174. Synthesis and Configuration of Some Hydroxymilbemycin Derivatives Including 22,23-Dihydroavermectin B_{1b} Aglycone

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Dedicated to Prof. *Oskar Jeger*

(17.IV.90)

The synthesis of several configurationally defined hydroxymilbemycin derivatives is described. One of these allylic alcohols is the known 5-*O*-[(*tert*-butyl)dimethylsilyl]-13α-hydroxymilbemycin D (= 5-*O*-[(*tert*-butyl)-dimethylsilyl]-22,23-dihydroavermectin B_{1b} aglycone; **15D**), the synthesis of which represents a conversion of the milbemycin to the avermectin series of natural products. The configurations at C(13), C(14), and C(15) of the new milbemycin derivatives were determined by NMR experiments and force-field calculations.

1. Introduction. – The milbemycins, *e.g.* **1A**[4]) and **1D**[4]) (see *Table 1*), are a family of 16-membered ring macrolides isolated from the *Streptomyces hygroscopicus* subspecies *aureolacrimosus* [1]. These compounds, isolated by *Sankyo* chemists in 1973, possess high anthelmintic, acaricidal, and insecticidal activity [2]. The avermectins **2** and **3**, compounds with similar structures and biological activity as the milbemycins, are produced by a culture of *Streptomyces avermitilis* [3]. A mixture of 22,23-dihydroavermectin B_{1a} and B_{1b} is sold as an antiparasitic agent under the generic name *Ivermectin* (**4**) [4]. The biological activity of this family of compounds is believed to be caused by interference with the nervous system of the parasite [5]. The interesting structure of this class has generated an enormous effort towards partial and total syntheses of the milbemycins and avermectins [6].

Avermectin B_{1b} (**3**) has been converted to milbemycin D (**1D**) by hydrogenation of the 22,23-double bond (*cf.* **4**), hydrolysis of the dioleandrose unit (*cf.* **5**), and deoxygenation of the aglycone [7]. In this paper, a functionalization of the milbemycin molecule (**1A** and **1D**) at position 13 is reported, whereby several allylic-alcohol isomers were synthesized including 13β-hydroxymilbemycin D (**6D**) and its known 5-*O*-protected C(13)-epimer **15D** (5-*O*-[(*tert*-butyl)dimethylsilyl]-13α-hydroxymilbemycin D[5]).

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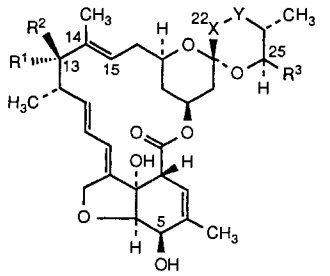
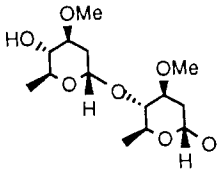
[4]) The terms **A** and **D** are used to describe structures in the milbemycin A_4 and D series, respectively. Numbering of the milbemycin molecule is according to [1]. The α and β nomenclature is defined with respect to structures of type **I** (*Table 1*).

[5]) A direct microbiological hydroxylation of the milbemycin nucleus at C(13) has been reported recently [8a], and a direct hydroxylation at C(13) using SeO_2 has also been published [8b].



I

Table 1. *Structures of Avermectins and Milbemycins*

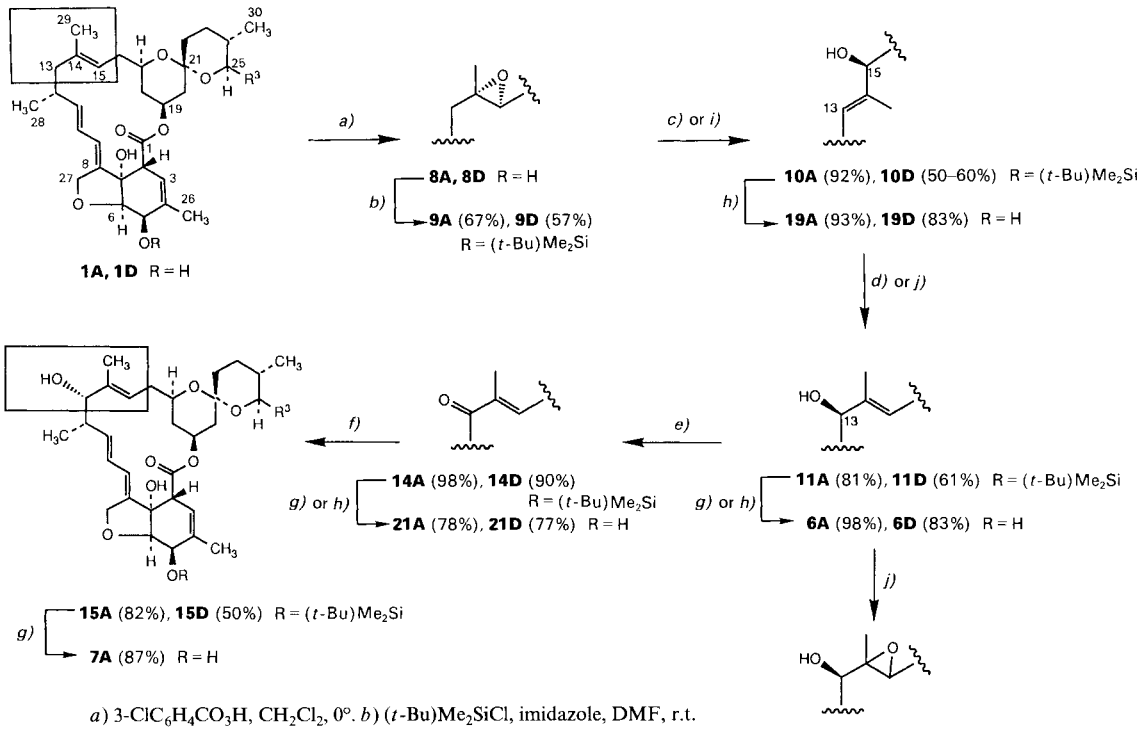
	Name	R^1	R^2	R^3	X–Y
1A[4])	Milbemycin A_4	H	H	Et	CH_2–CH_2
1D[4])	Milbemycin D	H	H	i-Pr	CH_2–CH_2
2	Avermectin B_{1a}		H	*s*-Bu	CH=CH
3	Avermectin B_{1b}		H	i-Pr	CH=CH
4	*Ivermectin*		H	*s*-Bu/i-Pr 80:20	CH_2–CH_2
5	*Ivermectin* aglycone	OH	H	*s*-Bu/i-Pr 80:20	CH_2–CH_2
6A[4])	13β-Hydroxymilbemycin A_4	H	OH	Et	CH_2–CH_2
6D[4])	13β-Hydroxymilbemycin D	H	OH	i-Pr	CH_2–CH_2
7A[4])	13α-Hydroxymilbemycin A_4	OH	H	Et	CH_2–CH_2
7D[4])	13α-Hydroxymilbemycin D	OH	H	i-Pr	CH_2–CH_2

2. Results and Discussion. – Selective epoxidation of one of the four double bonds of the milbemycins **1A** and **1D** has been reported [9]. Thus, epoxidation with 3-chloroperbenzoic acid occurs at C(14)=C(15) stereoselectively on the α-face of the milbemycin skeleton furnishing **8A** and **8D**, respectively. The β-face is substantially sterically shielded at this part of the molecule, as shown by examination of the crystal structure of avermectin B_{1a} aglycone [10]. After protection of the 5-OH group as its (*tert*-butyl)-dimethylsilyl ether, the epoxides **9A** and **9D** were obtained in 67 and 57% yields, respectively (*Scheme 1*).

Upon treatment with a suitable acidic reagent, epoxide **9** opens to the more stabilized tertiary cation, and elimination in the ring produces the desired allylic alcohol **10** [11]. The reagent used initially was Et_2AlN_3 in THF [12][6]), in a reaction reminiscent of the Et_2AlNR_2 method of *Yamamoto* and *Nozaki* [13]. Using this reagent, **9D** was converted to allylic alcohol **10D** in 50–60% yield. However, other *Lewis* and *Bronsted* acids were also found to be useful for this rearrangement (see *Table 2*), the best being 9-borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate (9-BBN triflate) in the presence of excess 2,6-dimethylpyridine (2,6-lutidine) [14] which afforded **10A** in 92% yield. The (13*E*)-compound is not necessarily a kinetically formed thermodynamically unfavourable isomer. The C(12)–C(13)–C(14)–C(15) torsion angle of 118° observed in the crystal structure of avermectin aglycone [10] is closer to (*E*)- than to (*Z*)-configuration.

[6]) In toluene as solvent, the azidoalcohol was formed [12a].

Scheme 1



a) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 0°. *b*) (*t*-Bu)Me_2SiCl, imidazole, DMF, r.t. *c*) 9-BBN triflate, 2,6-lutidine, CH_2Cl_2/Et_2O 1:10, r.t. *d*) PVPDC, DMF, 70°. *e*) 1. $(COCl)_2$, Me_2SO, CH_2Cl_2, −60°, 2. Et_3N, −60°→0°. *f*) $NaBH_4$, EtOH, r.t. *g*) 40% HF, MeCN 5:95, r.t. *h*) TsOH, MeOH, r.t. *i*) Et_3Al, HN_3, THF, 60°. *j*) PDC, DMF, r.t.

Table 2. *Rearrangement of the Epoxides* **9A** *and* **9D** *to the Allylic Alcohols* **10A** *and* **10D**, *Respectively*

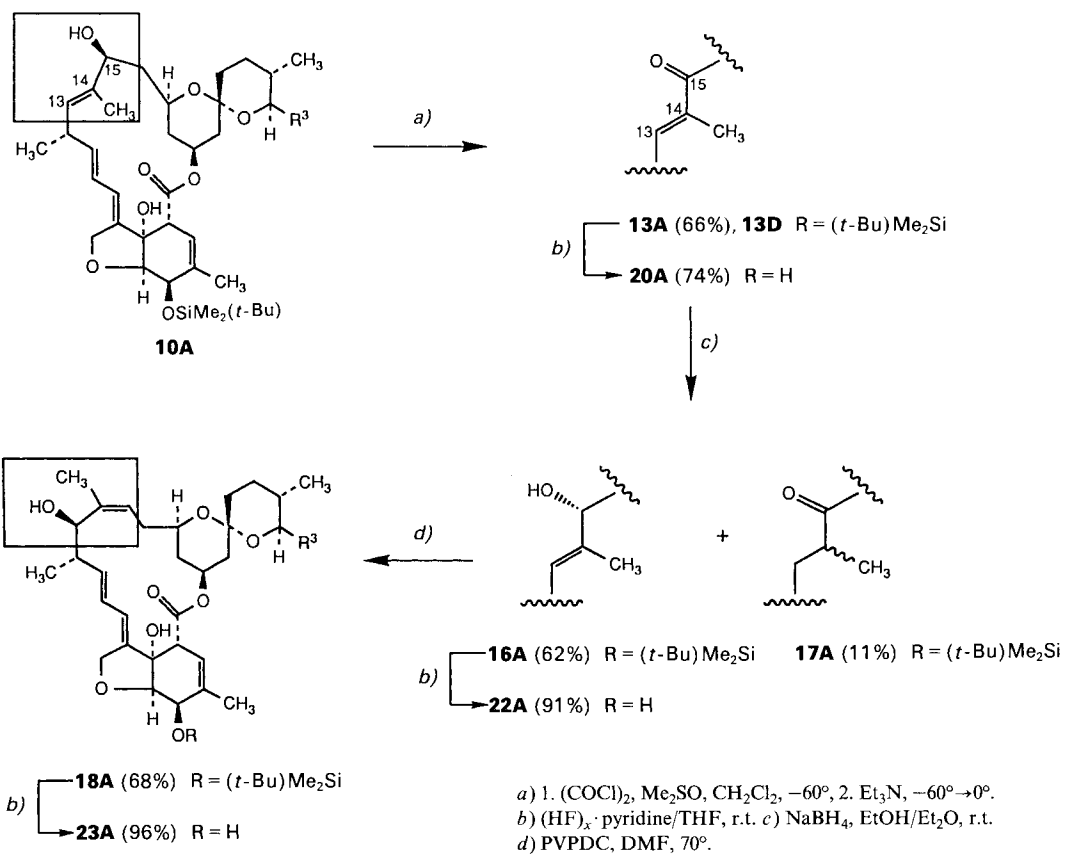
Epoxide	Reagent[a])	Solvent	Temp.	Product (Yield)
9D	HN_3/Et_3Al 1:0.6	THF	reflux	**10D** (50–60%)
9A	HN_3/Et_3Al 1:0.6	THF	reflux	**10A** (50–60%)
	9-BBN triflate/2,6-lutidine	CH_2Cl_2/Et_2O 1:10	r.t.	**10A** (85–95%)
	$(Bu)_2B$ triflate/2,6-lutidine	CH_2Cl_2/Et_2O 1:10	r.t.	**10A** (78%)
	(±)-camphor-10-sulfonic acid	CH_2Cl_2	reflux	**10A** (25–30%), **11A** (25–30%)
	TsOH	CH_2Cl_2	reflux	**10A** (16%), **11A** (15%)

[a]) The formation fo the allylic alcohols **10A** and **10D** was not observed under the following conditions: *i*) tetramethylpiperidine/Et_3Al, toluene, r.t.; *ii*) pyridinium toluene-4-sulfonate, $CHCl_3$, reflux; *iii*) Al(i-PrO)$_3$, toluene, reflux.

The rearrangement of the allylic alcohols **10A** and **10D** to the protected 13β-hydroxymilbemycins **11A** and **11D**, respectively, was accomplished using Cr(VI) reagents [15]. With pyridinium dichromate (PDC) or pyridinium chlorochromate (PCC) at r.t., the allylic alcohol **11D** was produced regio- and stereoselectively, presumably through a

hetero-*Claisen* reaction, in *ca.* 60% yield, accompanied by a small amount of epoxide **12D**. After longer reaction times, the *Sharpless*-type epoxide **12D** became the main product [16]. It is noteworthy that the synfacial allylic rearrangement is the only reaction observed: ketone **13D** (see below, *Scheme 2*) was not found, and the 13-oxomilbemycin derivative **14D** was isolated from the reaction mixture in only 4% yield. Using polymer-bound PDC (PVPDC) in DMF at 60° for this transformation, the side reactions were suppressed, and pure **11A** was obtained in 81% yield. Although Cr(VI) reagents were unsuitable for the oxidation of the 13β-allylic alcohols **11A** and **11D** to the 13-oxomilbemycin derivatives **14A** and **14D**, these ketones could be synthesized using DMSO-based reagents[7]). *Kornblum* oxidation [17] of the trifluoroacetate of **11D** with DMSO and *Hünig*'s base at 110° yielded **14D** in 23% yield. *Ganem*'s silver-assisted variant [18] starting from 13β-bromo-5-*O*-[(*tert*-butyl)dimethylsilyl]milbemycin D [19] offered no improvement, yielding **13D** and **14D** in only 11 and 3% yields, respectively. High yields of the ketones **14A** and **14D** were obtained, however, after oxidation of **11A** and **11D**

Scheme 2



a) 1. $(COCl)_2$, Me_2SO, CH_2Cl_2, −60°, 2. Et_3N, −60°→0°. *b*) $(HF)_x$·pyridine/THF, r.t. *c*) $NaBH_4$, EtOH/Et_2O, r.t. *d*) PVPDC, DMF, 70°.

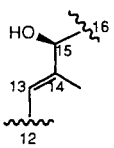
[7]) Oxidation of the 13α-hydroxy derivatives **15A** and **15D** with PDC in DMF afforded the ketones **14A** and **14D** in good yield [6b].

under *Swern* conditions [20] (*Scheme 1*). Reduction of the ketones **14A** and **14D** with $NaBH_4$ proved to be highly stereoselective producing the 13α-hydroxymilbemycin derivatives **15A** and **15D** in 82 and 50% yields, respectively. The epimeric 13β-hydroxy derivative **11A** was isolated as a by-product in 6% yield. The silylated 13α-hydroxymilbemycin D derivative **15D** was shown by 300-MHz ^{1}H-NMR to be identical with an authentic sample of 5-*O*-[(*tert*-butyl)dimethylsilyl]-22,23-dihydroavermectin B_{1b} aglycone prepared from commercially available *Ivermectin* according to *Mrozik et al.* [7].

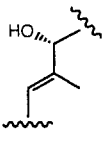
An entry into the 13-substituted milbemycin series with the unnatural (14*Z*)-double bond was obtained by rearrangement of the (15*R*)-allyl alcohol **16A** (*Scheme 2*). This intermediate was derived from **10A** through an oxidation-reduction sequence. *Swern* oxidation [20] of **10A** afforded the enone **13A** in 66% yield. The subsequent reduction with $NaBH_4$ proceeded with high stereoselectivity, forming the allylic alcohol **16A** (62%) and its C(15) epimer **10A** (4%), together with the 1,4-reduction product **17A** (11%). Treatment of **16A** with polymer-bound PDC in DMF at 70° produced the (14*Z*)-allylic alcohol **18A** (68%). This synfacial allylic rearrangement, as found for the rearrangements **10A** → **11A** and **10D** → **11D**, is clearly highly regio- and stereospecific, as no other isomer of product **18A** was found.

Apart from the interconversion of the two series of natural products, we have now in hand a number of highly functionalized, suitably protected compounds which have served as intermediates in the stereoselective synthesis of a range of new highly biologically active molecules [21].

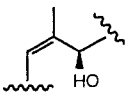
3. Configurational Assignments. – For the 15-OH compounds (R=H) synthesized above, **19A**, **22A**, **24**, and **25** are possible stereoisomers, for the 13-OH derivatives (R=H), stereoisomers **6A**, **7A**, **23A**, and **26** could be considered, and for the 13- and 15-oxo compounds (R=H) the (*E*)-isomers **21A** and **20A** and the (*Z*)-isomers **27** and **28** were taken into account. The assignment of the (*E*/*Z*)- and (*R*/*S*)-configurations was



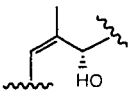
19A (13*E*,15*S*)



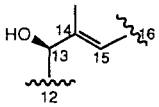
22A (13*E*,15*R*)



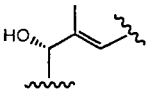
24 (13*Z*,15*S*)



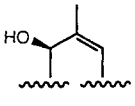
25 (13*Z*,15*R*)



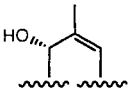
6A (14*E*,13*R*)



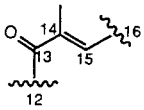
7A (14*E*,13*S*)



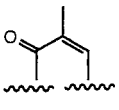
23A (14*Z*,13*R*)



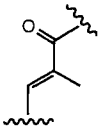
26 (14*Z*,13*S*)



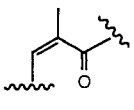
21A (14*E*)



27 (14*Z*)



20A (13*E*)



28 (13*Z*)

carried out using a combination of NMR spectroscopy and force-field calculations as described below. Spectral measurements were made predominately with the 5-OH derivatives (R=H). For this purpose, the 5-*O*-silyl derivatives **10A**, **10D**, **11A**, **11D**, **13A**, **14A**, **14D**, **15A**, **16A**, and **18A** were deprotected either with TsOH/MeOH, $HF/H_2O/MeCN$ [22], or $(HF)_x \cdot$ pyridine/THF [23] to the corresponding alcohols **19A**, **19D**, **6A**, **6D**, **20A**, **21A**, **21D**, **7A**, **22A**, and **23A**, respectively.

Position of the Double Bond (at C(13) or C(14)). The double-bond position was derived from the *multiplet* structures of H–C(13) and H–C(15) in the ^{1}H-NMR spectra: H–C(13) of the C(14)=C(15) isomers couples primarily with only H–C(12), whereas H–C(15) of the C(13)=C(14) isomers couples with 2H–C(16).

Distinction between (E)- and (Z)-Configuration. The 13- or 14-double-bond configuration was established by examining the ^{13}C-NMR chemical-shift value of the CH_3–C(14) resonance which is influenced by three γ-substituents. The three γ-effects can be estimated [24] from the torsion angles calculated for all possible configurations of the 13-OH and 15-OH compounds listed in *Table 3*. The γ-effect due to the *cis*- or *trans*-disposed C-atoms across the double bond is the dominant one and allows an unequivocal assignment of the (*E*/*Z*)-configuration to the double bonds of the compounds described here.

Table 3. *Chemical-Shift Values of CH_3–C(14) and Dihedral Angles*

	Configuration	Chemical shift[a])	Torsion angles [°] between CH_3–C(14) and		
			C(12) or C(16) (double bond)	C(13)–OH or C(15)–OH	C(12) or C(16) (single bond)
7A	(14*E*,13*S*)[b])	14.8	–1	157	–78
22A	(13*E*,15*R*)	15.0	–3	180	72
6A	(14*E*,13*R*)	10.1	–1	66	–57
19A	(13*E*,15*S*)	10.7	–4	–55	68
23A	(14*Z*,13*R*)	17.6	179	51	–71
24	(13*Z*,15*S*)		180	61	–61
26	(14*Z*,13*S*)		180	156	–78
25	(13*Z*,15*R*)		180	155	–78

a) In ppm. *vs.* TMS.
b) Assignment from X-ray [10].

Thus, the chemical shifts observed for CH_3–C(14) of **22A**, **7A**, **19A**, and **6A** (10.1–15.0 ppm) when compared with the value for $CH_3CH{=}CH_2$ (19.4 ppm), experience a large negative γ-effect due to the (*E*)-double bond. This (*E*)-configuration has been established for **7A** by X-ray analysis [10]. The chemical shifts for CH_3–C(14) of the two ketones **20A** and **21A** (12.8 and 12.9 ppm) are again compatible only with an (*E*)-configuration, and **23A** must be (*Z*)-configurated to comply with the chemical shift of 17.6 ppm (no large negative γ-shift).

A striking feature of *Table 3* is the fact that the chemical-shift values may be grouped into C(13)=C(14) and C(14)=C(15) isomer pairs. Since there are only two independent torsion angles and one of them may assume only two values, this correspondance of the chemical shifts suggests that a symmetry relationship exists between the fragments C(13)=C(CH_3)–C(15) and C(13)–C(CH_3)=C(15) with respect to the torsion angles. This is nicely corroborated by the calculated torsion angles which allow the configurations of the 13-OH and 15-OH compounds to be easily grouped in two (*Z*)- and two (*E*)-pairs.

This concordance may reflect the ability of the allylic alcohol moiety to determine its own conformation, despite the restraining influence of the macrocycle.

Configurations at the Tertiary C-Atoms C(15) and C(13). The configurations were derived from a comparison of experimental NMR coupling constants and nuclear *Overhauser* enhancements (NOE) with the corresponding calculated dihedral angles and distances.

A 7% NOE at H–C(15) was observed upon irradiation of H–C(17) in **19A**. This value is in keeping with a force-field-derived H–H distance of 2.52 Å for **19A** and is inconsistant with the correspondingly derived H–H distance of 3.72 Å for **22A**. The 15% NOE at H–C(15) observed on irradiation of H–C(13) in **19A**, is again consistent with the 2.26 Å H–H distance derived for **19A** and incompatible with the value of 3.55 Å derived for the (15*R*)-epimer **22A**. Furthermore, the *J*(H–C(15),H–C(16)) of 12.8 and 4.5 Hz of **19A** are in agreement with the force-field-derived torsion angles of 168 and 55°, respectively, while **22A** shows unresolved coupling (< 5 Hz) between these protons, in agreement with the calculated torsion angles of 49° and −64°.

Isomer **23A** was distinguished from its hypothetical C(13) epimer **26** on the basis of its *J*(H–C(12),H–C(13)) of 10 Hz which is compatible with the force-field-derived torsion angle of −176°, rather than −56° for **26**. For **23A**, no NOE of CH_3–C(14) was observed upon irradiation of H–C(13), in agreement with the calculated CH_3–H distance of 4.02 Å. An NOE would be expected, however, for **26**, with a CH_3–H distance of 3.0 Å.

The configuration of alcohol **7A** has been determined by X-ray analysis as 13*S* (α-OH). Consequently, **6A** has (13*R*)-configuration (β-OH). There is good agreement between the theoretical and experimental parameters (see *Table 3* and *Exper. Part*).

4. Computational Methods. – Force-field calculations were carried out using the MACROMODEL molecular-modeling system [25] on a *DEC VAX 8650* running the *VMS* operating system. Low-energy conformers of structures **19A**, **6A**, **22A**, **7A**, and **23A** were modeled in order to calculate torsion angles and H–H distances for comparison with experimental chemical-shift values, ^{1}H-NMR coupling constants, and NOE-derived distances as described above. The structures were modeled from the avermectin B_{1a} aglycone X-ray coordinates [10]. Conformers were generated by rotation about the ring torsion angles between C(11) and C(17) and the three ester ring torsion angles using the MULTIC submode in MACROMODEL [26]. A 60° torsion increment and minimum and maximum closure distances of 1.0 and 4.0 Å, respectively, were used in the systematic search. The C(14)=C(15) or C(13)=C(14) bond was used to define the closure bond. All of the conformers generated by the systematic search were minimized using the modified MM2 parameter set [27]. The ring torsion angles of the lowest-energy conformer of **7A** were within 20° of the avermectin X-ray ring torsion angles.

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Experimental Part

General. See [28], except as noted below. Flash chromatography (FC): silica gel *60, Merck*, 0.040–0.063 mm, 230–400 mesh ASTM (SiO_2), according to [29]; for inner diameter (i.d.) and length of SiO_2 column, see text. Anal. pure samples were obtained, in general, after repeated FC on SiO_2; in some cases further purification was necessary with an HPLC (*Du Pont Instruments, Model 830*, UV detector; 25 cm × 23.6 mm SiO_2 column). ^{1}H-NMR spectra: in $CDCl_3$ solns.; *Bruker-WM-250* (250 MHz) or- *WM-300* (300 MHz) instrument; only the relevant signals are given. Field-desorption mass spectra (FD-MS): *Varian-MAT-CH5-DF* spectrometer.

1. *Epoxides* **8A**, **8D**, **9A**, *and* **9D**. *1.1.* To a well stirred mixture of milbemycin A_4 (**1A**; 63.5 g, 117 mmol) in CH_2Cl_2 (700 ml) and 5% aq. $NaHCO_3$ soln. (450 ml) at 5° was added, within 4 h, a soln. of 3-chloroperbenzoic acid (26.9 g, 155 mmol) in CH_2Cl_2 (200 ml). After stirring for 1 h at 5°, the mixture was poured into H_2O (500 ml) and extracted with 3 × 500 ml of CH_2Cl_2. The combined org. phases were washed with sat. aq. NaCl soln. (500 ml), dried ($MgSO_4$), and evaporated. FC (i.d. 15 cm; 50 cm of SiO_2, hexane/AcOEt 2:1) afforded **8A** (50.5 g, 77%). For spectral data, see [8a].

To a soln. of **8A** (50.5 g, 90 mmol) in DMF (80 ml) were added imidazole (7.4 g, 108 mmol) and (*t*-Bu)Me_2SiCl (14.9 g, 99 mmol). After stirring for 4 h at r.t., the mixture was poured into H_2O (500 ml) and extracted with

3 × 500 ml of Et_2O. The org. extracts were washed with H_2O (250 ml) and sat. aq. NaCl soln. (250 ml), dried ($MgSO_4$), and evaporated. FC (i.d. 15 cm; 50 cm of SiO_2, hexane/AcOEt 6:1) afforded *(14S,15R)-5-O-[(*tert*-butyl)dimethylsilyl]-14,15-epoxy-14,15-dihydromilbemycin* A_4 (**9A**; 52.7 g, 87%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.11 (*s*, Me_2Si); 0.80 (*d*, *J* = 6, 3 H–C(30)); 0.92 (*s*, (*t*-Bu)Si); 0.97 (*t*, *J* = 7.5, 3 H–C(32)); 0.98 (*d*, *J* = 7, 3 H–C(28)); 1.23 (*s*, 3 H–C(29)); 1.79 (br. *s*, 3 H–C(26)); 2.38 (*m*, H–C(12)); 2.58 (*d*, *J* = 10, H–C(15)); 3.05 (*dt*, J_d = 2, 5, J_t = 9, H–C(25)); 3.38 (*m*, H–C(2)); 3.52 (*s*, OH); 3.72 (br. *t*, *J* = 12, H–C(17)); 3.82 (*d*, *J* = 6, H–C(6)); 4.41 (*m*, H–C(5)); 4.60 (*dd*, *J* = 15, 2, H–C(27)); 4.70 (*dd*, *J* = 15, 2, H–C(27)); 5.28 (*m* (sym. 7-line system), H–C(19)); 5.35 (br. *s*, H–C(3)); 5.43 (*dd*, *J* = 15, 10, H–C(11)); 5.75 (*dt*, J_d = 11, J_t = 2.5, H–C(9)); 5.88 (*dd*, *J* = 15, 11, H–C(10)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

1.2. To a stirred mixture of milbemycin **1D** (40.0 g, 71.9 mmol) and NaOAc (14.4 g, 180 mmol) in CH_2Cl_2 (800 ml) was added 3-chloroperbenzoic acid (17.6 g, 86 mmol). The mixture was stirred for 4 h at r.t. under Ar, quenched by the addition of 400 ml of 10% aq. $Na_2S_2O_5$ soln., and then extracted with 3 × 250 ml of CH_2Cl_2. The combined org. phases were washed with sat. aq. $NaHCO_3$ (400 ml) and sat. aq. NaCl soln. (400 ml) dried ($MgSO_4$), and evaporated: 40.5 g of crude **8D**.

Crude **8D** (40.5 g) was treated as described in *1.1* with imidazole (19.3 g, 283 mmol) in DMF (81 ml) and (*t*-Bu)Me_2Si (21.3 g, 141 mmol), for 2 h at r.t. Workup (pouring into H_2O (800 ml)) and FC afforded *(14S,15R)-5-O-[(*tert*-butyl)dimethylsilyl]-14,15-epoxy-14,15-dihydromilbemycin D* (**9D**). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.09 (*s*, Me_2Si); 0.81 (*d*, *J* = 6, 3 H–C(30)); 0.89, 1.02 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 0.93 (*s*, (*t*-BuSi)); 1.05 (*d*, *J* = 7, 3 H–C(28)); 1.24 (*s*, 3 H–C(29)); 1.80 (br. *s*, 3 H–C(26)); 2.59 (*d*, *J* = 10, H–C(15)); 3.06 (br. *d*, *J* = 10, H–C(25)); 3.38 (*m*, H–C(2)); 3.55 (*s*, OH); 3.76 (*m*, H–C(17)); 3.83 (*d*, *J* = 5, H–C(6)); 4.43 (*m*, H–C(5)); 4.60 (*dd*, *J* = 15, 2, H–C(27)); 4.73 (*dd*, *J* = 15, 2, H–C(27)); 5.26 (*m*, H–C(19)); 5.36 (br. *s*, H–C(3)); 5.44 (*dd*, *J* = 14.5, 10, H–C(11)); 5.76 (br. *d*, *J* = 11, H–C(9)); 5.90 (*dd*, *J* = 14.5, 11, H–C(10)). MS: 687 (18), 686 (36, $M^{+\cdot}$, $C_{39}H_{62}OSi$), 668 (10), 629 (10), 611 (32), 593 (9), 444 (56), 426 (16), 372 (10), 331 (12), 295 (24), 225 (41), 209 (62), 181 (71), 150 (35), 122 (22), 121 (25), 109 (30), 107 (32), 97 (57), *95* (100), 74 (72), 73 (84), 71 (65), 55 (73).

2. *Allylic Alcohols* **10A**, **10D**, **19A**, *and* **19D**. *2.1.* To a stirred soln. of **9A** (10.1 g, 15.0 mmol) and 2,6-lutidine (4.40 ml, 37.5 mmol) in Et_2O (120 ml) and CH_2Cl_2 (12 ml) was added at r.t., within 10 min, 9-BBN triflate (66 ml of a 0.5M soln. in hexane, 33.0 mmol). After stirring for 1 h at r.t. under Ar, the soln. was treated at 0° with H_2O (37.5 ml), 2N NaOH (33.0 ml), and 30% aq. H_2O_2 soln. (75 ml). The resulting mixture was stirred for 2 h at r.t., then poured into H_2O (150 ml), and extracted with 3 × 250 ml of Et_2O. The combined org. phases were washed with sat. aq. $NaHCO_3$ (250 ml) and sat. aq. NaCl soln. (250 ml), dried ($MgSO_4$), and evaporated. FC (i.d. 6.5 cm; 50 cm of SiO_2, hexane/AcOEt 4:1) afforded *(13E,15S)-5-O-[(*tert*-butyl)dimethylsilyl]-13,14-didehydro-14,15-dihydro-15-hydroxymilbemycin* A_4 (**10A**; 9.30 g, 92%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.11 (*s*, Me_2Si); 0.80 (*d*, *J* = 6, 3 H–C(30)); 0.92 (*s*, (*t*-Bu)Si); 0.97 (*t*, *J* = 7.5, 3 H–C(32)); 1.06 (*d*, *J* = 7, 3 H–C(28)); 1.59 (br. *s*, 3 H–C(29)); 1.77 (br. *s*, 3 H–C(26)); 2.97 (*dt*, J_d = 2.5, J_t = 10, H–C(25)); 3.06 (*m*, H–C(12)); 3.33 (*m*, H–C(2), H–C(17)); 3.86 (*d*, *J* = 6, H–C(6)); 3.96 (*s*, OH)); 4.05 (*dt*, J_d = 10, J_t = 3, H–C(15)); 4.41 (br. *d*, *J* = 6, H–C(5)); 4.53 (*dd*, *J* = 15, 2.5, H–C(27)); 4.65 (*dd*, *J* = 15, 2.5, H–C(27)); 4.85 (*m* (sym. 7-line system), H–C(19)); 5.12 (*d*, *J* = 9, H–C(13)); 5.20 (*dd*, *J* = 15, 10, H–C(11)); 5.32 (br. *s*, H–C(3)); 5.64 (*dt*, J_d = 11, J_t = 2, H–C(9)); 5.78 (*dd*, *J* = 15, 11, H–C(10)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

To a stirred soln. of Et_3Al (21.9 ml, 160 mmol) in THF (50 ml) at −78° was added a 2M soln. of HN_3 [30] in Et_2O (48.1 ml, 96.2 mmol). The mixture was allowed to warm to 0° and then treated with a soln. of **9D** (22.0 g, 32.0 mmol) in THF (30 ml). After heating at reflux for 24 h, the mixture was poured into Et_2O (500 ml), then *Celite* (50 g) and a sat. aq. potassium sodium tartrate soln. (30 ml) were added. After stirring for 1 h, the mixture was filtered, dried ($MgSO_4$), and evaporated. FC (i.d. 5 cm; 40 cm SiO_2, hexane/AcOEt 4:1) afforded **9D** (5.9 g, conversion 73%) and *(13E,15S)-5-O-[(*tert*-butyl)dimethylsilyl]-13,14-didehydro-14,15-dihydro-15-hydroxymilbemycin* A_4 (**10D**; 9.4 g, 59% based on converted **9D**). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.14 (*s*, MeSi); 0.80 (*d*, *J* = 6, 3 H–C(30)); 0.90, 1.02 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 1.07 (*d*, *J* = 7, 3 H–C(28)); 1.60 (br. *s*, 3 H–C(29)); 1.79 (br. *s*, 3 H–C(26)); 3.02 (br. *d*, *J* = 9, H–C(25)); 3.08 (*m*, H–C(12)); 3.29–3.46 (*m*, H–C(2), H–C(17)); 3.87 (*d*, *J* = 6, H–C(6)); 3.95 (*s*, OH); 4.08 (br. *dd*, *J* = 11, 4, H–C(15)); 4.43 (br. *d*, *J* = 6, H–C(15)); 4.54 (*dd*, *J* = 15, 2, H–C(27)); 4.68 (*dd*, *J* = 15, 2, H–C(27)); 4.86 (*m* (sym. 7-line system), H–C(19)); 5.13 (*d*, *J* = 10, H–C(13)); 5.21 (*dd*, *J* = 14.5, 10.5, H–C(11)); 5.33 (br. *s*, H–C(3)); 5.66 (br. *d*, *J* = 11, H–C(9)); 5.78 (*dd*, *J* = 14.5, 11, H–C(10)). MS: 687 (20), 686 (38, $M^{+\cdot}$, $C_{39}H_{62}OSi$), 643 (4), 611 (17), 593 (4), 455 (6), 444 (13), 426 (44), 408 (12), 387 (8), 372 (16), 330 (13), 321 (18), 303 (10), 275 (11), 264 (22), 225 (24), 209 (78), *181* (100), 147 (30), 97 (50), 95 (80), 74 (54), 73 (62), 69 (62), 55 (54).

2.2. A soln. of **10A** (91 mg, 0.135 mmol) in 1% TsOH in MeOH (1 ml) was stirred at r.t. for 2 h, then poured into 5% aq. $NaHCO_3$ soln. and extracted with Et_2O. The org. phase was dried and evaporated. FC (SiO_2, hexane/AcOEt 1:4) afforded *(13E,15S)-13,14-didehydro-14,15-dihydro-15-hydroxymilbemycin* A_4 (**19A**; 70 mg,

93%). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.84 (*d*, *J* = 6, 3 H–C(30)); 0.99 (*t*, *J* = 7, 3 H–C(32)); 1.09 (*d*, *J* = 7, 3 H–C(28)); 1.58 (*s*, 3 H–C(29)); 1.88 (*s*, 3 H–C(26)); 1.98 (br. *t*, *J* = 10, H–C(25)); 2.10 (*m*, H–C(12)); 2.28 (*m*, H–C(2)); 2.36 (br. *t*, *J* = 9, H–C(17)); 2.81 (*s*, OH); 4.05 (*d*, *J* = 6, H–C(6)); 4.09 (*m*, H–C(15)); 4.33 (*m*, H–C(5)); 4.69 (br. *d*, *J* = 14, H–C(27)); 4.75 (br. *d*, *J* = 14, H–C(27)); 4.92 (*m*, H–C(19)); 5.18 (br. *d*, *J* = 11, H–C(13)); 5.27 (*dd*, *J* = 14, 11, H–C(11)); 5.47 (br. *s*, H–C(3)); 5.73 (br. *d*, *J* = 12, H–C(9)); 5.83 (*dd*, *J* = 14, 12, H–C(10)). FD-MS: 558 ($M^{+\cdot}$, $C_{32}H_{46}O_8$).

A soln. of **10D** (30 mg, 0.044 mmol) in 1% TsOH in MeOH (1 ml) was treated as described above affording *(13E,15S)-13,14-didehydro-14,15-dihydro-15-hydroxymilbemycin D* (**19D**; 21 mg, 83%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80 (*d*, *J* = 6, 3 H–C(30)); 0.89, 1.03, 1.07 (3*d*, *J* = 7, 3 H–C(28), 3 H–C(32), 3 H–C(33)); 1.59 (*d*, *J* = 1, 3 H–C(29)); 1.88 (*t*, *J* = 2, 3 H–C(26)); 3.02 (br. *d*, *J* = 8, H–C(25)); 3.09 (*m*, H–C(12)); 3.26 (*m*, H–C(2)); 3.38 (br. *t*, *J* = 10, H–C(17)); 3.77 (*s*, OH); 4.02 (*d*, *J* = 6, H–C(6)); 4.07 (*dd*, *J* = 11, 5, H–C(15)); 4.30 (*m*, H–C(5)); 4.67 (*dd*, *J* = 15, 2, H–C(27)); 4.72 (*dd*, *J* = 15, 2, H–C(27)); 4.87 (*m*, H–C(19)); 5.13 (*dd*, *J* = 9, 1, H–C(13)); 5.23 (*dd*, *J* = 14, 10 H–C(11)); 5.46 (*m*, H–C(2)); 5.72 (*dt*, J_d = 11, J_t = 2, H–C(9)); 5.80 (*dd*, *J* = 14, 11, H–C(10)). MS: 572 (10, $M^{+\cdot}$, $C_{33}H_{48}O_8$), 444 (14), 426 (24), 330 (11), 264 (15), 209 (51), 181 (37), 151 (29), 123 (23), 111 (28), 107 (26), 97 (34), 95 (87), 83 (46), 81 (22), 69 (44), 67 (32), 59 (47), 55 (69), *43* (100), 41 (53).

3. *Allylic Alcohols* **6A**, **6D**, **11A**, *and* **11D**. *3.1.* To a soln. of **10A** (9.20 g, 13.67 mmol) in DMF (40 ml) was added poly(4-vinylpyridinium dichromate) (PVPDC; 5.70 g, 13.67 mmol). After stirring for 5 h at 70°, Et_2O (200 ml) was added, the mixture filtered over *Celite*, and the filter cake washed with 3 × 100 ml of Et_2O. The filtrate was washed with 1N HCl (200 ml), sat. aq. $NaHCO_3$ (200 ml) and sat. aq. NaCl soln. (200 ml), dried ($MgSO_4$), and evaporated. FC (i.d. 5 cm; 50 cm SiO_2, hexane/AcOEt 4:1) afforded *5-O-[(*tert*-butyl)dimethylsilyl]-13β-hydroxymilbemycin* A_4 (**11A**; 7.41 g, 81%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.12 (*s*, MeSi); 0.82 (*d*, *J* = 6, 3 H–C(30)); 0.92 (*s*, (*t*-Bu)Si); 0.98 (*t*, *J* = 7.5, 3 H–C(32)); 1.12 (*d*, *J* = 7, 3 H–C(28)); 1.59 (br. *s*, 3 H–C(29)); 1.79 (br. *s*, H–C(26)); 3.06 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.36 (*m*, H–C(2)); 3.56 (*m*, H–C(17)); 3.72 (*dd*, *J* = 10, 2.5, H–C(13)); 3.81 (*d*, *J* = 6, H–C(6)); 4.04 (*s*, OH); 4.42 (*m*, H–C(5)); 4.58 (*dd*, *J* = 15, 2, H–C(27)); 4.68 (*dd*, *J* = 15, 2, H–C(27)); 5.18–5.37 (*m*, H–C(11), H–C(15), H–C(19)); 5.31 (br. *s*, H–C(3)); 5.68–5.85 (*m*, H–C(9), H–C(10)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

A soln. of **10D** (500 mg, 0.728 mmol) in DMF (3 ml) was treated with pyridinium dichromate (PDC; 140 mg, 372 mmol). After stirring for 30 min at r.t., i-PrOH (1.0 ml) was added and the mixture poured into 50 ml of Et_2O. SiO_2 (1.0 g) and *Celite* (5 g) were added. After stirring for 15 min, the mixture was filtered and evaporated. FC (100 g of SiO_2) afforded **10D** (60 mg, 12%) and *5-O-[(*tert*-butyl)dimethylsilyl]-13β-hydroxymilbemycin D* (**11D**; 304 mg, 61%). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.14 (*s*, MeSi); 0.82 (*d*, *J* = 6, 3 H–C(30)); 0.88, 1.04 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 0.95 (*s*, (*t*-Bu)Si); 1.15 (*d*, *J* = 6.5, 3 H–C(28)); 1.60 (br. *s*, 3 H–C(29)); 1.80 (br. *s*, 3 H–C(26)); 3.07 (br. *d*, *J* = 9, H–C(25)); 3.36 (*m*, H–C(2)); 3.59 (*m*, H–C(17)); 3.72 (*d*, *J* = 10, H–C(13)); 3.82 (*d*, *J* = 6, H–C(6)); 4.03 (*s*, OH); 4.45 (*m*, H–C(5)); 4.60 (br. *d*, *J* = 15, H–C(27)); 4.69 (br. *d*, *J* = 15, H–C(27)); 5.14–5.43 (*m*, H–C(11), H–C(15), H–C(19)); 5.33 (br. *s*, H–C(3)); 5.69–5.87 (*m*, H–C(9), H–C(10)). FD-MS: 686 ($M^{+\cdot}$, $C_{39}H_{62}O_8Si$).

3.2. A soln. of **11A** (27 mg, 0.040 mmol) in 40% aq. HF soln./MeCN 5:95 (1 ml) was stirred at r.t. for 1 h, then poured into sat. aq. $NaHCO_3$ soln. (50 ml) and extracted with 3 × 50 ml of Et_2O. The combined org. phases were washed with sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. FC (SiO_2, hexane/AcOEt 1:1) afforded *13β-hydroxymilbemycin* A_4 (**6A**; 22 mg, 98%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81 (*d*, *J* = 6, 3 H–C(30)); 0.98 (*t*, *J* = 7.5, 3 H–C(32)); 1.12 (*d*, *J* = 7, 3 H–C(28)); 1.57 (br. *s*, 3 H–C(29)); 1.87 (br. *s*, 3 H–C(26)); 3.05 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.25 (*m*, H–C(2)); 3.56 (*m*, H–C(17)); 3.71 (*dd*, *J* = 10, 3, H–C(13)); 3.95 (*d*, *J* = 6, H–C(6)); 4.02 (*s*, OH); 4.28 (br. *t*, *J* = 6, H–C(5)); 4.65 (*d*, *J* = 15, H–C(27)); 4.71 (*d*, *J* = 15, H–C(27)); 5.23 (br. *t*, *J* = 8, H–C(15)); 5.28–5.42 (*m*, H–C(11), H–C(19)); 5.70–5.81 (*m*, H–C(9), H–C(10)). FD-MS: 558 ($M^{+\cdot}$, $C_{32}H_{46}O_8$).

Deprotection of **11D** (105 mg, 0.153 mmol) in 1% TsOH in MeOH (1 ml) as described in *2.2* gave, after FC (SiO_2, acetone/CH_2Cl_2 1:4), *13β-hydroxymilbemycin D* (**6D**; 73 mg, 83%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81 (*d*, *J* = 6, 3 H–C(30)); 0.87, 1.04 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 1.13 (*d*, *J* = 6, 3 H–C(28)); 1.58 (*s*, 3 H–C(29)); 1.87 (*t*, *J* = 1.5, 3 H–C(26)); 3.07 (*dd*, *J* = 10, 2, H–C(25)); 3.27 (*m*, H–C(2)); 3.61 (*m*, H–C(17)); 3.71 (*d*, *J* = 10, H–C(13)); 3.95 (*d*, *J* = 6, H–C(6)); 4.00 (*s*, OH); 4.29 (*m*, H–C(5)); 4.68 (br. *s*, 2H–C(27)); 5.22 (*m*, H–C(15)); 5.28–5.39 (*m*, H–C(10), H–C(19)); 5.41 (*d*, *J* = 1, H–C(3)); 5.77–5.80 (*m*, H–C(9), H–C(10)). MS: 572 (4, $M^{+\cdot}$, $C_{33}H_{48}O_8$), 554 (9), 294 (16), 293 (77), 261 (11), 221 (16), 209 (22), 181 (46), 179 (45), 157 (33), 152 (36), 151 (38), 139 (28), 137 (78), 123 (22), 121 (20), 111 (26), 109 (29), 97 (60), 96 (22), 95 (98), 94 (20), 93 (36), 83 (44), 81 (39), 79 (37), 69 (50), *55* (100).

4. *5-O-[(*tert*-Butyl)dimethylsilyl]-14,15-epoxy-14,15-dihydro-13β-hydroxymilbemycin D* (**12D**). A soln. of **10D** (158 mg, 0.23 mmol) and PDC (500 mg, 1.329 mmol) in DMF (1 ml) was stirred at r.t. for 1 h. CH_2Cl_2 (20 ml)

was then added and the mixture filtered through SiO_2, the latter washed with acetone/CH_2Cl_2 1:9, and the solvent evaporated. FC (SiO_2, AcOEt/hexane 1:4) afforded **12D** (64 mg, 40%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.14 (*s*, MeSi); 0.81 (*d*, *J* = 6, 3 H–C(30)); 0.88, 1.05 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 0.93 (*s*, (*t*-Bu)Si); 1.12 (*d*, *J* = 7, 3 H–C(28)); 1.27 (*s*, 3 H–C(29)); 1.80 (*d*, *J* = 1, H–C(26)); 2.38 (*m*, H–C(12)); 2.78 (*dd*, *J* = 10, 1.5, H–C(15)); 2.83 (*d*, *J* = 10, H–C(13)); 3.06 (br. *d*, *J* = 7, H–C(25)); 3.39 (*m*, H–C(2)); 3.35 (*s*, OH); 3.76 (*m*, H–C(17)); 3.83 (*d*, *J* = 6, H–C(6)); 4.42 (*m*, H–C(5)); 4.62 (*dd*, *J* = 15, 2, H–C(27)); 4.72 (*dd*, *J* = 15, 2, H–C(27)); 5.24 (*m*, H–C(19)); 5.38 (*m*, H–C(3)); 5.38 (*dd*, *J* = 15, 10, H–C(11)); 5.75 (br. *t*, *J* = 11, H–C(9)); 5.96 (*dd*, *J* = 15, 11, H–C(10)). MS: 702 (3, $M^{+\cdot}$, $C_{39}H_{62}O_9Si$), 460 (23), 317 (12), 309 (13), 226 (10), 225 (45), 209 (56), 181 (74), 163 (22), 157 (27), 151 (70), 150 (43), 139 (35), 137 (20), 123 (35), 121 (33), 111 (32), 109 (32), 107 (29), 97 (68), 95 (97), 93 (49), 75 (94), *73* (100), 69 (61), 67 (38), 57 (32), 55 (69), 43 (69), 41 (38).

5. *Enones* **14A**, **14D**, **21A**, *and* **21D**. *5.1.* To a stirred soln. of oxalyl chloride (3.60 ml, 39.9 mmol) in CH_2Cl_2 (150 ml) at −60° was added a soln. of DMSO (5.70 ml, 79.0 mmol) in CH_2Cl_2 (50 ml) within 10 min. Then, a soln. of **11A** (25.60 g, 38.0 mmol) in CH_2Cl_2 (75 ml) was added within 30 min. After stirring for 30 min at −60°, the mixture was treated with Et_3N (16.7 ml, 119.7 mmol), stirred for 5 min at −60°, allowed to warm to 0°, poured into 0.5N HCl (250 ml), and extracted with 3 × 250 ml of Et_2O. The combined org. phases were washed with H_2O (250 ml) and sat. aq. NaCl soln. (250 ml), dried ($MgSO_4$), and evaporated. FC (i.d. 6.5 cm; 50 cm SiO_2, hexane/Et_2O 3:1) afforded *5-O-[(*tert*-butyl)dimethylsilyl]-13-oxomilbemycin* A_4 (**14A**; 25.0 g, 98%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.12 (*s*, MeSi); 0.82 (*d*, *J* = 6, 3 H–C(30)); 0.91 (*s*, (*t*-Bu)Si); 0.94 (*t*, *J* = 7.5, 3 H–C(32)); 1.14 (*d*, *J* = 7, 3 H–C(28)); 1.78 (*s*, 3 H–C(26)); 1.83 (*s*, 3 H–C(29)); 3.03 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.39 (*m*, H–C(2)); 3.50–3.67 (*m*, H–C(12), H–C(17)); 3.82 (*d*, *J* = 6, H–C(6)); 4.35 (*s*, OH); 4.43 (*m*, H–C(5)); 4.59 (*dd*, *J* = 2, 15, H–C(27)); 4.72 (*dd*, *J* = 2, 15, H–C(27)); 5.25–5.44 (*m*, H–C(11), H–C(19)); 5.30 (br. *s*, H–C(3)); 5.80 (*dt*, J_d = 11, J_t = 2.5, H–C(9)); 6.03 (*dd*, *J* = 11, 15, H–C(10)); 6.21 (br. *t*, *J* = 8, H–C(15)). FD-MS: 670 ($M^{+\cdot}$, $C_{38}H_{58}O_8Si$).

Oxidation as above, with oxalyl chloride (280 µl, 3.258 mmol) in CH_2Cl_2 (5 ml), DMSO (460 µl, 6.476 mmol; neat, within 5 min), and **11D** (1.112 g, 1.619 mmol) in CH_2Cl_2 (5 ml; within 5 min). Workup as above, with Et_3N (2.30 ml, 16.50 mmol), pouring into H_2O (50 ml), and extraction with 3 × 100 ml of Et_2O. FC (i.d. 5 cm; 20 cm SiO_2, hexane/Et_2O 2:1) afforded *5-O-[(*tert*-butyl)dimethylsilyl]-13-oxomilbemycin D* (**14D**; 991 mg, 90%). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.12 (*s*, Me_2Si); 0.81 (*d*, *J* = 6, 3 H–C(30)); 0.86, 0.99 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 0.95 (*s*, (*t*-Bu)Si); 1.16 (*d*, *J* = 7, 3 H–C(28)); 1.80 (br. *s*, 3 H–C(26)); 1.83 (br. *s*, 3 H–C(29)); 3.06 (*d*, *J* = 9, H–C(25)); 3.41 (*m*, H–C(2)); 3.51–3.69 (*m*, H–C(12), H–C(17)); 3.83 (*d*, *J* = 5.5, H–C(6)); 4.36 (*s*, OH); 4.44 (*m*, H–C(5)); 4.61 (*dd*, *J* = 15, 2, H–C(27)); 4.73 (*dd*, *J* = 15, 2, H–C(27)); 5.30 (*m*, H–C(19)); 5.33 (br. *s*, H–C(3)); 5.40 (*dd*, *J* = 15, 11, C(11)); 5.81 (*dt*, J_d = 11, J_t = 2, H–C(9)); 6.04 (*dd*, *J* = 15, 11, H–C(10)); 6.22 (br. *t*, *J* = 8, H–C(15)). FD-MS: 684 ($M^{+\cdot}$, $C_{39}H_{60}O_8Si$).

5.2. A soln. of **14A** (54 mg, 0.0805 mmol) in 40% aq. HF soln./MeCN 5:95 (1 ml) was stirred at r.t. for 45 min. Workup as in *3.2* and FC (SiO_2, hexane/AcOEt 2:1) afforded *13-oxomilbemycin* A_4 (**21A**; 35 mg, 78%). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.83 (*d*, *J* = 7, 3 H–C(30)); 0.93 (*t*, *J* = 7.5, 3 H–C(32)); 1.16 (*d*, *J* = 7, 3 H–C(28)); 1.82 (br. *s*, 3 H–C(26)); 1.87 (br. *s*, 3 H–C(29)); 3.03 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.30 (*m*, H–C(2)); 3.51–3.65 (*m*, H–C(12), H–C(17)); 4.94 (*d*, *J* = 7.5, H–C(6)); 4.22 (*s*, OH); 4.29 (br. *t*, *J* = 7.5, H–C(5)); 4.67 (*dd*, *J* = 2, 15, H–C(27)); 4.73 (*dd*, *J* = 2, 15, H–C(27)); 5.28–5.48 (*m*, H–C(11), H–C(19)); 5.38 (br. *s*, H–C(3)); 5.83 (*dt*, J_d = 11, J_t = 2, H–C(9)); 6.03 (*dd*, *J* = 11, 15, H–C(10)); 6.21 (br. *t*, *J* = 8, H–C(15)). MS: 557 (4), 556 (14, $M^{+\cdot}$, $C_{32}H_{44}O_8$), 538 (2), 528 (16), 295 (72), 277 (10), 261 (24), 237 (14), 195 (70), *167* (100), 143 (94), 125 (32), 97 (40), 95 (68), 83 (54), 69 (28), 55 (78), 41 (32).

To a soln. of **14D** (53 mg, 0.077 mmol) in MeOH (1 ml) was added a 2% soln. (1 ml) of TsOH in MeOH. After stirring for 80 min at r.t., the mixture was poured into sat. aq. $NaHCO_3$ soln. (50 ml) and extracted with 3 × 50 ml of Et_2O. The combined org. phases were washed with sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. FC (SiO_2, hexane/AcOEt 1:1) afforded *13-oxomilbemycin D* (**21D**; 34 mg, 77%). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.83 (*d*, *J* = 6, 3 H–C(30)); 0.86, 0,99 (2*d*, *J* = 7, 3 H–C(32), 3 H–C(33)); 1.18 (*d*, *J* = 6, 3 H–C(28)); 1.83 (br. *s*, 3 H–C(26)); 1.88 (br. *s*, 3 H–C(29)); 3.05 (br. *d*, *J* = 9, H–C(25)); 3.32 (*m*, H–C(2)); 3.55–3.74 (*m*, H–C(12), H–C(17)); 3.99 (*d*, *J* = 6.5, H–C(6)); 4.24 (*s*, OH); 4.31 (br. *t*, *J* = 6.5, H–C(5)); 4.70 (*dd*, *J* = 15, 2, H–C(27)); 4.77 (*dd*, *J* = 15, 2, H–C(27)); 5.24–5.50 (*m*, H–C(11), H–C(19)); 5.42 (br. *s*, H–C(3)); 5.86 (*dt*, J_d = 11, J_t = 2, H–C(9)); 6.04 (*dd*, *J* = 14.5, 11, H–C(10)); 6.24 (br. *t*, *J* = 8.5, H–C(15)). FD-MS: 570 ($M^{+\cdot}$, $C_{33}H_{46}O_8$).

6. *Allylic Alcohols* **15A**, **15D**, *and* **7A**. *6.1.* To a stirred soln. of **14A** (392 mg, 0.584 mmol) in EtOH (3 ml) was added $NaBH_4$ (22 mg, 0.582 mmol). After stirring for 15 min at r.t., the reaction was quenched with sat. aq. NH_4Cl soln. (2 ml). The mixture was poured into sat. aq. NaCl soln. (50 ml) and extracted with 3 × 50 ml of Et_2O. The combined org. phases were dried ($MgSO_4$) and evaporated. FC (SiO_2, hexane/AcOEt 6:1) afforded epimer **11A**

(22 mg, 6%) and *5-O-[(tert-butyl)dimethylsilyl]-13α-hydroxymilbemycin A_4* (**15A**; 23 mg, 82%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.13 (*s*, Me_2Si); 0.82 (*d*, *J* = 7, 3 H–C(30)); 0.92 (*s*, (*t*-Bu)Si); 0.99 (*t*, *J* = 7.5 3 H–C(32)); 1.16 (*d*, *J* = 7, 3 H–C(28)); 1.54 (br. *s*, 3 H–C(29)); 1.70 (br. *s*, 3 H–C(26)); 3.07 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.65 (*m*, H–C(17)); 3.81 (*d*, *J* = 6, H–C(6)); 4.00 (br. *s*, H–C(13)); 4.13 (*s*, OH); 4.43 (*m*, H–C(5)); 4.57 (*d*, *J* = 15, H–C(27)); 4.67 (*d*, *J* = 15, H–C(27)); 5.24–5.42 (*m*, H–C(15), H–C(19)); 5.30 (br. *s*, H–C(3)); 5.59–5.82 (*m*, H–C(9), H–C(10), H–C(11)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

A soln. of **14D** (8 mg, 11.7 μmol) in EtOH (1 ml) was treated with a soln. of $NaBH_4$ (1 mg) in EtOH (0.1 ml). After 5 min, the reaction was quenched with sat. aq. NH_4Cl soln. and diluted with Et_2O (8 ml). The suspension was filtered through a plug of SiO_2, and FC (SiO_2, hexane/AcOEt 1:4) gave **15D** (4 mg, 50%). This material was identical to an authentic sample prepared according to [7] (TLC, ^{1}H-NMR (300 MHz)).

6.2. Deprotection of **15A** (25 mg, 0.037 mmol) as described in *3.2* gave, after FC (SiO_2, hexane/AcOEt 3:2), *13α-hydroxymilbemycin A_4* (**7A**; 18 mg, 87%). ^{1}H-NMR (250 MHz, $CDCl_3$): 0.84 (*d*, *J* = 6, 3 H–C(30)); 1.01 (*t*, *J* = 7.5, 3 H–C(32)); 1.18 (*d*, *J* = 7, 3 H–C(28)); 1.54 (br. *s*, 3 H–C(29)); 1.88 (br. *s*, 3 H–C(26)); 3.08 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.27 (*m*, H–C(2)); 3.67 (*m*, H–C(17)); 3.97 (*d*, *J* = 6, H–C(6)); 4.02 (br. *s*, H–C(13)); 4.11 (*s*, OH); 4.31 (br. *t*, *J* = 7.5, H–C(5)); 4.65 (*d*, *J* = 15, H–C(27)); 4.73 (*d*, *J* = 15, H–C(27)); 5.29–5.46 (*m*, H–C(15), H–C(19)); 5.40 (br. *s*, H–C(3)); 5.66–5.85 (*m*, H–C(9), H–C(10), H–C(11)). MS: 558 (4, $M^{+\cdot}$, $C_{32}H_{46}O_8$), 540 (10), 430 (6), 412 (4), *279* (100), 261 (18), 221 (8), 195 (20), 167 (60), 151 (66), 143 (56), 125 (26), 97 (42), 95 (82), 83 (50), 67 (30), 55 (76), 43 (48).

7. *Enones* **13A** *and* **20A**. *7.1.* As described for **14A** (*5.1*), with oxalyl chloride (155 μl, 1.714 mmol) in CH_2Cl_2 (6 ml), DMSO (203 μl, 2.856 mmol) in CH_2Cl_2 (2 ml; within 5 min), and **10A** (961 mg, 1.428 mmol) in CH_2Cl_2 (3 ml; within 12 min). Workup with Et_3N (597 μl, 4.284 mmol: 10 min stirring), pouring into 0.5N HCl (50 ml), extraction with 3 × 100 ml of Et_2O, and washing with H_2O (100 ml) and sat. aq. NaCl soln. (100 ml). FC (i.d. 5 cm; 20 cm SiO_2, hexane/Et_2O 3:1) afforded *(13E)-5-O-[(tert-butyl)dimethylsilyl]-13,14-didehydro-14,15-dihydro-15-oxomilbemycin A_4* (**13A**; 633 mg, 66%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.12 (*s*, Me_2Si); 0.80 (*d*, *J* = 6.5, 3 H–C(30)); 0.90 (*s*, (*t*-Bu)Si); 0.93 (*t*, *J* = 7.5, 3 H–C(32)); 1.14 (*d*, *J* = 6.5, 3 H–C(28)); 1.75 (br. *s*, 3 H–C(26)); 1.82 (br. *s*, 3 H–C(29)); 2.70 (*dd*, *J* = 7, 13, H–C(16)); 3.00 (*dt*, J_d = 2.5, J_t = 10, H–C(25)); 3.05 (*dd*, *J* = 4.5, 13, H–C(16)); 3.22 (*m*, H–C(12)); 3.28 (*m*, H–C(2)); 3.79 (*m*, H–C(17)); 3.83 (*d*, *J* = 6, H–C(6)); 4.22 (*s*, OH); 4.41 (br. *s*, H–C(5)); 4.51 (*dd*, *J* = 2, 15, H–C(27)); 4.67 (*dd*, *J* = 2, 15, H–C(27)); 5.22 (*m*, H–C(19)); 5.24 (br. *s*, H–C(3)); 5.37 (*dd*, *J* = 10, 14.5, H–C(11)); 5.75 (*dt*, J_d = 11, J_t = 2, H–C(9)); 5.83 (*dd*, *J* = 11, 14.5, H–C(10)); 6.06 (br. *d*, *J* = 10, H–C(13)). FD-MS: 670 ($M^{+\cdot}$, $C_{38}H_{58}O_8Si$).

7.2. A soln. of **13A** (50 mg, 0.0745 mmol) in $(HF)_x$·pyridine/pyridine/THF [23] (1 ml) was stirred at r.t. for 16 h, then poured into sat. aq. $NaHCO_3$ soln. (50 ml) and extracted with 3 × 50 ml of Et_2O. The combined org. phases were washed with sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. FC (SiO_2, hexane/AcOEt 2:1) afforded *(13E)-13,14-didehydro-14,15-dihydro-15-oxomilbemycin A_4* (**20A**; 31 mg, 74%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.78 (*d*, *J* = 6.5, 3 H–C(30)); 0.92 (*t*, *J* = 7.5, 3 H–C(32)); 1.15 (*d*, *J* = 6.5, 3 H–C(28)); 1.81 (br. *s*, 3 H–C(26)); 1.84 (br. *s*, 3 H–C(29)); 2.70 (*dd*, *J* = 7, 13, H–C(16)); 3.00 (*dt*, J_d = 2.5, J_t = 10, H–C(25)); 3.07 (*dd*, *J* = 4.5, 13, H–C(16)); 3.19 (*m*, H–C(2)); 3.23 (*m*, H–C(12)); 3.80 (*m*, H–C(17)); 4.99 (*d*, *J* = 6, H–C(6)); 4.06 (*s*, OH); 4.27 (br. *t*, *J* = 6, H–C(5)); 4.61 (*dd*, *J* = 1.5, 15, H–C(27)); 4.69 (*dd*, *J* = 1.5, 15, H–C(27)); 5.23 (*m* (sym. 7-line system), H–C(19)); 5.33 (br. *s*, H–C(3)); 5.39 (*dd*, *J* = 10, 13, H–C(11)); 5.75–5.91 (*m*, H–C(9), H–C(10)); 6.07 (br. *d*, *J* = 10, H–C(13)). FD-MS: 556 ($M^{+\cdot}$, $C_{32}H_{44}O_8$).

8. *Allylic Alcohols* **16A**, **22A**, **18A**, *and* **23A**. *8.1.* As described for **15A** (*6.1*), with **13A** (716 mg, 1.067 mmol) in EtOH (10 ml) and Et_2O (25 ml), $NaBH_4$ (42 mg, 1.12 mmol), sat. aq. NH_4Cl soln. (10 ml), sat. aq. NaCl soln. (100 ml), and 3 × 100 ml of Et_2O. FC (i.d. 5 cm; 30 cm SiO_2, hexane/AcOEt 4:1) afforded **17A** (76 mg, 11%), **10A** (28 mg, 4%), and **16A** (443 mg, 62%).

(13E,15R)-5-O-[(tert-Butyl)dimethylsilyl]-13,14-didehydro-14,15-dihydro-15-hydroxymilbemycin A_4 (**16A**). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.12 (*s*, Me_2Si); 0.80 (*d*, *J* = 6, 3 H–C(30)); 0.90 (*s*, (*t*-Bu)Si); 1.02 (*t*, *J* = 7.5, 3 H–C(32)); 1.05 (*d*, *J* = 6, 3 H–C(28)); 1.53 (br. *s*, 3 H–C(29)); 1.76 (br. *s*, 3 H–C(26)); 3.03 (*dt*, J_d = 2.5, J_t = 10, H–C(25)); 3.07 (*m*, H–C(12)); 3.33 (*m*, H–C(2)); 3.69 (br. *t*, *J* = 10, H–C(17)); 3.86 (*d*, *J* = 6, H–C(6)); 4.05 (*s*, OH); 4.21 (br. *s*, H–C(13)); 4.41 (br. *d*, *J* = 6, H–C(5)); 4.52 (*dd*, *J* = 2.5, 15, H–C(27)); 4.65 (*dd*, *J* = 2.5, 15, H–C(27)); 4.83 (*m*, sym. 7-line system), H–C(19)); 5.20–5.34 (*m*, H–C(3), H–C(11), H–C(13), H–C(19)); 5.65 (*dt*, J_d = 11, J_t = 2, H–C(9)); 5.75 (*dd*, *J* = 11, 14.5, H–C(10)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

5-O-[(tert-Butyl)dimethylsilyl]-14,15-dihydro-15-oxomilbemycin A_4 (**17A**). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.10 (*s*, Me_2Si); 0.78 (*d*, *J* = 6, 3 H–C(30)); 0.84 (*d*, *J* = 7.5, 3 H–C(29)); 0.89 (*s*, (*t*-Bu)Si); 0.98 (*t*, *J* = 7.5, 3 H–C(32)); 1.00 (*d*, *J* = 6.5, 3 H–C(28)); 1.76 (br. *s*, 3 H–C(26)); 3.00 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.36 (*m*, H–C(2)); 3.79 (*d*, *J* = 6, H–C(6)); 4.08 (*m*, H–C(17)); 4.16 (*s*, OH); 4.41 (*m*, H–C(5)); 4.53 (br. *d*, *J* = 15,

H–C(27)); 4.65 (br. *d*, *J* = 15, H–C(27)); 5.30 (br. *s*, H–C(3)); 5.32–5.53 (*m*, H–C(11), H–C(15)); 5.65–5.79 (*m*, H–C(9), H–C(10)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

Deprotection of **16A** (50 mg, 0.074 mmol) in $(HF)_x$·pyridine/pyridine/THF (1 ml); 17 h and FC as described in *7.2* afforded *(13E,15R)-13,14-didehydro-14,15-dihydro-15-hydroxymilbemycin* A_4 (**22A**; 38 mg, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80 (*d*, *J* = 6, 3 H–C(30)); 1.03 (*t*, *J* = 7.5, 3 H–C(32)); 1.06 (*d*, *J* = 6, 3 H–C(28)); 1.53 (br. *s*, 3 H–C(29)); 1.86 (br. *s*, 3 H–C(26)); 3.03 (*dt*, J_d = 2.5, J_t = 10, H–C(25)); 3.08 (*m*, H–C(12)); 3.24 (*m*, H–C(2)); 3.69 (br. *t*, *J* = 10, H–C(17)); 3.86 (*s*, OH); 4.02 (*d*, *J* = 6, H–C(6)); 4.20 (br. *s*, H–C(15)); 4.28 (br. *t*, *J* = 12, H–C(5)); 4.65 (*dd*, *J* = 2, 15, H–C(27)); 4.71 (*dd*, *J* = 2, 15, H–C(27)); 4.87 (*m* (sym. 7-line system), H–C(19)); 5.26 (*d*, *J* = 10, H–C(13)); 5.30 (*dd*, *J* = 3.5, 12, H–C(11)); 5.45 (br. *s*, H–C(3)); 5.70 (*dt*, J_d = 11, J_t = 2, H–C(9)); 5.77 (*dd*, *J* = 11, 12, H–C(10)). FD-MS: 558 ($M^{+\cdot}$, $C_{32}H_{46}O_8$).

8.2. As described for **11A** (*3.1*), with **16A** (50 mg, 0.074 mmol), DMF (1 ml), PVPDC (89 mg, 0.223 mmol; 4 h stirring), Et_2O (50 ml), and 3 × 20 ml of Et_2O (washing with H_2O (50 ml) and sat. aq. NaCl soln. (50 ml)). CC (SiO_2, hexane/AcOEt 2:1) afforded *(14Z)-5-O-[(*tert*-butyl)dimethylsilyl)]-13β-hydroxymilbemycin* A_4 (**18A**; 34 mg, 68%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.15 (*s*, Me_2Si); 0.83 (*d*, *J* = 6.5, 3 H–C(30)); 0.93 (*s*, (*t*-Bu)Si); 0.95 (*t*, *J* = 7, 3 H–C(32)); 1.12 (*d*, *J* = 6.5, 3 H–C(28)); 1.76 (br. *s*, 3 H–C(29)); 1.80 (br. *s*, 3 H–C(26)); 3.02 (*dt*, J_d = 2.5, J_t = 10, H–C(25)); 3.37 (*m*, H–C(2)); 3.77 (*m*, H–C(17)); 3.81 (*d*, *J* = 6, H–C(6)); 4.20 (*dd*, *J* = 11, 3, H–C(13)); 4.45 (*m*, H–C(5)); 4.57 (*dd*, *J* = 15, 2, H–C(27)); 4.68 (*dd*, *J* = 15, 2, H–C(27)); 4.71 (*s*, OH); 5.19–5.47 (*m*, H–C(11), H–C(15), H–C(19)); 5.30 (br. *s*, H–C(3)); 5.63–5.84 (*m*, H–C(9), H–C(10)). FD-MS: 672 ($M^{+\cdot}$, $C_{38}H_{60}O_8Si$).

Deprotection of **18A** (32 mg, 0.048 mmol) in $(HF)_x$·pyridine/pyridine/THF [23] (1 ml; 17 h) as described in *7.2* and FC (SiO_2, hexane/AcOEt 1:1) afforded *(14Z)-13β-hydroxymilbemycin* A_4 (**23A**; 26 mg, 96%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80 (*d*, *J* = 6.5, 3 H–C(30)); 0.94 (*t*, *J* = 7, 3 H–C(32)); 1.11 (*d*, *J* = 6.5, 3 H–C(28)); 1.72 (br. *s*, 3 H–C(29)); 1.87 (br. *s*, 3 H–C(26)); 3.00 (*dt*, J_d = 2.5, J_t = 9.5, H–C(25)); 3.27 (*m*, H–C(2)); 3.78 (*m*, H–C(17)); 3.94 (*d*, *J* = 6, H–C(6)); 4.18 (*dd*, *J* = 10, *J* = 4, H–C(13)); 4.29 (br. *t*, *J* = 6, H–C(5)); 4.58 (*s*, OH); 4.65 (br. *d*, *J* = 15, H–C(27)); 4.71 (br. *d*, *J* = 15, H–C(27)); 5.18–5.49 (*m*, H–C(11), H–C(15), H–C(19)); 5.37 (br. *s*, H–C(3)); 5.66–5.83 (*m*, H–C(9), H–C(10)). FD-MS: 558 ($M^{+\cdot}$, $C_{32}H_{46}O_8$).

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