, H–C(2)); 4.94 (br. *dd*, *J* = 9.9, 1.2, H–C(20/29)); 4.07 (*dd*, *J* = 7.8, 1.6); 3.97 (*m*); 3.70 (*m*); 3.60–3.30 (overl. *m*s); 3.22 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.92 (br. *s*, OH); 2.64 (*m*, 2 H–C(23)); 2.80 (br. *s*, OH); 2.48 (*m*, H–C(11)); 2.40–0.80 (overl. *m*s); minor rotamer: 8.03 (*s*, HC=O); 5.35 (*d*, *J* = 9.0, H–C(20/29)); 5.23 (*d*, *J* = 8.5, H–C(26)); 4.94 (br. *dd*, *J* = 9.9, 1.2, H–C(20/29)); 4.32 (br. *d*); 4.26 (*d*, *J* = 4.9, H–C(2)); 4.07 (*dd*, *J* = 7.8, 1.6); 3.97 (*m*); 3.70 (*m*); 3.60–3.30 (overl. *m*s); 3.22 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.80 (*m*, H–C(6)); 2.64 (*m*, 2 H, H–C(23)); 2.48 (*m*, H–C(11)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR of both rotamers: 212.1; 212.0*; 173.6; 169.8*; 169.5; 162.3*; 161.8; 138.42*; 138.35; 134.1*; 133.8; 130.8; 130.7*; 124.2; 84.11; 84.07*; 82.9*; 82.52; 82.47*; 82.3; 77.3; 77.2*; 73.6; 73.5*; 73.4; 67.0; 66.9*; 57.5; 57.0*; 56.7; 56.3; 54.4; 50.7; 48.5*; 48.4; 45.9*; 45.8; 44.0; 38.8; 38.7*; 38.2*; 34.9; 34.8; 34.7*; 34.4; 33.3; 32.2; 31.2; 30.2; 27.2*; 26.9; 26.4; 25.5; 24.2; 24.1; 21.5; 21.4*; 19.6*; 19.5; 17.0; 16.4; 12.22; 12.18*; 11.6; 8.90; 8.86*. HR-MS: 786.4765 ($[M+Na]^+$; calc. 786.4728).

Data of **7**. White foam. ^{1}H-NMR: 5.63 (*dt*, *J* = 15.7, 6.4, H–C(21)); 5.46 (br. *d*, *J* = 3.2, H–C(26)); 5.32 (*dt*, *J* = 15.7, 1.6, H–C(20)); 4.94 (*dm*, *J* = 9.0, H–C(29)); 4.56 (*d*, *J* = 1.7, HO–C(10)); 4.38 (*dm*, *J* = 14.0, 1 H–C(6)); 4.35 (*dd*, *J* = 6.0, 2.0, H–C(2)); 3.81 (*m*, H–C(24)); 3.58 (*d*, *J* = 1.9, HO–C(24)); 3.57 (*dd*, *J* = 9.6, 1.3, H–C(14)); 3.49 (*ddd*, *J* = 10.3, 3.4, 1.3, H–C(15)); 3.41 (*s*, MeO); 3.38 (*m*, H–C(13); H–C(33)); 3.35 (*s*, MeO); 3.30 (*s*, MeO); 3.05–2.95 (*m*, 1 H–C(6), 1 H–C(23), H–C(32)); 2.71 (br. *s*, HO–C(33)); 2.40–0.70 (overl. *m*s); 1.64 (*d*, *J* = 1.4, Me–C(27)); 1.15 (*s*, Me–C(19)). Anal calc. for $C_{43}H_{69}N_1O_{12}$: C 65.21, H 8.78, N 1.77; found: C 64.9, H 8.6, N 1.7. HR-MS: 812.4926 ($[M+Na]^+$; calc. 812.4925).

Data of **8**. White foam. ^{1}H-NMR: 5.83 (*t*, *J* = 2.3, H–C(6)); 5.48 (*dt*, *J* = 15.6, 6.4, H–C(21)); 5.42 (*dd*, *J* = 5.7, 2.1, H–C(2)); 5.20 (*m*, H–C(20), H–C(26), H–C(29)); 4.49 (*d*, *J* = 1.6, OH); 4.36 (*d*, *J* = 7.8, HO–C(9)/H–C(9)); 4.19 (*d*, *J* = 7.8, HO–C(9)/H–C(9)); 4.07 (*s*, OH); 3.72 (*dd*, *J* = 9.5, 1.4, H–C(14)); 3.65 (br. *t*, *J* = 9.7); 3.52 (*m*); 3.41 (*s*, MeO); 3.35–3.20 (overl. *m*s); 3.33 (*s*, MeO); 3.27 (*s*, MeO); 3.11 (*s*, MeO); 3.01 (*m*, H–C(32)); 2.78 (br. *s*, OH); 2.64 (*d*, *J* = 17.8, H_a–C(23)); 2.40–0.80 (overl. *m*s); 1.62 (*s*, Me–C(27)); 1.35 (*s*, Me–C(19)). ^{13}C-NMR: 216.1 (C(22)); 173.8 (C(1/8)); 171.0 (C(1/8)); 134.2 (C(20)); 131.7 (C(21)); 129.8 (C(27)); 129.0 (C(29)); 122.4 (C(20)); 97.3 (C(10)); 84.3 (C(32)); 80.4 (C(6)); 76.8; 75.5; 74.8; 73.5; 73.3; 72.4; 71.0; 56.9; 56.6; 56.5; 56.2; 52.5; 52.3; 45.7; 40.4; 38.7; 35.9; 35.0; 34.94; 34.90; 33.6; 31.3; 30.5; 30.1; 25.7; 25.3; 25.0; 20.0; 18.9; 16.4; 15.5; 14.3; 13.5; 11.3. Anal calc. for $C_{44}H_{73}N_1O_{13}$: C 64.13, H 8.93, N 1.70; found: C 64.8, H 9.2, N 1.6.

Compounds **2b** *and* **4b**. Prepared analogously to **2a** starting from **1b** according to *GP B*.

Data of **2b**. White foam. Yield: 66%. ^{1}H-NMR (*ca.* 4:1 mixture of rotamers): major rotamer: 5.83 (*t*, *J* = 2.6, H–C(6)); 5.45 (*dd*, *J* = 5.4, 1.9, H–C(2)); 5.29 (*d*, *J* = 8.7, H–C(20/29)); 5.07 (br. *s*, H–C(26)); 4.89 (*d*, *J* = 10.5, H–C(20/29)); 4.55 (*m*, H–C(33)); 4.49 (*s*, HO–C(10)); 4.42 (*s*, H–C(9), HO–C(9)); 3.78 (*dd*, *J* = 9.5, 1.4, H–C(14)); 3.60 (*m*, H–C(15), H–C(24)); 3.50–3.10 (overl. *m*s); 3.10 (*s*, MeO–C(6)); 2.80 (*dd*, *J* = 18.1, 3.5, 1 H–C(23)); 2.40 (*dd*, *J* = 18.1, 5.9, 1 H–C(23)); 2.40–0.80 (overl.

*m*s); minor rotamer: 6.14 (*s*, HO–C(10)); 5.53 (br. *s*, H–C(6)); 5.11 (*d*, *J* = 8.8, H–C(20/29)); 5.04 (br. *s*, H–C(26)); 4.83 (*d*, *J* = 9.7, H–C(20/29)); 4.69 (*dd*, *J* = 6.7, 4.2, H–C(2)); 4.55 (*m*, H–C(33)); 4.38 (br. *s*, H–C(9)/HO–C(9)); 4.26 (br. *s*, H–C(9)/HO–C(9)); 3.90 (*m*, H–C(24)); 3.85 (*dd*, *J* = 9.5, 2.1, H–C(14)); 3.73 (*s*, OH); 3.60 (*m*, H–C(15)); 3.50–3.10 (overl. *m*s); 2.59 (*dd*, *J* = 16.6, 2.0, 1 H–C(23)); 2.40–0.70 (overl. *m*s). ^{13}C-NMR: major rotamer: 214.0 (C(22)); 173.3 (C(8)); 170.7 (C(1)); 139.7 (C(19)); 131.0 (C(27)); 129.4 (C(29)); 123.8 (C(20)); 97.0 (C(10)); 80.5 (C(6)); 79.3; 77.6; 75.2; 74.7; 73.4; 72.5; 71.8; 59.3; 57.1; 56.29; 56.27; 55.6; 54.2; 52.1; 49.2; 43.7; 40.2; 36.0; 34.9; 33.8; 33.4; 31.9; 31.8; 30.5; 26.1; 25.7; 25.1; 22.6; 20.1; 16.0; 15.3; 15.0; 14.8; 14.0; 11.3; 11.0. ^{13}C-NMR: minor rotamer: 213.2 (C(22)); 174.2 (C(8)); 168.4 (C(1)); 140.5 (C(19)); 131.2 (C(27)); 129.0 (C(29)); 122.7 (C(20)); 99.7 (C(10)); 84.4 (C(6)); 76.9; 76.7; 73.4; 70.8; 70.1; 69.4; 59.3; 57.5; 56.0; 55.8; 54.9; 52.3; 48.6; 43.9; 41.0; 36.5; 34.8; 32.9; 32.2; 29.8; 26.9; 25.4; 25.2; 23.4; 18.0; 16.2; 16.1; 15.0; 14.1; 11.5; 9.8. HR-MS: 864.4649 ($[M+Na]^+$; calc. 864.4641).

Data of **4b**. White foam. Yield: 10%. ^{1}H-NMR (*ca.* 5:2 mixture of rotamers): major rotamer: 8.08 (*s*, HC=O); 5.39 (*d*, *J* = 8.7, H–C(20/29)); 5.21 (*d*, *J* = 8.1, H–C(26)); 5.13 (*d*, *J* = 5.4, H–C(2)); 4.94 (*d*, *J* = 9.9, H–C(20/29)); 4.53 (br. *d*, *J* = 2.7, H–C(33)); 4.06 (*dd*, *J* = 7.8, 1.6); 3.98 (*m*); 3.69 (*m*); 3.60–3.30 (overl. *m*s); 3.22 (*m*, H–C(21)); 2.88 (br. *s*, OH); 2.64 (*m*, 2 H–C(23)); 2.48 (*m*, H–C(11)); 2.40–0.80 (overl. *m*s); minor rotamer: 8.02 (*s*, HC=O); 5.39 (*d*, *J* = 8.7, H–C(20/29)); 5.23 (*d*, *J* = 7.6, H–C(26)); 4.94 (*d*, *J* = 9.9, H–C(20/29)); 4.53 (br. *d*, *J* = 2.7, H–C(33)); 4.32 (br. *d*, *J* = 12.9, H_a–C(6)); 4.25 (*d*, *J* = 5.2, H–C(2)); 4.06 (*dd*, *J* = 7.8, 1.6); 3.98 (*m*); 3.69 (*m*); 3.60–3.30 (overl. *m*s); 3.22 (*m*, H–C(21)); 2.80 (*m*, H_b–C(6)); 2.64 (*m*, 2 H–C(23)); 2.48 (*m*, H–C(11)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: both rotamers: 212.1; 212.0*; 173.6; 169.8*; 169.5; 162.3*; 161.9; 138.5*; 138.4; 133.7*; 133.6; 131.2; 131.0*; 124.2; 82.6; 82.5; 82.0; 79.4; 79.3*; 77.2; 73.64; 73.56*; 67.1; 59.31; 59.26*; 57.6; 57.0*; 56.8; 55.8; 54.5; 50.7; 48.5*; 48.4; 45.9*; 45.7; 44.0; 39.0; 38.9*; 38.2*; 35.0; 34.9; 34.8*; 33.3; 32.2; 31.8; 31.5; 27.3*; 26.9; 26.5; 25.5; 25.3; 24.3; 24.2*; 21.43; 21.39*; 19.6*; 19.5; 17.0; 16.4; 12.4; 11.6; 8.94; 8.87*.

Compound **2c**. Prepared analogously to **2a** starting from **1c** according to *GP B.* White foam. Yield: 30%. Anal. HPLC of the crude photolysate indicated a yield of *ca.* 70%. No attempt was made to isolate **4c**. ^{1}H-NMR (*ca.* 5:2 mixture of rotamers): major rotamer: 5.83 (br. *t*, *J* = 2.8, H–C(6)); 5.70 (*m*, H–C(37)); 5.45 (*dd*, *J* = 5.5, 1.9, H–C(2)); 5.22 (*d*, *J* = 8.9, H–C(20/29)); 5.08 (br. *s*, H–C(26)); 5.03 (*dm*, *J* = 17.0, 1 H–C(38)); 4.97 (*dm*, *J* = 11.2, 1 H–C(38)); 4.91 (*d*, *J* = 10.5, H–C(20/29)); 4.50 (*s*, HO–C(10)); 4.42, 4.40 (2*d* as *ABq*, H–C(9), HO–C(9)); 3.78 (*dd*, *J* = 9.6, 1.4, H–C(14)); 3.60 (*m*, H–C(15), H–C(24)); 3.50–3.20 (overl. *m*s); 3.10 (*s*, MeO–C(6)); 3.00 (*m*, H–C(32)); 2.84 (br. *s*, OH); 2.81 (*dd*, *J* = 18.1, 3.5, 1 H–C(23)); 2.55–0.70 (overl. *m*s); minor rotamer: 6.12 (*d*, *J* = 1.6, HO–C(10)); 5.70 (*m*, H–C(37)); 5.56 (br. *s*, H–C(6)); 5.05–4.95 (*m*, H–C(20/29), H–C(26), H–C(38)); 4.86 (*d*, *J* = 9.7, H–C(20/29)); 4.68 (*dd*, *J* = 6.8, 4.4, H–C(2)); 4.58 (br. *s*, HO–C(9)); 4.37 (br. *s*, H–C(9)); 3.91 (*m*, H–C(24)); 3.84 (*dd*, *J* = 9.5, 2.2, H–C(14)); 3.65 (*s*, OH); 3.60 (*m*, H–C(15)); 3.50–3.20 (overl. *m*s); 3.00 (*m*, H–C(32)); 2.84 (br. *s*, OH); 2.59 (*dd*, *J* = 16.6, 2.0, 1 H–C(23)); 2.55–0.70 (overl. *m*s). ^{13}C-NMR: major rotamer: 213.2 (C(22)); 173.3 (C(8)); 170.7 (C(1)); 139.9 (C(19)); 135.7 (C(37)); 131.2 (C(27)); 129.7 (C(29)); 123.3 (C(20)); 116.5 (C(38)); 97.0 (C(10)); 84.3 (C(32)); 80.5 (C(6)); 77.7 (C(26)); 75.3 (C(9)); 74.8 (C(15)); 73.5 (C(33)); 73.4 (C(13)); 72.6 (C(14)); 71.8 (C(24)); 57.1 (MeO); 56.5 (MeO); 56.3 (2 MeO); 52.6 (C(21)); 52.1 (C(2)); 49.2 (C(18)); 43.6 (C(23)); 40.4 (C(25)); 36.0 (C(11)); 35.0; 34.8; 34.0; 33.8; 33.5; 31.4; 30.5; 30.2; 26.2; 25.7; 25.1; 20.1; 16.1; 15.4; 14.9; 13.9; 11.1; minor rotamer: 212.3 (C(22)); 174.4 (C(8)); 168.4 (C(1)); 140.7 (C(19)); 135.6 (C(37)); 131.2 (C(27)); 129.1 (C(29)); 122.1 (C(20)); 116.4 (C(38)); 99.8 (C(10)); 84.4 (C(6)); 84.3 (C(32)); 77.0 (C(15/26)); 76.9 (C(15/26)); 73.9 (C(13)); 73.5 (C(33)); 70.8 (C(14)); 70.1 (C(24)); 69.6 (C(9)); 57.6; 56.0; 55.8; 52.9 (C(21)); 52.3 (C(2)); 48.6 (C(18)); 44.1 (C(23)); 41.2 (C(25); 36.6; 35.0; 34.9; 34.6; 32.9; 32.2; 30.3; 29.9; 25.4; 25.0; 23.4; 18.0; 16.20; 16.17; 15.1; 14.2; 9.9. HR-MS: 858.4985 ($[M+Na]^+$; calc. 858.4980).

Compound **2d**. Prepared analogously to **2a** starting from **1d** according to *GP B.* **1d** (1.0 g, 1.29 mmol) gave crude **2d** (1.04 g, 100%) which was taken to the next step without purification.

Compound **2e**. Prepared analogously to **2a** starting from **1a**/EtOH according to *GP B.* White foam. Yield: 34% ^{1}H-NMR (*ca.* 8:3 mixture of rotamers): major rotamer: 5.92 (*t*, *J* = 2.7, H–C(6)); 5.45 (*dd*, *J* = 5.5, 1.9, H–C(2)); 5.28 (*d*, *J* = 2.0, H–C(26)); 5.25 (*d*, *J* = 9.0, H–C(20/29)); 4.86 (*d*, *J* = 9.2, H–C(20/29)); 4.52 (*s*, HO–C(10)); 4.47 (*d*, *J* = 7.4, H–C(9)/HO–C(9)); 4.34 (*d*, *J* = 7.4, H–C(9)/HO–C(9)); 3.76 (*dd*, *J* = 9.6, 1.4, H–C(14)); 3.72 (*m*, H–C(24)); 3.58 (*m*, H–C(15)); 3.45–3.15 (overl.

*m*s); 2.99 (*m*, H–C(32)); 2.76 (*dd*, *J* = 18.0, 3.1, 1 H–C(23)); 2.74 (br. *s*, OH); 2.50–0.70 (overl. *m*s); minor rotamer: 6.19 (*s*, HO–C(10)); 5.60 (br. *s*, H–C(6)); 5.07 (*m*, H–C(20/29), H–C(26)); 4.85 (*d*, H–C(20/29)); 4.65 (*dd*, *J* = 6.6, 4.4, H–C(2)); 4.32 (br. *s*, H–C(9)); 4.07 (br. *s*, HO–C(9)); 3.89 (*m*, H–C(24)); 3.85 (*dd*, *J* = 9.5, 2.2, H–C(14)); 3.65 (*s*, OH); 3.50–3.20 (overl. *m*s); 2.99 (*m*, H–C(32)); 2.74 (br. *s*, OH); 2.58 (*dd*, *J* = 16.5, 2.0, 1 H–C(23)); 2.50–0.70 (overl. *m*s). ^{13}C-NMR: major rotamer: 214.0 (C(22)); 173.1 (C(8)); 170.3 (C(1)); 139.7 (C(19)); 132.6 (C(27)); 130.1 (C(29)); 123.9 (C(20)); 96.9 (C(10)); 84.2 (C(32)); 78.2 (C(6)); 76.9 (C(26)); 75.3 (C(9)); 74.9 (C(15)); 73.52; 73.46; 72.5 (C(14)); 71.1 (C(24)); 63.7 (Me*C*H$_2$O); 57.2 (MeO)); 56.4 (MeO); 56.3 (MeO); 54.0 (C(2/21)); 52.2(C(2/21)); 49.1 (C(18)); 43.2 (C(23)); 41.6 (C(25)); 36.1 (C(11)); 34.9; 34.7; 33.8; 33.0; 31.3; 30.9; 30.3; 26.1; 25.8; 22.9; 20.1; 16.0; 15.4; 14.9; 14.7; 13.9; 11.4; 11.1; minor rotamer: 212.4 (C(22)); 174.3 (C(8)); 168.5 (C(1)); 140.6 (C(19)); 132.2 (C(27)); 129.2 (C(29)); 122.6 (C(20)); 99.8 (C(10)); 84.2 (C(32)); 82.3 (C(6)); 76.8; 73.9 (C(13)); 73.5 (C(33)); 70.8 (C(14)); 70.2 (C(24)); 69.3 (C(9)); 63.4 (Me*C*H$_2$O); 57.6; 56.4; 56.0; 54.9 (C(21)); 52.4 (C(2)); 48.7 (C(18)); 43.8 (C(23)); 41.8 (C(25)); 36.6; 34.8; 32.9; 32.3; 30.5; 30.2; 25.5; 25.2; 23.7; 18.0; 16.23; 16.18; 15.2; 14.8; 14.2; 11.5; 10.0. HR-MS: 860.5138 ($[M+Na]^+$; calc. 860.5136).

Compound **2f**. Prepared analogously to **2a** starting from **1a**/PrOH according to *GP B*. White foam. Yield: 9%. ^{1}H-NMR (*ca.* 3:1 mixture of rotamers): major rotamer: 5.93 (*t*, *J* = 2.6, H–C(6)); 5.47 (*dd*, *J* = 5.5, 1.9, H–C(2)); 5.28 (*d*, *J* = 1.6, H–C(26)); 5.25 (*d*, *J* = 8.9, H–C(20/29)); 4.88 (*d*, *J* = 10.4, H–C(20/29)); 4.53 (*s*, HO–C(10)); 4.49 (*d*, *J* = 7.2, H–C(9)/HO–C(9)); 4.35 (*d*, *J* = 7.2, H–C(9)/HO–C(9)); 3.78 (*dd*, *J* = 9.6, 1.3, H–C(14)); 3.74 (*m*, H–C(24)); 3.59 (*m*, H–C(15), OH); 3.45–3.15 (overl. *m*s); 3.00 (*m*, H–C(32)); 2.77 (*dd*, *J* = 18.0, 3.0, H$_a$–C(23)); 2.70 (br. *s*, OH); 2.50–0.70 (overl. *m*s); minor rotamer: 6.19 (*s*, HO–C(10)); 5.62 (br. *s*, H–C(6)); 5.07 (*m*, H–C(20/29), H–C(26)); 4.88 (*d*, *J* ≈ 10, H–C(20/29)); 4.67 (*dd*, *J* = 6.8, 4.3, H–C(2)); 4.35 (br. *s*, H–C(9)); 4.06 (br. *s*, HO–C(9)); 3.90 (*m*, H–C(24)); 3.86 (*dd*, *J* = 9.5, 2.2, H–C(14)); 3.69 (*m*, MeC*H*$_2$O); 3.50–3.20 (overl. *m*s); 2.99 (*m*, H–C(32)); 2.70 (br. *s*, OH); 2.59 (*dd*, *J* = 16.5, 2.0, H$_a$–C(23)); 2.50–0.70 (overl. *m*s). HR-MS: 874.5303 ($[M+Na]^+$; calc. 874.5293).

Compound **3a**. According to *GP D*, **2a** (12.4 g, 15.05 mmol), CH_2Cl_2 (108 ml), $Cu(OAc)_2 \cdot H_2O$ (138 mg, 0.7 mmol), pyridine (123 µl, 1.5 mmol), 4-Å mol. sieves (11.5 g), r.t., 18 h. FC (SiO_2-2.5% $NaHCO_3$) gave **3a** (11.9 g, 96%). White foam. ^{1}H-NMR (DMSO; *ca.* 2:1 mixture of rotamers): major rotamer: 5.68 (*t*, *J* = 2.9, H–C(6)); 5.20 (*d*, *J* = 8.9, H–C(20/29)); 5.10 (br. *s*, H–C(26)); 4.91 (*d*, *J* = 10.1, H–C(20/29)); 4.47 (br. *d*, *J* = 5.2, H–C(2)); 4.20 (*d*, *J* = 1.2, HO–C(10)); 3.73 (*m*, H–C(24)); 3.72 (*dd*, *J* = 9.6, 1.2, H–C(14)); 3.65–3.05 (overl. *m*s); 3.02 (*m*, H–C(32)); 2.75–2.60 (*m*, 1 H–C(23), OH); 2.40–0.80 (overl. *m*s); minor rotamer: 5.31 (*s*, HO–C(10)); 5.18 (*s*, H–C(26)); 5.06 (*m*, H–C(6)); 5.02 (*d*, *J* = 9.0, H–C(20/29)); 5.00 (*d*, *J* = 10.0, H–C(20/29)); 4.67 (*t*, *J* = 6.5, H–C(2)); 3.98 (*m*, H–C(24)); 3.92 (*dd*, *J* = 9.5, 2.0, H–C(14)); 3.65–3.05 (overl. *m*s); 3.02 (*m*, H–C(32)); 2.75–2.60 (*m*, 1 H–C(23), OH); 2.40–0.80 (overl. *m*s). ^{13}C-NMR (both rotamers): 214.1*; 213.6; 195.4; 190.4*; 169.1; 167.7*; 167.3; 166.9*; 139.6*; 138.8; 131.2; 131.0*; 129.9; 129.3*; 123.7; 123.1*; 98.5*; 96.9; 84.3; 83.4*; 79.4; 78.0; 77.2*; 76.0*; 74.7; 73.62; 73.56; 73.47*; 72.7; 71.6*; 71.3; 69.3*; 57.3; 56.9; 56.5; 56.4; 56.3; 55.7*; 54.8*; 54.5; 54.2; 53.0*; 49.0*; 48.8; 44.1*; 43.6; 40.8; 40.7*; 36.2*; 35.1; 34.9*; 34.8; 33.2*; 32.94; 32.90*; 32.8; 31.31; 31.27*; 30.4; 30.2; 29.4*; 26.4; 25.7; 25.5*; 24.4; 23.65*; 23.59; 20.2; 18.8; 16.2; 16.1; 16.0; 15.9; 15.2*; 15.0; 14.2*; 14.0; 11.6*; 11.0; 10.7; 10.0*. HR-MS: 844.4827 ($[M+Na]^+$; calc. 844.4823).

Compound **3b**. Prepared analogously to **3a** starting from **2b** according to *GP D*. White foam. Yield: 10%. ^{1}H-NMR (*ca.* 2:1 mixture of rotamers): major rotamer: 5.68 (*t*, *J* = 3.0, H–C(6)); 5.27 (*d*, *J* = 8.6, H–C(20/29)); 5.09 (br. *s*, H–C(26)); 4.92 (*d*, *J* = 10.0, H–C(20/29)); 4.55 (*m*, H–C(33)); 4.47 (br. *d*, *J* = 5.5, H–C(2)); 4.18 (*d*, *J* = 1.2, HO–C(10)); 3.73 (*m*, H–C(24)); 3.71 (*dd*, *J* = 9.5, 1.1, H–C(14)); 3.65–3.05 (overl. *m*s); 2.67 (*dd*, *J* = 15.5, 3.3, 1 H–C(23)); 2.40–0.80 (overl. *m*s); minor rotamer: 5.36 (*s*, HO–C(10)); 5.19 (*s*, H–C(26)); 5.07 (overl. *d*, H–C(20/29)); 5.06 (br. *s*, H–C(6)); 5.02 (*d*, *J* = 9.2, H–C(20/29)); 4.65 (*t*, *J* = 6.6, H–C(2)); 4.55 (*m*, H–C(33)); 3.98 (*m*, H–C(24)); 3.92 (*dd*, *J* = 9.5, 2.4, H–C(14)); 3.65–3.05 (overl. *m*s); 2.70 (br. *d*, *J* ≈ 17, 1 H–C(23)); 2.40–0.80 (overl. *m*s). HR-MS: 862.4487 ($[M+Na]^+$; calc. 862.4484).

Compound **3c**. Prepared analogously to **3a** starting from **2c** according to *GP D*. White foam. Yield: 63%. ^{1}H-NMR (*ca.* 2:1 mixture of rotamers): major rotamer: 5.70 (*m*, H–C(6), H–C(37)); 5.21 (*d*, *J* = 8.9, H–C(20/29)); 5.11 (br. *s*, H–C(26)); 5.08–4.96 (*m*, H–C(38)); 4.93 (*d*, *J* = 10.1, H–C(20/29)); 4.45 (*dd*, *J* = 5.2, 1.8, H–C(2)); 4.20 (*d*, *J* = 1.2, HO–C(10)); 3.75 (*m*, H–C(24)); 3.72 (*dd*, *J* = 9.6, 1.3,

H–C(14)); 3.65–3.15 (overl. *m*s); 3.01 (*m*, H–C(32), OH); 2.70 (br. *s*, OH); 2.66 (*dd*, *J* = 17.2, 3.2, 1 H–C(23)); 2.40–0.80 (overl. *m*s); minor rotamer: 5.70 (*m*, H–C(37)); 5.26 (*s*, HO–C(10)); 5.18 (*s*, H–C(26)); 5.08–4.96 (*m*, H–C(6), H–C(20), H–C(29), 2 H–C(38)); 4.67 (*t*, *J* = 6.5, H–C(2)); 3.98 (*m*, H–C(24)); 3.92 (*dd*, *J* = 9.5, 2.0, H–C(14)); 3.65–3.05 (overl. *m*s); 3.01 (*m*, H–C(32), OH); 2.70 (br. *s*, OH); 2.67 (*dd*, *J* ≈ 17, H–C(23)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR (both rotamers): 213.2*; 212.9; 195.4; 190.4*; 169.1; 167.7*; 167.3; 166.9*; 139.8*; 139.0; 135.5; 135.4*; 131.2; 130.9*; 129.9; 129.3*; 123.1; 122.4*; 116.70; 116.65*; 98.5*; 96.9; 84.2; 83.4*; 79.4; 77.9; 77.2*; 75.9*; 74.7; 73.57; 73.55; 73.43*; 72.6; 71.5*; 71.3; 69.2*; 57.3; 56.9; 56.5; 56.33; 56.30; 55.7*; 54.6; 54.2; 52.9*; 52.8; 52.7; 48.9*; 48.7; 44.4*; 43.6; 40.71; 40.66*; 36.1*; 35.5*; 35.0; 34.90; 34.86; 34.81; 34.76; 33.2*; 32.9; 32.7; 31.3; 31.2*; 30.4; 30.1; 29.5*; 26.3; 25.6; 25.5*; 23.7*; 20.2; 18.7*; 16.2; 16.1; 15.8; 15.3*; 15.1; 14.2*; 14.0; 10.8; 10.0*. HR-MS: 856.4828 ([*M* + Na]$^+$; calc. 856.4823).

Compound **3e**. Prepared analogously to **3a** starting from **2e** according to *GP D*. White foam. Yield: 79%. ^{1}H-NMR (*ca.* 3 : 2 mixture of rotamers): major rotamer: 5.77 (br. *t*, *J* = 3.0, H–C(6)); 5.27 (*d*, *J* = 1.5, H–C(26)); 5.22 (*d*, *J* = 8.9, H–C(20/29)); 4.93 (*d*, *J* = 9.9, H–C(20/29)); 4.43 (*d*, *J* = 5.0, H–C(2)); 4.17 (br. *s*, HO–C(10)); 3.81 (*m*, H–C(24)); 3.69 (*dd*, *J* = 9.6, 1.1, H–C(14)); 3.65–3.10 (overl. *m*s); 3.04 (*d*, *J* = 4.9, OH); 2.99 (*m*, H–C(32)); 2.65 (*dd*, *J* = 17.0, 3.0, 1 H–C(23)); 2.50–0.80 (overl. *m*s); minor rotamer: 5.36 (*d*, *J* = 1.5, H–C(26)); 5.20 (*s*, HO–C(10)); 5.15 (br. *d*, H–C(6)); 5.03 (*d*, *J* ≈ 8.0, H–C(20/29)); 5.01 (*d*, *J* ≈ 8.5, H–C(20/29)); 4.65 (*t*, *J* = 6.8, H–C(2)); 3.96 (*m*, H–C(24)); 3.91 (*dd*, *J* = 9.5, 2.3, H–C(14)); 3.86 (*m*, MeC*H*$_2$O); 3.65–3.10 (overl. *m*s); 2.99 (*m*, H–C(32)); 2.70 (br. *s*, OH); 2.68 (br. *d*, *J* ≈ 17, 1 H–C(23)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR (both rotamers): 214.3*; 213.6; 195.7; 190.3*; 169.0; 167.6*; 167.3; 166.6*; 139.7*; 138.8; 132.1; 131.5*; 130.3; 129.2*; 123.5; 123.0*; 98.5*; 97.0; 84.2; 81.7*; 77.4; 76.8; 76.0*; 74.8; 73.7; 73.53; 73.47*; 72.8; 71.5*; 70.8; 69.4*; 63.8; 63.3*; 57.3; 56.9; 56.5; 56.4; 56.3; 54.7*; 54.5; 53.1; 52.9*; 49.0*; 48.6; 43.7*; 43.1; 41.3; 40.7*; 36.2*; 35.0; 34.9; 34.8; 34.7; 33.1*; 32.8; 32.6; 31.24; 31.21*; 30.6; 30.5; 30.3; 29.7*; 26.4; 25.7; 25.5; 24.6; 23.7*; 23.6; 20.3; 18.8*; 16.2*; 16.1; 15.94*; 15.89; 15.32; 15.25; 14.9; 14.5; 14.3; 14.0; 11.7*; 11.6; 10.6; 10.0*. HR-MS: 858.4980 ([*M* + Na]$^+$; calc. 858.4980).

Compound **3f**. Prepared analogously to **3a** starting from **2f** according to *GP D*. White foam. Yield: 74%. ^{1}H-NMR (*ca.* 5 : 4 mixture of rotamers): major rotamer: 5.77 (br. *t*, *J* = 2.6, H–C(6)); 5.27 (*d*, *J* = 1.7, H–C(26)); 5.21 (*d*, *J* = 8.9, H–C(20/29)); 4.94 (*d*, *J* = 9.9, H–C(20/29)); 4.43 (br. *d*, *J* = 5.5, H–C(2)); 4.18 (br. *s*, HO–C(10)); 3.82 (*m*, H–C(24)); 3.69 (*dd*, *J* = 9.6, 1.1, H–C(14)); 3.65–3.10 (overl. *m*s); 3.04 (*d*, *J* = 5.1, OH); 3.00 (*m*, H–C(32)); 2.69 (br. *s*, OH); 2.66 (*dd*, *J* = 17.0, 3.1, 1 H–C(23)); 2.50–0.80 (overl. *m*s); minor rotamer: 5.41 (*d*, *J* = 1.5, H–C(26)); 5.20 (*s*, HO–C(10)); 5.14 (*dm*, H–C(6)); 5.02 (*m*, H–C(20), H–C(29)); 4.62 (*dd*, *J* = 7.5, 6.2, H–C(2)); 3.97 (*m*, H–C(24)); 3.91 (*dd*, *J* = 9.5, 2.2, H–C(14)); 3.77 (*dt*, *J* = 9.2, 6.7, MeCH$_2$C*H*$_2$O); 3.65–3.10 (overl. *m*s); 3.00 (*m*, H–C(32)); 2.69 (*m*, 1 H–C(23), OH); 2.40–0.80 (overl. *m*s). HR-MS: 872.5145 ([*M* + Na]$^+$; calc. 872.5136).

Compound **5a**. According to *GP E*, **2a** (13.0 g, 15.78 mmol), NH_4Cl (474 mg, 8.94 mmol), DMF (1 l), 78°, 4 h, and purification by prep. HPLC gave **5a** (11.62 g, 93%). Colorless crystals. M.p. 132–137° (Et_2O/pentane). ^{1}H-NMR (*ca.* 7 : 3 mixture of rotamers): major rotamer: 7.01 (*d*, *J* = 8.6, H–C(6)); 5.40 (*d*, *J* = 1.8, HO–C(10)); 5.08 (*d*, *J* = 3.6, H–C(26)); 5.10–4.90 (*m*, H–C(2), H–C(5), H–C(20), H–C(29)); 4.47 (*d*, *J* = 11.6, H–C(9)); 4.05 (br. *d*, J = 11.6, HO–C(9)); 3.97 (*m*, H–C(24)); 3.75 (*dd*, *J* = 9.5, 1.8, H–C(14)); 3.52 (*m*, H–C(15)); 3.45–3.15 (overl. *m*s, H–C(13), H–C(21), H–C(33), OH, 3 MeO); 2.99 (*m*, H–C(32)); 2.88 (*d*, *J* = 1.3, OH); 2.70 (*dd*, *J* = 16.6, 2.9, 1 H–C(23)); 2.50–0.80 (overl. *m*s); minor rotamer: 7.22 (*d*, *J* = 9.7, H–C(6)); 5.60 (br. *t*, H–C(2)); 5.27 (br. *s*, H–C(26)); 5.19 (*m*, H–C(5)); 5.17 (br. *s*, HO–C(10)); 5.10–4.90 (*m*, H–C(20), H–C(29)); 4.17 (*d*, *J* = 8.1, H–C(9)); 3.99 (*d*, *J* = 8.1, HO–C(9)); 3.86 (*m*, H–C(24)); 3.73 (*dd*, *J* = 9.5, 1.3, H–C(14)); 3.60 (*m*, H–C(15)); 3.45–3.15 (overl. *m*s, H–C(13), H–C(21), H–C(33), OH, 3 MeO); 2.99 (*m*, H–C(32)); 2.84 (*d*, *J* = 1.3, OH); 2.76 (*dd*, *J* = 16.6, 3.0, 1 H–C(23)); 2.50–0.80 (overl. *m*s). ^{13}C-NMR (both rotamers): 213.8; 212.9; 171.2; 169.6; 169.5; 168.8; 140.2; 139.5; 132.4; 131.9; 130.2; 129.9; 125.3; 123.8; 123.2; 123.0; 111.0; 106.7; 99.5; 97.7; 84.2; 84.1; 78.6; 77.7; 77.2; 75.5; 74.0; 73.8; 73.51; 73.48; 73.0; 72.3; 71.6; 70.7; 69.8; 69.0; 57.6; 57.4; 56.5; 56.2; 56.0; 55.4; 54.7; 54.3; 52.8; 49.5; 48.1; 43.6; 43.2; 40.9; 39.9; 36.1; 35.3; 34.9; 34.84; 34.78; 33.1; 32.8; 32.7; 32.1; 31.2; 30.5; 30.50; 30.46; 26.5; 26.2; 24.0; 23.9; 23.3; 20.4; 19.3; 19.1; 16.22; 16.16; 15.5; 14.1; 11.65; 11.60; 10.1; 9.6. Anal calc. for $C_{43}H_{69}N_1O_{12}$ (792.03): C 65.2, H 8.78, N 1.77; found: C 64.41, H 8.29, N 1.77.

Compound **5b**. A soln. of **1b** (3 g, 3.70 mmol) in MeCN (500 ml) was irradiated for 15 h according to *GP B*. The solvent was stripped off, and the residue was purified by FC (SiO_2-5% $NaHCO_3$; toluene/AcOEt 1:2) to give two fractions which were further purified by prep. HPLC (*Polygosyl 10 CN* column, cyclohexane/i-PrOH 9:1 and 85:15) to give the 33-epichloro analog of **9** (1.13 g, 38%; this derivative is not discussed in the publication), **4b** (98 mg, 3%), and **5b** (50 mg, 2%). It is likely that **5b** could well be prepared through elimination of MeOH from **2b** analogously to the preparation of **5a**; however, this was not checked.

Data of **5b**. Anal. HPLC (*Polygosyl60 10 CN* column, cyclohexane/i-PrOH 85:15, 1 ml/min isocratic): t_R 5.57 min. ^{1}H-NMR (*ca.* 7:3 mixture of rotamers): characteristic signals: 7.24* (*d*, *J* = 9.7, H–C(6)); 7.01 (*d*, *J* = 8.6, H–C(6)).

Compound **5c**. Prepared analogously to **5a** starting from **2c** according to *GP E*. White foam. Yield: 77%. ^{1}H-NMR (*ca.* 2:1 mixture of rotamers): major rotamer: 7.00 (*d*, *J* = 8.6, H–C(6)); 5.70 (*m*, H–C(37)); 5.37 (*d*, *J* = 1.8, HO–C(10)); 5.10–4.95 (*m*, H–C(2), H–C(20), H–C(26), H–C(29), H–C(38)); 4.94 (*m*, H–C(5)); 4.48 (br. *d*, H–C(9)); 4.00 (*m*, HO–C(9), H–C(24)); 3.76 (*dd*, *J* = 9.6, 1.8, H–C(14)); 3.52 (*m*, H–C(15)); 3.45–3.15 (overl. *m*s, H–C(13), H–C(21), H–C(33), OH, 3 MeO); 2.99 (*m*, H–C(32)); 2.85 (br. *s*, OH); 2.70 (*dd*, *J* = 16.8, 3.0, 1 H–C(23)); 2.50–0.80 (overl. *m*s); minor rotamer: 7.22 (*d*, *J* = 9.6, H–C(6)); 5.70 (*m*, H–C(37)); 5.60 (br. *t*, H–C(2)); 5.27 (br. *s*, H–C(26)); 5.19 (*m*, H–C(5)); 5.18 (*s*, HO–C(10)); 5.10–4.90 (*m*, H–C(20), H–C(29), H–C(38)); 4.17 (*d*, H–C(9)); 4.00 (HO–C(9)); 3.85 (*m*, H–C(24)); 3.73 (*dd*, *J* = 9.6, 1.2, H–C(14)); 3.60 (*m*, H–C(15)); 3.45–3.15 (overl. *m*s, H–C(13), H–C(21), H–C(33), OH, 3 MeO); 2.99 (*m*, H–C(32)); 2.81 (br. *s*, OH); 2.77 (*dd*, *J* = 16.6, 3.0, 1 H–C(23)); 2.50–0.80 (overl. *m*s). ^{13}C-NMR: major rotamer: 211.1 (C(22)); 171.2 (C(1/8)); 168.9 (C(1/8)); 140.4 (C(19)); 135.4 (C(37)); 132.3 (C(27)); 130.3 (C(29)); 125.3 (C(6)); 122.4 (C(20)); 116.5 (C(38)); 106.7 (C(5)); 99.4 (C(10)); 84.1 (C(32)); 78.7 (C(26)); 77.1 (C(15)); 74.0 (C(13)); 73.5 (C(33)); 71.6 (C(14)); 69.7 (C(24)); 69.0 (C(9)); 57.6 (MeO); 56.5 (MeO); 56.0 (MeO); 53.3 (C(21)); 52.8 (C(2)); 48.0 (C(18)); 43.5 (C(23)); 41.0 (C(25)); 36.1 (C(16)); 35.1 (C(30/31/36)); 34.9 (C(30/31/36)); 34.8 (C(30/31/36)); 32.8 (C(11)); 32.1 (C(12)); 31.3 (C(34)); 30.5 (C(35)); 26.5 (C(17)); 23.3 (C(3)); 19.2 (*Me*–C(17)); 19.0 (C(4)); 16.3 (*Me*–C(11/19)); 16.2 (*Me*–C(11/19)); 14.1 (*Me*–C(27)); 10.2 (*Me*–C(25)). ^{13}C-NMR: minor rotamer: 213.1 (C(22)); 169.7 (C(1/8)); 169.4 (C(1/8)); 139.8 (C(19)); 135.6 (C(37)); 131.8 (C(27)); 129.9 (C(29)); 123.8 (C(6)); 122.6 (C(20)); 116.5 (C(38)); 111.1 (C(5)); 97.7 (C(10)); 84.2 (C(32)); 77.6 (C(26)); 75.5 (C(15)); 73.8 (C(13)); 73.5 (C(33)); 72.9 (C(9)); 72.2 (C(14)); 70.7 (C(24)); 57.4 (MeO); 56.6 (MeO); 56.2 (MeO); 54.7 (C(2)); 52.6 (C(21)); 49.4 (C(18)); 43.5 (C(23)); 39.9 (C(25)); 35.3 (C(11)); 34.9 (C(30/31/36)); 34.7 (C(30/31/36)); 33.0 (C(12); 32.7 (C(16)); 31.2 (C(34)); 30.5 (C(35)); 26.2 (C(17)); 23.9 (C(3)); 20.4 (*Me*–C(17)); 19.3 (C(4)); 16.2 (*Me*–C(11)); 15.6 (*Me*–C(19)); 14.1 (*Me*–C(27)); 9.7 (*Me*–C(25)). HR-MS: 826.4723 ($[M + Na]^+$; calc. 826.4717).

Compound **5d**. Prepared analogously to **5a** starting from crude **2d** (1.0 g, 1.23 mmol) according to *GP E*. Purification by prep. HPLC (*Polygosyl 10 CN* column; cyclohexane/i-PrOH 9:1, isocratic) gave **5d** (375 mg, 39%) as a foam. Anal. HPLC (*Polygosyl 10 CN* column; cyclohexane/i-PrOH 9:1, 2 ml/min, isocratic): t_R 4.66 min.

Compound **6a**. According to *GP D*, **5a** (0.1 g, 0.13 mmol), cupric bis(2-ethylhexanoate) (2.2 mg, 5 mol-%), pyridine (1 µl, 10 mol-%), 4-Å mol. sieves (0.5 g), CH_2Cl_2 (2 ml), O_2 balloon, r.t., 3 d, followed by purification by prep HPLC gave **6a** (91 mg, 91%). The reaction also worked well employing $Cu(OAc)_2$ under the same conditions. Using 1 equiv. of the Cu^{II} catalyst, the reaction time was reduced to 4 h. Colorless crystals from Et_2O/pentane. M.p. 169–172°. ^{1}H-NMR (*ca.* 10:7 mixture of rotamers): major rotamer: 6.81 (*d*, *J* = 8.3, H–C(6)); 5.20 (*d*, *J* = 2.9, H–C(26)); 5.10–5.02 (*m*, H–C(5), H–C(20), H–C(29), HO–C(10)); 4.94 (*m*, H–C(2)); 3.99 (*m*, H–C(24)); 3.88 (*dd*, *J* = 9.6, 2.7, H–C(14)); 3.56 (*m*, H–C(15)); 3.45 (*m*, H–C(13)); 3.41 (*m*, H–C(33)); 3.40 (*s*, MeO); 3.38 (*s*, MeO); 3.30 (*s*, MeO); 3.20 (*m*, H–C(21)); 3.00 (*ddd*, *J* = 11.2, 8.8, 4.3, H–C(32)); 2.75 (*s*, OH); 2.73 (*dd*, *J* = 17.3, 2.2, 1 H–C(23)); 2.44 (*m*, 1 H–C(3)); 2.40–0.80 (overl. *m*s); minor rotamer: 7.13 (*d*, *J* = 8.7, H–C(6)); 5.30 (*m*, H–C(5)); 5.27 (*d*, *J* = 3.9, H–C(26)); 5.08 (overl. *d*, H–C(29)); 4.98 (br. *d*, *J* = 10.2, H–C(20)); 4.96 (*m*, H–C(2)); 4.42 (*s*, HO–C(10)); 3.91 (*m*, H–C(24)); 3.66 (*dd*, *J* = 9.6, 1.2, H–C(14)); 3.56 (*m*, H–C(15)); 3.45–3.35 (*m*, H–C(13), H–C(33)); 3.40 (*s*, MeO); 3.37 (*s*, MeO); 3.33 (*s*, MeO); 3.26 (*m*, H–C(21)); 3.00 (*ddd*, *J* = 11.2, 8.8, 4.3, H–C(32)); 2.90 (*d*, *J* = 3.7, OH); 2.83 (*dd*, *J* = 15.4, 3.9,

1 H–C(23)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: major rotamer: 213.8 (C(22)); 190.8 (C(9)); 167.6 (C(1)); 162.9 (C(8)); 139.4 (C(19)); 131.9 (C(27)); 129.7 (C(29)); 123.2 (C(20)); 121.9 (C(6)); 112.0 (C(5)); 98.9 (C(10)); 84.2 (C(32)); 78.1 (C(26)); 76.5 (C(15)); 73.57 (C(13)); 73.51 (C(33)); 72.3 (C(14)); 69.2 (C(24)); 57.6 (MeO); 56.5 (MeO); 56.1 (MeO); 54.8 (C(21)); 53.0 (C(2)); 48.7 (C(18)); 43.5 (C(23)); 40.3 (C(25)); 35.4 (C(16)); 34.9 (C(30/31)); 34.8 (C(30/31)); 33.6; 32.5; 31.2 (C(34)); 30.5 (C(35)); 26.0 (C(17)); 25.5 (C(36)); 23.1 (C(3)); 19.3 (*Me*–C(17)); 18.8 (C(4)); 16.0 (*Me*–C(11)); 15.8 (*Me*–C(19)); 14.2 (*Me*–C(27)); 11.7 (C(37)); 9.9 (*Me*–C(25)); minor rotamer: 213.0 (C(22)); 194.6 (C(9)); 168.1 (C(1)); 162.2 (C(8)); 138.7 (C(19)); 131.6 (C(27)); 130.5 (C(29)); 123.9 (C(20)); 123.4 (C(6)); 109.7 (C(5)); 97.6 (C(10)); 84.2 (C(32)); 78.8 (C(26)); 75.5 (C(15)); 73.8 (C(13)); 73.5 (C(33)); 73.0 (C(14)); 69.8 (C(24)); 57.1 (MeO); 56.5 (MeO); 56.3 (MeO); 53.3 (C(2)); 55.1 (C(21)); 49.0 (C(18)); 44.5 (C(23)); 39.7 (C(25)); 34.9 (C(30)); 34.7 (C(31)); 34.4 (C(11)); 33.5 (C(16)); 32.4 (C(12)); 31.2 (C(34)); 30.5 (C(35)); 26.4 (C(17)); 24.4 (C(36)); 23.5 (C(3)); 20.4 (*Me*–C(17)); 19.3 (C(4)); 16.0 (*Me*–C(11)); 15.8 (*Me*–C(19)); 13.7 (*Me*–C(27)); 11.7 (C(37)); 9.7 (*Me*–C(25)). Anal calc. for $C_{43}H_{67}N_1O_{12}$: C 65.38, H 8.55, N 1.77; found: C 65.58, H 8.69, N 1.65.

Compound **6b**. To a mixture of Ph_3PCl_2 (44.4 mg of a 80% pure reagent, 0.11 mmol) and 2 ml of toluene was added, under Ar, collidine (43.7 µl, 0.33 mmol), followed by a soln. of **6a** (70 mg, 0.09 mmol) in 3 ml of toluene. The mixture was heated at 60° for 1 h, washed with H_2O, aq. 0.01N HCl, aq. $NaHCO_3$, and brine, dried and stripped of the solvent. The residue was purified by prep. HPLC (*Polygosil* column; cyclohexane/i-PrOH 82:8) to give **6b** (39 mg, 54%) as a foam. It is likely that **6b** could also be prepared through oxidation of **5b** according to *GP D* analogously to **6a**; this was, however, not carried out. ^{1}H-NMR (*ca.* 10:7 mixture of rotamers): major rotamer: 6.84 (*d*, *J* = 8.4, H–C(6)); 5.21 (*d*, *J* = 2.1, H–C(26)); 5.15 (*d*, *J* = 1.6, HO–C(10)); 5.08 (*m*, H–C(5); H–C(20/29)); 5.01 (br. *d*, *J* = 9.6, H–C(20/29)); 4.94 (*m*, H–C(2)); 4.55 (*m*, H–C(33)); 3.98 (*m*, H–C(24)); 3.89 (*dd*, *J* = 9.6, 2.7, H–C(14)); 3.60–3.25 (overl. *m*s, H–C(13), H–C(15), H–C(32), HO–C(24), 3 MeO); 3.18 (*m*, H–C(21)); 2.73 (*dd*, *J* = 17.3, 2.0, 1 H–C(23)); 2.46 (*m*, 1 H–C(3)); 2.40–0.80 (overl. *m*s); minor rotamer: 7.13 (*d*, *J* = 8.6, H–C(6)); 5.30 (*m*, H–C(5)); 5.29 (*d*, *J* = 2.8, H–C(26)); 5.08 (*m*, H–C(20), H–C(29)); 4.94 (*m*, H–C(2)); 4.55 (*m*, H–C(33)); 4.36 (*d*, J = 1.3, HO–C(10)); 3.92 (*m*, H–C(24)); 3.63 (*dd*, *J* = 9.6, 1.1, H–C(14)); 3.60–3.25 (overl. *m*s, H–C(13), H–C(15), H–C(32), 3 MeO); 3.23 (*m*, H–C(21)); 2.95 (*d*, *J* = 3.5, HO–C(24)); 2.82 (*dd*, *J* = 15.5, 3.3, 1 H–C(23)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: both rotamers: 214.2; 213.3; 168.2; 167.6; 162.9; 139.6; 138.9; 132.1; 131.8; 129.8; 129.2; 123.9; 123.23; 123.16; 121.9; 112.1; 109.8; 98.9; 97.5; 79.3; 78.0; 77.5; 76.5; 75.4; 73.8; 73.6; 73.2; 72.2; 70.1; 69.5; 59.4; 59.3; 57.6; 57.1; 56.3; 56.2; 55.7; 55.3; 55.1; 54.9; 53.0; 48.9; 48.7; 43.8; 43.0; 39.9; 39.3; 35.5; 34.8; 34.4; 33.6; 33.3; 32.6; 32.5; 32.0; 31.7; 26.6; 26.0; 25.5; 24.7; 24.5; 23.5; 23.1; 20.5; 19.4; 18.8; 16.1; 15.8; 15.7; 14.4; 14.1; 11.7; 9.8, 9.5.

Compound **6c**. Prepared analogously to **6a** starting from **5c** according to *GP D*. White foam. Yield: 70%. ^{1}H-NMR (*ca.* 10:7 mixture of rotamers): major rotamer: 6.81 (*d*, *J* = 8.4, H–C(6)); 5.71 (*m*, H–C(37)); 5.20 (*d*, *J* = 2.5, H–C(26)); 5.10–4.90 (overl. *m*s, H–C(2), H–C(5), H–C(20), H–C(29), H–C(38), HO–C(10)); 4.00 (*m*, H–C(24)); 3.88 (*dd*, *J* = 9.5, 2.7, H–C(14)); 3.57 (*m*, H–C(15)); 3.60–3.40 (overl. *m*s, H–C(13), H–C(21), H–C(33), 3 MeO); 3.00 (*m*, H–C(32)); 2.73 (*dd*, *J* = 17.3, 2.0, 1 H–C(23)); 2.71 (*s*, OH); 2.50–0.80 (overl. *m*s); minor rotamer: 7.13 (*d*, *J* = 8.5, H–C(6)); 5.71 (*m*, H–C(37)); 5.30 (*m*, H–C(5)); 5.26 (*d*, *J* = 2.6, H–C(26)); 5.10–4.90 (overl. *m*s, H–C(2), H–C(20), H–C(29), H–C(38)); 4.45 (*d*, *J* = 1.2, HO–C(10)); 3.91 (*m*, H–C(24)); 3.68 (*dd*, *J* = 9.6, 1.3, H–C(14)); 3.57 (*m*, H–C(15)); 3.60–3.40 (overl. *m*s, H–C(13), H–C(21), H–C(33), 3 MeO); 3.00 (*m*, H–C(32)); 2.86 (*d*, *J* = 3.8, OH); 2.82 (*dd*, *J* = 15.5, 3.3, 1 H–C(23)); 2.50–0.80 (overl. *m*s). ^{13}C-NMR: both rotamers: 212.9; 212.2; 194.5; 190.9; 168.1; 167.7; 162.8; 162.0; 139.6; 138.9; 135.42; 135.39; 131.9; 131.6; 130.6; 129.8; 123.9; 122.7; 122.6; 121.9; 116.69; 116.66; 112.1; 109.7; 98.9; 97.6; 84.2; 78.8; 78.1; 76.4; 75.4; 73.7; 73.545; 73.52; 73.0; 72.3; 69.8; 69.0; 57.6; 57.2; 56.5; 56.1; 55.2; 53.1; 53.0; 52.9; 49.0; 48.6; 44.7; 43.9; 40.4; 39.8; 35.5; 35.40; 35.35; 34.9; 34.7; 34.3; 33.7; 33.5; 32.5; 32.4; 31.2; 30.54; 30.48; 26.3; 26.1; 23.5; 23.1; 20.3; 19.4; 19.3; 18.8; 16.0; 15.9; 14.1; 13.7; 9.9; 9.7. HR-MS: 824.4570 ($[M+Na]^+$; calc. 824.4561).

Compound **6d**. Prepared analogously to **6a** starting from **5d** according to *GP D*. White foam. Yield: 64%. ^{1}H-NMR (*ca.* 10:7 mixture of rotamers): major rotamer: 6.79 (*d*, *J* = 8.4, H–C(6)); 5.21 (*d*, *J* = 2.4, H–C(26)); 5.15–4.90 (overl. *m*s, H–C(2), H–C(5), H–C(20), H–C(29), HO–C(10)); 3.99 (*m*,

H–C(24)); 3.86 (*dd*, *J* = 9.6, 2.7, H–C(14)); 3.56 (*m*, H–C(15)); 3.50–3.25 (overl. *m*s, H–C(13), H–C(21), H–C(33), 3 MeO); 3.00 (*m*, H–C(32)); 2.76 (*dd*, *J* = 17.3, 2.0, H_a–C(23)); 2.67 (*s*, OH); 2.50–0.80 (overl. *m*s); minor rotamer: 7.13 (*d*, *J* = 8.5, H–C(6)); 5.30 (*d*, *J* = 2.5, H–C(26)); 5.29 (*m*, H–C(5)); 5.10–4.90 (overl. *m*s, H–C(2), H–C(20), H–C(29)); 4.39 (*d*, *J* = 1.1, HO–C(10)); 3.89 (*m*, H–C(24)); 3.66 (*dd*, *J* = 9.6, 1.1, H–C(14)); 3.56 (*m*, H–C(15)); 3.50–3.25 (overl. *m*s, H–C(13), H–C(21), H–C(33), 3 MeO); 3.11 (*d*, *J* = 1.8, OH); 3.00 (*m*, H–C(32)); 2.87 (*dd*, *J* = 15.5, 3.3, 1 H–C(23)); 2.67 (br. *s*, OH); 2.50–0.80 (overl. *m*s).

Compounds **9**, **7**, *and* **4a**. According to *GP A*, **1a** (0.2 g, 0.252 mmol) in MeCN/H_2O 4:1 (50 ml) was irradiated at r.t. for 2 h. 25 such batches (total 5 g, 6.31 mmol) were combined and purified by prep. HPLC to give **9** (two isomers; 0.548 g, 11%), **7** (1.489 g, 30%), **4a** (0.482 g, 10%), and unchanged starting material **1a** (1.288 g, 26%).

Data of **9**, *Major C(9)-Isomer*. White foam. ^{1}H-NMR: 5.24 (br. *s*, H–C(26)); 5.24 (*m*, H–C(6)); 5.14 (*dd*, *J* = 8.8, 1.1, H–C(20/29)); 4.91 (*d*, *J* = 9.0, H–C(20/29)); 4.68 (*d*, *J* = 1.5, HO–C(10)); 4.60 (*d*, *J* = 7.1, H–C(2)); 4.27 (*d*, *J* = 1.2, H–C(9)); 4.12 (*m*, H–C(24)); 3.66 (*dd*, *J* = 9.5, 2.0, H–C(14)); 3.51 (*dm*, *J* = 11.3, H–C(15)); 3.45–3.35 (*m*, H–C(13), H–C(33)); 3.39 (*s*, MeO); 3.35 (*s*, MeO); 3.30 (*s*, MeO); 3.28 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.74 (*dd*, *J* = 17.9, 1.6, 1 H–C(23)); 2.69 (br. *s*, OH); 2.38 (*dd*, *J* = 17.9, 10.2, 1 H–C(23)); 2.30 (*m*); 2.20–0.80 (overl. *m*s). ^{13}C-NMR: 214.7 (C(22)); 170.5 (C(1/8)); 168.5 (C(1/8)); 139.8 (C(19)); 131.5 (C(27)); 129.0 (C(29)); 122.4 (C(20)); 97.8 (C(10)); 87.0 (C(6)); 84.2 (C(32)); 76.9; 76.14; 76.09; 74.0; 73.5; 71.5; 69.1; 56.9; 56.6; 56.2; 54.4; 52.6; 48.6; 43.0; 39.7; 35.1; 34.84; 34.79; 32.4; 31.8; 31.2; 30.9; 30.7; 26.4; 25.8; 25.3; 25.2; 19.5; 18.3; 15.8; 15.2; 14.4; 11.7; 10.2. HR-MS: 814.4722 ($[M+Na]^+$; calc. 814.4717).

Data of **9**, *Minor C(9)-Isomer:* White foam. ^{1}H-NMR: 5.30 (*ddd*, *J* = 10.0, 3.7, 2.0, H–C(6)); 5.08 (*d*, *J* = 1.8, H–C(26)); 5.05 (*d*, *J* = 9.0, H–C(29)); 4.90 (*d*, *J* = 6.0, H–C(2)); 4.86 (*d*, *J* = 9.8, H–C(20)); 4.37 (*d*, *J* = 2.0, H–C(9)); 3.75 (*m*, H–C(24)); 3.71 (*dd*, *J* = 9.5, 2.1, H–C(14)); 3.65 (*d*, *J* = 2.9, HO–C(24)); 3.54 (*m*, H–C(15)); 3.45–3.35 (*m*, H–C(13), H–C(33)); 3.41 (*s*, MeO); 3.37 (*s*, MeO); 3.32 (*s*, MeO); 3.22 (*m*, H–C(21)); 3.11 (*d*, *J* = 1.8, HO–C(10)); 3.01 (*m*, H–C(32)); 2.83 (*dd*, *J* = 16.9, 3.6, 1 H–C(23)); 2.73 (br. *s*, HO–C(33)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: 212.1 (C(22)); 169.4 (C(1/8)); 166.4 (C(1/8)); 140.0 (C(19)); 131.8 (C(27)); 129.6 (C(29)); 123.7 (C(20)); 97.6 (C(10)); 86.0 (C(6)); 84.1 (C(32)); 80.2 (C(9)); 78.1; 77.0; 74.0; 73.5; 72.6; 69.6; 57.1; 56.5; 56.0; 55.0; 51.9; 47.5; 44.7; 40.5; 35.2; 34.9; 34.7; 34.3; 33.5; 32.3; 31.2; 30.6; 26.7; 26.1; 23.5; 19.9; 18.8; 16.7; 16.1; 14.4; 11.7; 9.2.

Compounds **11** *and* **12**. Prepared analogously to **2a** starting from **10** according to *GP B*. Purification by prep. HPLC gave the α-MeO and β-MeO compounds, **11** (8%) and **12** (24%), resp., as white foams.

Data of **11**. ^{1}H-NMR: 5.50 (*d*, *J* = 4.6, H–C(5)); 5.23 (*d*, *J* = 1.6, HO–C(10)); 5.01 (*m*, H–C(26), H–C(20/29)); 4.99 (*d*, *J* = 9.5, H–C(20/29)); 4.63 (*d*, *J* = 9.1, H–C(2)); 4.47 (br. *s*, H–C(9)); 4.03 (br. *s*, OH); 3.97 (*m*, H–C(24)); 3.72 (*dd*, *J* = 9.6, 1.8, H–C(14)); 3.52 (*m*); 3.45–3.30 (overl. *m*s); 3.41 (*s*, MeO); 3.38 (*s*, MeO); 3.36 (*s*, MeO); 3.28 (*s*, MeO); 3.15 (*m*, H–C(21)); 3.12 (br. *s*, OH); 3.00 (*m*, H–C(32)); 2.74 (*dd*, *J* = 16.9, 3.3, 1 H–C(23)); 2.73 (br. *s*, OH); 2.40 (*dd*, *J* = 16.9, 8.1, 1 H–C(23)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: 213.0 (C(22)); 173.0 (C(1/8)); 170.6 (C(1/8)); 140.0 (C(19)); 132.3 (C(27)); 130.3 (C(29)); 123.6 (C(20)); 99.2 (C(10)); 88.4 (C(5)); 84.1 (C(32)); 79.0 (C(26)); 77.3; 74.2; 73.5; 72.2; 71.2; 69.9; 59.7; 57.4; 56.5; 56.1; 55.8; 54.0; 47.5; 42.7; 40.4; 35.8; 34.8; 34.7; 32.8; 32.1; 31.1; 30.5; 28.7; 27.0; 24.9; 24.0; 20.0; 16.9; 16.2; 13.9; 11.7; 10.6; 9.6. HR-MS: 832.4829 ($[M+Na]^+$; calc. 832.4823).

Data of **12**. ^{1}H-NMR (6:1 mixture of rotamers or C(9)-isomers): major isomer: 5.95 (*d*, *J* = 1.3, HO–C(10)); 5.92 (*d*, *J* = 3.8, H–C(5)); 5.10 (*d*, *J* = 3.3, H–C(26)); 5.02 (*d*, *J* = 9.1, H–C(20/29)); 4.88 (*d*, *J* = 9.6, H–C(20/29)); 4.43 (*d*, *J* = 9.2, H–C(9)); 4.38 (*t*, *J* = 8.5, H–C(2)); 4.05 (br. *d*, *J* = 9.2, HO–C(9)); 4.01 (*m*, H–C(24)); 3.83 (*dd*, *J* = 9.5, 1.9, H–C(14)); 3.54 (*m*); 3.45–3.30 (overl. *m*s); 3.40 (*s*, MeO); 3.38 (*s*, MeO); 3.36 (*s*, 2 MeO); 3.24 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.86 (br. *s*, OH); 2.69 (*dd*, *J* = 16.3, 3.1, 1 H–C(23)); 2.50–0.8 (overl. *m*s); minor isomer: 5.60 (*d*, *J* = 4.2, H–C(5)); 5.45 (*dd*, *J* = 9.3, 5.2, H–C(2)); 5.19 (br. *s*, H–C(26)); 5.11 (overl. *d*, H–C(20/29)); 5.00 (overl. *d*, H–C(20/29)); 4.82 (br. *s*, OH); 4.19 (*d*, *J* = 8.5, H–C(9)); 3.89 (*d*, *J* = 8.5, HO–C(9)); 3.73 (*d*, *J* = 7.9, H–C(14)); 3.60–0.80 (overl. *m*s). ^{13}C-NMR (major isomer): 213.1 (C(22)); 173.2 (C(1/8)); 169.2 (C(1/8)); 140.2 (C(19)); 131.8 (C(27)); 130.0 (C(29)); 122.8 (C(20)); 99.6 (C(10)); 88.3 (C(5)); 84.2 (C(32)); 78.5 (C(26)); 77.0; 74.0; 73.5; 71.6; 71.2; 70.8; 69.3; 59.7 (C(2)); 57.5; 56.5; 56.1; 55.3; 54.2; 48.8; 44.7; 41.2; 36.2; 34.8; 34.7;

32.8; 32.2; 31.3; 31.2; 30.5; 25.7; 25.0; 23.8; 18.8; 16.2; 15.5; 13.9; 11.6; 9.7. HR-MS: 832.4827 ($[M+Na]^+$; calc. 832.4823).

Compound **13**. Prepared analogously to **5a** starting from **12** according to *GP E*. Purification by prep. HPLC gave **13** (24%). White foam. ^{1}H-NMR: 7.26 (*dt*, *J* = 4.4, 2.1, H–C(5)); 6.26 (*s*, OH); 5.17 (*dt*, *J* = 4.4, 2.5, H–C(4)); 5.14 (*d*, *J* = 3.5, H–C(26)); 5.04 (*d*, *J* = 9.1, H–C(20/29)); 4.93 (*d*, *J* = 9.3, H–C(20/29)); 4.72 (*dd*, *J* = 11.4, 3.8, H–C(2)); 4.35 (br. *s*, H–C(9)); 4.01 (*m*, H–C(24)); 3.81 (*dd*, *J* = 9.5, 1.9, H–C(14)); 3.54 (*m*, H–C(15)); 3.45–3.30 (*m*, H–C(13), H–C(33)); 3.40 (*s*, MeO); 3.37 (*s*, MeO); 3.36 (*s*, MeO); 3.28 (br. *s*, OH); 3.21 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.95 (*m*, 1 H–C(3)); 2.84 (br. *s*, OH); 2.70 (*dd*, *J* = 16.4, 3.1, 1 H–C(23)); 2.43 (*m*, 1 H–C(3)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: 213.3 (C(22)); 170.0 (C(1/8)); 168.9 (C(1/8)); 140.3 (C(19)); 132.1 (C(27)); 130.5 (C(5/29)); 130.4 (C(5/29)); 122.9 (C(20)); 109.3 (C(4)); 99.9 (C(10)); 84.1 (C(32)); 78.9 (C(26)); 74.1; 73.5; 71.4; 70.5; 69.4; 59.0 (C(2)); 57.6; 56.5; 56.0; 55.5; 48.4; 43.9; 41.1; 36.1; 34.8; 34.7; 32.8; 32.0; 31.8; 31.2; 30.5; 26.1; 24.1; 19.2; 16.2; 15.9; 13.9; 11.7; 9.9. HR-MS: 800.4560 ($[M+Na]^+$; calc. 800.4561).

Compound **14**. Prepared analogously to **3a** starting from **11** according to *GP D*. Purification by prep. HPLC gave **14** (60%). White foam. ^{1}H-NMR (7:1 mix of rotamers): 6.04 (*d*, *J* = 1.5, HO–C(10)); 5.71 (*d*, *J* = 4.2, H–C(5)); 5.18 (*d*, *J* = 2.6, H–C(26)); 5.01 (*m*, H–C(20), H–C(29)); 4.45 (*d*, *J* = 9.5, H–C(2)); 4.00 (*m*, H–C(24)); 3.91 (*dd*, *J* = 9.5, 2.3, H–C(14)); 3.57 (*m*, H–C(15)); 3.50–3.35 (*m*, H–C(13), H–C(33), OH); 3.40 (*s*, MeO); 3.37 (*s*, MeO); 3.30 (*s*, MeO); 3.19 (*s*, MeO); 3.18 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.70 (*dd*, *J* = 16.8, 2.3, 1 H–C(23)); 2.69 (br. *s*, OH); 2.50–0.80 (overl. *m*s). ^{13}C-NMR: 214.5 (C(22)); 188.1 (C(9)); 168.6 (C(1)); 164.4 (C(8)); 140.2 (C(19)); 132.3 (C(27)); 129.5 (C(29)); 122.7 (C(20)); 98.7 (C(10)); 88.8 (C(5)); 84.2 (C(32)); 78.0 (C(26)); 76.1; 73.5; 71.7; 69.2; 59.0 (C(2)); 57.0; 56.5; 56.3; 55.6; 55.3; 49.0; 44.3; 43.2; 40.8; 36.0; 34.8; 34.7; 33.2; 32.6; 31.2; 30.8; 30.6; 25.8; 25.3; 24.5; 19.0; 16.1; 15.5; 14.2; 11.7; 9.8. HR-MS: 830.4664 ($[M+Na]^+$; calc. 830.4667).

Compound **15**. Prepared analogously to **3a** starting from **12** according to *GP D*. FC (SiO_2; AcOEt) gave **15** (42%). White foam. ^{1}H-NMR (*ca.* 6:1 mixture of rotamers): 6.01 (*d*, *J* = 1.8, HO–C(10)); 5.47 (*d*, *J* = 4.0, H–C(5)); 5.17 (*d*, *J* = 2.8, H–C(26)); 5.03 (*d*, *J* = 9.1, H–C(20/29)); 4.94 (*d*, *J* = 9.5, H–C(20/29)); 4.49 (*t*, *J* = 9.2, H–C(2)); 4.03 (*m*, H–C(24)); 3.95 (*dd*, *J* = 9.5, 2.3, H–C(14)); 3.58 (*m*, H–C(15)); 3.50–3.30 (*m*, H–C(13), H–C(33), OH); 3.41 (*s*, MeO); 3.39 (*s*, 2 MeO); 3.35 (*s*, MeO); 3.25 (*m*, H–C(21)); 3.01 (*m*, H–C(32)); 2.69 (*dd*, *J* = 16.3, 2.5, 1 H–C(23)); 2.67 (br. *s*, OH); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: 213.6 (C(22)); 188.0 (C(9)); 168.1 (C(1)); 163.9 (C(8)); 139.9 (C(19)); 131.6 (C(27)); 130.0 (C(29)); 123.1 (C(20)); 99.1 (C(10)); 88.6 (C(5)); 84.2 (C(32)); 78.4 (C(26)); 76.1; 73.57; 73.56; 71.4; 69.1; 59.0 (C(2)); 57.5; 56.5; 56.3; 55.2; 55.0; 49.0; 44.5; 41.2; 36.2; 34.9; 34.7; 33.0; 32.74; 32.67; 31.2; 30.5; 25.5; 25.1; 23.9; 18.5; 16.1; 15.4; 14.0; 11.6; 9.7. HR-MS: 830.4666 ($[M+Na]^+$; calc. 830.4667).

Compound **16**. Prepared analogously to **3a** starting from **13** according to *GP D*. FC (SiO_2-5% $NaHCO_3$; AcOEt) gave **16** (65%). White foam. ^{1}H-NMR (7:1 mixture of rotamers): major rotamer: 7.23 (*dt*, *J* = 4.4, 2.2, H–C(5)); 6.20 (*d*, *J* = 1.8, HO–C(10)); 5.34 (*dt*, *J* = 4.4, 2.6, H–C(4)); 5.22 (*d*, *J* = 3.1, H–C(26)); 5.06 (*d*, *J* = 9.1, H–C(20/29)); 4.94 (*d*, *J* = 9.2, H–C(20/29)); 4.73 (*dd*, *J* = 11.3, 4.8, H–C(2)); 4.02 (*m*, H–C(24)); 3.94 (*dd*, *J* = 9.5, 2.3, H–C(14)); 3.57 (*m*, H–C(15)); 3.50–3.30 (*m*, H–C(13), H–C(33)); 3.40 (*s*, MeO); 3.38 (*s*, MeO); 3.36 (*s*, MeO); 3.31 (*d*, *J* = 2.5); 3.23 (*m*, H–C(21)); 3.00 (*m*, H_a–C(3), H–C(32)); 2.69 (*dd*, *J* = 16.4, 2.8, 1 H–C(23)); 2.65 (br. *s*, OH); 2.61 (*m*, 1 H–C(3)); 2.50–0.80 (overl. *m*s). ^{13}C-NMR: 213.7 (C(22)); 187.0 (C(9)); 167.7 (C(1)); 159.0 (C(8)); 140.3 (C(19)); 132.0 (C(27)); 130.4 (C(5/29)); 129.4 (C(5/29)); 122.8 (C(20)); 113.2 (C(4)); 99.2 (C(10)); 84.2 (C(32)); 79.0 (C(26)); 76.5; 73.58; 73.55; 71.5; 69.08; 59.0 (C(2)); 57.7; 56.5; 56.2; 55.4; 48.9; 44.0; 41.2; 36.0; 34.9; 34.7; 33.0; 32.6; 32.2; 31.2; 30.6; 26.9; 25.8; 24.2; 18.8; 16.1; 15.5; 13.9; 11.7; 9.6.

Compounds **17a** *and* **17b**. Prepared analogously to **2a** starting from 22-dihydro-33-*O*-^{t}BuMe$_2$Si-ascomycin (**17**) according to *GP A*. Prep. HPLC gave the β-MeO and α-MeO compounds, **17a** (37%) and **17b** (9%), resp., as white foams.

Data of **17a**. ^{1}H-NMR: 5.84 (br. *s*, H–C(6)); 5.29 (*d*, *J* = 4.1, H–C(2)); 5.21 (*d*, *J* = 9.9, H–C(20/29); 5.20 (br. *d*, *J* = 4.1, H–C(26)); 5.02 (*d*, *J* = 10.4, H–C(20/29); 4.80 (br. *s*, OH); 4.62 (br. *d*, *J* = 8.6, HO–C(9)); 4.34 (*d*, *J* = 8.6, H–C(9)); 3.95 (br. *d*, *J* = 8.5, H–C(24)); 3.72 (*dd*, *J* = 9.6, 1.3, H–C(14)); 3.65 (*m*, 2 H); 3.43 (*s*, MeO); 3.42 (*m*); 3.36 (*s*, MeO); 3.34 (*s*, MeO); 3.27 (*m*); 3.15 (*s*, MeO); 2.97 (*m*, H–C(32)); 2.68 (br. *s*, OH); 2.40–0.80 (overl. *m*s), 0.90 (*s*, *t*-Bu); 0.09 (*s*, MeSi); 0.08 (*s*, MeSi). ^{13}C-NMR: 173.9; 170.7; 136.8; 130.4; 129.4; 125.6; 97.3; 84.3; 80.1; 77.7; 75.23; 75.18; 74.4; 73.6; 73.1; 73.0;

72.1; 57.9; 57.3; 56.3; 55.9; 52.9; 49.4; 46.2; 40.0; 38.3; 36.7; 35.6; 35.2; 34.0; 33.8; 30.7; 30.6; 26.0; 25.9; 24.4; 19.9; 18.1; 16.1; 15.3; 14.9; 14.2; 11.7; 10.6; −4.6; −4.8.

Data of **17b**. ^{1}H-NMR: 6.40 (*s*, OH); 6.25 (*d*, *J* = 4.1, OH); 5.62 (*s*, H−C(6)); 5.32 (br. *s*, H−C(2)); 5.23 (*s*, H−C(26)); 5.03 (*d*, *J* = 8.9); 4.75 (*d*, *J* = 10.1); 4.15 (*d*, *J* = 4.0, H−C(9)); 4.08 (*s*, OH); 3.73 (*d*); 3.65 (*m*); 3.59 (*t*); 3.50 (*d*); 3.43 (*s*, MeO); 3.41 (*s*, MeO); 3.39 (*s*, MeO); 3.34 (*s*, MeO); 3.24 (*m*); 2.97 (*m*, H−C(32)); 2.58 (br. *s*, OH); 2.50–0.80 (overl. *m*s); 0.90 (*s*, *t*-Bu); 0.09 (*s*, MeSi); 0.07 (*s*, MeSi). ^{13}C-NMR: 173.8; 172.2; 137.7; 131.7; 128.5; 128.2; 99.3; 84.2; 81.5; 79.5; 76.8; 75.74; 75.65; 75.5; 75.2; 73.8; 71.3; 69.5; 58.8; 58.1; 57.1; 56.1; 54.7; 47.3; 46.8; 41.7; 39.1; 36.7; 35.0; 33.8; 33.3; 32.1; 31.9; 31.0; 27.8; 25.8; 24.4; 23.7; 22.3; 20.0; 18.1; 16.2; 15.9; 14.8; 13.0; 11.4; 9.6; −4.5; −4.4.

Compound **18a**. According to *GP C*, **17a** was oxidized in MeOH and worked up. The crude product was desilylated using MeCN/1N HCl 10:1 at 0–5°, and purified by FC (SiO_2; CH_2Cl_2/MeOH 100:5) to give **18a** (34%). White foam. ^{1}H-NMR: 5.68 (*t*, *J* = 2.6, H−C(6)); 5.19 (*d*, *J* = 8.9, H−C(29)); 5.06 (*d*, *J* = 10.3, H−C(20)); 5.02 (*d*, *J* = 2.0, H−C(26)); 4.55 (*d*, *J* = 3.9, H−C(2)); 4.18 (*d*, *J* = 1.3, HO−C(10)); 3.96 (br. *d*, *J* = 9.9, H−C(22)); 3.71 (*dd*, *J* = 10.5, 1.0, H−C(14)); 3.64 (*m*, H−C(15), H−C(24)); 3.40 (*m*, H−C(13/33)); 3.40 (*s*, MeO); 3.38 (*s*, MeO); 3.33 (*m*, H−C(13/33)); 3.28 (*s*, MeO); 3.16 (*s*, MeO); 3.02 (*m*, H−C(32)); 2.96 (br. *s*, OH); 2.78 (*s*, OH); 2.46 (br. *s*, OH); 2.29 (*m*, 2H); 2.20–0.80 (overl. *m*s). ^{13}C-NMR: 195.1 (C(9)); 169.4 (C(1/8); 167.5 (C(1/8); 136.5 (C(19)); 130.6 (C(27)); 129.0 (C(29); 125.2 (C(20)); 96.4 (C(10)); 84.2 (C(32)); 79.4 (C(6)); 78.2; 74.5; 73.54; 73.50; 73.2; 72.4; 71.1; 56.8; 56.5; 56.4; 56.2; 53.8; 49.3; 45.8; 39.9; 37.3; 35.0; 34.87; 34.85; 33.1; 32.8; 31.3; 30.3; 30.2; 26.0; 25.8; 20.0; 16.2; 15.9; 14.9; 14.1; 11.8; 11.2. HR-MS: 846.4973 ($[M+Na]^+$; calc. 846.4980).

Compound **18b**. According to *GP C* and analogously to **18a**, **17b** was oxidized in MeOH and purified by FC (SiO_2; CH_2Cl_2/MeOH 100:3) to give the tricarbonyl product (40%) which was desilylated using MeCN/1N HCl 10:1) at 0–5° and purified by FC (SiO_2; CH_2Cl_2/MeOH 100:4) to give **18b** (91%). White foam. ^{1}H-NMR: 5.06 (*d*, *J* = 10.3, H−C(20)); 5.05 (*s*, H−C(26)); 4.96 (*t*, *J* = 2.8, H−C(6)); 4.90 (*d*, *J* = 9.0, H−C(29)); 4.22 (*d*, *J* = 1.8, HO−C(10)); 4.19 (*dd*, *J* = 8.5, 3.7, H−C(2)); 4.06 (br. *s*, OH); 3.91 (*m*, H−C(22)); 3.77 (br. *s*, OH); 3.67 (*dd*, *J* = 11.2, 3.6), 3.63 (*d*, *J* = 9.6) (H−C(14)); 3.50–3.30 (*m*, 3H); 3.41 (*s*, MeO); 3.40 (*s*, MeO); 3.38 (*s*, MeO); 3.33 (*s*, MeO); 3.01 (*m*, H−C(32)); 2.82 (br. *s*, OH); 2.40–0.80 (overl. *m*s); 1.64 (*d*, *J* = 1.0, Me−C(27)); 1.57 (*s*, Me−C(19)). ^{13}C-NMR: 195.0 (C(9)); 168.1 (C(1)); 165.5 (C(8)); 134.9 (C(19)); 131.5 (C(27)); 127.9 (C(20/29); 127.7 (C(20/29); 98.6 (C(10)); 84.9 (C(6)); 84.2 (C(32)); 77.5; 75.7; 73.5; 72.3; 71.7; 57.2; 56.6; 56.2; 55.1; 53.1; 50.3; 46.3; 38.3; 38.2; 34.9; 34.8; 34.2; 33.0; 32.3; 31.2; 30.6; 29.4; 26.6; 25.3; 23.9; 20.4; 17.2; 16.1; 16.0; 14.4; 12.0; 10.3. HR-MS: 846.4978 ($[M+Na]^+$; calc. 846.4980).

Compound **19**. A mixture of the but-1-enyl derivative **7** (53 mg, 0.067 mmol) and cat. Pd/C in AcOEt (5 ml) was stirred under H_2 balloon for 2.6 h at r.t. The catalyst was filtered off on *Celite*, and the filtrate was concentrated to give a residue which, upon FC (SiO_2; toluene/AcOEt 2:5), gave **19** (40 mg, 75%). White foam. ^{1}H-NMR: 5.40 (*d*, *J* = 2.8, H−C(26)); 4.97 (*d*, *J* = 9.0, H−C(29)); 4.45 (*d*, *J* = 1.5, HO−C(10)); 4.43 (*d*, *J* = 4.6, H−C(2)); 4.40 (*dd*, *J* = 13.6, 3.4, 1H−C(6)); 3.88 (*m*, H−C(24)); 3.82 (*d*, *J* = 1.7, HO−C(24)); 3.59 (*dd*, *J* = 9.6, 1.1, H−C(14)); 3.48 (*dd*, *J* = 10.4, 4.0, H−C(13/15)); 3.45–3.35 (*m*, H−C(13/15), H−C(33)); 3.41 (*s*, MeO); 3.35 (*s*, MeO); 3.29 (*s*, MeO); 3.02 (*m*, H−C(32)); 3.00 (*dd*, *J* = 14.8, 1.7, 1H−C(23)); 2.93 (br. *t*, *J* = 13.6, 1H−C(6)); 2.40–0.80 (overl. *m*s), 1.66 (*s*, Me−C(27)); 1.04 (*s*, Me−C(19)). ^{13}C-NMR: 219.2 (C(22)); 196.1 (C(9)); 169.0 (C(1/8); 165.7 (C(1/8); 131.6 (C(27)); 128.4 (C(29)); 97.4 (C(10)); 84.2 (C(32)); 77.2; 75.1; 73.54; 73.52; 72.0; 69.9; 57.0; 56.8; 56.6; 56.1; 52.4; 46.8; 40.5; 39.1; 38.7; 38.3; 35.4; 34.9; 34.8; 34.4; 32.5; 31.2; 30.7; 26.5; 26.4; 26.1; 25.4; 24.1; 23.2; 21.8; 21.3; 20.6; 18.3; 16.0; 14.5; 13.8; 10.9. HR-MS: 816.4879 ($[M+Na]^+$; calc. 816.4874).

Compound **20**. According to *GP C* **8**, upon oxidation with $Cu(OAc)_2$ in MeOH (24 h), followed by FC (SiO_2; AcOEt), gave **20** (35%). White foam. ^{1}H-NMR: 5.69 (br. *s*, H−C(6)); 5.51 (*dt*, *J* = 15.6, 6.4, H−C(21)); 5.22 (*d*, *J* = 15.6, H−C(20)); 5.22 (*s*, H−C(26)); 5.13 (*d*, *J* = 9.0, H−C(29)); 4.45 (br. *s*, H−C(2)); 4.35 (br. *s*, OH); 3.87 (br. *s*, OH); 3.71 (*m*, H−C(14), H−C(24)); 3.50–3.30 (*m*, H−C(13), H−C(15), H−C(33)); 3.41 (*s*, MeO); 3.36 (*s*, MeO); 3.28 (*s*, MeO); 3.23 (*s*, MeO); 3.01 (*m*, H−C(32)); 2.71 (*s*, OH); 2.58 (br. *d*, *J* = 17.3, 1H−C(23)); 2.30 (H−C(30)); 2.19 (*dd*, *J* = 17.3, 10.7, 1H−C(23)); 2.20–0.80 (overl. *m*s); 1.63 (*s*, Me−C(27)); 1.18 (*s*, Me−C(19)). HR-MS: 844.4817 ($[M+Na]^+$; calc. 844.4823).

Compound **21**. 1N HCl (2 ml) was added to a suspension of MeO-**2a** (1.0 g, 1.2 mmol) in MeCN (40 ml) at 0°. The mixture was stirred at 0° for 3 h and at r.t. for 5 h and worked up with aq. $NaHCO_3$ and AcOEt. The org. extracts were dried, concentrated, and the residue was subjected to FC (SiO_2; CH_2Cl_2/MeOH 100:4 to 100:8) to give **21** (732 mg, 75%). White foam. ^{1}H-NMR (1:0.18 mixture of isomers): major isomer: 9.80 (*s*, H–C(6)); 7.35 (*d*, NH); 6.56 (*s*, HO–C(10)); 5.23 (*d*, H–C(26)); 5.04 (*d*, H–C(20/29)); 4.98 (*d*, H–C(20/29)); 4.86 (*d*, H–C(9)); 4.12 (*d*, HO–C(9)); 4.05 (*m*, H–C(2), H–C(24)); 3.83 (*dd*, H–C(14)); 3.59 (*ddd*, H–C(15)); 3.50 (*d*, OH); 3.40 (*m*, H–C(33)); 3.40 (*s*, MeO); 3.38 (*s*, MeO), 3.37 (*s*, MeO); 3.20 (*m*, H–C(21)); 3.07 (br. *s*); 3.00 (*m*, H–C(32)); 2.74 (br. *s*), 2.70 (*dd*, 1 H–C(23)); 2.56 (*m*, 2 H); 2.5–0.8 (overl. *m*s); 1.67 (*s*, Me–C(19), Me–C(27)); 0.97 (*d*, J = 6.6, Me–C(11)); 0.92 (*d*, J = 7.2, Me–C(25)); 0.88 (*t*, J = 7.3, Me–C(37)); 0.78 (*d*, J = 6.4, Me–C(17)). ^{13}C-NMR: 214.3 (C(22)); 200.9 (C(6)); 176.1; 169.2; 140.3 (C(19)); 131.6 (C(27)); 130.7 (C(29); 122.7 (C(20)); 99.8 (C(10)); 84.1 (C(32)); 78.8; 77.1; 73.9; 73.5; 71.03; 70.96; 68.6; 57.5; 56.5; 56.0; 55.3; 53.1; 49.3; 44.2; 43.0; 41.5; 36.6; 34.8; 34.7; 32.7; 31.7; 31.4; 30.5; 29.8; 25.2; 24.1; 18.7; 18.4; 16.1; 15.3; 13.9; 11.7; 10.2. HR-MS: 832.4823 ($[M+Na]^+$; calc. 832.4823).

Compound **22**. A soln. of **21** (1 g, 1.2 mmol) and resorcinol (175 mg, 1.6 mmol) in a mixture of 30 ml *t*-BuOH and 20 ml acetate buffer (pH 4.0) was stirred at −10°. A soln. of aq. $NaClO_2$ (0.9M soln., 13 ml, 12 mmol) was added in 4 equal portions in intervals of 5 min to the mixture. The mixture turned violet and then pink. After 30 min of total reaction time, it was extracted with Et_2O, washed with brine, dried, and stripped of the solvent. The residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 9:1 to 4:1) to give **22** (760 mg, 75%). ^{1}H-NMR: 7.67 (br. *s*, NH); 6.43 (br. *s*, OH); 5.19 (*d*, J = 1.8, H–C(26)); 5.07 (*d*, J = 8.7, H–C(20/29)); 4.97 (*d*, J = 8.9, H–C(20/29)); 4.25 (*s*, H–C(9)); 4.17 (*m*, H–C(2)); 4.03 (*ddd*, J = 10.1, 3.9, 1.4, H–C(24)); 3.79 (*dd*, J = 9.6, 1.8, H–C(14)); 3.61 (*m*, H–C(13/15)); 3.46 (*m*, H–C(13/15)); 3.40 (*s*, MeO); 3.39 (*s*, MeO); 3.36 (*m*, H–C(33)); 3.35 (*s*, MeO); 3.14 (*m*, H–C(21)); 3.05 (*ddd*, J = 11.2, 9.2, 4.4, H–C(32)); 2.69 (*d*, J = 17.0, 1 H–C(23)); 2.50–0.80 (overl. *m*s); 1.64 (*d*, J = 1.0, Me–C(27)); 1.62 (*s*, Me–C(19)); 0.95 (*d*, J = 6.9, Me–C(11)); 0.89 (*d*, J = 7.3, Me–C(25)); 0.88 (*t*, J = 7.3, Me–C(37)); 0.77 (*d*, J = 6.6, Me–C(17)). ^{13}C-NMR: 214.5 (C(22)); 175.8; 169.7; 140.1 (C(19)); 131.8 (C(27)); 130.2 (C(29)); 122.8 (C(20)); 99.9 (C(10)); 84.2 (C(32)); 78.3; 77.7; 73.9; 73.4; 71.0; 70.9; 68.9; 57.5; 56.6; 55.9; 55.3; 53.3; 49.2; 43.7; 41.0; 36.6; 34.89; 34.83; 33.5; 32.8; 31.8; 31.7; 29.9; 29.7; 25.5; 24.5; 21.2; 18.8; 16.0; 15.4; 14.2; 11.7; 10.1. HR-MS: 848.4769 ($[M+Na]^+$; calc. 848.4767).

Compound **23**. A mixture of the acid **22** (100 mg, 0.12 mmol), 2 ml of CH_2Cl_2, and 3 ml of ethereal CH_2N_2 was stirred for 15 min at 0°. The solvent was removed, and the residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 100:3) to afford **23** (72 mg, 70%). ^{1}H-NMR: 7.32 (*d*, J = 5.7, NH); 6.60 (br. *s*, OH); 5.22 (*d*, J = 3.0, H–C(26)); 5.02 (*d*, J = 9.0, H–C(20/29)); 4.97 (*d*, J = 9.1, H–C(20/29)); 4.11 (*s*, H–C(9)); 4.05 (*m*, H–C(2), H–C(24)); 3.70 (*s*, COOMe); 3.57 (*ddd*, J = 10.8, 5.5, 2.1, H–C(15)); 3.39 (*m*, H–C(13), H–C(33)); 3.39 (*s*, MeO); 3.36 (*s*, 2 MeO); 3.17 (*m*, H–C(21)); 2.99 (*ddd*, J = 11.2, 8.7, 4.2, H–C(32)); 2.68 (*dd*, J = 16.7, 1.8, 1 H–C(23)); 2.32 (*dd*, J = 16.7, 10.3, 1 H–C(23)); 2.50–0.80 (overl. *m*s); 1.66 (*d*, J = 1.2, Me–C(27)); 1.65 (*s*, Me–C(19)); 0.96 (*d*, J = 6.6, Me–C(11)); 0.90 (*d*, J = 7.3, Me–C(25)); 0.87 (*t*, J = 7.3, Me–C(37)); 0.76 (*d*, J = 6.4, Me–C(17)). HR-MS: 862.4924 ($[M+Na]^+$; calc. 862.4923).

Compound **24a**. According to *GP D*, oxidation of **22** (100 mg, 0.12 mmol) in CH_2Cl_2, followed by FC (SiO_2; CH_2Cl_2/MeOH 97:3 to 80:20) gave **24a** (65 mg, 65%). White foam. ^{1}H-NMR (*ca.* 5:4 mixture of six-membered-ring (*) and seven-membered-ring (**) hemiketals): 7.48* (*d*, J = 6.6, NH); 7.24** (*d*, J = 8.2, NH); 5.29* (br. *s*, HO–C(10)); 5.15*.** (br. *s*, H–C(26)); 5.08** (*d*, J = 8.9, H–C(20/29)); 5.02* (*d*, J = 8.9, H–C(20/29)); 4.99* (*d*, J = 9.4, H–C(20/29)); 4.93** (*d*, J = 9.4, H–C(20/29)); 4.52** (*m*, H–C(2)); 4.23* (*m*, H–C(2)); 4.94** (*m*, H–C(24)); 4.00* (*m*, H–C(24)); 3.85* (*dd*, J = 9.6, 1.4, H–C(14)); 3.70–3.25 (overl. *m*s, H–C(13), H–C(15), H–C(33), 3 MeO); 3.22*.** (*m*, H–C(21)); 3.02*.** (*m*, H–C(32)); 2.78** (*dd*, J = 17.6, 3.9, 1 H–C(23)); 2.66* (*dd*, J = 16.7, 2.8, 1 H–C(23)); 2.60–0.70 (overl. *m*s). HR-MS: 846.4613 ($[M+Na]^+$; calc. 846.4610).

Compound **24b**. According to *GP D*, oxidation of **23** (100 mg, 0.12 mmol) in CH_2Cl_2, followed by FC (SiO_2; CH_2Cl_2/MeOH 99.5:0.5 to 97.5:2.5), gave **24b** (72 mg, 72%). White foam. ^{1}H-NMR (mixture of 4 isomers which transformed over 24 h to a 5:2 mixture of six-membered-ring and seven-membered-ring hemiketals): major isomer: 7.42 (*d*, J = 6.9, NH); 5.29 (br. *s*, HO–C(10)); 5.16 (*d*, J = 2.7, H–C(26)); 5.04 (*d*, J = 9.0, H–C(20/29)); 4.96 (*d*, J = 9.4, H–C(20/29)); 4.22 (*m*, H–C(2)); 3.90 (*m*, H–C(24)); 3.97 (*dd*,

J = 9.6, 2.0, H–C(14)); 3.69 (*s*, COOMe); 3.57 (*ddd*, J = 11.0, 5.3, 2.0, H–C(15)); 3.55–3.30 (overl. *m*s); 3.22 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.65 (*dd*, J = 16.8, 3.5, 1 H–C(23)); 2.60–0.80 (overl. *m*s). HR-MS: 860.4770 ($[M+Na]^+$; calc. 860.4767).

Compound **25**. According to *GP C*, oxidation of **21** (200 mg, 0.25 mmol) using $Cu(OAc)_2$ in THF at r.t. for 22 h, followed by removal of the solvent at r.t. and aq. $NaHCO_3/CH_2Cl_2$ workup gave crude **25** (166 mg, 83%). Light yellow foam. The material contained *ca.* 30% starting material (^{1}H-NMR). Longer reaction times and higher temps. during workup, or attempted chromatography on silica resulted in partial transformation of the aldehyde to **26a** and **26b**. ^{1}H-NMR (5:2 mixture of isomers): characteristic signals: 9.78* (*t*, J = 1.0, HC=O); 9.74 (*t*, J = 1.4, HC=O); 7.42* (*d*, J = 7.2, NH); 7.22 (*d*, J = 9.1, NH). HR-MS: 830.4668 ($[M+Na]^+$; calc. 830.4667).

Compounds **26a** *and* **26b**. 250 µl of 40% aq. HF was added to a soln. of **3a** (200 mg, 0.24 mmol) in MeCN (10 ml) at 0°. The mixture was stirred for 4.25 h at ice-bath temp., basified with 100 ml of aq. $NaHCO_3$ and extracted with AcOEt. The org. extracts were washed with brine, dried, and concentrated to give a residue which, after FC (SiO_2; CH_2Cl_2/MeOH 100:3 to 100:5), gave unchanged starting material **3a** (96 mg, 48%), **26b** (32 mg, 16%), and **26a** (50 mg, 25%).

Data of **26a**. ^{1}H-NMR (*ca.* 3:1 mixture of 2 isomers): major isomer: 6.02 (br. *s*, OH), 5.09 (*dd*, J = 10, 3.5, H–C(6)); 5.08 (*s*, H–C(26)); 5.03 (*d*, J = 9.0, H–C(20/29)); 4.90 (*d*, J = 6.3, H–C(2)); 4.76 (*d*, J = 9.7, H–C(20/29)); 3.85 (br. *s*, OH); 3.71 (*m*, H–C(24)); 3.68 (*m*, H–C(14)); 3.60–3.30 (overl. *m*s); 3.25 (*m*, H–C(21)); 3.01 (*m*, H–C(32), OH)); 2.91 (*s*, OH); 2.80 (*dd*, 1 H–C(23)); 2.40–0.70 (overl. *m*s); minor isomer: 5.37 (*dd*, J = 10, 4, H–C(6)); 5.26 (br. *s*, H–C(26)); 5.18 (*d*, J = 9.5, H–C(20/29)); 4.94 (*d*, J = 9, H–C(20/29)); 4.58 (*d*, J = 7.5, H–C(2)); 4.22 (*m*, 2 H), 3.96 (br. *s*, OH), 3.60–3.20 (overl. *m*s); 3.01 (*m*, H–C(32), OH); 2.75 (1 H–C(23)); 2.49 (*dd*, 1 H–C(23)); 2.40–0.70 (overl. *m*s). ^{13}C-NMR: major isomer: 212.2 (C(22)); 169.7 (C(1/8); 166.6 (C(1/8); 139.9 (C(19)); 131.8 (C(27)); 129.2 (C(29)); 123.6 (C(20)); 101.4 (C(9/10)); 99.6 (C(9/10)); 84.10 (C(6/32)); 84.01 (C(6/32)); 77.9; 77.3; 73.5; 73.4; 71.5; 70.0; 57.2; 56.7; 56.2; 54.7; 52.1; 48.4; 44.9; 40.8; 34.92; 34.87; 34.80; 34.0; 32.5; 31.9; 31.2; 30.7; 25.7; 25.5; 23.2; 19.2; 19.1; 17.1; 15.8; 14.7; 11.6; 9.0. HR-MS: 830.4669 ($[M+Na]^+$; calc. 830.4667).

Data of **26b**. ^{1}H-NMR: 5.82 (br. *s*, OH); 5.69 (*d*, J = 8.2); 5.20 (*d*, J = 9.0); 4.85 (*dd*, J = 10.0, 3.4); 4.63 (*d*, J = 10.2); 4.33 (*d*, J = 1.7); 3.96 (*dd*, J = 5.2, 8.5); 3.82 (*t*, J = 5.0); 3.68 (*dd*, J = 9.4, 1.8); 3.47 (br. *d*, J = 11.1); 3.45–3.25 (*m*, H–C(13), H–C(21), H–C(33)); 3.38 (*s*, MeO); 3.36 (*s*, MeO); 3.31 (*s*, MeO); 3.07 (br. *s*, OH); 2.99 (*m*, H–C(32)); 2.92 (br. *s*, OH); 2.87 (*dd*, J = 13.9, 10.0, 1 H–C(23)); 2.4–0.7 (overl. *m*s); 1.70 (*s*, Me–C(19)); 1.51 (*d*, J = 1.0, Me–C(27)); 1.15 (*d*, J = 6.7, Me–C(11)); 1.05 (*d*, J = 6.9, Me–C(25)); 0.80 (*t*, J = 7.4, Me–C(37)); 0.76 (*d*, J = 6.3, Me–C(17)). ^{13}C-NMR: 210.8 (C(22)); 170.3 (C(1/8); 169.8 (C(1/8); 139.8 (C(19)); 133.7 (C(27)); 131.7 (C(29)); 123.5 (C(20)); 100.1 (C(9/10)); 99.8 (C(9/10)); 85.8 (C(6)); 84.1 (C(32)); 75.9; 73.7; 73.5; 71.0; 69.9; 57.4; 56.7; 56.22; 56.15; 54.5; 49.3; 47.6; 41.0; 36.6; 34.70; 34.65; 34.1; 33.3; 32.4; 31.3; 30.4; 27.9; 25.2; 23.8; 19.4; 18.1; 16.6; 15.5; 11.6; 11.5; 9.0. HR-MS: 830.4669 ($[M+Na]^+$; calc. 830.4667).

Compound **27a**. A mixture of **21** (2.0 g, 2.47 mmol) and benzyl (triphenylphosphoranylidene)acetate (1.42 g, 3.46 mmol) in 20 ml of toluene was stirred for 2 d at r.t. The solvent was evaporated, and the residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 99:1 to 97:3) to give **27a** (1.97 g, 85%). White foam. ^{1}H-NMR: 7.40–7.30 (*m*, 5 arom. H); 7.16 (*d*, J = 5.6, NH); 6.99 (*dt*, J = 15.7, 6.8, H–C(6)); 6.58 (*d*, J = 1.3, HO–C(10)); 5.92 (*d*, J = 15.7, H–C(6′)); 5.22 (*d*, J = 2.9, H–C(26)); 5.18 (*s*, PhCH_2); 5.00 (*d*, J = 9.4, H–C(29)); 4.98 (*d*, J = 9.6, H–C(20)); 4.22 (*d*, J = 11.0, HO–C(9)); 4.10 (*d*, J = 11.0, H–C(9)); 4.06 (*m*, H–C(2)); 4.03 (*m*, H–C(24)); 3.82 (*dd*, J = 9.5, 2.0, H–C(14)); 3.55 (*ddd*, J = 10.8, 4.8, 2.0, H–C(15)); 3.45 (*d*, J = 2.1, HO–C(24)); 3.38 (*s*, MeO–C(32)); 3.38 (*m*, H–C(33)); 3.37 (*m*, H–C(13)); 3.35 (*s*, MeO–C(13)); 3.30 (*s*, MeO–C(15)); 3.16 (*m*, H–C(21)); 2.98 (*ddd*, J = 11.2, 8.8, 4.2, H–C(32)); 2.73 (*d*, J = 1.4, HO–C(33)); 2.68 (*dd*, J = 16.6, 1.6, 1 H–C(23)); 2.31 (*dd*, J = 16.6, 10.4, 1 H–C(23)); 2.28 (*m*, 2 H–C(5)); 2.26 (*m*, H–C(30)); 2.24 (*m*, H–C(18a)); 2.04 (*m*, H–C(11)); 2.01 (*m*, H–C(12), 1 H–C(31)); 2.00 (*m*, 1 H–C(34)); 1.92 (*m*, H–C(3)); 1.85 (*m*, H–C(25)); 1.76 (*m*, 1 H–C(3)); 1.71 (*m*, 1 H–C(36)); 1.70 (*m*, H–C(18b)); 1.70–1.60 (*m*, 2 H–C(4)); 1.65 (*s*, Me–C(27)); 1.64 (*s*, Me–C(19)); 1.61 (*m*, 1 H–C(35)); 1.57 (*m*, H–C(17)); 1.54 (*m*, 1 H–C(12)); 1.49 (*m*, 1 H–C(36)); 1.35 (*m*, 2 H–C(16), 1 H–C(34)); 1.03 (*m*, 1 H–C(35)), 0.96 (*d*, J = 6.6, Me–C(11)); 0.94 (*m*, 1 H–C(34)); 0.89 (*d*, J = 7.0, Me–C(25)); 0.87 (*t*, J = 7.4, Me–C(37)); 0.76 (*d*, J = 6.5, Me–C(17)). ^{13}C-NMR: 214.7 (C(22)); 175.9 (C(8)); 169.2 (C(1)); 166.0 (C(6″)); 147.8 (C(6)); 140.3 (C(19)); 135.9 (arom. C_q); 131.6

(C(27)); 130.5 (C(29)); 128.6 (arom. CH); 128.3 (arom. CH); 122.7 (C(20)); 122.0 (C(6′)); 99.7 (C(10)); 84.1 (C(32)); 78.6 (C(26)); 77.0 (C(15)); 73.9 (C(13)); 73.5 (C(33)); 71.1 (C(14)); 70.8 (C(9)); 68.7 (C(24)); 66.2 (Ph*C*H$_2$); 57.4 (MeO–C(15)); 56.5 (MeO–C(32)); 56.0 (MeO–C(13)); 55.3 (C(21)); 52.8 (C(2)); 49.3 (C(18)); 43.7 (C(23)); 41.4 (C(25)); 36.6 (C(16)); 34.8 (C(30)); 34.7 (C(31)); 32.9 (C(11)); 31.7 (C(12)); 31.2 (C(34)); 31.2 (C(5)); 30.6 (C(35)); 29.9 (C(3)); 25.2 (C(17)); 24.3 (C(36)); 24.1 (C(4)); 18.8 (*Me*–C(17)); 16.1 (*Me*–C(11)); 15.2 (*Me*–C(19)); 14.0 (*Me*–C(27)); 11.7 (C(37)); 10.1 (*Me*–C(25)). HR-MS: 964.5387 ([M + Na]$^+$; calc. 964.5393).

Compound **27b**. A mixture of **21** (2.0 g, 2.47 mmol), methyl (triphenylphosphoranylidene)acetate (1.16 g, 3.46 mmol) in 10 ml of toluene was stirred for 20 h at r.t. The solvent was evaporated, and the residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 99 : 1 to 97 : 3) to give **27b** (1.878 g, 88%). White foam. ^{1}H-NMR (contains *ca.* 8 % *cis*-isomer): 7.17 (*d*, *J* = 5.7, NH); 6.95 (*dt*, *J* = 15.6, 6.6, H–C(6)); 6.58 (*d*, *J* = 1.6, HO–C(10)); 5.88 (*dt*, *J* = 16.6, 1.6, H–C(6′)); 5.23 (*d*, *J* = 3.0, H–C(26)); 5.00 (*d*, *J* ≈ 9, H–C(29)); 4.99 (*d*, *J* ≈ 9, H–C(20)); 4.70 (br. *s*, HO–C(9)); 4.10 (br. *s*, H–C(9)); 4.06 (*m*, H–C(2)); 4.03 (*m*, H–C(24)); 3.82 (*dd*, *J* = 9.6, 2.1, H–C(14)); 3.74 (*s*, COOMe); 3.58 (*ddd*, *J* = 11.0, 5.0, 2.1, H–C(15)); 3.46 (br. *s*, HO–C(24)); 3.40–3.35 (*m*, H–C(13), H–C(33)); 3.39 (*s*, MeO); 3.36 (*s*, 2 MeO); 3.18 (*m*, H–C(21)); 2.99 (*ddd*, *J* = 11.0, 8.7, 4.1, H–C(32)); 2.69 (*dd*, *J* = 16.7, 2.1, 1 H–C(23)); 2.69 (br. *s*, HO–C(33)); 2.33 (*dd*, *J* = 16.7, 6.4, 1 H–C(23)); 2.30–2.20 (*m*, 2 H–C(5), 1 H–C(18), H–C(30)); 2.08 (*m*, H–C(11)); 1.66 (*s*, Me–C(19), Me–C(27)); 2.10–1.20 (overl. *m*s); 1.03 (*m*, 1 H–C(35)); 0.97 (*d*, *J* = 6.6, Me–C(11)); 0.94 (*m*, 1 H–C(31); 0.90 (*d*, *J* = 7.1, Me–C(25)); 0.87 (*t*, *J* = 7.3, Me–C(37)); 0.77 (*d*, *J* = 6.4, Me–C(17)). HR-MS: 888.5080 ([M + Na]$^+$; calc. 888.5080).

Compound **28a**. According to *GP C*, oxidation of **27a**, followed by FC (SiO_2; CH_2Cl_2/MeOH 99 : 1 to 99 : 3) gave **28a** (83%). White foam. HR-MS: 962.5230 ([M + Na]$^+$; calc. 962.5236). This compound was transformed to **29a**, which was fully characterized.

Compound **28b**. According to *GP C*, oxidation of **27b**, followed by FC (SiO_2; CH_2Cl_2/MeOH 99 : 1 to 95 : 5) gave **28b** (88%). Foam. ^{1}H-NMR (1 : 1 mixture equilibrating in 24 h to 20 : 1 mixture of six-membered-ring/seven-membered-ring hemiketals); major isomer: 7.22 (*d*, *J* = 7.4, NH); 6.91 (*dt*, *J* = 14.2, 7.0, H–C(6)); 5.84 (*dt*, *J* = 14.2, 1.4, H–C(6′)); 3.86 (*m*, H–C(24)); 3.85 (*dd*, *J* = 9.6, 2.0, H–C(14)); 3.72 (*s*, COOMe); 3.58 (*ddd*, *J* = 11.1, 4.5, 2.0, H–C(15)); 3.48 (*m*, H–C(13/33)); 3.39 (*s*, MeO); 3.37 (*s*, MeO); 3.36 (*m*, H–C(13/33)); 3.34 (*s*, MeO); 3.20 (*m*, H–C(20)); 3.00 (*m*, H–C(32)); 2.64 (*dd*, *J* = 16.8, 3.2, 1 H–C(23)); 2.55 (*m*, H–C(5)); 2.40–0.80 (overl. *m*s). ^{13}C-NMR: 212.5 (C(22)); 189.0 (C(9)); 169.5; 166.6; 160.0; 147.3 (C(6)); 139.5 (C(19)); 131.4 (C(27)); 130.0 (C(29)); 123.2 (C(20/6′)); 122.1 (C(20/6′)); 98.5 (C(10)); 84.3 (C(32)); 78.9 (C(26)); 76.4; 73.6; 73.5; 72.0; 69.2 (C(24)); 57.7 (MeO); 56.5 (MeO); 56.1 (MeO); 55.3 (C(21)); 52.5 (C(2)); 51.5 (COO*Me*); 49.0; 44.1; 40.7; 34.93; 34.90; 34.7; 33.1; 32.3; 31.3; 31.2; 30.6; 30.2; 26.5; 24.3; 24.0; 19.6; 15.9; 15.7; 14.0; 11.6; 9.6. HR-MS: 886.4922 ([M + Na]$^+$; calc. 886.4923).

Compound **29a**. A mixture of **28a** (100 mg, 0.105 mmol) and Pd/C (10 mg) in AcOEt (10 ml) was stirred under H_2 balloon for 1 d, filtered, stripped of the solvent, and the residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 100 : 1 to 100 : 6) to give **29a** (20 mg, 22%). White foam. ^{1}H-NMR (5 : 2 mixture of six-membered-ring- and seven-membered-ring hemiketals): six-membered-ring hemiketal: 7.20 (br. *d*, *J* ≈ 7, NH); 5.37 (br. *s*, HO–C(10)); 5.16 (*d*, *J* = 2.6, H–C(26)); 5.00 (*d*, *J* = 9.0, H–C(20), H–C(29)); 4.20 (*m*, H–C(2)); 3.92 (*m*, H–C(24)); 3.86 (*dd*, *J* = 9.7, 2.0, H–C(14)); 3.60 (*ddd*, *J* = 11.0, 4.4, 2.0, H–C(15)); 3.46 (*m*, H–C(13)); 3.43 (*m*, H–C(33)); 3.41 (*s*, MeO–C(32)); 3.38 (*s*, MeO–C(13)); 3.36 (*s*, MeO–C(15)); 3.22 (*m*, H–C(21)); 3.02 (*ddd*, *J* = 11.3, 8.6, 4.2, H–C(32)); 2.65 (*dd*, *J* = 16.8, 2.9, 1 H–C(23)); 2.44 (*m*, H–C(11)); 2.35 (*dd*, *J* = 16.8, 8.6, 1 H–C(23)); 2.32 (*t*, *J* = 7.0, 2 H–C(6′)); 2.27 (*m*, H–C(30)); 2.14 (*m*, 1 H–C(18)); 2.11 (*m*, 1 H–C(12)); 2.04 (*m*, 1 H–C(31)); 1.99 (*m*, 1 H–C(34)); 1.93 (*m*, 1 H–C(3)); 1.92 (*m*, 1 H–C(18)); 1.85 (*m*, H–C(25)); 1.77 (*m*, 1 H–C(3)); 1.71 (*m*, 1 H–C(36)); 1.65 (*d*, *J* = 1.1, Me–C(27)); 1.62 (*s*, Me–C(19)); 1.62 (*m*, H–C(17)); 1.60 (*m*, 1 H–C(35)); 1.55 (*m*, 1 H–C(16)); 1.49 (*m*, 1 H–C(12), 1 H–C(36)); 1.40 (*m*, 2 H–C(5), 2 H–C(6)); 1.35 (*m*, 1 H–C(34)); 1.24 (*m*, 1 H–C(16)); 1.05 (*m*, 1 H–C(35)); 1.00 (*m*, 1 H–C(31)); 0.93 (*d*, *J* = 7.1, Me–C(25)); 0.88 (*d*, *J* = 6.6, Me–C(11)); 0.85 (*d*, *J* = 6.8, Me–C(17)); 0.85 (*t*, *J* = 7.3, Me–C(37)). ^{13}C-NMR: 169.7 (C(1)); 52.4 (C(2)); 30.2 (C(3)); 27.8 (C(5/6)); 24.5 (C(5/6); 33.2 (C(6′)); 166.5 (C(6″)); 160.2 (C(8)); 98.5 (C(10)); 32.9 (C(11)); 32.2 (C(12)); 73.53 (C(13/33)); 71.7 (C(14)); 76.6 (C(15)); 35.1 (C(16)); 26.6 (C(17)); 48.7 (C(18)); 139.5 (C(19)); 122.9 (C(20)); 55.1 (C(21)); 213.1 (C(22)); 43.9

(C(23)); 69.4 (C(24)); 40.5 (C(25)); 78.6 (C(26)); 131.4 (C(27)); 129.6 (C(29)); 34.8 (C(30)); 34.7 (C(31)); 84.3 (C(32)); 73.43 (C(13/33); 31.2 (C(34)); 30.5 (C(35)); 24.5 (C(36)); 11.6 (C(37)); 15.9 (*Me*–C(11)); 19.4 (*Me*–C(17)); 15.9 (*Me*–C(19)); 9.7 (*Me*–C(25)); 14.1 (*Me*–C(27)); 56.1 (*Me*O–C(13)); 57.7 (*Me*O–C(15)); 56.6 (*Me*O–C(32)); seven-membered-ring hemiketal: 7.35 (*d*, *J* = 3.3, OH); 7.18 (br. *d*, *J* ≈ 8, NH); 5.08 (*d*, *J* = 9.2, H–C(29)); 4.94 (*d*, *J* = 9.2, H–C(20)); 4.49 (*m*, H–C(2)); 3.92 (*m*, H–C(24)); 3.67 (*m*, H–C(15)); 3.66 (*m*, H–C(13)); 3.55 (*m*, H–C(11)); 3.43 (*m*, H–C(33)); 3.41 (*s*, MeO–C(32)); 3.37 (*s*, MeO–C(13/15)); 3.32 (*s*, MeO–C(13/15)); 3.32 (*m*, H–C(14)); 3.22 (*m*, H–C(21)); 3.02 (*ddd*, *J* = 11.3, 8.6, 4.2, H–C(32)); 2.80 (*dd*, *J* = 17.7, 4.0, 1 H–C(23)); 2.49 (*dd*, *J* = 17.7, 6.8, 1 H–C(23)); 2.35 (*m*, 1 H–C(12)); 2.31 (*t*, *J* = 7.0, 2 H–C(6′)); 2.27 (*m*, H–C(30)); 2.18 (*m*, 1 H–C(18)); 2.04 (*m*, 1 H–C(31)); 1.99 (*m*, 1 H–C(34)); 1.93 (*m*, 1 H–C(3)); 1.85 (*m*, H–C(25)); 1.77 (*m*, 1 H–C(3), 1 H–C(18)); 1.71 (*m*, 1 H–C(36)); 1.72 (*s*, Me–C(19)); 1.62 (*s*, Me–C(27)); 1.60 (*m*, 1 H–C(16), 1 H–C(35)); 1.49 (*m*, 1 H–C(36)); 1.40 (*m*, 2 H–C(5), 2 H–C(6)); 1.35 (*m*, 1 H–C(34)); 1.26 (*m*, 1 H–C(12); 1.18 (*d*, *J* = 6.6, Me–C(11)); 1.05 (*m*, 1 H–C(35)); 1.00 (*m*, 1 H–C(16), 1 H–C(31)); 0.91 (*d*, *J* = 7.3, Me–C(25)); 0.84 (*d*, *J* = 6.6, Me–C(17)). ^{13}C-NMR (not all C-atoms detected): 212.6 (C(10)); 166.5 (C(6″)); 139.3 (C(19)); 130.7 (C(27)); 129.7 (C(29)); 123.8 (C(20)); 97.7 (C(9)); 84.3 (C(32)); 77.1 (C(13)); 77.1 (C(15)); 77.0 (C(14)); 73.5 (C(33)); 68.4 (C(24)); 57.5 (MeO); 57.1 (MeO); 56.5 (MeO); 54.8 (C(21)); 52.0 (C(2)); 50.2 (C(18)); 45.1 (C(23)); 40.4 (C(25)); 38.0 (C(11)); 38.0 (C(12)); 34.9 (C(30)); 34.7 (C(31)); 33.2 (C(6′)); 31.2 (C(34)); 30.5 (C(35)); 30.2 (C(3)); 27.8 (C(5/6)); 24.5 (C(5/6)); 24.5 (C(36)); 20.1 (*Me*–C(17)); 16.2 (*Me*–C(11)); 16.1 (*Me*–C(19)); 13.8 (*Me*–C(27)); 11.6 (C(37)); 9.7 (*Me*–C(25)). HR-MS: 874.4927 ([*M* + Na]$^+$; calc. 874.4923).

Compound **29b**. A mixture of **28b** (50 mg, 0.058 mmol) and Pd/C (5 mg) in AcOEt (7 ml) was stirred under H_2 balloon for 6 h, filtered, stripped of the solvent, and the residue was purified by FC (SiO_2; AcOEt/i-PrOH 100 : 0 to 100 : 30) to give **29b** (28 mg, 56%). White foam. R_f (CH_2Cl_2/MeOH 10 : 1) 0.45. ^{1}H-NMR (complex mixture; selected signals): 7.40 (*d*, *J* = 8.3, NH); 5.23 (*s*, H–C(26)); 5.18 (*m*); 5.09 (*d*, *J* = 9.0, H–C(29)); 4.95 (*d*, *J* = 9.0, H–C(20)). ESI-MS: 882.1 ([*M* + H]$^+$).

Compounds **30a** *and* **31a**. An Et_2O soln. of CH_2N_2 (22 ml) was added in small portions under stirring over a period of 3 h to a mixture of 5,6-dehydroascomycin (**6a**; 0.5 g, 0.633 mmol) and bis(2,4-pentandionato)copper (0.1 g) in CH_2Cl_2 at r.t. The mixture was stirred for further 4 h, diluted with AcOEt, and washed successively with aq. $NaHCO_3$ and brine. The org. layer was dried and stripped of the solvent to give a residue, which after repeated purification by prep. HPLC (*Polygosyl 10 CN* column, cyclohexane/i-PrOH 90 : 10) gave pure samples of **30a** and **31a** as colorless foams. Estimated yields of **30a** and **31a** are 6 and 24%.

Data of **30a**. ^{1}H-NMR: 7.41 (br. HO–C(10)); 5.13 (*d*, *J* = 2.5, H–C(26)); 5.05 (*d*, *J* = 9.4, H–C(20)); 4.95 (*d*, *J* = 9.0, H–C(29)); 4.36 (*dd*, *J* = 6.1, 2.7, H–C(2)); 4.01 (*m*, H–C(24)); 3.95 (*dd*, *J* = 9.5, 2.3, H–C(14)); 3.59 (*m*, H–C(15)); 3.5–3.3 (*m*, H–C(13), H–C(33)); 3.41 (*s*, MeO–C(32)); 3.39 (*s*, MeO–C(13)); 3.36 (*s*, MeO–C(15)); 3.19 (*m*, H–C(21)); 3.01 (*m*, H–C(32)); 2.84 (*m*, H–C(6)); 2.71 (*dd*, *J* = 14.8, 2.3, 1 H–C(23)); 2.66 (*s*, HO–C(33)); 2.38 (*dd*, *J* = 17.8, *ca.* 10, 1 H–C(23)); 1.66 (*s*, Me–C(19/27)); 1.65 (*s*, Me–C(19/27)); 1.04 (*d*, *J* = 6.6, Me–C(11)); 0.91 (*d*, *J* = 7.2, Me–C(25)); 0.89 (*t*, *J* = 7.3, H–C(37)); 0.84 (*d*, *J* = 6.5, Me–C(17)); 0.75 (*m*, 1 H–C(6′)). HR-MS: 826.4711 ([*M* + Na]$^+$; calc. 826.4712).

Data of **31a**. ^{1}H-NMR (*ca.* 2 : 1 mixture of isomers): major isomer: 5.41 (*s*, HO–C(10)); 5.22 (*d*, *J* = 3.0, H–C(26)); 5.05 (*d*, *J* = 8.9, H–C(29)); 5.02 (*d*, *J* = 8.7, H–C(20)); 4.40 (*dd*, *J* = 8.7, 6.2, H–C(2)); 4.02 (*m*, H–C(24)); 3.86 (*dd*, *J* = 9.6, 2.5, H–C(14)); 3.56 (*m*, H–C(15)); 3.44 (*m*, H–C(13)); 3.40 (*m*, H–C(33)); 3.40 (*s*, MeO–C(32)); 3.38 (*s*, MeO–C(13)); 3.32 (*s*, MeO–C(15)); 3.19 (*m*, H–C(21)); 3.06 (*m*, H–C(6)); 3.00 (*m*, H–C(32)); 2.70 (*dd*, *J* = 17.0, 1.8, 1 H–C(23)); 2.34 (*dd*, *J* = 17.0, 9.6, 1 H–C(23)); 2.29 (*m*, H–C(30)); 1.67 (*d*, *J* = 0.9, Me–C(27)); 1.65 (*s*, Me–C(19)); 1.30 (*m*, H–C(5)); 1.05 (*d*, *J* = 6.4, Me–C(11)); 0.90 (*d*, *J* = 7.3, Me–C(25)); 0.87 (*t*, *J* = 7.3, H–C(37)); 0.81 (*d*, *J* = 6.4, Me–C(17)); 0.82 (*m*, 1 H–C(6′)); 0.60 (*m*, 1 H–C(6′)); minor isomer: 5.34 (*d*, *J* = 3.0, H–C(26)); 5.11 (*d*, *J* = 9.2, H–C(29)); 5.02 (*d*, *J* = 8.7, H–C(20)); 4.38 (br. *s*, H–C(2)); 4.31 (*s*, HO–C(10)); 3.92 (*m*, H–C(24)); 3.62 (*dd*, *J* = 9.8, 1.1, H–C(14)); 3.56 (*m*, H–C(15)); 3.41 (*s*, MeO–C(32)); 3.40 (*m*, H–C(33)); 3.37 (*s*, MeO–C(13)); 3.34 (*m*, H–C(13)); 3.29 (*s*, MeO–C(15)); 3.19 (*m*, H–C(21)); 3.15 (*m*, H–C(6)); 3.00 (*m*, H–C(32)); 2.83 (*dd*, *J* = 15.4, 3.4, 1 H–C(23)); 2.29 (*m*, H–C(30)); 1.63 (*d*, *J* =

0.9, Me–C(27)); 1.60 (*s*, Me–C(19)); 1.30 (*m*, H–C(5)); 1.03 (*m*, 1 H–C(6′)); 0.98 (*d*, *J* = 6.6, Me–C(11)); 0.93 (*d*, *J* = 6.4, Me–C(17)); 0.89 (*d*, *J* = 7.3, Me–C(25)); 0.36 (*m*, 1 H–C(6′)). HR-MS: 826.4713 ($[M+Na]^+$; calc. 826.4712).

Compounds **30b** *and* **31b**. 110 ml of an Et_2O soln. of CH_2N_2 was added in small portions under stirring over 2.5 h to a mixture of *9-deoxo-5,6-dehydroascomycin* (**32**; 300 mg, 0.387 mmol) and bis(2,4-pentadionato)copper (0.1 g) in 1.5 ml of Et_2O at r.t. The mixture was filtered through *Celite*, and the filtrate was washed successively with aq. $NaHCO_3$ and brine. The org. layer was separated, dried and the solvent was removed to give a residue. FC of the residue (SiO_2-5% $NaHCO_3$, AcOEt) gave a mixture which was purified by prep. HPLC (*Polygosyl 10 CN* column, cyclohexane/i-PrOH 9 :1) to give the *β*-isomer **30b** (28 mg, 9%) as the first, and the *α*-isomer **31b** (47 mg, 15%) as the second fraction, both as colorless foams. Anal. HPLC (*Polygosyl 10 CN* column; cyclohexane/i-PrOH: 9 :1): t_R (**30b**) 10.3 min, t_R (**31b**) 11.9 min.

Data of **30b**. ^{1}H-NMR: 6.51 (*d*, *J* = 1.4, HO–C(10)); 5.11 (*d*, *J* = 2.5, H–C(26)); 5.01 (*d*, *J* = 8.9, H–C(20)); 4.91 (*d*, *J* = 9.2, H–C(29)); 4.34 (*dd*, *J* = 6.4, 1.6, H–C(2)); 4.01 (*ddd*, *J* = 10.1, 3.9, 1.8, H–C(24)); 3.84 (*dd*, *J* = 9.4, 2.0, H–C(14)); 3.51 (*ddd*, *J* = 10.5, 5.0, 2.0, H–C(15)); 3.41 (*m*, H–C(13)); 3.39 (*m*, H–C(33)); 3.39 (*s*, MeO–C(32)); 3.37 (*s*, MeO–C(13)); 3.36 (*s*, MeO–C(15)); 3.14 (*m*, H–C(21)); 3.14 (*d*, *J* = 14.9 , 1 H–C(9)); 2.99 (*ddd*, *J* = 11.2, 8.7, 4.4, H–C(32)); 2.79 (*ddd*, *J* = 8.7, 6.2, 3.7, H–C(6)); 2.71 (*dd*, *J* = 17.0, 1.8, 1 H–C(23)); 2.61 (*d*, *J* = 14.9, 1 H–C(9)); 2.37 (*dd*, *J* = 17.0, 10.1, 1 H–C(23)); 2.32 (*m*, 1 H–C(18)); 2.26 (*m*, H–C(30)); 2.09 (*m*, 1 H–C(4)); 2.01 (*m*, H–C(31)); 1.98 (*m*, 1 H–C(3), 1 H–C(12), H–C(34)); 1.84 (*m*, H–C(25)); 1.80 (*m*, 1 H–C(3)); 1.69 (*m*, 1 H–C(36)); 1.66 (*m*, 1 H–C(18)); 1.65 (*m*, H–C(11)); 1.64 (*d*, *J* = 1.2, Me–C(27)); 1.62 (*s*, Me–C(19)); 1.58 (*m*, 1 H–C(35)); 1.57 (*m*, H–C(17)); 1.56 (*m*, 1 H–C(12)); 1.50 (*m*, 1 H–C(36)); 1.44 (*m*, 2 H–C(16)); 1.34 (*m*, H–C(5), H–C(34)); 1.01 (*m*, 1 H–C(35)); 0.96 (*d*, *J* = 6.6, Me–C(11)); 0.95 (*m*, 1 H–C(4)); 0.93 (*m*, 1 H–C(31)); 0.89 (*m*, 1 H–C(6′)); 0.87 (*t*, *J* = 7.3, Me–C(37)); 0.87 (*d*, *J* = 7.1, Me–C(25)); 0.79 (*d*, *J* = 6.4, Me–C(17)); 0.51 (*m*, 1 H–C(6′)). ^{13}C-NMR: 169.4 (C(1)); 54.0 (C(2)); 25.2 (C(3)); 18.9 (C(4)); 13.0 (C(5)); 26.2 (C(6)); 14.6 (C(6′)); 176.0 (C(8)); 38.4 (C(9)); 98.5 (C(10)); 38.5 (C(11)); 32.5 (C(12)); 74.5 (C(13)); 71.0 (C(14)); 77.5 (C(15)); 36.2 (C(16)); 25.6 (C(17)); 49.1 (C(18)); 140.5 (C(19)); 122.5 (C(20)); 55.4 (C(21)); 214.7 (C(22)); 43.1 (C(23)); 69.3 (C(24)); 40.5 (C(25)); 77.6 (C(26)); 132.3 (C(27)); 129.2 (C(29)); 34.85 (C(30)); 34.81 (C(31)); 84.2 (C(32)); 73.6 (C(33)); 31.2 (C(34)); 30.6 (C(35)); 24.8 (C(36)); 11.8 (C(37)); 17.0 (*Me*–C(11)); 19.6 (*Me*–C(17)); 15.6 (*Me*–C(19)); 9.8 (*Me*–C(25)); 14.3 (*Me*–C(27)); 56.1 (*Me*O–C(13)); 57.7 (*Me*–C(15)); 56.5 (*Me*O–C(32)). HR-MS: 812.4917 ($[M+Na]^+$; calc. 812.4925).

Data of **31b**. ^{1}H-NMR: 6.79 (*d*, *J* = 1.2, HO–C(10)); 5.20 (*d*, *J* = 2.0, H–C(26)); 5.02 (*d*, *J* = 9.2, H–C(29)); 4.99 (*d*, *J* = 8.9, H–C(20)); 4.46 (*t*, *J* = 6.4, H–C(2)); 4.02 (*dd*, *J* = 10.3, 3.7, H–C(24)); 3.82 (*dd*, *J* = 9.4, 2.3, H–C(14)); 3.51 (*m*, H–C(15), HO–C(24/33)); 3.43 (*m*, H–C(13)); 3.40 (*s*, MeO–C(32)); 3.39 (*m*, H–C(33)); 3.37 (*s*, MeO–C(13)); 3.34 (*s*, MeO–C(15)); 3.14 (*m*, H–C(21)); 3.07 (*d*, *J* = 15.1, 1 H–C(9)); 3.00 (*ddd*, *J* = 11.2, 8.7, 4.1, H–C(32)); 2.70 (*m*, H–C(6)); 2.66 (*d*, *J* = 17.2, 1 H–C(23)); 2.63 (*d*, *J* = 15.1, 1 H–C(9)); 2.28 (*dd*, *J* = 17.2, 10.3, 1 H–C(23)); 2.28 (*m*, H–C(30)); 2.27 (*m*, 1 H–C(18)); 2.04 (*m*, 1 H–C(31)); 1.99 (*m*, 1 H–C(34)); 1.98 (*m*, 1 H–C(4), 1 H–C(12)); 1.86 (*m*, H–C(25)); 1.85 (*m*, 2 H–C(3)); 1.70 (*m*, 1 H–C(36)); 1.67 (*s*, Me–C(27)); 1.65 (*s*, Me–C(19)); 1.65 (*m*, H–C(18)); 1.64 (*m*, H–C(11)); 1.63 (*m*, 1 H–C(35)); 1.61 (*m*, H–C(17)); 1.55 (*m*, 1 H–C(12)); 1.50 (*m*, 1 H–C(36)); 1.42 (*m*, 1 H–C(4)); 1.36 (*m*, 1 H–C(34)); 1.35 (*m*, 2 H–C(16)); 1.32 (*m*, H–C(5)); 1.07 (*m*, 1 H–C(35)); 0.99 (*m*, 1 H–C(6′)); 0.97 (*d*, *J* = 6.6, Me–C(11)); 0.96 (*m*, 1 H–C(31)); 0.88 (*d*, *J* = 7.3, Me–C(25)); 0.87 (*t*, *J* = 7.3, H–C(37)); 0.75 (*d*, *J* = 6.0, Me–C(17)); 0.59 (*m*, 1 H–C(6′)). ^{13}C-NMR: 169.7 (C(1)); 52.5 (C(2)); 23.9 (C(3)); 19.4 (C(4)); 13.4 (C(5)); 26.8 (C(6)); 14.1 (C(6′)); 175.6 (C(8)); 37.8 (C(9)); 98.5 (C(10)); 38.5 (C(11)); 32.5 (C(12)); 74.4 (C(13)); 70.7 (C(14)); 77.0 (C(15)); 36.4 (C(16)); 25.4 (C(17)); 48.8 (C(18)); 140.8 (C(19)); 122.3 (C(20)); 55.3 (C(21)); 214.9 (C(22)); 43.1 (C(23)); 69.0 (C(24)); 40.9 (C(25)); 77.5 (C(26)); 132.2 (C(27)); 129.7 (C(29)); 34.9 (C(30)); 34.8 (C(31)); 84.2 (C(32)); 73.6 (C(33)); 31.2 (C(34)); 30.6 (C(35)); 24.5 (C(36)); 11.7 (C(37)); 16.9 (*Me*–C(11)); 18.8 (*Me*–C(17)); 15.4 (*Me*–C(19)); 10.0 (*Me*–C(25)); 14.3 (*Me*–C(27)); 56.1 (*Me*O–C(13)); 57.4 (*Me*O–C(15)); 56.5 (*Me*O–C(32)). HR-MS: 812.4926 ($[M+Na]^+$; calc. 812.4925).

Compound **32**. H_2S Gas was passed for 10 min through a mixture of **6a** (0.2 g, 0.253 mmol) and pyridine (0.3 ml) in DMF (5 ml). The mixture was stirred for 3 d at r.t., stripped of the volatiles under vacuum, and worked up using aq. $NaHCO_3$ and AcOEt. FC of the residue (SiO_2-5% $NaHCO_3$; AcOEt) gave **32** (157 mg, 80%). White foam. ^{1}H-NMR (*ca.* 3:1 mixture of rotamers): 6.60 (*s*, HO–C(10)); 6.59* (*d*, *J* = 8.0, H–C(6)); 6.52 (*d*, *J* = 8.5, H–C(6)); 5.20 (*d*, *J* = 0.5, H–C(26)); 5.16* (*s*); 5.13* (*d*, *J* = 9.1); 5.10–4.95 (*m*, 3 H); 4.88 (*s*); 4.75* (*s*); 4.72* (*m*); 4.50* (*d*, *J* = 9.1); 4.10* (*m*, H–C(24)); 4.00 (br. *d*, *J* = 10.5, H–C(24)); 3.90* (*d*, *J* = 3.90)); 3.86 (*dd*, *J* = 9.5, 2.4, H–C(14)); 3.61* (*d*, *J* = 9.5, 2.1, H–C(14)); 3.57* (*s*); 3.53 (*m*); 3.50–3.20 (overl. signals); 3.18 (*m*); 3.00 (*m*, H–C(32), H–C(32*)); 2.75 (*d*, *J* = 5.7, H_a–C(9)); 2.68 (*d*, *J* = 5.7, H_b–C(9)); 2.68 (*m*, H_a–C(23), H_a–C(23*)); 2.52* (H_b–C(23)); 2.36 (br. *d*, *J* = 10.6); 2.30–0.70 (overl. *m*s). ^{13}C-NMR (main rotamer): 214.8; 170.9; 168.1; 140.9; 132.6; 129.2; 123.7; 122.3; 107.3; 98.5; 84.2; 77.4; 76.9; 74.2; 73.6; 70.9; 69.4; 57.7; 56.6; 56.1; 55.4; 52.6; 48.7; 42.6; 40.8; 38.4; 37.4; 36.2; 34.89; 34.85; 32.5; 31.2; 30.6; 25.7; 24.6; 23.3; 19.0; 18.8; 16.9; 15.5; 14.4; 11.7; 9.7. HR-MS: 798.4768 ($[M+Na]^+$; calc. 798.4768).

Compound **33**. An Et_2O soln. of CH_2N_2 (10 ml) was added in small portions to a soln. of **6a** (0.5 g, 0.633 mmol) and stirred for 4 h. The solvents were removed, and the residue was passed through a short column (SiO_2-5% $NaHCO_3$; AcOEt) for removing polymeric materials. The residue was purified by prep. HPLC (*Polygosyl 10 CN* column, cyclohexane/i-PrOH 85:15) to give a minor isomer (19%) and a major isomer (41%), both as colorless foams.

Data of Minor C(9)-Isomer of **33**. ^{1}H-NMR: 7.08 (*dt*, *J* = 8.5, 1.1, H–C(6)); 5.26 (*d*, *J* = 4.1, H–C(26)); 5.19 (*t*, *J* = 3.6, H–C(2)); 5.12 (*m*, H–C(5)); 5.08 (*d*, *J* = 9.0, H–C(20/29)); 5.03 (*d*, *J* = 9.8, H–C(20/29)); 4.00 (*m*, H–C(24)); 3.41 (*s*, MeO); 3.35 (*s*, MeO); 3.29 (*s*, MeO)); 3.50–3.30 (*m*, H–C(13), H–C(14), H–C(15), H–C(33)); 3.18 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 3.00 (*d*, *J* = 5.1, 1 H–C(9′)); 2.91 (*dd*, *J* = 14.2, 3.8, 1 H–C(23)); 2.85 (*d*, *J* = 5.1, 1 H–C(9′)); 2.81 (br. *s*, OH)); 2.71 (br. *s*, OH)); 2.67 (*d*, *J* = 1.9, HO–C(10)); 2.45 (*dd*, *J* = 14.2 , 9.3, 1 H–C(23)); 2.43 (*m*, H–C(11)); 1.62 (*s*, Me–C(19/27)); 1.61 (*s*, Me–C(19/27)); 0.88 (*t*, *J* = 7.4, H–C(37)); 2.20–0.80 (overl. *m*s). ^{13}C-NMR: 213.0 (C(22)); 169.6 (C(1)); 164.1 (C(8)); 139.4 (C(19)); 132.3 (C(27)); 130.4 (C(29)); 123.4 (C(6)); C(20)); 109.5 (C(5)); 97.0 (C(10)); 84.4 (C(32)); 78.7; 75.8; 74.5; 74.0; 73.7; 70.3 (C(24)); 61.6 (C(9)); 57.2; 56.7; 56.52; 56.46; 55.9; 50.4 (C(9′/18)); 48.9 (C(9′/18)); 43.7 (C(23)); 39.9 (C(25)); 35.1; 35.0; 34.9; 33.9; 32.9; 31.4; 30.8; 27.1 (C(17)); 24.9; 23.8; 20.6; 19.4; 16.6; 16.1; 14.0; 12.0; 10.1. HR-MS: 826.4721 ($[M+Na]^+$; calc. 826.4717).

Data of Major C(9)-Isomer of **33**. ^{1}H-NMR: 7.04 (*d*, *J* = 8.5, H–C(6)); 5.95 (*t*, *J* = 3.0, H–C(2)); 5.56 (*s*, H–C(26)); 5.13 (*m*, H–C(5)); 5.09 (*d*, *J* = 9.1, H–C(20/29)); 5.03 (*d*, *J* = 8.7, H–C(20/29)); 4.24 (*m*, H–C(24)); 3.65 (*dd*, *J* = 11.8, 3.7, H–C(15)); 3.57 (*d*, *J* = 9.6, H–C(14)); 3.43 (*s*, MeO); 3.38 (*s*, MeO); 3.36 (*s*, MeO); 3.40 (*m*, H–C(33)); 3.19 (*m*, H–C(13)); 3.11 (*m*, H–C(21)); 3.09 (*d*, *J* = 4.5, 1 H–C(9′)); 3.02 (*m*, H–C(32)); 2.96 (*d*, *J* = 4.5, 1 H–C(9′)); 2.74 (br. *s*, OH)); 2.57 (*dd*, *J* = 15.8, 10.6, 1 H–C(23)); 2.44 (*m*); 2.24 (*dd*, *J* = 15.8, 2.2, 1 H–C(23)); 2.30–0.80 (overl. *m*s); 1.64 (*d*, *J* = 1.0, Me–C(27)); 1.55 (*s*, Me–C(19)); 1.03 (*d*, *J* = 6.5, Me–C(11)); 0.90 (*d*, *J* = 6.1, Me–C(17/25)); 0.88 (*t*, *J* = 6.4, Me–C(37)); 0.86 (*d*, *J* = 7.1, Me–C(17/25)). ^{13}C-NMR: 209.5 (C(22)); 169.7 (C(1)); 164.6 (C(8)); 140.1 (C(19)); 131.6 (C(27)); 129.2 (C(29)); 123.8 (C(6/20)); 123.5 (C(6/20)); 110.1 (C(5)); 95.9 (C(10)); 84.2 (C(32)); 79.1; 75.2; 73.8; 73.6; 72.5; 70.5 (C(24)); 61.9 (C(9)); 58.2 (MeO, C(2/21)); 56.7 (MeO, C(2/21)); 56.1 (MeO, C(2/21)); 55.8 (MeO, C(2/21)); 55.2 (MeO, C(2/21)); 49.7 (C(9′/18)); 48.6 (C(9′/18)); 43.3 (C(23)); 39.0 (C(25)); 36.6 (C(16)); 35.0 (C(30/31)); 34.8 (C(30/31)); 33.2 (C(11/12)); 31.2 (C(34)); 30.6 (C(35)); 26.5; 25.1; 24.3; 20.0; 19.8; 15.9; 15.3; 14.4; 11.7 (C(37)); 6.1 (C(25)).

Compound **34**. A mixture of **32** (300 mg, 0.387 mmol) and aq. 1N HCl (1 ml) in MeCN (10 ml) was stirred for 6 h at r.t. and worked up using aq. $NaHCO_3$/AcOEt. The residue was purified by prep. HPLC (*Polygosyl 10 CN* column, cyclohexane/i-PrOH 85:15) to give **34** (110 mg, 37%). White foam. ^{1}H-NMR: 5.28 (*d*, *J* = 8.7, H–C(20)); 5.25 (*s*, H–C(26)); 5.18 (*dd*, *J* = 8.9, 5.0, H–C(6)); 4.91 (*d*, *J* = 8.9, H–C(29)); 4.66 (*d*, *J* = 7.1, H–C(2)); 3.97 (*dd*, *J* = 10.5, 4.1, H–C(24)); 3.72 (br. *s*, OH)); 3.46 (*ddd*, *J* = 10.8, 9.4, 4.6, H–C(13)); 3.41 (*m*, H–C(15)); 3.39 (*s*, MeO–C(32)); 3.38 (*m*, H–C(33)); 3.35 (*s*, MeO–C(13)); 3.34 (*s*, MeO–C(15)); 3.30 (*d*, *J* = 9.4, H–C(14)); 3.11 (*m*, H–C(21)); 2.99 (*ddd*, *J* = 11.2, 8.9, 4.4, H–C(32)); 2.95 (*d*, *J* = 16.0, 1 H–C(9)); 2.77 (*d*, *J* = 17.5, 1 H–C(23)); 2.68 (br. *s*, OH); 2.50 (*d*, *J* = 16.0, 1 H–C(9)); 2.48 (*dd*, *J* = 17.5, 10.8, 1 H–C(23)); 2.26 (*m*, H–C(30)); 2.16 (*m*, 1 H–C(12)); 2.13 (*m*, 1 H–C(18)); 2.08 (*m*, 1 H–C(3), 1 H–C(5)); 2.01 (*m*, 1 H–C(31)); 1.97 (*m*, 1 H–C(34)); 1.95 (*m*, H–C(25)); 1.93

(*m*, 1 H–C(3), H–C(11)); 1.71 (*m*, 1 H–C(18)); 1.70 (*m*, 1 H–C(5)); 1.68 (*m*, 1 H–C(4)); 1.66 (*m*, 1 H–C(36)); 1.65 (*s*, Me–C(27)); 1.64 (*s*, Me–C(19)); 1.61 (*m*, 1 H–C(16)); 1.57 (*m*, 1 H–C(35)); 1.54 (*m*, 1 H–C(36)); 1.53 (*m*, H–C(17)); 1.34 (*m*, 1 H–C(34)); 1.30 (*m*, 1 H–C(4)); 1.26 (*m*, 1 H–C(16)); 1.14 (*m*, 1 H–C(12)); 1.00 (*m*, 1 H–C(35)); 0.93 (*m*, 1 H–C(31)); 0.91 (*d*, $J = 6.9$, Me–C(11)); 0.88 (*t*, $J = 7.3$, Me–C(37)); 0.86 (*d*, $J = 7.1$, Me–C(25)); 0.84 (*d*, $J = 6.4$, Me–C(17)). ^{13}C-NMR: 170.7 (C(1)); 54.6 (C(2)); 25.9 (C(3)); 17.0 (C(4)); 30.71 (C(5/35)); 80.9 (C(6)); 170.5 (C(8)); 32.0 (C(9)); 101.9 (C(10)); 37.7 (C(11)); 33.5 (C(12)); 73.5 (C(13)); 75.5 (C(14)); 76.7 (C(15)); 35.7 (C(16)); 27.5 (C(17)); 48.3 (C(18)); 139.6 (C(19)); 122.3 (C(20)); 56.0 (C(21)); 215.8 (C(22)); 40.8 (C(23)); 70.2 (C(24)); 39.7 (C(25)); 76.0 (C(26)); 132.4 (C(27)); 128.4 (C(29)); 34.8 (C(30)); 34.9 (C(31)); 84.2 (C(32)); 73.6 (C(33)); 31.2 (C(34)); 30.68 (C(5/35)); 25.7 (C(36)); 11.9 (C(37)); 16.4 (*Me*–C(11)); 19.3 (*Me*–C(17)); 16.9 (*Me*–C(19)); 9.7 (*Me*–C(25)); 14.5 (*Me*–C(27)); 56.4 (*Me*O–C(13)); 57.6 (*Me*O–C(15)); 56.6 (*Me*O–C(32)). HR-MS: 798.4756 ($[M + Na]^+$; calc. 798.4763).

Compound **36**. According to *GP B*, a soln. of **35** [14] (3 g, 2.6 mmol) in 0.5 l of MeOH was irradiated at 0° for 8 h. Removal of MeOH gave the crude product **36** which was taken to next step (acidic hydrolysis). A pure sample of **36** was obtained by FC (SiO_2-5% $NaHCO_3$; toluene/AcOEt 15 : 1 to 1 : 1) in 69% yield. White foam. ^{1}H-NMR: 5.78 (br. *s*, H–C(6)); 5.65 (*d*, $J = 2.4$, H–C(26)); 5.54 (br. *d*, $J = 5.6$, H–C(2)); 5.26 (*d*, $J = 9.2$, H–C(20/29)); 5.24 (*d*, $J = 10.0$, H–C(20/H–C(29)); 4.47 (*d*, $J = 7.3$, H–C(9)/HO–C(9)); 4.41 (*s*, HO–C(10)); 4.32 (*d*, $J = 7.3$, H–C(9)/HO–C(9)); 4.09 (br. *d*, $J = 10.8$, H–C(24)); 3.85 (*ddd*, $J = 11.4$, 3.9, 2.4, H–C(22)); 3.76 (br. *d*, $J = 9.5$, H–C(14)); 3.57 (*ddd*, $J = 11.6$, 4.7, 1.8, H–C(15)); 3.39 (*m*, H–C(13/33)); 3.38 (*s*, MeO)); 3.35 (*s*, MeO)); 3.28 (*m*, H–C(13/33)); 3.25 (*s*, MeO), 3.14 (*s*, MeO–C(6)); 2.93 (*ddd*, $J = 11.2$, 8.6, 4.5, H–C(32)); 1.69 (*s*, Me–C(19/27)); 1.57 (*s*, Me–C(19/27)); 0.89 (*s*, *t*-Bu), 0.08 (*s*, MeSi), 0.06 (*s*, MeSi), 2.3–0.8 (overl. *m*s). ^{13}C-NMR: 173.2 (C(1/8)); 169.3 (C(1/8)); 135.0 (C(19)); 134.0 (C(27)); 132.7 (C(29)); 125.5 (C(20)); 96.8 (C(10)); 84.2 (C(32)); 80.6 (C(6)); 76.6; 75.4; 75.1; 73.5; 72.4; 71.1; 69.9; 57.7 (MeO); 57.0 (MeO); 56.6 (MeO); 56.3 (MeO); 52.0 (C(2)); 49.4 (C(18)); 45.4; 42.5; 36.3; 36.1; 36.0; 34.9; 34.0; 33.7; 32.0; 31.0; 30.4; 27.1; 26.0; 25.9 (Me_3C); 25.4; 20.2; 18.2; 18.0; 17.9; 17.8; 17.6; 17.53; 17.50; 17.45; 16.0; 15.2; 14.8; 14.4; 13.8; 13.3; 12.73; 12.70; 12.2; 11.5; −4.5 (MeSi); −4.7 (MeSi). HR-MS: 1204.7526 ($[M + Na]^+$; calc. 1204.7518).

Compound **37**. According to *GP D*, a mixture of **36** (7 g, 5.92 mmol), anh. $Cu(OAc)_2$ (2.6 g, 14.3 mmol), pyridine (1.15 ml, 14.3 mmol), 4-Å mol. sieves (7 g) in 120 ml of CH_2Cl_2 was heated at 54° for 40 h under O_2. Workup, followed by FC (SiO_2-5% $NaHCO_3$; toluene/AcOEt 16 : 1 to 8 : 1) gave **37** (6.45 g, 92%). White foam. ^{1}H-NMR (*ca.* 5 : 2 mixture of isomers): 6.06* (*s*); 5.64 (br. *s*); 5.44 (*s*); 5.34* (*s*); 5.28 (*d*, $J = 8.7$); 5.23 (*d*, $J = 5.3$); 5.00* (*d*, $J = 2.7$); 4.93* (*d*, $J = 9.0$); 4.79* (*d*, $J = 9.4$); 4.76* (*t*, $J = 6.5$); 4.33 (br. *s*); 4.20 (br. *s*); 4.06 (*m*); 3.96* (*m*); 3.91* (*dd*, $J = 9.4$, 1.8); 3.84 (br. *d*, $J = 9.5$); 3.73 (*d*, $J = 9.5$), 3.60–3.10 (overl. *m*s); 2.94 (*m*, H–C(32)); 2.50–0.70 (overl. *m*s); 0.08 (*s*, MeSi); 0.07 (*s*, MeSi). ^{13}C-NMR (both isomers): 190.2; 168.4; 167.4; 167.2; 135.5; 134.3; 133.3; 131.5; 131.3; 128.3; 128.2; 126.0; 98.6; 97.1; 84.3; 84.2; 83.2; 79.6; 76.9; 75.3; 75.1; 73.7; 72.5; 71.4; 71.0; 69.6; 69.2; 68.6; 58.1; 57.8; 57.2; 56.6; 56.4; 56.3; 55.8; 54.2; 52.2; 49.3; 48.0; 46.1; 45.4; 43.2; 39.3; 36.8; 36.4; 36.1; 35.5; 35.0; 34.9; 34.0; 33.9; 33.3; 32.8; 32.7; 31.8; 30.7; 30.6; 30.3; 30.1; 26.3; 26.05; 25.97; 25.87; 25.6; 23.9; ;20.9; 20.6; 20.0; 18.2; 17.94; 17.86; 17.82; 17.64; 17.58; 17.53; 17.49; 17.42; 17.2; 16.3; 16.2; 16.1; 15.9; 15.8; 15.2; 14.6; 14.4; 13.74; 13.66; 13.60; 13.3; 12.8; 12.64; 12.60; 12.4; 12.3; 12.0; 10.2; −4.5; −4.7. HR-MS: 1202.7362 ($[M + Na]^+$; calc. 1202.7361).

Compound **38**. According to *GP B*, a soln. of **37** (4.2 g, 3.6 mmol) in 1 l of MeOH was irradiated at 0–5° for 6 h. Removal of MeOH gave the crude product. The crude (1 g) was purified by FC (SiO_2-5% $NaHCO_3$; toluene/AcOEt 2 : 1 to 0 : 1) to give **38** (440 mg, 44%). White foam. ^{1}H-NMR (*ca.* 4 : 1 mixture of isomers): 5.24 (*d*, $J = 5.8$, H–C(26)); 5.21 (*d*, $J = 8.8$, H–C(20/29)); 4.89 (*d*, $J = 9.9$, H–C(20/29)); 4.45 (*d*, $J = 1.8$, HO–C(10)); 4.22 (*m*, 2 H)); 3.87 (*m*, 2 H); 3.83 (*s*, MeO); 3.80* (*s*, MeO); 3.75* (*d*, $J = 1.6$, HO–C(10)); 3.68 (*s*, MeO); 3.61 (*m*, H–C(14/15)); 3.45–3.20 (*m*, H–C(13), H–C(33), 3 MeO); 2.94 (*m*, H–C(32)); 2.40–0.70 (overl. *m*s); 0.08 (*s*, MeSi); 0.07 (*s*, MeSi). Signals from the minor isomer are mostly overlapped or identical with those from the major isomer. ^{13}C-NMR (major isomer): 174.0; 172.1; 164.2; 135.0; 132.5; 132.4; 127.8; 99.2; 84.2; 78.2; 76.4; 75.2; 74.0; 73.34; 73.30; 70.2; 69.1; 58.9; 58.5; 57.9; 55.7; 52.7; 52.3; 48.3; 46.5; 41.3; 37.9; 36.3; 36.1; 35.0; 33.9; 32.2; 31.6; 30.7; 26.9; 25.9; 25.30; 25.25; 23.2; 18.84; 18.75; 17.67; 17.64; 17.59; 17.50; 17.46; 17.43; 16.5; 16.0; 13.95; 13.91; 13.3; 13.0; 12.8; 12.6; 10.8; −4.5; −4.7

Compound **39**. Aq. 0.1N HCl (75 ml) was added to a soln. of the crude **36** (8 g) in a mixture of 230 ml of MeCN and 75 ml of THF at 0°. The mixture was stirred overnight (0° to r.t.) and concentrated under vacuum. The residue was extracted with AcOEt, washed with sat. aq. $NaHCO_3$ and brine, and stripped of the solvent. FC (SiO_2, CH_2Cl_2/MeOH 100:2 to 100:8) of the residue yielded the aldehyde **39** desilylated at O–C(33) (4.72 g, 59% over two steps). A mixture of the aldehyde (12.51 g, 11.87 mmol), 1*H*-imidazole (2.42 g, 35.5 mmol), and TBSCl (2.68 g, 23.05 mmol) in DMF (70 ml) was stirred at r.t. for 3 h. Toluene was added to the mixture, and the precipitated imidazole salt was filtered off. The filtrate was concentrated, and the residue was worked up as usual. FC (SiO_2; CH_2Cl_2/MeOH 1:0 to 95:5) gave **39** (13.27 g, 96%). White foam. ^{1}H-NMR: 9.81 (*s*, H–C(6)); 7.23 (*d*, *J* = 6.9, NH); 7.09 (*s*, OH); 5.35 (*s*, H–C(26)); 4.85 (*d*, *J* = 8.9, H–C(29)); 4.73 (*d*, *J* = 9.2, H–C(20)); 4.17 (*m*, H–C(2)); 4.08 (*m*, H–C(24)); 4.07 (*s*, H–C(9)); 3.99 (*ddd*, *J* = 11.0, 4.8, 2.3, H–C(22)); 3.83 (*dd*, *J* = 9.6, 2.0, H–C(14)); 3.49 (*ddd*, *J* = 11.5, 4.8, 2.0, H–C(15)); 3.44 (*ddd*, *J* = 11.2, 9.6, 4.6, H–C(13)); 3.40 (*s*, MeO); 3.38 (*m*, H–C(33)); 3.36 (*s*, MeO); 3.35 (*s*, MeO); 2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.58 (*m*, 2 H–C(5)); 2.43 (*m*, H–C(21)); 2.30 (br. *d*, *J* = 12.4, 1 H–C(18)); 2.22 (*m*, H–C(30)); 2.1–0.8 (overl. *m*s); 1.59 (*s*, Me–C(27)); 1.49 (*s*, Me–C(19)); 0.95 (*d*, *J* = 6.4, Me–C(11)); 0.83 (*t*, *J* = 7.3, H–C(37)); 0.79 (*d*, *J* = 7.3, Me–C(25)); 0.77 (*d*, *J* = 6.6, Me–C(17)); 0.88 (*s*, *t*-Bu)); 0.07 (*s*, MeSi); 0.06 (*s*, MeSi). ^{13}C-NMR: 200.7 (C(6)); 175.2 (C(1/8)); 169.2 (C(1/8)); 136.0 (C(19)); 132.6 (C(27)); 128.4 (C(20/29)); 128.0 (C(20/29)); 99.6 (C(10)); 84.2 (C(32)); 78.5 (C(15/26)); 76.9 (C(15/26)); 75.2 (C(33)); 74.2 (C(13)); 71.2 (C(14)); 70.2 (C(9)); 69.6 (C(24)); 69.2 (C(22)); 58.0 (MeO–C(32)); 57.6 (MeO–C(15)); 56.0 (MeO–C(13)); 52.9 (C(2)); 50.0 (C(18)); 45.9 (C(21)); 43.2 (C(5)); 39.5 (C(25)); 36.7 (C(16), C(31)); 34.9 (C(30)); 33.8 (C(34)); 33.2 (C(11)); 31.4 (C(23)); 31.2 (C(3/4); C(12)); 30.9 (C(35)); 29.8 (C(3/4); C(12)); 25.9 (*Me*$_3$C)); 25.1 (C(17)); 20.9 (Me–C(17)); 20.5 (C(36)); 18.7 (C(3/4)); 18.1 (Me$_3$*C*); 17.65 (MeSi); 17.61 (MeSi); 17.56 (MeSi); 17.51 (MeSi); 17.11 (MeSi); 17.07 (MeSi); 16.28 (*Me*–C(11)); 14.8 (*Me*–C(19/27)); 13.7 (SiCH); 13.6 (SiCH); 12.86 (SiCH/C(37)); 12.81 (SiCH/C(37)); 12.4 (SiCH); 10.5 (*Me*–C(25)); –4.5 (MeSi); –4.7 (MeSi). HR-MS: 1190.7363 ([*M* + Na]$^+$; calc. 1190.7361).

Conversion of **39** *to* **35**. To a mixture of **39** (0.56 g, 0.479 mmol) in 14 ml of a 4:1 mixture THF/H_2O was added $NaBH_4$ (14 mg, 0.37 mmol) in small portions over a period of 30 min at 0°. The mixture was extracted with AcOEt, washed with brine, dried, and stripped of the solvent. The residue was purified by FC (SiO_2; MC/MeOH 100:2) to give 0.39 g (70%) of the C(6)-alcohol product (R_f (SiO_2; MC/MeOH 100:6) 0.33. A mixture of the above C(6)-alcohol (100 mg, 0.085 mmol), $Cu(OAc)_2$ (15.5 mg, 1.0 equiv.), and pyridine (0.69 µl, 0.1 equiv.) in 10 ml of CH_2Cl_2 was stirred at r.t. for 32 h. Workup, followed by FC (SiO_2; CH_2Cl_2/MeOH 100:2) gave 56 mg (56%) of the corresponding 9-keto product (R_f (SiO_2; MC/MeOH 100:8) 0.56. A mixture of the above C(9)=O product (45 mg, 0.039 mmol), Ph_3P (TPP; 20 mg, 2.0 equiv.) in 2 ml of THF was charged with diethyl azodicarboxylate (DEAD; 12 µl in 120 µl THF) and stirred for 28 h at r.t. Additional 1 equiv. of TPP and 1 equiv. of DEAD were added, and the mixture was stirred for a further 20 h, diluted with brine, and extracted with AcOEt. The extract was washed with brine, dried, and the solvent was removed. The residue was purified by FC (SiO_2; MC/MeOH 100:1 to 100:6) to give the cyclized compound **35** (20 mg, 44%).

Compound **40**. Vinylmagnesium bromide (5.1 ml of 0.5M soln. in Et_2O, 1.0 equiv.) was added to a soln. of **39** (3 g, 2.57 mmol) in 35 ml of THF under stirring and under Ar at –78°. Additional 10.2 ml of the reagent (2 equiv.) was added after 4 h, and the mixture was kept at –20° overnight. A further portion of 5.1 ml of the reagent (1 equiv.) was added, and stirring was continued at –20° for 2 h. The mixture was hydrolyzed with 0.05N HCl at 0° and extracted with Et_2O, washed with brine, dried, and stripped of the solvent. The residue, after FC (SiO_2; CH_2Cl_2/MeOH 100:0 to 96.5:3.5), afforded **40** (1.637 g, 53%). Foam. ^{1}H-NMR (1:1 mixture of isomers): 7.24 (*d*, *J* = 6.9, NH); 7.08 (*d*, *J* = 7.0, NH); 5.88 (*ddd*, *J* = 17.2, 10.3, 6.6, H–C(6′)); 5.87 (*ddd*, *J* = 17.2, 10.3, 6.6, H–C(6′)); 5.35 (br. *s*, H–C(26)); 5.34 (br. *s*, H–C(26)); 5.24 (*dt*, *J* = 17.2, 1.4, 1 H–C(6″)); 5.22 (*dt*, *J* = 17.2, 1.4, 1 H–C(6″)); 5.14 (br. *d*, *J* = 10.3, 1 H–C(6″)); 5.13 (br. *d*, *J* = 10.3, 1 H–C(6″)); 4.88 (br. *d*, *J* = 8.9, H–C(29)); 4.87 (br. *d*, *J* = 8.9, H–C(29)); 4.75 (*d*, *J* = 9.2, 2 H–C(20)); 4.2–4.0 (*m*, 2 H–C(2), 2 H–C(6), 2 H–C(24)); 4.07 (*s*, H–C(9)); 4.06 (*s*, H–C(9)); 3.99 (*m*, 2 H–C(22)); 3.81 (br. *d*, *J* = 9.6, 2 H–C(14)); 3.52 (*m*, 2 H–C(15)); 3.45–3.30 (*m*, 2 H–C(13), 2 H–C(33)); 3.41 (*s*, 2 MeO); 3.36 (*s*, 2 MeO); 3.34 (*s*, 2 MeO); 2.95 (*m*, 2 H–C(32)); 2.44 (*m*, 2 H–C(21)); 2.4–0.7 (overl. *m*s); 0.89 (*s*, 2 *t*-Bu); 0.08 (*s*, 2 MeSi); 0.06 (s, 2 MeSi). HR-MS: 1218.7670 ([*M* + Na]$^+$; calc. 1218.7674).

Compound **41**. According to *GP D*, a mixture of **40** (1.4 g, 1.17 mmol), $Cu(OAc)_2$ (212 mg, 1.17 mmol), and 10 µl of pyridine in 20 ml of CH_2Cl_2 was stirred under O_2 balloon at r.t. for 4 d. Usual workup gave 1.303 g of the crude 9-keto product. A mixture of 200 mg (0.17 mmol) of the above crude 9-keto product, 3 ml of dry CH_2Cl_2, 135 µl (10 equiv.) of pyridine, and 2 mg of 4-(dimethylamino)pyridine (DMAP) was stirred at 0° for 10 min. MeOCOCl (35 µl, 2.5 equiv.) was added to it in 3 portions over 2.5 h, and stirring was continued at 0° for a further 45 min. The mixture was diluted with AcOEt, washed with sat. citric acid and brine, dried, and stripped of the solvent. The residue was purified by FC (SiO_2; toluene/AcOEt 4:1) to afford the carbonate **41** (88 mg, 42% over two steps). White foam. ^{1}H-NMR (exclusively as seven-membered-ring hemiketal, *ca.* 1:1 mixture of C(6)-isomers): 6.72 (*d*, *J* = 8.5, NH); 5.74 (*ddd*, *J* = 17.2, 10.5, 6.6, H–C(6′)); 5.38 (*s*, H–C(26)); 5.28 (*ddd*, *J* = 17.2, 2.8, 1.4, 1 H–C(6″)); 5.20 (*dt*, *J* = 10.5, 1.1, 1 H–C(6″)); 5.20 (d, *J* ≈ 10.0, H–C(20)); 5.11, 5.105 (2*s*, 2 H, HO–C(10), both isomers); 5.02 (*d*, *J* = 8.5, H–C(29)); 5.00 (*m*, H–C(6)); 4.46 (*m*, H–C(2)); 4.02 (br. *d*, *J* = 11.0, H–C(24)); 3.96 (*ddd*, *J* = 11.5, 4.6, 1.2, H–C(22)); 3.76 (*s*, MeOCO)); 3.72 (*ddd*, *J* = 10.5, 8.7, 5.0, H–C(13)); 3.58 (*ddd*, *J* = 11.5, 3.7, 2.0, H–C(15)); 3.42 (*dd*, *J* = 8.7, 2.0, H–C(14)); 3.41 (*s*, MeO); 3.37 (*s*, MeO); 3.35 (*m*, H–C(33)); 3.29 (*m*, H–C(11)); 3.21 (*s*, MeO); 2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.32 (*dt*, *J* = 13.5, 4.4, 1 H–C(12)); 1.62 (*s*, Me–C(19), Me–C(27)); 1.21 (*d*, *J* = 6.6, Me–C(11)); 0.89 (*s*, *t*-Bu); 0.83 (*t*, *J* = 7.3, Me–C(37)); 2.3–0.8 (overl. *m*s); 0.07 (*s*, MeSi); 0.06 (*s*, MeSi).

Compound **42**. A mixture of **41** (300 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (10 mg, 5 mol%) in 15 ml of dry MeCN was stirred under Ar at r.t. for 2 h. The solvent was removed, and the residue was purified by FC (SiO_2; toluene/AcOEt 92:8) to afford **42** (202 mg, 72%). Alternatively, a mixture of the primary allyl carbonate **44** (16 mg, 0.013 mmol) and $Pd(PPh_3)_4$ (2.6 mg, 25 mol%) in 1 ml of dry MeCN was stirred under Ar at r.t. for 30 h. Workup and FC as described above gave **42** (9.4 mg, 63%). ^{1}H-NMR Data of **42** prepared either way are identical to each other. ^{1}H-NMR (mixture of 3 signal sets, C(6)-isomers, and amide rotamers *ca.* 3:2:1.3): 6.67 (*d*, *J* = 1.2, HO–C(10)); 6.61 (br. *s*, HO–C(10)); 6.19 (*ddd*, *J* = 17.5, 10.8, 4.6, H–C(6′)); 5.92 (*m*, H–C(6′)); 5.78 (*ddd*, *J* = 17.2, 10.5, 6.6, H–C(6′)); 5.50 (*d*, *J* = 1.4, HO–C(10)); 5.45–4.4 (overl. *m*s, H–C(2), H–C(6), 2 H–C(6″), H–C(20), H–C(26), H–C(29)); 4.2–3.6 (overl. *m*s, H–C(14), H–C(22), H–C(24)); 3.6–3.2 (overl. *m*s, H–C(13), H–C(15), H–C(33), MeO–C(13), MeO–C(15), MeO–C(32)); 2.43 (*m*, H–C(21)); 2.35–0.7 (overl. *m*s); 0.89 (*s*, *t*-Bu); 0.08 (*s*, MeSi); 0.07 (*s*, MeSi).

Compound **43**. A mixture of **39** (1.5 g, 1.28 mmol) and methyl (triphenylphosphoranylidene)acetate (0.52 g, 1.54 mmol) in 15 ml toluene was stirred at r.t. for 24 h. The solvent was removed, and the residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 100:2) to give the *Wittig* product (1.48 g, 94%). To a soln. of the above *Wittig* product (0.6 g, 0.49 mmol) in 18 ml of toluene kept at −78° was added under Ar ^{i}Bu$_2$AlH (DIBAH; 0.82 ml, 1.2M in toluene, 0.98 mmol). Two additional portions of 0.41 ml each of DIBAH were added after 1 h and 3 h. After a total reaction time of 5 h at −78°, the reaction was quenched with solid NH_4Cl, and the mixture was partitioned between cold 5% aq. citric acid and AcOEt. The org. phase was washed with aq. $NaHCO_3$ and brine, dried, and stripped of the solvent. The residue was purified by FC (SiO_2, CH_2Cl_2/MeOH 100:0 to 94:6) to give the allylic alcohol **43** (395 mg, 67%). White foam. ^{1}H-NMR: 7.15 (*d*, *J* = 7.7, NH); 5.75 (*m*, H–C(6)); 5.72 (*m*, H–C(6′)); 5.34 (*s*, H–C(26)); 4.89 (*d*, *J* = 8.8, H–C(29)); 4.74 (*d*, *J* = 9.1, H–C(20)); 4.25 (*td*, *J* = 7.1, 3.8, H–C(2)); 4.09 (*m*, 1 H–C(6″), H–C(24)); 4.04 (*s*, H–C(9)); 4.00 (*m*, 1 H–C(6″), H–C(22)); 3.81 (*dd*, *J* = 9.5, 2.0, H–C(14)); 3.57 (*ddd*, *J* = 11.8, 5.1, 2.0, H–C(15)); 3.42 (*s*, MeO); 3.41 (*s*, MeO); 3.39 (*m*, H–C(13), H–C(33)); 3.36 (*s*, MeO); 2.95 (*ddd*, *J* = 11.3, 8.5, 4.4, H–C(32)); 2.45 (*m*, H–C(21)); 1.59 (*s*, Me–C(27)); 1.50 (*s*, Me–C(18)); 0.96 (*d*, *J* = 6.6, Me–C(11)); 0.89 (*s*, *t*-Bu); 0.83 (*t*, *J* = 7.4, Me–C(37)); 0.78 (*d*, *J* = 7.0, Me–C(17), Me–C(25)); 2.3–0.8 (overl. *m*s); 0.08 (*s*, MeSi); 0.07 (*s*, MeSi). HR-MS: 1218.7667 ($[M+Na]^+$; calc. 1218.7674).

Compound **44**. According to *GP D*, a mixture of **43** (300 mg, 0.25 mmol), $Cu(OAc)_2$ (45 mg, 0.25 mmol), and 2 µl of pyridine in 60 ml of CH_2Cl_2 was stirred under O_2 balloon at r.t. for 4 d. Usual workup gave 292 mg of the crude 9-keto product. A mixture of 100 mg (0.084 mmol) of the above crude 9-keto product, 1.5 ml of dry CH_2Cl_2, 68 µl (10 equiv.) of pyridine, and 1.5 mg of DMAP was stirred at 0° for 10 min. MeOCOCl (14 µl, 1 equiv.) was added to it in 3 portions over 3 h. After a total reaction time of 4 h at 0°, the mixture was diluted with AcOEt, washed with aq. sat. citric acid and brine, dried, and stripped of the solvent. The residue was purified by FC (SiO_2; toluene/AcOEt 6:1) to afford the

carbonate **44** (30 mg, 29% over two steps). White foam. ^{1}H-NMR (exclusively as seven-membered-ring hemiketal): 6.77 (*d*, *J* = 8.5, NH); 5.74 (*dt*, *J* = 15.6, 6.6, H–C(6)); 5.57 (*dt*, *J* = 15.6, 6.4, H–C(6′)); 5.39 (*s*, H–C(26)); 5.21 (*d*, *J* = 10.1, H–C(20)); 5.12 (*s*, HO–C(9)); 5.01 (*d*, *J* = 9.2, H–C(29)); 4.54 (*d*, *J* = 6.4, H–C(6″)); 4.47 (*dt*, *J* = 8.5, 5.3, H–C(2)); 4.02 (*d*, *J* = 10.8, H–C(24)); 3.97 (*ddd*, *J* = 11.5, 5.0, 1.6, H–C(22)); 3.77 (*s*, OCOOMe); 3.72 (*ddd*, *J* = 10.3, 8.9, 5.0, H–C(13)); 3.59 (*ddd*, *J* = 11.2, 3.7, 2.0, H–C(15)); 3.41 (*dd*, *J* = 8.9, 2.0, H–C(14)); 3.40 (*s*, MeO); 3.37 (*s*, MeO); 3.36 (*m*, H–C(33)); 3.27 (*m*, H–C(11)); 3.21 (*s*, MeO); 2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.32 (*ddd*, *J* = 13.5, 4.8, 3.7, 1 H–C(12)); 1.62 (*s*, Me–C(19), Me–C(27)); 1.21 (*d*, *J* = 6.6, Me–C(11)); 0.89 (*s*, *t*-Bu); 2.3–0.8 (overl. *m*s); 0.07 (*s*, MeSi); 0.06 (*s*, MeSi).

Compound **45**. To a soln. of **42** (178 mg, 0.151 mmol) in 1.8 ml of CH_2Cl_2 and 6.5 ml of MeCN was added 0.65 ml of a soln. of 40% HF in MeCN at r.t. After stirring for 18 h at r.t., the mixture was worked up using AcOEt and aq. $NaHCO_3$ to give the crude product which, after FC (SiO_2; toluene/AcOEt 1:2, 1:4, 1:10), gave the desilylated product **45** (105 mg, 85%). White foam. ^{1}H-NMR (mixture of isomers at C(6) and rotamers): 6.17 (*ddd*, *J* = 17.4, 11.0, 5.3, H–C(6′)); 5.85 (*m*, H–C(6′)); 5.44 (*dd*, *J* = 17.2, 16.0, H_a–C(6″)); 5.39 (*dd*, *J* = 10.8, 2.1, H_b–C(6″)); 5.40–4.85 (overl. *m*s); 4.82 (br. *s*, OH); 4.76 (br. *s*, H–C(6)); 4.64 (*dd*, *J* = 6.0, 1.6, H–C(2)); 4.62 (br. *s*); 4.44 (br. *m*, H–C(6)); 4.35 (*m*); 4.29 (br. *m*); 4.16 (br. *s*, OH); 4.10–3.30 (overl. *m*s); 2.99 (*m*, H–C(32)); 2.69 (br. *s*, OH); 2.35–0.80 (overl. *m*s). HR-MS: 842.5024 ([*M* + Na]$^+$; calc. 842.5025).

Compound **46**. To a soln. of **45** (71 mg, 0.087 mmol) in 5.7 ml of CH_2Cl_2 was added pyridine (35 µl, 0.44 mmol), and *Dess–Martin*'s periodinane (= 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 37 mg, 0.087 mmol). After stirring at r.t. for 2 and 4 h, additional amounts of *Dess–Martin*'s periodinane (37 mg, 0.087 mmol) and pyridine (18 µl, 0.44 mmol) were added each time. After a total reaction time of 8 h, the solids were filtered off, and the filtrate was stripped of the solvent. The residue was purified by FC (SiO_2; toluene/AcOEt 1:4) to give **46** (44 mg, 62%). White foam. ^{1}H-NMR (mixture of isomers at C(6) and amide rotamers, shifts partially derived from ^{1}H,^{13}C-correlation [HSQC]): 6.10 (*ddd*, *J* = 17.7, 11.0, 4.4, H–C(6′)); 6.02 (*ddd*, *J* = 17.4, 10.5, 7.1, H–C(6′)); 5.87 (*m*, H–C(6′)); 5.56 (*s*, HO–C(10)); 5.46 (*s*, HO–C(10)); 5.40 (s, HO–C(10)); 5.30 (H–C(26)); 5.28 (H–C(26)); 5.38, 5.18 (H–C(6″)); 5.22, 5.15 (H–C(6″)); 5.20 (H–C(6″)); 5.19, 5.10 (H–C(6″)); 5.17 (H–C(26)); 5.14 (H–C(26)); 5.07 (H–C(6)); 5.10–5.00 (*m*, H–C(20)); 5.12 (H–C(29)); 5.01 (H–C(29)); 4.96 (H–C(29)); 4.87 (br. *s*, H–C(6)); 4.79 (br. *s*, H–C(6)); 4.69 (*t*, *J* = 6.6, H–C(2)); 4.56 (*dd*, *J* = 6.4, 1.8, H–C(2)); 4.52 (*m*, H–C(6)); 4.46 (*m*, H–C(2)); 4.41 (br. *s*, OH); 3.20 (*m*, H–C(32)); 4.0–3.8 (*m*, H–C(14), H–C(24)); 3.7–3.3 (overl. *m*s, 3 MeO, H–C(13), H–C(15), H–C(33)); 3.20 (*m*, H–C(21)); 3.00 (*m*, H–C(32)); 2.9–2.6 (*m*, 1 H–C(23)); 2.5–0.8 (overl. *m*s). ^{13}C-NMR: 214.3 (C(22)); 213.0 (C(22)); 196.0 (C(9)); 169.7 (C(1/8)); 169.1 (C(1/8)); 168.3 (C(1/8)); 167.6 (C(1/8)); 166.0 (C(1/8)); 139.9 (C(19)); 138.9 (C(19)); 138.6 (C(6′)); 138.4 (C(6′)); 137.0 (C(6′)); 136.7 (C(6′)); 132.1 (C(27)); 132.0 (C(27)); 131.6 (C(27)); 130.2 (C(29)); 129.3 (C(29)); 123.1 (C(20)); 123.0 (C(20)); 117.0 (C(6″)); 116.2 (C(6″)); 116.0 (C(6″)); 98.6 (C(10)); 97.4 (C(10)); 84.2 (C(32)); 78.6 (C(26)); 78.12 (C(26)); 78.19 (C(26)); 77.6 (C(26)); 76.2; 76.1; 75.4; 74.0; 73.8; 73.6 (C(33)); 73.1; 71.9 (C(14)); 71.5 (C(14)); 70.0 (C(24)); 69.7 (C(24)); 69.1 (C(24)); 57.4; 57.2; 57.0; 56.6; 56.3; 56.2; 55.8 (C(2)); 55.6 (C(2)); 54.99 (C(21)); 54.96 (C(21)); 54.2 (C(6)); 53.8 (C(2)); 53.6 (C(6)); 53.2 (C(2)); 52.4 (C(6)); 51.4 (C(6)); 49.1 (C(18)); 48.7 (C(18)); 43.9 (C(23)); 43.7 (C(23)); 43.6 (C(23)); 40.6 (C(25)); 40.4 (C(25)); 39.9 (C(25)); 36.3; 35.7; 34.9 (C(30)); 34.8 (C(31)); 33.4 (C(11)); 33.3; 33.1 (C(11)); 32.8; 32.6; 31.2 (C(34)); 30.5 (C(35)); 28.0; 26.8; 26.5 (C(17)); 26.4; 26.1 (C(17)); 25.4 (C(17)); 24.5; 24.4; 24.2; 22.7; 20.5; 19.4; 18.9; 16.9; 16.3; 16.2; 16.1; 15.8; 15.3; 14.9; 14.3; 13.9; 11.7 (C(37)); 9.9 (*Me*–C(25)); 9.7 (*Me*–C(25)). HR-MS: 840.4866 ([*M* + Na]$^+$; calc. 840.4868).

Compound **47**. Lithium hexamethyldisilazide (LiHMDS; 3.38 ml of 1M soln. in THF, 3.5 equiv.) was added in one portion to an ice-cold suspension of (methoxymethyl)triphenylphosphonium chloride (3.88 g, 4 equiv.) in 128 ml of dry THF. The white suspension turned to a deep red soln. The mixture was stirred at 0° for 30 min and cooled to −78°. A soln. of **39** (3.2 g, 2.7 mmol) in 32 ml of dry THF was added dropwise over 10 min. The mixture was stirred at −78° for 2 h and let warm up to 0° over 30 min, and then further to r.t. over 1 h. The mixture was diluted with Et_2O, washed with aq. $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by FC (SiO_2-3% $NaHCO_3$; toluene/AcOEt 4:1) to give the *Wittig* product **47** (972 mg, 30%). White foam. ^{1}H-NMR (mixture of two isomers (*E*)/(*Z*) *ca.*

2:1): (*E*)-isomer: 7.17 (*dd*, *J* = 1.2, OH)); 7.04 (*d*, *J* = 7.1, NH); 6.35 (*d*, *J* = 12.6, H–C(5″)); 5.35 (*s*, H–C(26)); 4.87 (*d*, *J* = 9.2, H–C(29)); 4.74 (*d*, *J* = 9.2, H–C(20)); 4.70 (*dt*, *J* = 12.6, 7.3, H–C(5′)); 4.15 (*ddd*, *J* = 9.2, 7.1, 3.9, H–C(2)); 4.09 (*ddd*, *J* = 11.2, 6.6, 2.9, H–C(24)); 4.05 (br. *s*, OH); 4.00 (*ddd*, *J* = 11.4, 5.0, 2.8, H–C(22)); 3.83 (*dd*, *J* = 9.4, 2.1, H–C(14)); 3.52 (*s*, MeO–C(5″)); 3.50 (*dd*, *J* = 5.0, 2.1, H–C(13)); 3.44 (*m*, H–C(15)); 3.41 (*s*, MeO–C(32)); 3.40 (*m*, H–C(33)); 3.37 (*s*, MeO–C(13/15)); 3.36 (*s*, MeO–C(13/15)); 2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.44 (*m*, H–C(21)); 1.59 (*s*, Me–C(27)); 1.49 (*s*, Me–C(19)); 0.96 (*d*, *J* = 6.4, Me–C(11)); 0.83 (*t*, *J* = 7.3, H–C(37)); 0.79 (*d*, *J* = 7.3, Me–C(25)); 0.77 (*d*, *J* = 6.4, Me–C(17)); 0.89 (*s*, *t*-Bu); 2.3–0.8 (overl. *m*s); 1.1–0.9 (Me_2CHSi); (*Z*)-isomer: 7.19 (*d*, *J* = 1.2, OH); 7.08 (*d*, *J* = 7.1, NH); 5.93 (*dt*, *J* = 6.2, 1.4, H–C(5″)); 5.34 (*s*, H–C(26)); 4.87 (*d*, *J* = 9.2, H–C(29)); 4.74 (*d*, *J* = 9.2, H–C(20)); 4.34 (*dt*, *J* = 7.3, 6.2, H–C(5′)); 4.15 (*ddd*, *J* = 9.2, 7.1, 3.9, H–C(2)); 4.09 (*ddd*, *J* = 11.2, 6.6, 2.9, H–C(24)); 4.05 (br. *s*, OH)); 4.00 (*ddd*, *J* = 11.4, 5.0, 2.8, H–C(22)); 3.83 (*dd*, *J* = 9.4, 2.1, H–C(14)); 3.61 (*s*, MeO–C(5″)); 3.52 (*m*, H–C(13)); 3.44 (*m*, H–C(15)); 3.40 (*s*, MeO–C(32)); 3.40 (*m*, H–C(33)); 3.37 (*s*, MeO–C(13/15)); 3.36 (*s*, MeO–C(13/15)); 2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.44 (*m*, H–C(21)); 1.59 (*s*, Me–C(27)); 1.49 (*s*, Me–C(17)); 0.96 (*d*, *J* = 6.4, Me–C(11)); 0.83 (*t*, *J* = 7.3, Me–C(37)); 0.79 (*d*, *J* = 7.3, Me–C(25)); 0.77 (*d*, *J* = 6.4, Me–C(17)); 0.89 (*s*, *t*-Bu); 2.3–0.8 (overl. *m*s); 1.1–0.9 (Me_2CHSi). HR-MS: 1218.7668 ($[M+Na]^+$; calc. 1218.7674).

Compound **48**. A soln. of **47** (0.8 g, 0.67 mmol) in a mixture of 7.2 ml of MeCN and 4.8 ml of THF was added to a prestirred ice-cold mixture of $Pd(OAc)_2$ (160 mg, 1.06 equiv.), 3.2 ml of MeCN, and 0.32 ml of aq. 5% $NaHCO_3$. The mixture turned first to orange brown and then to black. The mixture was stirred at 0° for 3 h and then refrigerated overnight. It was diluted with AcOEt, washed with brine, dried, and stripped of the solvent to give the corresponding crude unsaturated aldehyde (847 mg). DIBAH (480 µl of a 1.2M soln. in toluene, 0.58 mmol) was added to the mixture of the above crude aldehyde (480 mg, 0.41 mmol) and 3 ml of toluene at −78° under Ar. After 45 min, additional DIBAH (480 µl of a 1.2M soln. in toluene, 0.58 mmol) was added. After a total reaction time of 2.3 h at −78°, the reaction was quenched with aq. NH_4Cl, and the mixture was extracted with AcOEt. The org. phase was washed with cold aq. 0.01N HCl, brine, dried, and stripped of the solvent. The residue, after FC (SiO_2; toluene/AcOEt 100:0 to 36:65) afforded the allylic alcohol **48** (223 mg, 50% over two steps). White foam. ^{1}H-NMR: 7.12 (*d*, *J* = 6.9, NH); 5.78 (*dt*, *J* = 15.6, 6.2, H–C(5)); 5.70 (*dt*, *J* = 15.6, 5.7, H–C(5′)); 5.36 (*s*, H–C(26)); 4.87 (*d*, *J* = 8.9, H–C(29)); 4.72 (*d*, *J* = 9.2, H–C(20)); 4.19 (*ddd*, *J* = 8.5, 6.9, 4.6, H–C(2)); 4.09 (*ddd*, *J* = 11.5, 6.4, 2.0, H–C(24)); 4.04 (*s*, H–C(9)); 4.00 (*ddd*, *J* = 11.2, 5.0, 2.8, H–C(22)); 3.91 (*d*, *J* = 5.5, H–C(5″)); 3.83 (*dd*, *J* = 9.4, 2.3, H–C(14)); 3.49 (*ddd*, *J* = 11.5, 5.0, 2.3, H–C(15)); 3.46 (*m*, H–C(13)); 3.41 (*s*, MeO–C(32)); 3.38 (*m*, H–C(33)); 3.37 (*s*, MeO); 3.36 (*s*, MeO); 2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.44 (*m*, H–C(21)); 1.60 (*d*, *J* = 0.9, Me–C(27)); 1.49 (*s*, Me–C(19)); 0.96 (*d*, *J* = 6.4, Me–C(11)); 0.89 (*s*, *t*-Bu); 0.84 (*d*, *J* = 7.3, Me–C(37)); 0.80 (*d*, *J* = 7.3, Me–C(25)); 0.78 (*d*, *J* = 6.4, Me–C(17)); 0.08 (*s*, MeSi); 0.06 (*s*, MeSi); 2.4–1.0 (overl. *m*s); 1.1–0.9 (Me_2CHSi).

Compound **49**. According to *GP D*, a mixture of **48** (1.91 g, 1.62 mmol), $Cu(OAc)_2$ (440 mg, 1.5 equiv.), pyridine (13 µl, 0.1 equiv.), and 3.6 g of 4-Å mol. sieves in 100 ml of CH_2Cl_2 was stirred at r.t. under O_2 balloon. After stirring for 1 and 2 d, additional amounts each of $Cu(OAc)_2$ (440 mg, 1.5 equiv.) and pyridine (13 µl, 0.1 equiv.) were added. After a total reaction time of 5 d, the solvents were removed, and the residue was taken up in AcOEt, washed with aq. $NaHCO_3$, cold aq. 0.1N HCl, and brine, dried, and stripped of the solvent to give the crude 9-keto product (1.84 g, 96%). To a mixture of this crude product (1 g, 0.847 mmol), pyridine (683 µl, 10 equiv.) and DMAP (10.3 mg, 0.1 equiv.) in 25 ml of CH_2Cl_2 at 0° was added MeOCOCl (262 µl, 4 equiv.) in 4 equal portions over 4 h, and the mixture was stirred further at r.t. for 1 h. The mixture was diluted with AcOEt, and washed twice with aq. 10% citric acid and brine, dried, and stripped of the solvent. The residue, after FC (SiO_2; toluene/AcOEt 9:1 to 0:1), afforded the allylic carbonate **49** (700 mg, 67% over 2 steps). White foam. ^{1}H-NMR (20:1 mixture seven-membered-ring/six-membered-ring hemiketals): 6.79 (*d*, *J* = 8.5, NH); 5.75 (*dt*, *J* = 15.5, 6.4, H–C(5)); 5.59 (*dt*, *J* = 15.5, 6.2, H–C(5′)); 5.40 (*s*, H–C(26)); 5.20 (*d*, *J* = 9.9, H–C(20)); 5.14 (*s*, HO–C(9)); 5.01 (*d*, *J* = 9.2, H–C(29)); 4.54 (*d*, *J* = 6.2, 2 H–C(5″)); 4.48 (*dt*, *J* = 8.5, 4.8, H–C(2)); 4.02 (br. *d*, *J* = 11.0, H–C(24)); 3.97 (*ddd*, *J* = 11.7, 5.0, 1.6, H–C(22)); 3.76 (*s*, COOMe)); 3.72 (*ddd*, *J* = 10.8, 8.7, 5.0, H–C(13)); 3.58 (*ddd*, *J* = 11.5, 3.9, 2.1, H–C(15)); 3.41 (*dd*, *J* = 8.7, 2.1, H–C(14)); 3.40 (*s*, MeO–C(32)); 3.37 (*m*, H–C(33)); 3.37 (*s*, MeO–C(13)); 3.27 (*m*, H–C(11)); 3.21 (*s*, MeO–C(15));

2.94 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.32 (*m*, 1 H–C(12)); 2.23 (*m*, 1 H–C(18)); 2.21 (*m*, H–C(30)); 2.12 (*m*, 2 H–C(4)); 2.04 (*m*, H–C(17)); 2.03 (*m*, 1 H–C(3)); 1.96 (*m*, H–C(25)); 1.95 (*m*, 1 H–C(31)); 1.94 (*m*, H–C(21)); 1.82 (*m*, 1 H–C(34)); 1.77 (*m*, 1 H–C(18)); 1.73 (*m*, 1 H–C(3), 1 H–C(23)); 1.69 (*m*, 1 H–C(16)); 1.61 (*s*, Me–C(19), Me–C(27)); 1.50 (*m*, 1 H–C(35)); 1.47 (*m*, 1 H–C(36)); 1.38 (*m*, 1 H–C(36)); 1.33 (*m*, 1 H–C(34)); 1.26 (*m*, 1 H–C(12)); 1.21 (*d*, *J* = 6.6, Me–C(11)); 1.09 (*m*, 1 H–C(16), 1 H–C(23)); 1.00 (*m*, 1 H–C(31)); 0.98 (*m*, 1 H–C(35)); 0.91 (*d*, *J* = 7.3, Me–C(25)); 0.89 (*s*, *t*-Bu)); 0.84 (*d*, *J* = 6.6, Me–C(17)); 0.82 (*t*, *J* = 7.3, H–C(37)); 1.10–0.80 (Me_2CHSi); 0.07 (*s*, MeSi); 0.06 (*s*, MeSi). ^{13}C-NMR: 168.8 (C(1)); 52.0 (C(2)); 32.0 (C(3)); 28.3 (C(4)); 134.35 (C(5)); 124.8 (C(5′)); 68.1 (C(5″)); 167.1 (C(8)); 97.1 (C(9)); 211.7 (C(10)); 37.9 (C(11)); 38.3 (C(12)); 77.3 (C(13)); 76.34 (C(14/26)); 77.2 (C(15)); 32.5 (C(16)); 24.3 (C(17)); 50.9 (C(18)); 134.46 (C(19)); 126.2 (C(20)); 46.6 (C(21)); 70.26 (C(22/24)); 37.6 (C(23)); 70.18 (C(22/24)); 41.0 (C(25)); 76.28 (C(14/26)); 131.9 (C(27)); 129.4 (C(29)); 34.8 (C(30)); 36.8 (C(31)); 84.2 (C(32)); 75.5 (C(33)); 33.8 (C(34)); 30.8 (C(35)); 26.8 (C(36)); 12.3 (C(37)); 16.3 (*Me*–C(11)); 20.1 (*Me*–C(17)); 16.1 (*Me*–C(19)); 10.7 (*Me*–C(25)); 14.4 (*Me*–C(27)); 57.4 (*Me*O–C(13)); 56.8 (*Me*O–C(15)); 58.0 (*Me*O–C(32)); 155.6 (OC(=O)O); 54.7 (*Me*OCOO); 25.9 (Me_3C); 18.2 (Me_3C); –4.5 (MeSi); –4.7 (MeSi); 17.9 (Me); 17.76 (Me); 17.71 (Me); 17.54 (Me); 17.51 (Me); 17.45 (Me); 17.42 (Me); 14.2 (SiCH); 13.8 (SiCH); 13.2 (SiCH); 12.7 (SiCH). HR-MS: 1260.7421 ($[M+Na]^+$; calc. 1260.7416).

Compounds **50a** *and* **51a**. A mixture of **49** (600 mg, 0.484 mmol), $Pd(Ph_3)_4$ (20 mg, 3 mol-%) in 30 ml of MeCN was stirred under Ar for 2 d at 50°. After addition of further $Pd(Ph_3)_4$ (20 mg, 3 mol-%) stirring was continued for additional 2 d at 50°. After addition of additional $Pd(Ph_3)_4$ (20 mg, 3 mol-%), stirring was continued for a further 16 h at 70°. The solvent was removed, and the residue, after FC (SiO_2; heptane/AcOEt 12 : 1, 6 : 1, 1 : 1), gave the α-vinyl product **50a** (152 mg, 27%) and the β-vinyl product **51a** (169 mg, 30%) as white foams.

Data of **50a**. ^{1}H-NMR: 7.09 (*d*, *J* = 1.1, HO–C(10)); 5.72 (*ddd*, *J* = 17.2, 10.5, 5.5, H–C(5′)); 5.37 (*s*, H–C(26)); 5.17 (br. *t*, *J* ≈ 5.5, H–C(5)); 5.09 (*d*, *J* = 10.5, 1 H–C(5′)); 5.02 (*d*, *J* = 17.2, 1 H–C(5′)); 4.90 (*d*, *J* = 9.2, H–C(29)); 4.91 (*d*, *J* = 9.6, H–C(20)); 4.51 (*dd*, *J* = 8.9, 2.1, H–C(2)); 4.10 (*ddd*, *J* = 11.2, 6.4, 1.8, H–C(24)); 3.98 (*ddd*, *J* = 11.5, 4.8, 2.8, H–C(22)); 3.90 (*dd*, *J* = 9.4, 2.3, H–C(14)); 3.50 (*m*, H–C(15)); 3.48 (*m*, H–C(13)); 3.41 (*s*, MeO–C(32)); 3.38 (*m*, H–C(33)); 3.37 (*s*, MeO–C(13)); 3.32 (*s*, MeO–C(15)); 2.95 (*ddd*, *J* = 11.2, 8.5, 4.4, H–C(32)); 2.53 (*d*, *J* = 11.2, 1 H–C(18)); 2.46 (*m*, H–C(21)); 2.23 (*m*, H–C(30)); 2.18 (*m*, 1 H–C(3)); 2.12 (*m*, 1 H–C(4)); 2.02 (*m*, H–C(25)); 2.01 (*m*, H–C(11)); 2.00 (*m*, 1 H–C(12)); 1.96 (*m*, 1 H–C(3)); 1.94 (*m*, 1 H–C(31)); 1.85 (*m*, 1 H–C(36)); 1.82 (*m*, 1 H–C(4)); 1.81 (*m*, 1 H–C(34)); 1.61 (*m*, 1 H–C(23)); 1.61 (*d*, *J* = 1.0, Me–C(27)); 1.56 (*m*, 1 H–C(16)); 1.53 (*s*, Me–C(19)); 1.51 (*m*, 1 H–C(35)); 1.50 (*m*, 1 H–C(12), H–C(17)); 1.47 (*m*, 1 H–C(18)); 1.45 (*m*, 1 H–C(23)); 1.39 (*m*, 1 H–C(16)); 1.34 (*m*, 1 H–C(34)); 1.10 (*m*, 1 H–C(36)); 1.10–0.90 (*m*, Me_2CHSi); 0.95 (*m*, 1 H–C(31)); 0.95 (*d*, *J* = 6.2, Me–C(11)); 0.91 (*m*, 1 H–C(35)); 0.89 (*s*, *t-Bu*); 0.84 (*t*, *J* = 7.3, Me–C(37)); 0.81 (*d*, *J* = 7.3, Me–C(25)); 0.80 (*d*, *J* = 6.3, Me–C(17)); 0.08 (*s*, MeSi); 0.06 (*s*, MeSi). ^{13}C-NMR: 168.4 (C(1)); 60.0 (C(2)); 25.4 (C(3)); 30.5 (C(4)); 59.6 (C(5)); 137.1 (C(5′)); 116.5 (C(5″)); 164.5 (C(8)); 187.3 (C(9)); 99.4 (C(10)); 33.0 (C(11)); 31.7 (C(12)); 73.9 (C(13)); 71.7 (C(14)); 78.0 (C(15)); 36.5 (C(16)); 25.6 (C(17)); 49.8 (C(18)); 135.9 (C(19)); 127.9 (C(20)); 46.1 (C(21)); 69.3 (C(22)); 31.0 (C(23)); 69.7 (C(24)); 39.2 (C(25)); 76.2 (C(26)); 133.1 (C(27)); 128.0 (C(29)); 34.8 (C(30)); 36.8 (C(31)); 84.2 (C(32)); 75.2 (C(33)); 33.8 (C(34)); 31.0 (C(35)); 20.5 (C(36)); 12.82 (C(37)); 16.3 (*Me*–C(11)); 21.0 (*Me*–C(17)); 15.2 (*Me*–C(19)); 10.3 (*Me*–C(25)); 15.0 (*Me*–C(27)); 56.2 (*Me*O–C(13)); 57.2 (*Me*O–C(15)); 58.1 (*Me*O–C(32)); 25.9 (Me_3C); 18.2 (Me_3C); –4.7 (MeSi); 17.63 (Me); 17.57 (Me); 17.52 (Me); 17.1 (Me); 13.7 (CH); 12.4 (CH). HR-MS: 1184.7247 ($[M+Na]^+$; calc. 1184.7255).

Data of **51a**. ^{1}H-NMR: 6.79 (*d*, *J* = 1.6, HO–C(10)); 5.82 (*ddd*, *J* = 17.2, 10.8, 4.1, H–C(5′)); 5.43 (*ddd*, *J* = 17.2 , 1.6, 0.9, 1 H–C(5″)); 5.39 (*s*, H–C(26)); 5.18 (*ddd*, *J* = 10.8, 1.6, 1.6, 1 H–C(5″)); 4.84 (*d*, *J* = 9.2, H–C(29)); 4.80 (*d*, *J* = 9.2, H–C(20)); 4.58 (br. *dd*, *J* = 6.5, 4.5, H–C(5)); 4.47 (*t*, *J* = 7.8, H–C(2)); 4.09 (*ddd*, *J* = 11.2, 6.2, 2.3, H–C(24)); 4.00 (*ddd*, *J* = 11.2, 4.8, 2.3, H–C(22)); 3.95 (*dd*, *J* = 9.6, 2.5, H–C(14)); 3.51 (*m*, H–C(15)); 3.48 (*m*, H–C(13)); 3.41 (*s*, MeO–C(32)); 3.38 (*s*, MeO–C(15)); 3.38 (*m*, H–C(33)); 3.35 (*s*, MeO–C(13)); 2.95 (*ddd*, *J* = 11.2, 8.5, 4.6, H–C(32)); 2.46 (*m*, H–C(21)); 2.37 (*m*, 1 H–C(3)); 2.35 (*m*, 1 H–C(18)); 2.23 (*m*, H–C(30)); 2.11 (*m*, H–C(11)); 2.06 (*m*, 1 H–C(12), H–C(25)); 2.01 (*m*, 1 H–C(4)); 1.98 (*m*, 1 H–C(3)); 1.93 (*m*, 1 H–C(31)); 1.89

(*m*, 1 H–C(36)); 1.81 (*m*, H–C(34)); 1.61 (*m*, 1 H–C(23)); 1.59 (*d*, *J* = 1.0, Me–C(27)); 1.54 (*m*, 1 H–C(18)); 1.53 (*s*, Me–C(19)); 1.53 (*m*, 1 H–C(12)); 1.52 (*m*, 1 H–C(16), H–C(17)); 1.49 (*m*, 1 H–C(35)); 1.43 (*m*, 1 H–C(23)); 1.34 (*m*, 1 H–C(16), 1 H–C(34)); 1.10–0.90 (2 Me_2CHSi)); 1.07 (*m*, 1 H–C(36)); 0.95 (*d*, *J* = 6.4, Me–C(11)); 0.94 (*m*, 1 H–C(31)); 0.89 (*s*, *t-Bu*)); 0.89 (*m*, 1 H–C(35)); 0.84 (*t*, *J* = 7.4, Me–C(37)); 0.81 (*d*, *J* = 6.0, Me–C(17)); 0.77 (*d*, *J* = 7.3, Me–C(25)); 0.08 (*s*, MeSi); 0.06 (*s*, MeSi). ^{13}C-NMR: 167.5 (C(1)); 59.2 (C(2)); 25.80 (C(3)); 32.2 (C(4)); 61.3 (C(5)); 136.5 (C(5′)); 116.7 (C(5″)); 165.8 (C(8)); 187.8 (C(9)); 99.2 (C(10)); 32.7 (C(11)); 31.8 (C(12)); 73.9 (C(13)); 71.3 (C(14)); 77.8 (C(15)); 36.3 (C(16)); 25.4 (C(17)); 49.9 (C(18)); 135.7 (C(19)); 128.6 (C(20)); 45.9 (C(21)); 69.1 (C(22)); 31.4 (C(23)); 69.5 (C(24)); 38.8 (C(25)); 76.1 (C(26)); 132.4 (C(27)); 127.9 (C(29)); 34.8 (C(30)); 36.8 (C(31)); 84.2 (C(32)); 75.3 (C(33)); 33.8 (C(34)); 30.9 (C(35)); 20.52 (C(36)); 12.81 (C(37)); 56.2 (*Me*O–C(13)); 57.5 (*Me*O–C(15)); 58.1 (*Me*O–C(32)); 16.1 (*Me*–C(11)); 20.59 (*Me*–C(17)); 15.3 (*Me*–C(19)); 10.2 (*Me*–C(25)); 14.9 (*Me*–C(27)); 25.86 (Me_3C); 18.2 (Me_3C)); –4.5 (MeSi); –4.7 (MeSi); 17.6 (Me); 17.5 (Me); 17.2 (Me); 17.1 (Me); 13.6 (Me_2CHSi); 12.4 (Me_2CHSi). HR-MS: 1184.7253 ([*M* + Na]$^+$; calc. 1184.7255).

Compound **50b**. To a mixture of **50a** (70 mg, 0.06 mmol)), 1 ml CH_2Cl_2 and 2 ml MeCN was added at r.t. a mixture of 1 ml MeCN and 325 µl of 40% HF in MeCN. After stirring overnight at r.t., the mixture was worked up using AcOEt and aq. $NaHCO_3$, and the residue was purified by FC (SiO_2; toluene/AcOEt 1:2, 1:4, 1:6) to give the α-vinyl product **50b** (37 mg, 76%) as a white foam. ^{1}H-NMR (~1:1 mixture of rotamers): 7.12 (br. *s*, HO–C(10)); 5.73 (*m*, H–C(6)); 5.69 (*m*, H–C(6)); 5.29 (br. *s*, H–C(26)); 5.20–4.85 (several overl. *m*s, 6.5 H, H–C(2), 2 H–C(5), 2 H–C(6′), 2 H–C(20), H–C(26), 2 H–C(29), HO–C(10)); 4.70 (*dd*, *J* = 8.3, 2.3, H–C(2)); 4.10–3.90 (*m*, 1.5 H, H–C(22), 2 H–C(24)); 3.77 (*dd*, *J* = 9.6, 2.0, H–C(14)); 3.70 (*dd*, *J* = 9.6, 1.3, H–C(14)); 3.70–3.50 (*m*, 2.5 H, 2 H–C(15), H–C(22), 2 OH); 3.45–3.25 (*m*, 11 H, 2 H–C(13), 2 H–C(33), MeO); 3.01 (*m*, 2 H–C(32); 2.85 (br. *s*, OH); 2.70 (br. *s*, 2 OH); 2.53 (br. *s*, OH); 2.40–0.80 (overl. *m*s). HR-MS: 828.4874 ([*M* + Na]$^+$; calc. 828.4868).

Compound **51b**. To a mixture of **51a** (80 mg, 0.069 mmol), 1 ml of CH_2Cl_2, and 2 ml of MeCN was added at r.t. a mixture of 1 ml of MeCN and 325 µl of 40% HF in MeCN. After stirring overnight at r.t., the mixture was worked up using AcOEt and aq. $NaHCO_3$, and the residue was purified by FC (SiO_2; toluene/AcOEt 1:2, 1:4, 1:6, 1:10) to give the β-vinyl product **51b** (31 mg, 56%). White foam. ^{1}H-NMR (mixture of rotamers): 6.37 (*s*, HO–C(10)); 5.82 (*ddd*, *J* = 17.4, 10.8, 5.3, H–C(5′)); 5.36 (*d*, *J* = 17.4, 1 H–C(5″)); 5.16 (*d*, *J* = 10.8, 1 H–C(5″)); 5.16 (br. *s*, H–C(26)); 5.06 (*d*, *J* = 9.9, H–C(20)); 4.93 (*d*, *J* = 9.2, H–C(29)); 4.82 (br. *ddd*, *J* = 7.8, 5.0, 2.5, H–C(5)); 4.55 (*t*, *J* = 8.3, H–C(2)); 3.94 (br. *t*, *J* = 8.5, H–C(24)); 3.77 (*dd*, *J* = 9.6, 1.8, H–C(14)); 3.72 (*m*, H–C(22)); 3.54 (*ddd*, *J* = 10.8, 3.2, 1.8, H–C(15)); 3.40 (*s*, MeO–C(32)); 3.39 (*m*, H–C(33)); 3.38 (*m*, H–C(13)); 3.37 (*s*, MeO–C(13)); 3.33 (*s*, MeO–C(15)); 3.01 (*m*, H–C(32)); 2.69 (br. *s*, HO–C(24)); 2.47 (br. *s*, HO–C(22)); 2.28 (*m*, H–C(30)); 2.27 (*m*, 1 H–C(3)); 2.24 (*m*, H–C(21)); 2.20 (*m*, H–C(11)); 2.08 (*m*, 1 H–C(4)); 2.07 (*m*, 1 H–C(12)); 2.05 (*m*, H–C(18)); 2.02 (*m*, 1 H–C(31)); 1.98 (*m*, 1 H–C(34)); 1.97 (*m*, 1 H–C(3)); 1.88 (*m*, 1 H–C(4)); 1.80 (*m*, H–C(25)); 1.71 (*m*, 1 H–C(16)); 1.63 (*s*, Me–C(27)); 1.62 (*m*, H–C(17)); 1.60 (*s*, Me–C(19)); 1.57 (*m*, 1 H–C(35)); 1.55 (*m*, 2 H–C(23)); 1.52 (*m*, 1 H–C(36)); 1.46 (*m*, 1 H–C(12)); 1.35 (*m*, 1 H–C(34)); 1.28 (*m*, 1 H–C(36)); 1.15 (*m*, 1 H–C(16)); 1.00 (*m*, 1 H–C(35)); 0.96 (*d*, *J* = 7.1, Me–C(25)); 0.95 (*m*, 1 H–C(31)); 0.90 (*d*, *J* = 6.4, Me–C(17)); 0.86 (*d*, *J* = 6.6, Me–C(11)); 0.85 (*t*, *J* = 7.4, Me–C(37)). ^{13}C-NMR: 168.6 (C(1)); 60.1 (C(2)); 26.3 (C(3)); 32.0 (C(4)); 61.2 (C(5)); 136.8 (C(5′)); 117.05 (C(5″)); 163.0 (C(8)); 193.2 (C(9)); 98.9 (C(10)); 33.4 (C(11)); 32.7 (C(12)); 73.9 (C(13)); 72.7 (C(14)); 76.5 (C(15)); 34.6 (C(16)); 26.9 (C(17)); 48.9 (C(18)); 136.2 (C(19)); 126.9 (C(20)); 45.9 (C(21)); 72.1 (C(22)); 39.5 (C(23)); 70.9 (C(24)); 40.8 (C(25)); 77.7 (C(26)); 131.7 (C(27)); 128.2 (C(29)); 34.78 (C(30)); 34.81 (C(31)); 84.2 (C(32)); 73.6 (C(33)); 31.2 (C(34)); 30.7 (C(35)); 25.2 (C(36)); 11.6 (C(37)); 16.0 (*Me*–C(11)); 20.1 (*Me*–C(17)); 16.2 (*Me*–C(19)); 10.2 (*Me*–C(25)); 14.5 (*Me*–C(27)); 56.2 (*Me*O–C(13)); 57.4 (*Me*O–C(15)); 56.6 (*Me*O–C(32)). HR-MS: 828.4870 ([*M* + Na]$^+$; calc. 828.4868).

Compound **52**. A mixture of **51b** (26 mg, 0.033 mmol), pyridine (12.9 µl, 0.16 mmol), and *Dess–Martin* periodinane (13.6 mg, 0.033 mmol) in 2 ml of CH_2Cl_2 was stirred at r.t. for 4 h. The solids were filtered off, and the filtrate was co-evaporated with toluene, and the residue was purified by FC (SiO_2; toluene/AcOEt 1:1) to give the β-vinyl product **52** (16 mg, 62%). White foam. ^{1}H-NMR: 6.11 (*s*, HO–C(10)); 5.85 (*ddd*, *J* = 17.2, 10.5, 4.4, H–C(5′)); 5.43 (br. *d*, *J* = 17.2, 1 H–C(5″)); 5.19 (*ddd*, *J* =

10.5, 1.3, 1.1, 1 H–C(5″)); 5.15 (*d*, *J* = 3.0, H–C(26)); 4.98 (*d*, *J* = 9.2, H–C(29)); 4.93 (*d*, *J* = 9.4, H–C(20)); 4.79 (br. *dd*, *J* = 6.6, 4.4, H–C(5)); 4.41 (*t*, *J* = 8.4, H–C(2)); 4.01 (*ddd*, *J* = 9.9, 4.1, 3.0, H–C(24)); 3.94 (*dd*, *J* = 9.6, 2.4, H–C(14)); 3.57 (*ddd*, *J* = 11.2, 4.4, 2.4, H–C(15)); 3.42 (*m*, H–C(13)); 3.40 (*s*, MeO–C(32)); 3.39 (*m*, H–C(33)); 3.38 (*s*, MeO–C(13)); 3.35 (*s*, MeO–C(15)); 3.23 (*m*, H–C(21)); 3.00 (*ddd*, *J* = 11.2, 8.9, 4.4, H–C(32)); 2.68 (*dd*, *J* = 16.3, 2.8, 1 H–C(23)); 2.36 (*m*, 1 H–C(18)); 2.33 (*m*, 1 H–C(23)); 2.28 (*m*, 1 H–C(3)); 2.27 (*m*, H–C(30)); 2.16 (*m*, H–C(11)); 2.08 (*m*, 1 H–C(12)); 2.03 (*m*, 1 H–C(4)); 2.02 (*m*, 1 H–C(31)); 1.98 (*m*, 1 H–C(34)); 1.96 (*m*, 1 H–C(3)); 1.93 (*m*, 1 H–C(4)); 1.80 (*m*, 1 H–C(18)); 1.79 (*m*, H–C(25)); 1.73 (*m*, 1 H–C(36)); 1.70 (*s*, Me–C(19)); 1.65 (*m*, H–C(17)); 1.65 (*d*, *J* = 1.2, Me–C(27)); 1.59 (*m*, 1 H–C(35)); 1.48 (*m*, 1 H–C(12), 1 H–C(36)); 1.47 (*m*, 1 H–C(16)); 1.37 (*m*, 1 H–C(16)); 1.35 (*m*, 1 H–C(34)); 1.01 (*m*, 1 H–C(35)); 0.94 (*d*, *J* = 6.4, Me–C(11)); 0.93 (*m*, 1 H–C(31)); 0.92 (*d*, *J* = 6.9, Me–C(25)); 0.86 (*t*, *J* = 7.3, Me–C(37)); 0.80 (*d*, *J* = 6.4, Me–C(17)). ^{13}C-NMR: 168.3 (C(1)); 60.3 (C(2)); 26.1 (C(3)); 32.0 (C(4)); 61.3 (C(5)); 136.7 (C(6)); 164.0 (C(8)); 187.9 (C(9)); 99.0 (C(10)); 32.9 (C(11)); 32.0 (C(12)); 73.6 (C(13/33)); 71.4 (C(14)); 76.4 (C(15)); 36.1 (C(16)); 25.6 (C(17)); 49.1 (C(18)); 140.1 (C(19)); 123.0 (C(20)); 55.2 (C(21)); 213.6 (C(22)); 44.4 (C(23)); 69.2 (C(24)); 41.0 (C(25)); 78.4 (C(26)); 131.9 (C(27)); 129.7 (C(29)); 34.8 (C(30)); 34.7 (C(31)); 84.2 (C(32)); 73.7 (C(13/33)); 31.2 (C(34)); 30.6 (C(35)); 24.0 (C(36)); 11.6 (C(37)); 16.1 (*Me*–C(11)); 18.7 (*Me*–C(17)); 15.4 (*Me*–C(19)); 9.6 (*Me*–C(25)); 14.1 (*Me*–C(27)); 56.3 (*Me*O–C(13)); 57.5 (*Me*O–C(15)); 56.5 (*Me*O–C(32)). HR-MS: 826.4711 ([*M* + Na]$^+$; calc. 826.4712).

Compound **53**. A mixture of **50b** (29 mg, 0.036 mmol), pyridine (14.5 µl, 0.18 mmol), and *Dess–Martin* periodinane (15.2 mg, 0.036 mmol) in 2 ml of CH_2Cl_2 was stirred at r.t. for 4 h. The solids were filtered off, and the filtrate was co-evaporated with toluene, and the residue was purified by FC (SiO_2; toluene/AcOEt 1 : 1) to give the β-vinyl product **53** (14 mg, 48%). White foam. ^{1}H-NMR (*ca.* 3 : 1 mixture of isomers): major isomer: 6.20 (*d*, *J* = 1.6, HO–C(10)); 5.70 (*ddd*, *J* = 17.0, 10.5, 5.3, H–C(5′)); 5.20 (*m*, H–C(26)); 5.17 (*m*, H–C(5)); 5.10 (*dd*, *J* = 10.5, 1.3, 1 H–C(5″)); 5.02 (*m*, H–C(29)); 5.01 (*dd*, *J* = 17.0, 1.3, 1 H–C(5″)); 5.00 (*m*, H–C(20)); 4.46 (*dd*, *J* = 8.5, 2.0, H–C(2)); 4.01 (br. *d*, *J* = 10.1, H–C(24)); 3.90 (*dd*, *J* = 9.4, 2.3, H–C(14)); 3.57 (*ddd*, *J* = 11.2, 4.8, 2.3, H–C(15)); 3.40 (*s*, MeO–C(32)); 3.40 (*m*, H–C(13)); 3.39 (*m*, H–C(33)); 3.36 (*s*, MeO–C(13)); 3.32 (*s*, MeO–C(15)); 3.19 (*m*, H–C(21)); 3.00 (*ddd*, *J* = 11.2, 8.7, 4.4, H–C(32)); 2.68 (*dd*, *J* = 16.7, 2.3, 1 H–C(23)); 2.66 (br. *s*, HO–C(24)); 2.38 (br. *d*, *J* = 13.5, 1 H–C(18)); 2.31 (*dd*, *J* = 16.7, 10.1, 1 H–C(23)); 2.28 (*m*, H–C(30)); 2.20 (*m*, 1 H–C(3), 1 H–C(4)); 2.04 (*m*, 1 H–C(12), 1 H–C(31)); 2.00 (*m*, H–C(11)); 1.99 (*m*, 1 H–C(34)); 1.94 (*m*, 1 H–C(3)); 1.83 (*m*, H–C(25), 1 H–C(4)); 1.80 (*m*, 1 H–C(18)); 1.70 (*m*, 1 H–C(36)); 1.65 (*m*, H–C(17)); 1.61 (*m*, 1 H–C(35)); 1.60 (*s*, Me–C(19), Me–C(27)); 1.50 (*m*, 1 H–C(36)); 1.46 (*m*, 1 H–C(16), 1 H–C(12)); 1.41 (*m*, 1 H–C(16)); 1.36 (*m*, 1 H–C(34)); 1.03 (*m*, 1 H–C(35)); 0.95 (*m*, 1 H–C(31)); 1.00 (*d*, *J* = 6.4, Me–C(11)); 0.92 (*d*, *J* = 7.1, Me–C(25)); 0.88 (*t*, *J* = 7.3, Me–C(37)); 0.80 (*d*, *J* = 6.6, Me–C(17)). ^{13}C-NMR (major isomer): 168.5 (C(1)); 60.0 (C(2)); 25.6 (C(3)); 30.8 (C(4)); 60.1 (C(5)); 136.7 (C(5′)); 116.7 (C(5″)); 164.5 (C(8)); 188.1 (C(9)); 98.6 (C(10)); 33.1 (C(11)); 32.7 (C(12)); 73.6 (C(13)); 71.5 (C(14)); 76.2 (C(15)); 36.5 (C(16)); 25.7 (C(17)); 49.1 (C(18)); 140.4 (C(19)); 122.7 (C(20)); 55.4 (C(21)); 214.5 (C(22)); 43.4 (C(23)); 69.1 (C(24)); 41.0 (C(25)); 78.1 (C(26)); 132.3 (C(27)); 129.6 (C(29)); 34.8 (C(30)); 34.7 (C(31)); 84.2 (C(32)); 73.6 (C(33)); 31.2 (C(34)); 30.6 (C(35)); 24.4 (C(36)); 11.7 (C(37)); 16.2 (*Me*–C(11)); 18.9 (*Me*–C(17)); 15.5 (*Me*–C(19)); 9.8 (*Me*–C(25)); 14.2 (*Me*–C(27)); 56.2 (*Me*O–C(13)); 57.2 (*Me*O–C(15)); 56.6 (*Me*O–C(32)). HR-MS: 826.4714 ([*M* + Na]$^+$; calc. 826.4712).

X-Ray Crystal-Structure Analysis[3]). Unit-cell determination and intensity-data collection for **6a** were performed on a *Bruker AXS SMART 6000 CCD*, with graphite-monochromatized CuK_α radiation from a sealed tube generator. A semi-empirical absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings [16b]. The structure was solved by dual-space recycling methods and refined by full-matrix least-squares on F^2 [16c]. Non-H-atoms were refined with anisotropic displacement parameters, H-atoms were calculated in idealized positions and refined using a riding model.

Crystal Data for **6a**. Colorless rod from MeOH, size 0.39 · 0.20 · 0.14 mm^3, $C_{43}H_{67}NO_{12}$, M_r = 789.98, monoclinic, space group $P2_1$ (No. 4) with *a* = 14.572(2), *b* = 11.085(2), *c* = 14.933(6) Å, β = 116.922(4)°,

$V = 2150.7(6)$ Å^3, $Z = 2$, $D_c = 1.220\ g \cdot cm^{-3}$, 67261 reflections measured, 7701 independent ($R_{int} = 0.0360$), $3.32° < \theta < 68.27°$, $T = 100$ K, 517 parameters, 1 restraint, $R_1 = 0.0268$, $wR_2 = 0.0667$ for 7535 reflections with $I > 2\sigma(I)$, $R_1 = 0.0275$, $wR_2 = 0.0673$ for all 7701 data, GoF = 1.031, res. el. dens. = +0.16/ −0.19 e · Å^{-3}.

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