

# Synthetic Modifications of Ascomycin. V.\* Access to Novel Ascomycin Derivatives by Replacement of the Cyclohexylvinylidene Subunit

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**Keywords** Starting from the easily accessible 24-*O*-*tert*-butyldimethylsilyl-22(*R*)-dihydro-28-oxoascomycin, methodologies that allow replacement of the cyclohexylvinylidene moiety of ascomycin by various other substituents are described. In addition, a so far unknown reactivity of the masked tricarbonyl moiety of ascomycin towards a stabilized Wittig reagent is reported.

ascomycin  
immunosuppressiva  
aldol reaction  
oxime  
Wittig reaction  
oxidation

## INTRODUCTION

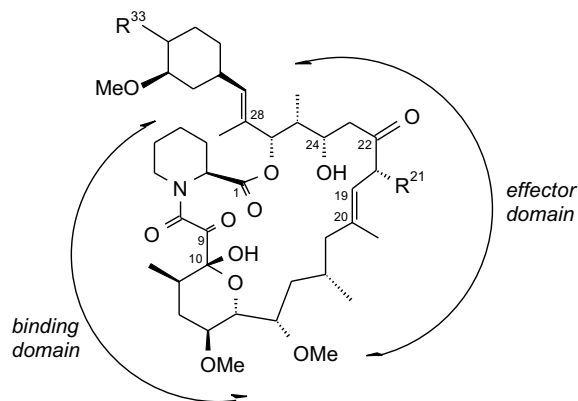
The 23-membered macrolactam ascomycin (**1**, Scheme 1), a fermentation product originally isolated from *Streptomyces hygroscopicus* var. *ascomyceticus*<sup>2</sup> for its antifungal activity, has later been shown to be a structurally closely related congener of the potent immunomodulator FK 506 (tacrolimus, **2**).<sup>3</sup> Pimecrolimus (Elidel®, SDZ ASM 981, **3**) derived from ascomycin and featuring a more lipophilic C-28 side chain has been shown to possess a high therapeutic potential for the treatment of inflammatory skin diseases. Pimecrolimus cream (1 %), which combines a skin selective, anti-inflammatory activity with a low risk of systemic side effects, has recently been launched on the market for the treatment of atopic der-

matitis.<sup>4</sup> As depicted in Scheme 1, macrolactams consist of two functional molecular domains:<sup>5</sup> a binding domain (left part of the molecule) responsible for binding to the intracellular cytosolic receptor (macrophilin) and an effector domain (right part of the molecule) interacting with the target enzyme. Consequently, only minor structural changes are tolerated within these domains without provoking a considerable loss of biological activities.<sup>3a</sup> The role of the cyclohexyl part is, however, not completely clear,<sup>6</sup> although there have been numerous reports describing modification of this part of the structure in FK 506 and its 21-ethyl analogue ascomycin.<sup>7</sup>

Previously, we reported a practical and versatile method for chemoselective removal of the cyclohexyl residue of precursor **4** leading to C-28-ketone **5**.<sup>8</sup> The

\* For Part IV see Ref. 1.

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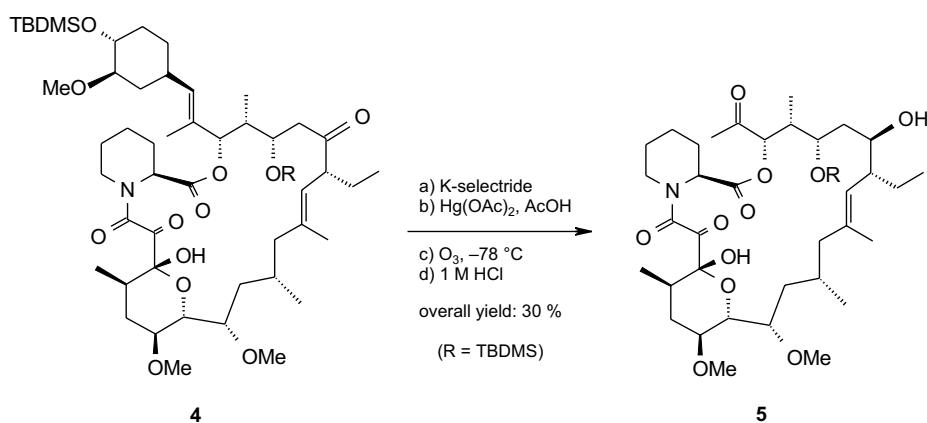


Scheme 1.

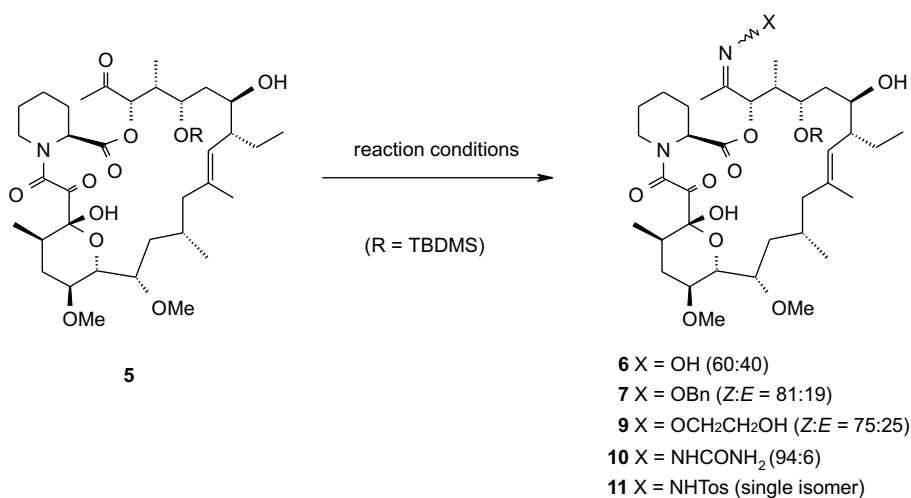
procedure is accomplished in four steps (Scheme 2). Starting from the 24,33-*O*-bis-silylated ascomycin derivative **4**, the synthesis of intermediate **5** involves protection of the C-19/C-20 double bond through reduction of the C-22-carbonyl group with K-selectride®, followed by 5-*endo*-cyclization of the resulting C-22-alcohol with the C-19/C-20 double bond using an oxymercuration reaction, ozonolysis of the exocyclic C-28/C-29 double bond and finally regeneration of the C-19/C-20 double bond by treatment with an acid. This paper provides the synthetic basis for replacements of the cyclohexyl-propenyl side chain.

## RESULTS AND DISCUSSION

Having the versatile 28-oxo-ascomycin derivative **5** in our hands, we first directed the addition of several hydroxylamine- and hydrazine nucleophiles to C-28 carbonyl group of **5** (Scheme 3). Thus, treatment of **5** with an



Scheme 2.



Reaction conditions. For **6**:  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , EtOH, r.t., 24 h, yield: 59 %; for **7**:  $\text{BnONH}_2$ , PPTS, benzene, r.t., 5 d, yield: 83 %; for **9**:  $\text{H}_2\text{NOCH}_2\text{CH}_2\text{OH}$  (**8**), PPTS, benzene, r.t., 6 d, yield: 88 %; for **10**:  $\text{H}_2\text{NCONHNH}_2 \cdot \text{HCl}$ , NaOAc, EtOH,  $\text{H}_2\text{O}$ ,  $70^\circ\text{C}$ , 48 h, yield: 51 %; for **11**:  $\text{TosNHNH}_2$ , AcOH, r.t., 25 h, yield: 53 %.

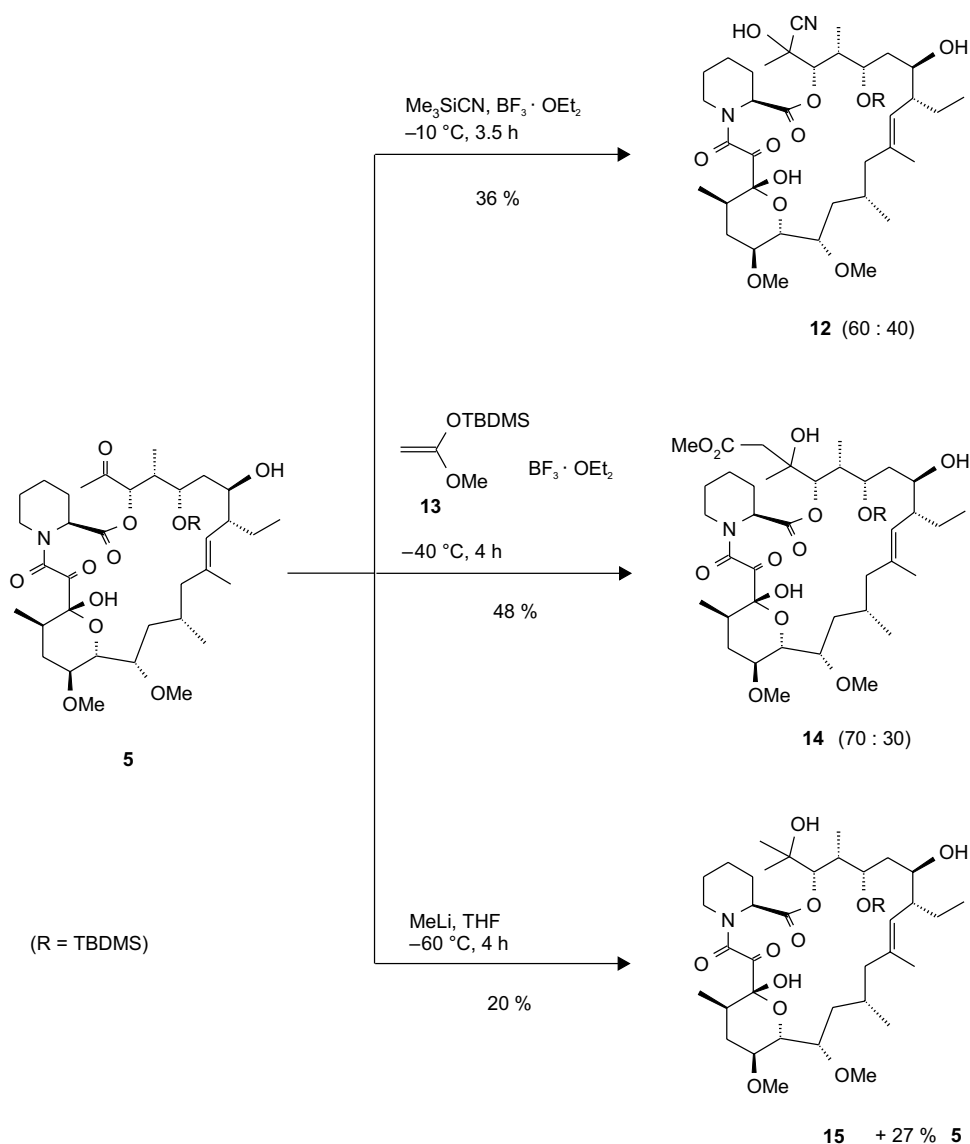
Scheme 3.

excess of hydroxylamine hydrochloride in ethanol at room temperature provided the expected oxime **6** in 59 % yield as a mixture of two geometrical isomers (60 : 40). In the presence of catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS), *O*-benzyl hydroxylamine converted ketone **5** into oxime ether **7** in a good yield (83 %) and with remarkable *Z*-selectivity (*Z*-**7** : *E*-**7** = 81:19). Analogously, the reaction of **5** with *O*-(2-hydroxyethyl)-hydroxylamine (**8**)<sup>9</sup> provided oxime ether **9** as a mixture of geometrical isomers in excellent yield (88 %; *Z*-**9** : *E*-**9** = 75 : 25). It is noteworthy that the *Z/E* ratios were deduced from the observed chemical shifts of the C=NR adjacent positions<sup>10</sup> and from NOESY experiments.

Similar results were obtained with semicarbazide hydrochloride and tosylhydrazine (Scheme 3). Thus, treatment of compound **5** with semicarbazide hydrochloride in the presence of sodium acetate at 70 °C afforded semicarbazone **10** in 51 % yield as a mixture of two iso-

mers in a 94 : 6 ratio. Preparation of tosylhydrazone **11** was achieved under standard reaction conditions, as described by Donaldson and Iida,<sup>11</sup> with tosylhydrazine in acetic acid. Notably, tosylhydrazone **11** was obtained as a single isomer. Gratifyingly, upon treatment of **5** with *N*-nucleophiles, no products reflecting C=N bond formation at C-9 could be detected as by-products, though such transformations are reported in the literature.<sup>12</sup>

Having accomplished the addition of *N*-nucleophiles on the C-28 carbonyl group of **5**, we explored the reactivity of **5** towards some *C*-nucleophiles (Scheme 4). Reaction with one of the simplest *C*-nucleophiles, *i.e.*, cyanotrimethylsilane in the presence of catalytic amounts of boron trifluoride etherate, converted **5** into an inseparable mixture of two diastereoisomeric cyanohydrins **12**, albeit in a low yield (36 %, ratio of the isomers 60 : 40). The low yield is not so surprising since it is known from the literature that the masked tricarbonyl moiety of asco-



Scheme 4.

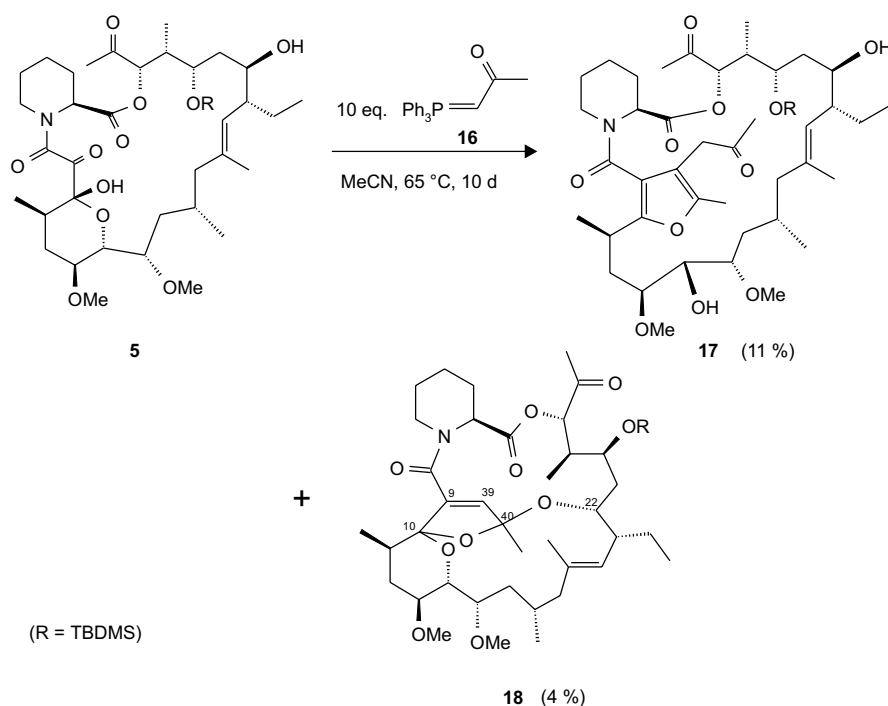
mycin is highly sensitive towards cyanide.<sup>13</sup> Similarly to the formation of **12**, the aldol type reaction of **5** with *O*-(*tert*-butyldimethylsilyl) ketene acetal **13** /  $\text{BF}_3 \cdot \text{OEt}_2$ <sup>14,15</sup> yielded the expected  $\beta$ -hydroxy ester **14** (48 %; **14a** : **14b** = 70 : 30). In contrast, employing silyl enol ethers as nucleophilic components, the expected Mukaiyama reaction failed; only the starting material could be recovered. Efforts to add organolithium reagents at the C-28 position of **5** gave only poor results. Although treatment of **5** with methyl lithium allowed isolation of the desired tertiary alcohol **15** in a low yield (20 %), no product was observed with phenyllithium and lithiated methoxyallene.<sup>16</sup> However, we had to learn that basic reaction conditions aggravate the regioselective addition of C-nucleophiles.

Attempts to establish a carbon-carbon double bond at C-28 of compound **5** *via* a Wittig or Wittig-Horner olefination reaction were unsuccessful. A variety of reaction conditions and various Wittig (or Wittig-Horner) reagents were examined, but almost no reaction took place and only the starting material could be recovered. Surprisingly, when the reaction of **5** was carried out with a large excess of stabilized Wittig reagent **16** under more forceful reaction conditions (65 °C, 10 d), we observed an unexpected reaction leading to the furano derivatives **17** (11 % yield) and **18** (4 % yield) (Scheme 5). Structure elucidations of **17** and **18** are based on <sup>1</sup>H and <sup>13</sup>C NMR spectra and are supplemented by NOE, HMBC and HSQC experiments. The resulting compound **18** possesses a furan moiety that incorporates the C-9 and C-10 atoms of the macrolide. A <sup>3</sup>J<sub>CH</sub> [C-40–O–C-22] long-range cou-

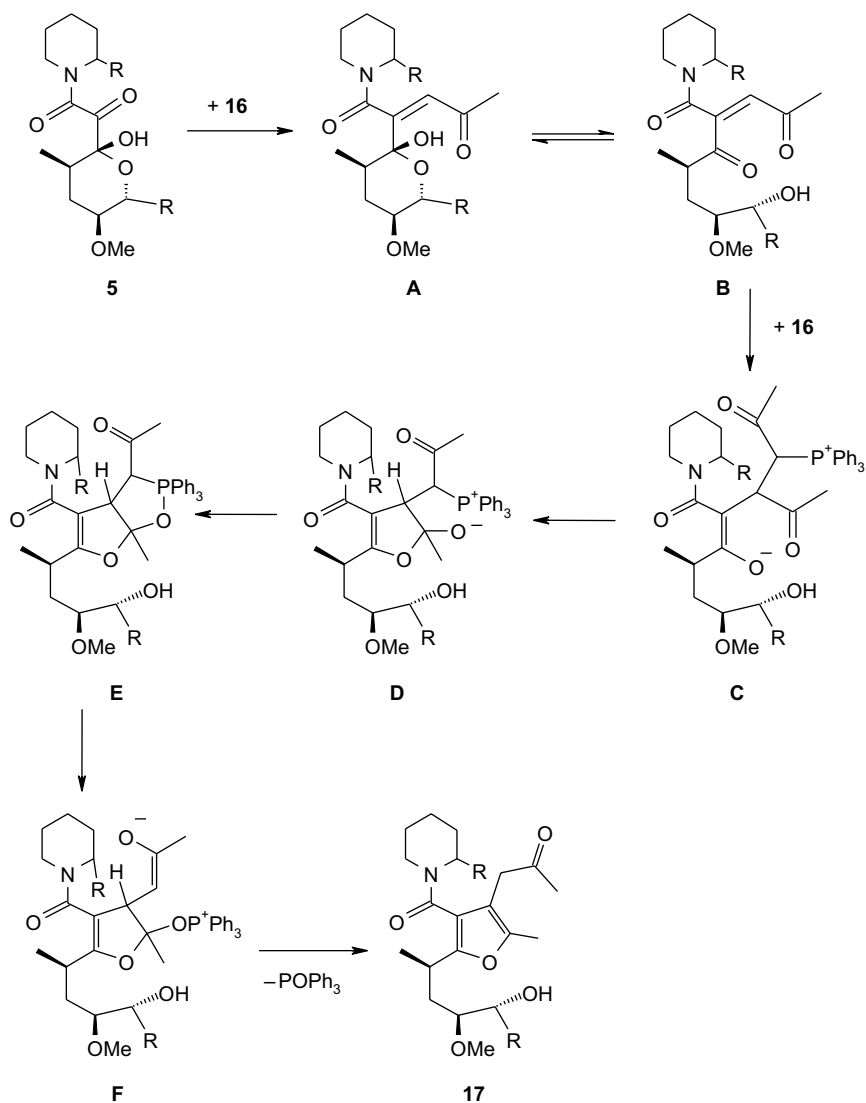
pling in compound **18** confirms that the furan unit and the C-22 atom are connected on the same oxygen atom.

Inspection of the carbon skeleton of **17** clearly reveals that two equivalents of the Wittig reagent **16** have been incorporated. A possible explanation for the formation of the surprising compound **17** is outlined in Scheme 6 and assumes that first a common Wittig reaction at C-9 carbonyl group in **5** gives the hemiketal **A**, which has the property of being in equilibrium with its ring opened structure **B**. Alternatively, liberation of the C-10 carbonyl group might occur first, followed by the olefination step to give the same intermediate **B** and 1,4-addition of a second equivalent of ylide **16** at the newly formed activated double bond of **B** in a Michael-type reaction<sup>17</sup> might produce the highly functionalized intermediate **C**, which upon hemiketal formation would give betaine **D**. Continuing from **D**, a carbon to oxygen shift of the phosphonium ligand, *i.e.*, *via* the unchanged intermediate **E**, would give the alternative betaine **F**, from which the formation of **17**, *via* tautomerization and elimination of triphenylphosphin-oxide (POPh<sub>3</sub>), can be easily explained.

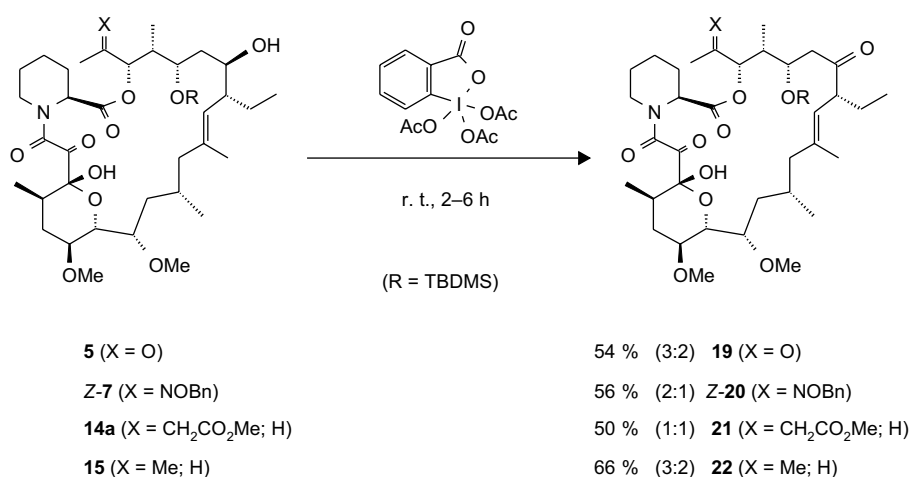
It should be borne in mind that the original FK 506 and ascomycin skeleton have a C=O functionality at position 22, which it was necessary to reduce in the reaction sequence to remove the cyclohexyl moiety (see Scheme 2). Finally, this position has to be restored to get back the intact effector domain (see Scheme 1). The oxidative restoration of the C-22 carbonyl in selected C-28 modified compounds was accomplished with Dess-Martin periodinane.<sup>18,19</sup> Applying these oxidation conditions to precursor **5** and its derivatives **Z-7**, **14a** and **15**, we obtained



Scheme 5.



Scheme 6.



Scheme 7.

the desired oxidation products **19–22** in reasonable yields (50–66 %, Scheme 7). According to the NMR studies, the resulting modified ascomycin compounds **19–22** exist

in deuteriochloroform solution as a mixture of two conformers (*cis/trans*-amide rotamers). Ratios of the conformers were 3 : 2 (**19**, **22**), 2 : 1 (**Z-20**) and 1 : 1 (**21**).

## EXPERIMENTAL

All reactions were performed in flame-dried reaction vessels under a slight pressure of dry Ar. Solvents were dried by standard methods. All other commercially available reagents were applied without further purification. All reactions were monitored by TLC on glass backed silica-gel plates with fluorescent stain (UV detection at  $\lambda_{\max} = 254$  nm); visualization of the reaction components was effected by spraying with a solution of molybdato-phosphoric acid (20 % in EtOH–H<sub>2</sub>O, 3 : 1). Column chromatography: silica gel (0.040–0.063 mm), from E. MERCK. <sup>1</sup>H and <sup>13</sup>C NMR Spectra: Bruker WM 250 and Bruker AMX 500; the solvent CDCl<sub>3</sub> was used as internal standard ( $\delta_{\text{H}} = 7.27$ ,  $\delta_{\text{C}} = 77.0$  ppm); due to complicated overlapping, only relevant <sup>1</sup>H NMR data are reported. Mass spectra: fast atom bombardment (FAB) spectra; VG 70-SE instrument (VG analytical) operating at 8 kV accelerating voltage.

(3*S*,4*R*,5*S*,7*R*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-5-(*tert*-Butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-3-(*N*-hydroxyethanimidoyl)-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-octadecahydro-3*H*-15,19-epoxyprido[2,1-*c*][1,4]-oxazacyclotricosine-1,20,21(23*H*)-trione (**6**)

NH<sub>2</sub>OH · HCl (116 mg, 1.67 mmol) was added to a solution of 28-oxoascomycin **5** (131 mg, 0.167 mmol) in dry ethanol (3 ml). After stirring at r.t. for 24 h, the solution was concentrated in vacuo. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and washed subsequently with H<sub>2</sub>O and brine. The organic phase was dried (MgSO<sub>4</sub>) and the solvent was evaporated in vacuo. The crude product was submitted to column chromatography (silica gel, toluene–AcOEt 6 : 1): **6** (79 mg, 59 %). Mixture of two isomers (60 : 40), major isomer: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 8.04 (s, 1 H, NOH); 5.65 (d,  $J = 2.5$  Hz, 1 H, 26-H); 5.38 (d,  $J = 2$  Hz, 1 H, 2-H); 4.88 (d,  $J = 10$  Hz, 1 H, 20-H); 3.38, 3.28 (2 s, 3 H each, 2 MeO); 1.85 (s, 3 H, 28-Me); 1.63 (s, 3 H, 19-Me); 1.02 (d,  $J = 6.5$  Hz, 3 H, 17-Me); 0.99 (s, 9 H, Si*t*Bu); 0.18, 0.16 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 198.3 (C-9); 169.1 (C-1); 166.1 (C-8); 155.5 (C-28); 136.4 (C-19); 125.4 (C-20); 99.0 (C-10); 76.5, 74.4, 74.1, 73.8, 73.7, 73.4 (C-13, C-14, C-15, C-22, C-24, C-26); 56.9, 56.4, 56.3 (C-2, 2 MeO); 49.3 (C-18); 44.7 (C-21); 39.2, 38.8 (C-6, C-25); 35.6, 34.7 (C-11, C-23); 33.0 (C-16); 32.5 (C-12); 27.9 (C-17); 26.8 (C-36); 26.5 (C-3); 26.0 (Si*t*Bu); 24.5 (C-5); 22.0, 21.5 (C-4, 17-Me); 18.2 (Si-C); 16.1, 15.4 (19-Me, 28-Me); 12.1, 11.8 (C-37, 11-Me); 10.7 (25-Me); –3.9, –4.6 (SiMe<sub>2</sub>). FAB-MS:  $m/z$ : 803 ([M + Li]<sup>+</sup>), 647, 629, 266, 242.

(3*S*,4*R*,5*S*,7*R*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-3-[*N*-(*Benzyl*oxy)ethanimidoyl]-5-(*tert*-butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-octadecahydro-3*H*-15,19-epoxyprido[2,1-*c*][1,4]-oxazacyclotricosine-1,20,21(23*H*)-trione (**7**)

*O*-Benzylhydroxyl amine (625 mg, 5.08 mmol) and PPTS (10 mg) were added to a solution of **5** (398 mg, 0.508 mmol)

in anhydrous benzene (10 ml) and the solution was stirred at r.t. for 5 d. Concentration of the solution and purification by column chromatography (silica gel, toluene–EtOAc 6 : 1) afforded **7** (375 mg, 83 %) as colorless foam. Mixture of two isomers (*Z*-**7** : *E*-**7** = 81 : 19). Major isomer *Z*-**7**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 7.38–7.13 (m, 5 H, Ph); 6.31 (d,  $J = 2.5$  Hz, 1 H, 26-H); 5.57 (d,  $J = 2$  Hz, 1 H, 10-OH); 5.10, 5.06 (AB system,  $J_{\text{AB}} = 12.5$  Hz, 2 H, CH<sub>2</sub>O); 4.91 (d,  $J = 10$  Hz, 1 H, 20-H); 4.46 (d,  $J = 12.5$  Hz, 1 H, 6-H<sub>eq</sub>); 4.25 (d,  $J = 6$  Hz, 1 H, 2-H); 3.35, 3.28 (2 s, 3 H each, 2 MeO); 3.04 (dt,  $J = 3$ , 13.5 Hz, 1 H, 6-H<sub>ax</sub>); 2.02 (t,  $J = 13.5$  Hz, 1 H, 3-H<sub>eq</sub>); 1.79 (s, 3 H, 28-Me); 1.60 (s, 3 H, 19-Me); 1.03 (d,  $J = 6.5$  Hz, 3 H, 17-Me); 0.94 (s, 9 H, Si*t*Bu); 0.08, 0.01 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 198.8 (C-9); 169.5 (C-1); 166.2 (C-8); 156.7 (C-28); 137.8, 136.2, 128.6, 128.2, 127.8 (C-19, Ph); 125.2 (C-20); 99.3 (C-10); 76.5 (C-15); 76.0 (OCH<sub>2</sub>); 74.8 (C-24); 74.5 (C-13); 73.8 (C-14); 73.4 (C-22); 72.0 (C-26); 56.7, 56.4, 56.3 (C-2, 2 MeO); 49.2 (C-18); 44.3 (C-21); 38.6 (C-6); 36.6 (C-25); 34.8, 34.7 (C-11, C-23); 33.4 (C-16); 32.5 (C-12); 28.0 (C-17); 26.8 (C-36); 26.4 (C-3); 26.0 (Si*t*Bu); 24.0 (C-5); 22.1, 22.0 (C-4, 17-Me); 18.3 (Si-C); 17.3 (28-Me); 16.2 (19-Me); 12.0 (C-37); 11.8 (25-Me); –4.6, –4.9 (SiMe<sub>2</sub>). Minor isomer *E*-**7**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 7.38–7.13 (m, 5 H, Ph); 5.62 (d,  $J = 2.5$  Hz, 1 H, 10-OH); 5.32 (d,  $J = 2$  Hz, 1 H, 26-H); 4.32 (d,  $J = 10$  Hz, 1 H, 20-H); 4.32 (d,  $J = 12.5$  Hz, 1 H, 6-H<sub>eq</sub>); 3.34, 3.25 (2 s, 3 H each, 2 MeO); 1.83 (s, 3 H, 28-Me); 0.98 (s, 9 H, Si*t*Bu); 0.16, 0.13 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 198.4 (C-9); 168.9 (C-1); 166.0 (C-8); 154.1 (C-28); 138.2, 136.2, 128.0, 127.7, 127.0 (C-19, Ph); 125.4 (C-20); 98.9 (C-10); 49.0 (C-18); 44.7 (C-21); 38.8 (C-6); –4.0, –5.0 (SiMe<sub>2</sub>). FAB-MS:  $m/z$ : 886 ([M + Li]<sup>+</sup>), 755, 737, 719, 332.

(3*S*,4*R*,5*S*,7*R*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-5-(*tert*-Butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-3-[*N*-(2-hydroxyethoxy)ethanimidoyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-octadecahydro-3*H*-15,19-epoxyprido[2,1-*c*][1,4]-oxazacyclotricosine-1,20,21(23*H*)-trione (**9**)

According to the preparation of **7**, a mixture of **5** (210 mg, 0.268 mmol), *O*-(2-hydroxyethyl)-hydroxylamine (**8**) (413 mg, 5.36 mmol) and PPTS (20 mg) in benzene–ethanol (5 : 1, 12 ml) was stirred for 6 days at r.t. Purification by column chromatography (hexane–EtOAc 1 : 1) afforded the 28-oxime ether **9** (198 mg, 88 %) as colorless foam. Mixture of two isomers (*Z*-**9** : *E*-**9** = 75 : 25). Major isomer *Z*-**9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ /ppm: 6.31 (d,  $J = 3.5$  Hz, 1 H, 26-H); 5.57 (d,  $J = 2$  Hz, 1 H, 10-OH); 4.92 (d,  $J = 10$  Hz, 1 H, 20-H); 4.46 (d,  $J = 13$  Hz, 1 H, 6-H<sub>eq</sub>); 4.28 (d,  $J = 7$  Hz, 1 H, 2-H); 4.16 (t,  $J = 4.5$  Hz, 2 H, OCH<sub>2</sub>); 3.95–3.78 (m, 4 H, 22-H, 24-H, CH<sub>2</sub>OH); 3.37, 3.29 (2 s, 3 H each, 2 MeO); 3.08 (d,  $J = 1.8$  Hz, 1 H, 22-OH); 3.02 (dt,  $J = 3$ , 13 Hz, 1 H, 6-H<sub>ax</sub>); 1.82 (s, 3 H, 28-Me); 1.62 (s, 3 H, 19-Me); 1.04 (d,  $J = 6.5$  Hz, 3 H, 17-Me); 1.02 (s, 9 H, Si*t*Bu); 0.95 (d,  $J = 7$  Hz, 3 H, 25-Me); 0.86 (t,  $J = 7.5$  Hz, 3 H, 37-H); 0.84 (d,  $J = 6.5$  Hz, 3 H, 11-Me); 0.20, 0.19 (2 s, 3 H each, SiMe<sub>2</sub>).



$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 198.7 (C-9); 169.9 (C-1); 166.2 (C-8); 157.6 (C-28); 136.3 (C-19); 125.2 (C-20); 99.3 (C-10); 76.7 (C-15); 74.7 (C-24,  $\text{OCH}_2$ ); 74.3 (C-13); 73.8 (C-14); 73.3 (C-22); 71.7 (C-26); 62.5 ( $\text{CH}_2\text{OH}$ ); 56.7 (C-2); 56.4, 56.3 (2 MeO); 49.2 (C-18); 44.4 (C-21); 38.7 (C-6); 37.1 (C-25); 34.8, 34.7 (C-11, C-23); 33.4 (C-16); 32.4 (C-12); 28.0 (C-17); 26.8 (C-36); 26.4 (C-3); 26.0 (Si*t*Bu); 24.0 (C-5); 22.0 (17-Me); 21.9 (C-4); 18.3 (Si-C); 17.2 (28-Me); 16.1 (19-Me); 15.2 (11-Me); 12.0 (C-37); 11.9 (25-Me); -4.5, -4.8 ( $\text{SiMe}_2$ ). FAB-MS:  $m/z$ : 803 ( $[\text{M} + \text{Li}]^+$ ), 709, 691, 673, 286, 266. Minor isomer *E*-**9**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 5.64 (d,  $J = 3$  Hz, 1 H, 26-H); 5.35 (d,  $J = 1.5$  Hz, 1 H, 10-OH); 4.78 (d,  $J = 10$  Hz, 1 H, 20-H); 4.27 (d,  $J = 10$  Hz, 1 H, 6- $\text{H}_{\text{eq}}$ ); 4.19 (d,  $J = 3$  Hz, 1 H, 2-H); 3.36, 3.28 (2 s, 3 H each, 2 MeO); 2.82 (d,  $J = 2$  Hz, 1 H, 22-OH); 1.83 (s, 3 H, 28-Me); 1.61 (s, 3 H, 19-Me); 1.03 (d,  $J = 6.5$  Hz, 3 H, 17-Me); 1.00 (s, 9 H, Si*t*Bu); 0.89 (d,  $J = 6$  Hz, 3 H, 25-Me); 0.86 (d,  $J = 6$  Hz, 3 H, 11-Me); 0.85 (t,  $J = 7$  Hz, 3 H, 37-H); 0.19, 0.16 (2 s, 3 H each,  $\text{SiMe}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 198.4 (C-9); 169.2 (C-1); 166.1 (C-8); 155.3 (C-28); 136.5 (C-19); 125.3 (C-20); 99.0 (C-10); 76.5 (C-15); 74.7 (C-24); 74.4 (C-13); 74.0, 73.8, 73.7 (C-14, (C-26,  $\text{OCH}_2$ ); 73.4 (C-22); 63.1 ( $\text{CH}_2\text{OH}$ ); 55.8 (C-2); 56.4, 56.3 (2 MeO); 49.2 (C-18); 44.8 (C-21); 39.0, 38.8 (C-6, C-25); 35.4 (C-11); 34.7 (C-23); 33.0 (C-16); 32.5 (C-12); 27.9 (C-17); 26.8 (C-36); 26.5 (C-3); 25.9 (Si*t*Bu); 24.1 (C-5); 21.9 (17-Me); 21.5 (C-4); 18.2 (Si-C); 16.0 (19-Me); 15.4 (11-Me); 12.4 (28-Me); 12.1 (C-37); 10.7 (25-Me); -4.0, -4.6 ( $\text{SiMe}_2$ ).

(3*S*,4*R*,5*S*,7*R*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-3-[*N*-(Aminocarbonyl)ethane-hydrizonoyl]-5-(*tert*-butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-octadecahydro-3*H*-15,19-epoxyprido[2,1-*c*][1,4]oxazacyclotricosine-1,20,21(23*H*)-trione (**10**)

A solution of **5** (150 mg, 0.191 mmol), semicarbazide hydrochloride (107 mg, 0.958 mmol) and NaOAc (110 mg, 1.34 mmol) in ethanol- $\text{H}_2\text{O}$  (5 : 1, 12 ml) was stirred at 70 °C for 48 h. After removal of the solvents, the residue was dissolved in EtOAc (10 ml) and the resulting solution was washed with  $\text{H}_2\text{O}$ . The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated in vacuo. Column chromatography ( $\text{CH}_2\text{Cl}_2$ -methanol 97 : 3) of the residue yielded **10** (82.5 mg, 51 %). Mixture of two isomers (94 : 6). Major isomer **10**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 5.64 (d,  $J = 2.5$  Hz, 1 H, NH); 5.43 (d,  $J = 1.5$  Hz, 1 H, 26-H); 4.89 (d,  $J = 10$  Hz, 1 H, 20-H); 4.41 (d,  $J = 10$  Hz, 1 H, 6- $\text{H}_{\text{eq}}$ ); 4.29 (d,  $J = 4$  Hz, 1 H, 2-H); 3.36, 3.29 (2 s, 3 H each, 2 MeO); 1.94 (s, 3 H, 28-Me); 1.61 (s, 3 H, 19-Me); 0.97 (s, 9 H, Si*t*Bu); 0.20, 0.17 (2 s, 3 H each,  $\text{SiMe}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 198.3 (C-9); 169.3 (C-1); 166.0 (C-8); 157.9 (C-28); 147.4 ( $\text{CONH}_2$ ); 136.4 (C-19); 125.3 (C-20); 99.0 (C-10); 76.4, 75.1, 74.2, 74.0, 73.7, 73.4 (C-13, C-14, C-15, C-22, C-24, C-26); 56.7, 56.3, 56.2 (C-2, 2 MeO); 49.2 (C-18); 44.7 (C-21); 39.9 (C-6); 38.7 (C-25); 35.3, 34.6 (C-11, C-23); 33.0 (C-16); 32.0 (C-12); 27.8 (C-17); 26.8 (C-36); 26.4 (C-3); 25.9 (Si*t*Bu); 24.0 (C-5); 21.9, 21.5 (C-4, 17-Me); 18.1 (Si-C); 16.0, 15.3, 13.4

(11-Me, 19-Me, 28-Me); 12.0 (C-37); 10.8 (25-Me); -4.0, -4.7 ( $\text{SiMe}_2$ ). FAB-MS:  $m/z$ : 839 ( $\text{M}^+$ ), 707, 689, 671, 522, 284, 266, 244, 220.

(3*S*,4*R*,5*S*,7*R*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-*N*'-{[5-(*tert*-Butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26*a*-docosahydro-3*H*-15,19-epoxyprido[2,1-*c*][1,4]-oxazacyclotricosin-3-yl]ethylidene}-4-methylbenzene sulfonohydrazide (**11**)

*p*-Toluenesulfonic acid hydrazide (36.5 mg, 0.196 mmol) was added to a solution of **5** (77 mg, 0.098 mmol) in AcOH (1 ml) and the mixture was stirred at r.t. for 25 h. The reaction mixture was poured into a sat. aq.  $\text{NaHCO}_3$  solution (2 ml) and extracted with EtOAc. The combined organic layers were washed with brine and dried ( $\text{MgSO}_4$ ). Removal of the solvent in vacuo and purification by column chromatography (hexane-EtOAc 2 : 1) afforded **11** (49 mg, 53 %) as colorless foam. One isomer.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 7.89 (br. s, 1 H, NH); 7.81-7.70, 7.30-7.25 (2 m, 2 H each,  $\text{C}_6\text{H}_4$ ); 5.55 (d,  $J = 2.5$  Hz, 1 H, 26-H); 4.86 (d,  $J = 10$  Hz, 1 H, 20-H); 4.33 (d,  $J = 13.5$  Hz, 1 H, 6- $\text{H}_{\text{eq}}$ ); 3.36, 3.29 (2 s, 3 H each, 2 MeO); 2.43 (s, 3 H,  $\text{C}_6\text{H}_4\text{Me}$ ); 1.73 (s, 3 H, 28-Me); 1.60 (s, 3 H, 19-Me); 0.97 (s, 9 H, Si*t*Bu); 0.63 (d,  $J = 7$  Hz, 3 H, 25-Me); 0.15, 0.12 (2 s, 3 H each,  $\text{SiMe}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 198.5 (C-9); 169.4 (C-1); 166.1 (C-8); 154.4 (C-28); 144.0, 136.5, 135.5, 129.5, 127.9 (C-19,  $\text{C}_6\text{H}_4$ ); 125.3 (C-20); 99.0 (C-10); 76.4, 75.0 (C-15, C-26); 74.3 (C-13); 73.9, 73.8, 73.3 (C-14, C-22, C-24); 56.8, 56.4, 56.3 (C-2, 2 MeO); 49.3 (C-18); 44.7 (C-21); 39.6, 38.7 (C-6, C-25); 35.3, 35.0 (C-11, C-23); 33.2 (C-16); 32.4 (C-12); 27.9 (C-17); 26.8, 26.4 (C-3, C-36); 25.9 (Si*t*Bu); 24.1 (C-5); 22.0, 21.6, 21.3 (C-4, 17-Me, 28-Me); 18.1 (Si-C); 16.1 (19-Me); 15.4 (11-Me); 13.5 ( $\text{C}_6\text{H}_4\text{Me}$ ); 12.1 (C-37); 10.3 (25-Me); -4.0, -4.7 ( $\text{SiMe}_2$ ).

(3*S*,4*R*,5*S*,7*R*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-[5-(*tert*-Butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26*a*-docosahydro-3*H*-15,19-epoxyprido[2,1-*c*][1,4]-oxazacyclotricosin-3-yl]-2-hydroxypropanenitrile (**12**)

A solution of **5** (125 mg, 0.160 mmol) and trimethylsilyl cyanide (158 mg, 1.60 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 ml) was treated with  $\text{BF}_3 \cdot \text{OEt}_2$  (10 drops) for 3.5 h at -10 °C. Work up with sat. aq.  $\text{NaHCO}_3$  solution, extraction with  $\text{CH}_2\text{Cl}_2$ , drying with  $\text{MgSO}_4$  and evaporation of the solvent afforded the crude product. Column chromatography (hexane-EtOAc 3 : 1) of the crude product gave the cyano-substituted derivative **12** (49 mg, 36 %) as colorless foam. Mixture of two diastereomers (60 : 40). Major isomer **12**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 5.40 (d,  $J = 2$  Hz, 1 H, 26-H); 5.13 (s, 1 H, 10-OH); 4.40 (d,  $J = 10$  Hz, 1 H, 20-H); 3.37, 3.29 (2 s, 3 H each, 2 MeO); 1.60 (s, 3 H, 19-Me); 1.26 (s, 3 H, 28-Me); 1.16 (d,  $J = 7$  Hz, 3 H, 17-Me); 0.97 (s, 9 H, Si*t*Bu); 0.19, 0.16 (2 s,

3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 198.6 (C-9); 173.1 (C-1); 166.1 (C-8); 137.0 (C-19); 125.0 (C-20); 119.8 (28-CN); 98.9 (C-10); 79.3, 77.1, 75.3, 74.2, 74.1, 73.7, 73.2 (C-13, C-14, C-15, C-22, C-24, C-26, C-28); 57.6, 56.4, 56.3 (C-2, 2 MeO); 49.3 (C-18); 45.0 (C-21); 38.3, 37.7, 36.0, 34.7, 32.9, 32.6 (C-6, C-11, C-12, C-16, C-23, C-25); 27.6, 26.7 (C-3, C-36); 25.0, 24.2 (C-4, C-5); 25.9 (Si<sub>t</sub>Bu); 21.7 (28-Me); 18.2 (Si-C); 16.0 (19-Me); 15.5 (11-Me); 12.1 (C-37); 10.7 (25-Me); -4.0, -4.5 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 810 (M<sup>+</sup>), 764, 706, 632, 614, 227.

*Methyl (3S,4R,5S,7R,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-[5-(tert-Butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-3H-15,19-epoxyprido[2,1-c][1,4]oxazacyclotricosin-3-yl]-3-hydroxybutanoate (14)*

According to the preparation of **12**, a mixture of **5** (110 mg, 0.140 mmol), *O*-silyl ketene acetal **13** (0.5 ml) and BF<sub>3</sub> · OEt<sub>2</sub> (10 drops) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was stirred for 4 h at -40 °C and then worked up. Purification by column chromatography (hexane–EtOAc 4 : 1) of the crude product gave **14** (57 mg, 48 %) as colorless foam. Mixture of two diastereomers (70 : 30). Major diastereomer **14**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.40 (d, *J* = 2 Hz, 1 H, 26-H); 4.90 (d, *J* = 1.5 Hz, 1 H, 10-OH); 4.82 (d, *J* = 10 Hz, 1 H, 20-H); 4.46 (d, *J* = 14 Hz, 1 H, 6-H<sub>eq</sub>); 4.36 (t, *J* = 3 Hz, 1 H, 2-H); 3.72 (s, 3 H, CO<sub>2</sub>Me); 3.36, 3.28 (2 s, 3 H each, 2 MeO); 3.30 (s, 1 H, OH); 2.52, 2.44 (AB system, *J*<sub>AB</sub> = 15 Hz, 2 H, 28-CH<sub>2</sub>); 1.63 (s, 3 H, 19-Me); 1.32 (s, 3 H, 28-Me); 1.01 (d, *J* = 7 Hz, 3 H, 17-Me); 0.98 (s, 9 H, Si<sub>t</sub>Bu); 0.80 (t, *J* = 7 Hz, 3 H, 37-H); 0.16, 0.10 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 198.2 (C-9); 172.2, 169.6 (C-1, CO<sub>2</sub>Me); 165.9 (C-8); 136.7 (C-19); 125.8 (C-20); 98.6 (C-10); 76.2, 76.0, 75.1, 74.1, 74.0, 73.7, 73.5 (C-13, C-14, C-15, C-22, C-24, C-26, C-28); 57.9, 56.4, 56.3 (C-2, 2 MeO); 51.8 (CO<sub>2</sub>Me); 49.4 (C-18); 45.3, 43.6 (C-21, 28-CH<sub>2</sub>); 39.1, 38.5 (C-6, C-25); 36.3, 34.8 (C-11, C-23); 32.6, 32.5 (C-12, C-16); 27.5 (C-17); 26.7, 26.6 (C-3, C-36); 26.1 (Si<sub>t</sub>Bu); 24.9, 24.0 (C-5, 28-Me); 22.1, 21.7 (C-4, 17-Me); 18.1 (Si-C); 15.9, 15.6 (11-Me, 19-Me); 12.6, 12.0 (C-37, 25-Me); -3.8, -4.4 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 856 (M<sup>+</sup>), 838 (M<sup>+</sup> - H<sub>2</sub>O), 820 (M<sup>+</sup> - 2 H<sub>2</sub>O), 706, 688, 281, 221, 183. Minor diastereomer **14**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.43 (d, *J* = 2 Hz, 1 H, 26-H); 4.82 (d, *J* = 9.5 Hz, 1 H, 20-H); 4.81 (d, *J* = 2 Hz, 1 H, 10-OH); 4.48 (d, *J* = 14 Hz, 1 H, 6-H<sub>eq</sub>); 4.41 (br. s, 1 H, 2-H); 4.19 (s, 1 H, OH); 3.74 (s, 3 H, CO<sub>2</sub>Me); 3.38, 3.23 (2 s, 3 H each, 2 MeO); 2.58, 2.40 (AB system, *J*<sub>AB</sub> = 16 Hz, 2 H, 28-CH<sub>2</sub>); 1.60 (s, 3 H, 19-Me); 1.26 (s, 3 H, 28-Me); 0.98 (s, 9 H, Si<sub>t</sub>Bu); 0.82 (t, *J* = 7 Hz, 3 H, 37-H); 0.16, 0.08 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 197.9 (C-9); 173.0, 169.2 (C-1, CO<sub>2</sub>Me); 165.8 (C-8); 136.4 (C-19); 126.2 (C-20); 98.3 (C-10); 75.9, 75.6, 75.1, 74.0, 73.9, 73.3, 73.1 (C-13, C-14, C-15, C-22, C-24, C-26, C-28); 51.9 (CO<sub>2</sub>Me); 49.3 (C-18); 45.2, 43.0 (C-21, 28-CH<sub>2</sub>); 39.1, 37.9 (C-6, C-25); 36.2, 34.8 (C-11, C-23); 32.6, 32.4 (C-12,

C-16); 27.3 (C-17); 26.7, 26.6 (C-3, C-36); 26.1 (Si<sub>t</sub>Bu); 24.4, 24.2 (C-5, 28-Me); 22.3, 21.5 (C-4, 17-Me); 18.1 (Si-C); 15.8, 15.7 (11-Me, 19-Me); 12.9, 11.8 (C-37, 25-Me); -3.8, -4.6 (SiMe<sub>2</sub>).

*(3S,4R,5S,7R,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-5-(tert-Butyldimethylsilyloxy)-8-ethyl-7,19-dihydroxy-3-(1-hydroxy-1-methylethyl)-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-3H-15,19-epoxyprido[2,1-c][1,4]-oxazacyclotricosine-1,20,21(23H)-trione (15)*

MeLi (0.48 ml, 0.768 mmol; 1.6 M solution in hexane) was added dropwise to a solution of **5** (150 mg, 0.192 mmol) in anhydrous THF (10 ml) at -60 °C. After stirring at -60 °C for 3.5 h, the mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution followed by extraction with *tert*-butyl methyl ether. The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by column chromatography (hexane–EtOAc 5 : 1): **15** (30 mg, 20 %) and the starting material **4** (41 mg, 27 %). Compound **15**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.33 (d, *J* = 2 Hz, 1 H, 26-H); 4.90 (d, *J* = 1.5 Hz, 1 H, 10-OH); 4.82 (d, *J* = 10 Hz, 1 H, 20-H); 4.45 (d, *J* = 13.5 Hz, 1 H, 6-H<sub>eq</sub>); 3.35, 3.27 (2 s, 3 H each, 2 MeO); 1.59 (s, 19-Me); 1.24, 1.20 (2 s, 3 H each, 28-Me); 1.00 (d, *J* = 7 Hz, 3 H, 17-Me); 0.97 (s, 9 H, Si<sub>t</sub>Bu); 0.15, 0.11 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 198.1 (C-9); 170.1 (C-1); 165.9 (C-8); 136.7 (C-19); 125.8 (C-20); 98.5 (C-10); 78.6 (C-26); 76.0, 75.1, 73.9, 73.7, 73.4, 73.2 (C-13, C-14, C-15, C-22, C-24, C-28); 57.8, 56.4, 56.3 (C-2, 2 MeO); 49.3 (C-18); 45.1 (C-21); 39.0, 38.7 (C-6, C-25); 36.1, 34.7, 34.5, 32.5 (C-11, C-12, C-16, C-23); 28.5 (C-17); 27.4, 26.7 (C-3, C-36); 26.0 (Si<sub>t</sub>Bu); 25.3, 24.3 (C-5, 28-Me); 21.9, 21.6 (C-4, 17-Me); 18.1 (Si-C); 15.9, 15.6 (11-Me, 19-Me); 12.2, 11.9 (C-37, 25-Me); -3.8, -4.4 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 799 (M<sup>+</sup>), 648, 630, 187, 130, 123, 111.

*Reaction of 24-O-tert-butyldimethylsilyl-22(R)-dihydro-28-oxoascomycin (5) with Wittig reagent 16*

The Wittig reagent **16** (777 mg, 2.44 mmol) was added to a solution of **5** (191 mg, 0.244 mmol) in dry MeCN (10 ml) and the mixture was stirred at 65 °C for 10 d. Then the suspension was filtered and the resulting filtrate was concentrated in vacuo. Column chromatography (cyclohexane–EtOAc 2 : 1) of the residue yielded **17** (22 mg, 11 %) and **18** (8 mg, 4 %). Compound **17**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.63 (d, *J* = 5 Hz, 1 H, 2-H); 5.22 (d, *J* = 5.5 Hz, 1 H, 26-H); 4.75 (d, *J* = 10.5 Hz, 1 H, 20-H); 3.90 (d, *J* = 12.5 Hz, 1 H, 6-H<sub>eq</sub>); 3.78 (q, *J* = 5.5 Hz, 1 H, 24-H); 3.26 (dd, *J* = 4, 11 Hz, 1 H, 15-H); 3.22 (s, 3 H, 15-OMe); 3.10 (dd, *J* = 9.5, 14 Hz, 1 H, 14-H); 2.78 (s, 3 H, 13-OMe); 2.70 (dd, *J* = 8, 9 Hz, 1 H, 13-H); 2.63 (br s, 1 H, 22-OH); 2.59 (d, *J* = 1 Hz, 1 H, 24-OH); 2.28 (s, 3 H, 28-Me); 2.18 (s, 3 H, MeCH=); 2.17 (s, 3 H, MeC=O); 1.64 (s, 3 H, 19-Me); 1.32 (d, *J* = 7 Hz, 3 H, 11-Me); 0.95 (d, *J* = 7 Hz, 3 H, 25-Me); 0.91 (s, 9 H, Si<sub>t</sub>Bu); 0.83 (d, *J* = 6.5 Hz, 3 H, 17-Me); 0.12, 0.09 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 205.7 (C=O);



203.9 (C-28); 172.8 (C-1); 166.0 (C-8); 154.0 (C-10); 147.9 (=C-O); 136.6 (C-19); 126.6 (C-20); 117.6 (C-9); 112.1 (=C-CH<sub>2</sub>); 79.4 (C-26); 77.9 (C-13); 77.3 (C-15); 74.3 (C-14); 74.1 (C-24); 73.6 (C-22); 58.1 (15-OMe); 55.6 (13-OMe); 50.9 (C-2); 49.9 (C-18); 47.5 (C-21); 45.3 (C-6); 40.4 (C-25); 38.9 (C-12); 38.5 (CH<sub>2</sub>C=O); 36.5 (C-23); 34.2 (C-16); 32.0 (C-11); 29.5 (MeC=O); 28.1 (28-Me); 26.4 (C-3); 26.4 (C-17); 25.9 (Si*t*Bu); 25.7 (C-5); 25.2 (C-36); 21.0 (C-4); 20.0 (17-Me); 18.5 (11-Me); 17.9 (Si-C); 15.9 (19-Me); 12.7 (25-Me); 11.4 (C-37, =CMe); -4.3, -4.7 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 868 ([M + Li]<sup>+</sup>), 249, 227. Compound **18**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 6.00 (s, 1 H, =CH); 5.92 (d, *J* = 2 Hz, 1 H, 26-H); 5.04 (d, *J* = 4.5 Hz, 1 H, 2-H); 4.81 (d, *J* = 10 Hz, 1 H, 20-H); 4.46 (d, *J* = 11 Hz, 1 H, 6-H<sub>eq</sub>); 3.89 (dd, *J* = 5.5, 12 Hz, 1 H, 24-H); 3.67 (br dd, *J* = 3.5, 9 Hz, 1 H, 22-H); 3.36, 3.29 (2 s, 3 H each, 2 MeO); 2.98 (dt, *J* = 3.5, 13.5 Hz, 1 H, 6-H<sub>ax</sub>); 2.13 (s, 3 H, 28-Me); 1.69 (s, 3 H, 19-Me); 1.49 (s, 3 H, MeC-O); 1.04 (d, *J* = 6.5 Hz, 3 H, 17-Me); 0.95 (s, 9 H, Si*t*Bu); 0.93 (d, *J* = 6.5 Hz, 3 H, 11-Me); 0.89 (d, *J* = 7 Hz, 3 H, 25-Me); 0.85 (t, *J* = 7 Hz, 3 H, 37-H); 0.70 (dd, *J* = 13.3, 13.5 Hz, 1 H, 16-H); 0.15, 0.13 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 207.1 (C-28); 171.8 (C-1); 166.2 (C-8); 138.6 (C-9, C-19); 131.2 (=CH); 125.4 (C-20); 111.6 (C-10); 110.6 (C-O); 77.3 (C-26); 76.5 (C-15); 76.2 (C-14); 74.5 (C-13); 73.0 (C-22); 72.1 (C-24); 58.4 (C-2); 56.4, 56.3 (2 OMe); 49.6 (C-18); 47.3 (C-21); 40.1 (C-25); 39.1 (C-6); 35.8 (C-23); 34.5 (C-11); 33.4 (C-12); 32.5 (C-16); 28.9 (C-17); 27.3 (28-Me); 26.1 (C-3, C-36); 25.9 (Si*t*Bu); 24.3 (C-5); 21.7, 21.6 (C-4, 17-Me); 21.1 (MeC-O); 18.1 (Si-C); 17.1 (19-Me); 16.3 (11-Me); 13.3 (C-37); 11.0 (25-Me); -3.7, -4.3 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 810 ([M + Li]<sup>+</sup>), 672, 654, 227.

*Oxidation of the C-22 Hydroxy Group by Dess Martin Periodinane; General Procedure.* – The appropriate 22(*R*)-dihydroascomyacin derivative (1 equiv.) and pyridine (6–12 equiv.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 ml/1 mmol of substrate). After addition of Dess Martin periodinane (3–4 equiv.), the suspension was stirred at r.t. for the time indicated. The reaction was quenched with 10 % Na<sub>2</sub>SO<sub>3</sub> solution and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The resulting crude product was purified by column chromatography (hexane–EtOAc 3 : 1 or 4 : 1).

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-3-Acetyl-8-ethyl-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-heptadecahydro-3*H*-15,19-epoxyprido[2,1-*c*]-[1,4]oxazacyclotricosine-1,7,20,21(23*H*)-tetrone (**19**)

According to the general procedure, compound **5** (0.113 g, 0.144 mmol), Dess Martin periodinane (0.188 g, 0.433 mmol) and pyridine (0.063 g, 0.796 mmol) afforded **19** (0.061 g, 54 %). Reaction time: 2 h. Mixture of two conformers (60 : 40). Major conformer: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.44 (d, *J* = 2.5 Hz, 1 H, 26-H); 4.78 (d, *J* = 10 Hz, 1 H, 20-H); 4.10 (d, *J* = 1 Hz, 1 H, 10-OH); 3.71 (dd, *J* = 1, 10 Hz, 1 H, 14-H); 3.38, 3.28 (2 s, 3 H each, 2 MeO); 2.80 (dt, *J* = 3,

13.5 Hz, 1 H, 6-H<sub>ax</sub>); 2.19 (s, 3 H, 28-Me); 1.60 (s, 3 H, 19-Me); 1.03 (d, *J* = 6.5 Hz, 3 H, 17-Me); 0.91 (s, 9 H, Si*t*Bu); 0.12, 0.05 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 211.0 (C-22); 203.0 (C-28); 196.4 (C-9); 169.7 (C-1); 164.6 (C-8); 138.8 (C-19); 123.5 (C-20); 97.5 (C-10); 77.2 (C-26); 74.9, 73.7, 72.8, 71.1 (C-13, C-14, C-15, C-24); 57.1, 56.3, 55.5 (C-2, 2 MeO); 48.6 (C-18); 44.3 (C-21); 39.4, 39.1 (C-6, C-25); 34.7, 33.0, 32.7, 32.2 (C-11, C-12, C-16, C-23); 27.1, 26.5, 26.1, 25.4 (C-3, C-17, C-36, 28-Me); 25.8 (Si*t*Bu); 24.0 (C-5); 20.4, 19.9 (C-4, 17-Me); 18.1 (Si-C); 16.2 (19-Me); 15.1 (11-Me); 11.4 (C-37); 10.1 (25-Me); -4.1, -4.9 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 786 ([M + Li]<sup>+</sup>), 762, 704, 630, 227, 199.

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-3-[(*Z*)-*N*-(benzyloxy)ethanimidoyl]-8-ethyl-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-octadecahydro-3*H*-15,19-epoxyprido[2,1-*c*]-[1,4]oxazacyclotricosine-1,7,20,21(23*H*)-tetrone (**Z-20**)

According to the general procedure, compound (*Z*)-**7** (0.088 g, 0.099 mmol), Dess Martin periodinane (0.168 g, 0.396 mmol) and pyridine (0.068 g, 0.860 mmol) afforded (*Z*)-**20** (0.049 g, 56 %). Reaction time: 4 h. Mixture of two conformers (67 : 33). Major conformer (*Z*)-**20**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 7.35–7.25 (m, 5 H, Ph); 6.14 (d, *J* = 3.5 Hz, 1 H, 26-H); 5.80 (s, 1 H, 10-OH); 5.08, 5.04 (AB system, *J*<sub>AB</sub> = 13 Hz, 2 H, CH<sub>2</sub>O); 4.79 (d, *J* = 10 Hz, 1 H, 20-H); 3.95 (dd, *J* = 2.5, 9.5 Hz, 1 H, 14-H); 3.35, 3.27 (2 s, 3 H each, 2 MeO); 1.78 (s, 3 H, 28-Me); 1.66 (s, 3 H, 19-Me); 1.05 (d, *J* = 6.5 Hz, 3 H, 17-Me); 0.82 (s, 9 H, Si*t*Bu); -0.01, -0.05 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 210.9 (C-22); 192.0 (C-9); 168.9 (C-1); 166.1 (C-8); 155.9 (C-28); 139.3, 128.3, 128.1, 127.9, 127.6 (C-19, Ph); 123.3 (C-20); 98.8 (C-10); 76.4, 76.0, 75.8, 75.5, 74.8, 74.6, 70.3 (C-13, C-14, C-15, C-22, C-24, C-26, OCH<sub>2</sub>); 57.5, 56.3, 55.3 (C-2, 2 MeO); 52.2, 48.7, 43.6 (C-18, C-21, C-23); 39.7, 36.3 (C-6, C-25); 33.3, 32.7, 32.4 (C-11, C-12, C-17); 26.8 (C-36); 26.4 (C-3); 25.8 (Si*t*Bu); 24.4, 23.3, 21.0 (C-4, C-5, 17-Me); 18.8 (Si-C); 17.2 (28-Me); 16.2 (19-Me); 15.7 (11-Me); 12.0 (C-37); 11.6 (25-Me); -4.7, -4.9 (SiMe<sub>2</sub>). FAB-MS: *m/z*: 884 ([M + Li]<sup>+</sup>), 754, 735, 376.

Methyl (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-[5-(*tert*-Butyldimethylsilyloxy)-8-ethyl-19-hydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,7,20,21-tetraoxo-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26*a*-docosahydro-3*H*-15,19-epoxyprido[2,1-*c*]-[1,4]oxazacyclotricosin-3-yl]-3-hydroxybutanoate (**21**)

According to the general procedure, compound **14a** (0.133 g, 0.155 mmol), Dess Martin periodinane (0.263 g, 0.620 mmol) and pyridine (0.147 g, 1.86 mmol) afforded **21** (0.066 g, 50 %). Reaction time: 6 h. Mixture of two conformers (50 : 50), both conformers of **21**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.26 (d, *J* = 3 Hz, 1 H, 26-H); 4.84, 4.77 (2 d, *J* = 10 Hz each, 1 H, 20-H); 3.70, 3.67 (2 s, 3 H, 2 CO<sub>2</sub>Me); 3.37, 3.36, 3.33, 3.25 (4 s, 3 H each, 4 MeO); 1.74, 1.57 (2 s, 3 H, 19-Me); 1.26, 1.23 (2 s, 3 H, 28-Me); 0.99, 0.91 (2 d, *J* = 6.5 Hz each, 3 H,

17-Me); 0.87, 0.85 (2 s, 9 H, 2 Si*t*Bu); 0.10, 0.06, 0.05, 0.04 (4 s, 6 H, 2 SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 210.6, 209.0 (C-22); 195.9, 194.7 (C-9); 172.3, 171.6, 169.7, 169.6, 166.0, 164.8 (C-1, C-8, CO<sub>2</sub>Me); 139.7, 137.7 (C-19); 124.0, 123.5 (C-20); 98.2, 96.9 (C-10); 78.9, 77.3, 76.6, 74.9, 73.7, 73.5, 73.4, 73.0, 72.6, 72.4, 71.7, 69.8 (C-13, C-14, C-15, C-22, C-24, C-26, C-28); 57.2, 57.0, 56.8, 56.3, 55.1, 54.0 (C-2, 4 MeO); 52.3, 51.8 (2 CO<sub>2</sub>Me); 48.7, 48.2 (C-18); 46.0, 44.4, 43.9, 42.2 (C-21, 28-CH<sub>2</sub>); 39.8, 39.3, 35.2, 34.7, 33.0, 32.8, 32.5, 32.4, 27.3, 26.3 (C-3, C-6, C-11, C-12, C-16, C-17, C-23, C-25, C-36); 25.9, 25.7 (2 Si*t*Bu); 24.7, 24.0, 23.1, 22.9, 21.2, 20.8, 20.2, 19.5 (C-4, C-5, 17-Me, 28-Me); 17.9 (Si-C); 16.2, 16.1, 15.9, 15.3 (11-Me, 19-Me); 13.6, 12.1 (C-37); 11.6, 11.5 (25-Me); -3.9, -4.3, -4.7, -4.8 (2 SiMe<sub>2</sub>). FAB-MS of the desilylated compound of **21** (HF/MeCN; r.t., 1 h): *m/z*: 777 ([M+Li]<sup>+</sup>), 776, 737, 736, 735, 719, 678, 332, 266, 216.

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-5-(*tert*-Butyldimethylsilyloxy)-8-ethyl-19-hydroxy-3-(1-hydroxy-1-methylethyl)-14,16-dimethoxy-4,10,12,18-tetramethyl-4,5,6,7,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-octadecahydro-3*H*-15,19-epoxyprido[2,1-*c*]-[1,4]oxazacyclotricosine-1,7,20,21(23*H*)-tetrone (**22**)

According to the general procedure, compound **15** (0.032 g, 0.040 mmol), Dess Martin periodinane (0.068 g, 0.160 mmol) and pyridine (0.038 g, 0.480 mmol) afforded **22** (0.021 g, 66 %). Reaction time: 4 h. Mixture of two conformers (60 : 40). Major conformer **22**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ/ppm: 5.22 (d, *J* = 2.5 Hz, 1 H, 26-H); 4.74 (d, *J* = 10 Hz, 1 H, 20-H); 3.37, 3.27 (2 s, 3 H each, 2 MeO); 1.61 (s, 3 H, 19-Me); 1.24 (s, 3 H, 28-Me); 0.89 (s, 9 H, Si*t*Bu); 0.14, 0.09 (2 s, 3 H each, SiMe<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ/ppm: 208.4 (C-22); 194.9 (C-9); 170.0 (C-1); 166.3 (C-8); 139.6 (C-19); 124.2 (C-20); 98.3 (C-10); 81.1, 73.7, 73.5, 72.7, 72.6, 71.6, 70.3 (C-13, C-14, C-15, C-24, C-26, C-28); 57.2, 56.9, 56.3 (C-2, 2 MeO); 48.3 (C-18); 45.2 (C-21); 40.3, 39.5, 36.2, 35.3, 32.8, 32.5 (C-6, C-11, C-12, C-16, C-23, C-25); 27.3, 26.7, 25.6 (C-3, C-17, C-36); 26.0 (Si*t*Bu); 25.1, 24.7, 22.9, 19.3 (C-4, C-5, 17-Me, 28-Me); 17.9 (Si-C); 16.0, 15.9 (11-Me, 19-Me); 14.3 (C-37); 11.6 (25-Me); -4.6, -5.1 (SiMe<sub>2</sub>). FAB-MS of the desilylated compound of **22** (HF/MeCN; r.t., 1.5 h): *m/z*: 741 (MH<sup>+</sup>), 722 (M<sup>+</sup> - H<sub>2</sub>O), 704 (M<sup>+</sup> - 2 H<sub>2</sub>O), 686, 266, 183, 169.

## CONCLUSION

In summary, we have developed methodologies that allow replacement of the cyclohexylvinylidene moiety of ascomycin (**1**) by various nitrogen and carbon substituents. Access to these novel macrolides with a modified subunit is particularly important for the establishment of structure-activity relationships.

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## SAŽETAK

### Preparativne modifikacije askomicina. V. Dobivanje novih derivata askomicina pomoću zamjene cikloheksilvinilidenske podjedinice

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Opisani su postupci koji počinju s lako pristupačnim 25-*O*-*tert*-butildimetilsilil-22(*R*)-dihidro-28-oksoaskomicinom i omogućuju zamjenu askomicinske cikloheksilvinilidenske podjedinice različitim substituentima.