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Regioselective Carbon–Carbon Bond Formation in the Effector Domain of Ascomycin

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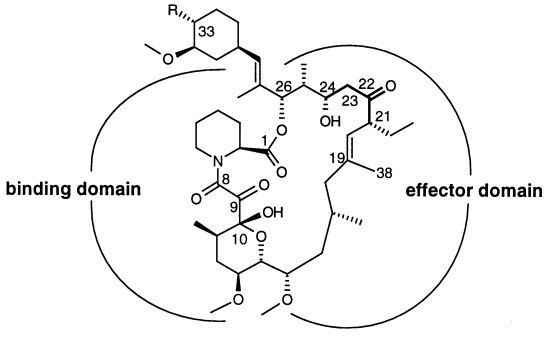
Abstract—Starting from 33-*O*-silyl-protected ascomycin or its 23,24-dehydration product, regio- and stereo-selective formal aldol reactions under carbon–carbon bond formation at C-22, C-23, or C-24 are demonstrated. Additionally, with the 22-silyl enol ether ascomycin derivative a rhodium(I)-catalysed shift of the 19,20 double bond into the 19,38 exocyclic position is observed at elevated temperature.

Introduction

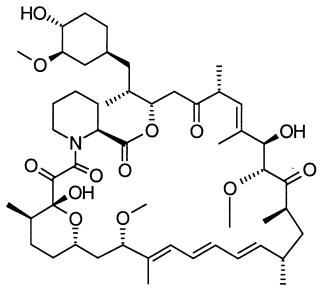
Ascomycin (**1**) is a macrolactam, isolated from the fermentation broth of the soil fungus *Streptomyces hygroscopicus* var. *ascomyceticus*.[1a–d] Derivatives of ascomycin have shown high anti-inflammatory activities in animal models for skin inflammation and clinical efficacy has been proven in patients with atopic dermatitis, allergic and irritant contact dermatitis as well as psoriasis.[2a–h] The first ascomycin derivative in development as a drug, SDZ ASM 981[3a–f] (**2**), is currently being extensively investigated in patients with inflammatory skin diseases.

Ascomycin has a complex macrocyclic structure (Fig. 1). The left part, the 'binding domain', is responsible for the binding to macrophilin, the intracellular cytosolic receptor. The right part, the 'effector domain', interacts with calcineurin, the target enzyme, and thus determines the specific biological activity.[4a–c] Rapamycin (**3**), another macrocyclic compound, shares the binding domain with ascomycin but has a different effector domain (Fig. 1). As a consequence it binds to macrophilin, but not to calcineurin, which results in different biological and pharmacological properties.[2b] In contrast to ascomycin and other calcineurin inhibitors, rapamycin does not have anti-inflammatory properties in animal models of skin inflammation.

On the basis of this knowledge we were interested to prepare new ascomycin derivatives with structural modifications in the effector domain, while leaving the binding domain



1 R = OH **ascomycin**
2 R = epi-Cl **SDZ ASM 981**



3 **rapamycin**

Figure 1.

Keywords: aldol reaction; enol ether; ketene acetals; regiospecificity; macrocycles.
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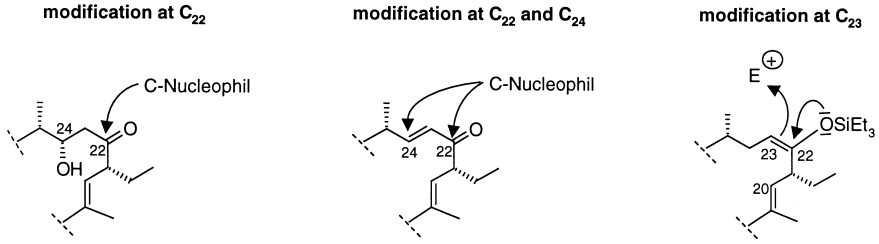


Scheme 1.

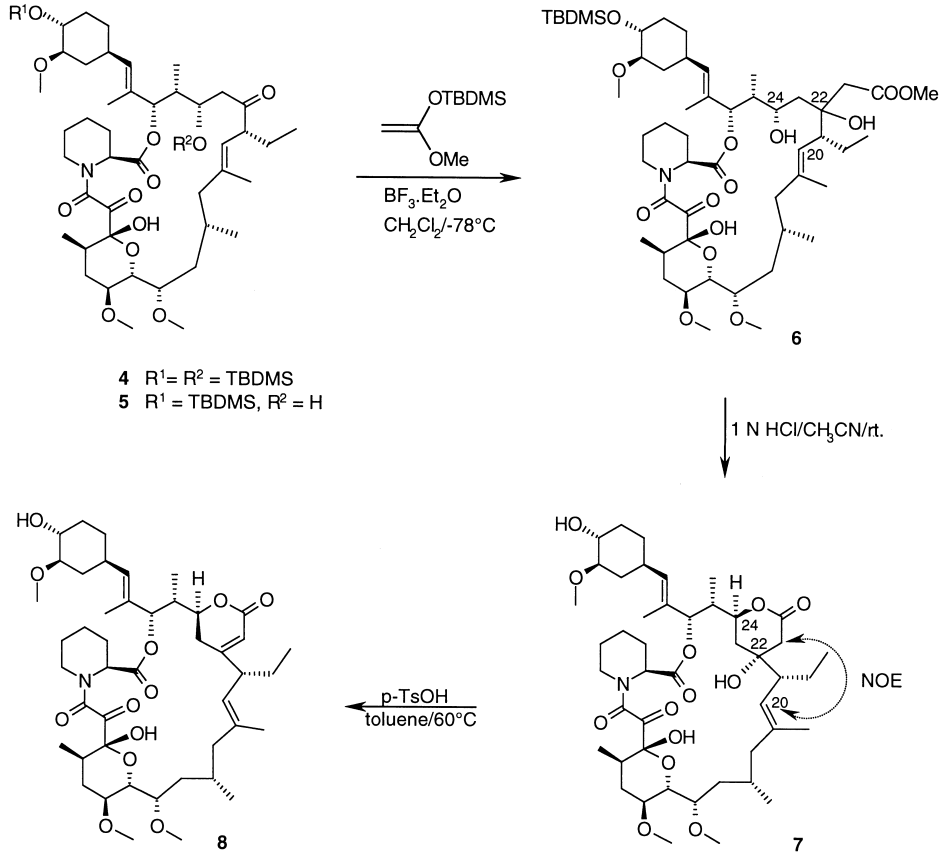
unchanged in a dedicated medicinal chemistry program. Here we report on the preparation of new ascomycin derivatives by selective C–C bond formation in the region C-22 to C-24 via aldol-type reactions. The synthetic strategy for selective C–C bond formation in the effector domain is shown in Scheme 1.

Results and Discussion

Regioselective C–C bond formation at carbon C-22

Ascomycin features four keto groups C-8, C-9, C-10 (C-10 masked as hemiketal) and C-22. (Fig. 1). The unique arrangement of three adjacent carbonyls in positions 8–10 suggests that nucleophiles should preferentially attack at the 9-keto group, especially under conditions where the free 10-carbonyl is in equilibrium with the hemiketal.[5] This expectation has been largely confirmed, but there are examples for selective reactions at the 22-ketone, e.g. treatment of ascomycin with ammonia or methylamine yielded C-9 imine and C-10 amine derivatives[2a,6] whereas hydrazine and hydroxylamine reacted selectively at the 22-keto group to give the corresponding hydrazone and oxime, respectively.[7] Alkyl and allyl Grignard reagents were reported to add to the 9-carbonyl, but with alkyl and aryllithium compounds preferential addition to the 22-keto group from the sterically less hindered β-face was observed.[8] Selectivity for C-9 versus C-22 attack in ascomycin is thus presumably determined by electronic as well as steric effects, which can further be modulated by ketone–hemiketal equilibrium and conformational changes.

Our efforts to achieve selective aldol reactions focused on acid catalysed reactions with silyl-enolates, since ascomycin is unstable in protic solvents under basic conditions.[1b,6,9] In a first attempt 24,33-*O*-bis(*tert*-butyldimethyl)silyl-ascomycin (**4**)[10] (Scheme 2) was treated with



Scheme 2.

tert-butyldimethylsilyloxy-1-methoxyethene[11a,b] in the presence of boron trifluoride etherate. However, no reaction was observed even after prolonged reaction times. We considered this failure to be due to steric hindrance by the bulky protective group (TBDMS) in position 24 of the ascomycin derivative, and therefore repeated the experiment using 33-*O*-(*tert*-butyldimethyl)silyl-ascomycin (**5**)[7a] with a free 24-OH group as starting material. Compound **5** readily and regioselectively reacted with *tert*-butyldimethylsilyloxy-1-methoxyethene to give after chromatographic purification 22-dihydro-22-(methoxy-carbonyl)-methyl-ascomycin derivative **6** in 36% yield (Scheme 2). Compound **6** was isolated as a single stereoisomer. The newly introduced methoxycarbonylmethyl group appears in the ^{1}H NMR spectrum ($CDCl_3$) as a singlet at 3.77 ppm and an AB system at 2.63 and 2.39 ppm (J_{AB}=17 Hz). The ^{13}C NMR spectrum deduced unambiguously addition at the C-22 due to the absence of the signal at δ=213.4 for C-22 carbonyl (signal of C-22 shifted to δ=76.1) and the unchanged signal for C-9 carbonyl at δ=195.9.

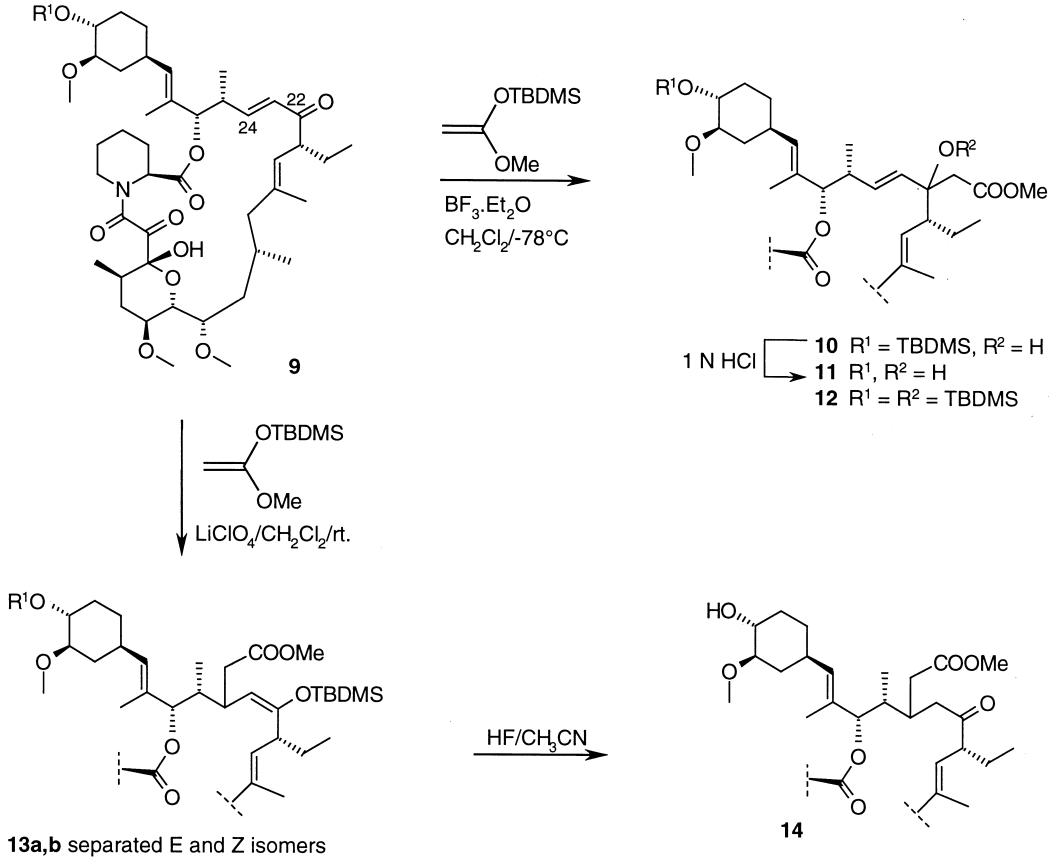
When the *tert*-butyldimethylsilyl group of **6** was removed under acidic conditions concomitant transesterification occurred yielding the lactone **7** which was further converted into its dehydration product **8** by treatment with a catalytic amount of *p*-toluenesulfonic acid in toluene at 60°C.

Compound **7** exists in $CDCl_3$ solution as a mixture of two rotamers regarding the amide bond. The signal of H-24 in the ^{1}H NMR spectrum of **7** is shifted downfield when compared to its position in the spectrum of **5** (3.93–4.62 ppm) due to the lactone formation. A positive NOE is observed between the signals at 4.93 ppm for H-20 and the AB system at 2. 65 and 2.55 ppm ($COCH_2$). This indicates that the OH substituent at C-22 is in an axial position and the configuration at C-22 is *R*. Attack of the silyl enol ether thus has occurred from the less bulky side of the molecule.

Regioselective C–C bond formation at C-22 and C-24

Introduction of a double bond ($\Delta^{23,24}$) created a new electrophilic center at carbon 24 and was expected to enable selective C–C bond formations at position 24. Enone **9**[12a,b] (Scheme 3) was prepared from protected ascomycin **5** by treatment with methanesulfonyl chloride and excess 4-dimethylaminopyridine. Treatment of **9** with *tert*-butyldimethylsilyloxy-1-methoxyethene in the presence of boron trifluoride etherate resulted, however, in a 1,2-addition to the 22-keto group (Scheme 3). The 22-β-hydroxy-methylester derivatives **10** (30%) and **12** (18%) were obtained as the main products together with traces of a third component (not elucidated). Deprotection of **10** was achieved with 1N HCl in acetonitrile to give compound **11** in 82% yield as a single isomer (configuration at the new stereogenic center in position 22 unknown, Scheme 3).

Predominant 1,4-addition was eventually achieved by replacing the catalyst boron trifluoride etherate by 3 mol% $LiClO_4$ in dichloromethane.[13] Under these conditions the Michael addition products **13a** (16%) and **13b** (29%) were



Scheme 3.

obtained as main products along with lower amounts (16%) of the 1,2-addtion product **12**. The compound **13a** exists in $CDCl_3$ solution as a mixture of (1:1) *trans–cis* amide rotamers in equal intensities, which made the interpretation of the spectrum difficult. Although the C–C bond formation at C-24 as well as the formed silyl enol ether at C22/23 of both **13a** and **13b** could be assigned from their NMR data, attempts to determine their absolute configuration at C-22, C-23 and C-24 via NMR spectroscopy failed. Deprotection of **13a** and **13b**, respectively, by treatment with aqueous HF in acetonitrile gave one single identical compound **14**. Consequently, compounds **13a** and **13b** are *E*/*Z* isomers regarding the formed silyl enol ether in position C22/23.

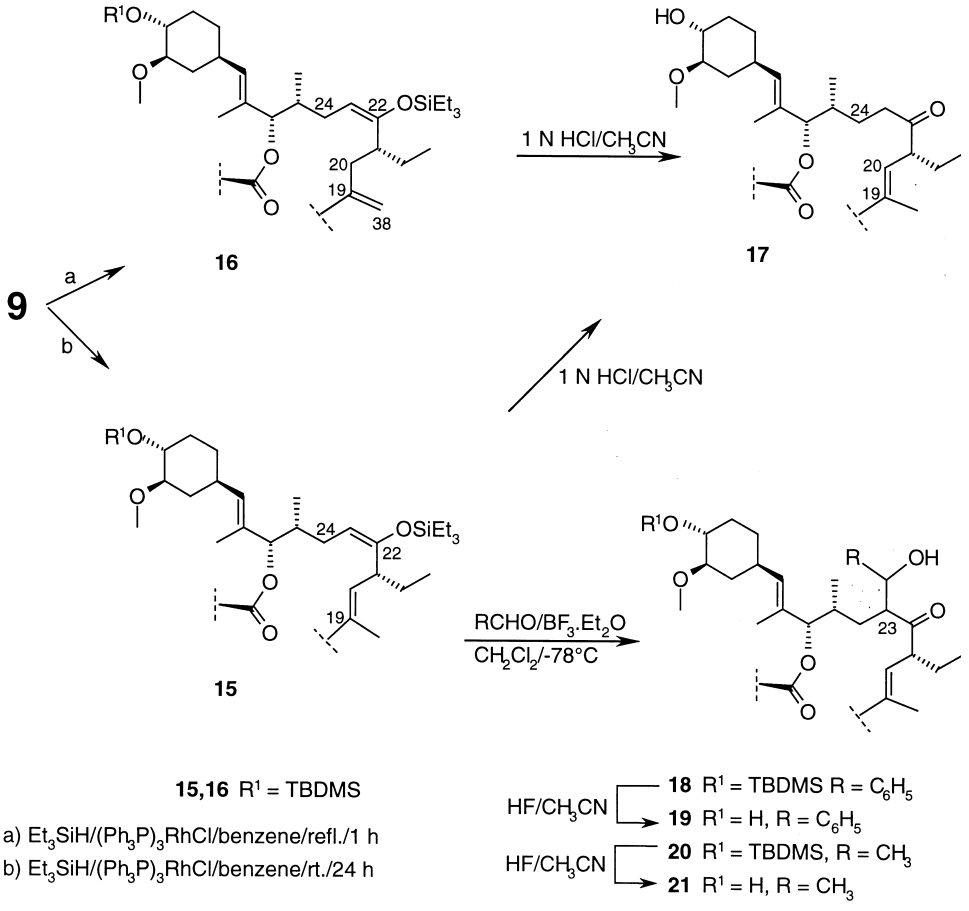
Regioselective C–C bond formation at position 23

In order to allow a selective C–C bond formation at position 23, regioselective conversion of the 22-carbonyl group into an enol ether with the double bond between positions 22 and 23 was envisaged. This was achieved by hydrosilylation of enone **9** (Scheme 4). Reaction of **9** with an excess of triethylsilane and a catalytic amount of Wilkinson's catalyst in benzene at room temperature for 24 h yielded the silyl enol ether **15** in 55% yield. Raising the temperature to 80°C in order to shorten the reaction time led to a complex mixture of compounds from which, besides **15** (15%), a new component **16** was isolated in 25% yield by multiple chromatography.

Compound **16** features an exocyclic C=CH_2 group as evidenced by 2-D $^1H/^{13}C$ NMR correlation (HMQC) analysis (new signal for olefinic protons at 4.68 and 4.61 ppm correlating with the signal for a C atom at 113.5 ppm). Obviously the C19/20 double bond was shifted into the C19/38 position under the influence of the Wilkinson's catalyst. Attempts to regenerate the 22-keto function of **16** led to reformation of the 19,20 double bond in the original conformation yielding **17**[12a,b] which was also obtained upon deprotection of the silyl enol ether **15** (Scheme 4).

The silyl ether **15** reacted with aldehydes (benzaldehyde, acetaldehyde) in the presence of boron trifluoride etherate to give the expected aldol products (**18**, 28% and **20**, 43% yield) under C–C bond formation at position 23 (Scheme 4). The compounds were obtained as single stereoisomers (configuration at the two new stereogenic centers unknown). Treatment with 2% HF in acetonitrile provided the deprotected analogues **19** and **21**, respectively (Scheme 4).

In summary, it has been shown that stereo- and regioselective alkylation at position 22, 23, and 24 in ascomycin can be achieved by acid catalysed aldol-type reactions in this complex molecule. In addition, the formation of a novel ascomycin derivative with a double bond shifted from the 19/20 to the exocyclic 19/38 position was observed.



Scheme 4.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 250 MHz (Bruker WM 250) and at 500 MHz (Bruker AMX 500) in $CDCl_3$ with $(Me_3)_4Si$ as internal standard. Due to hindered rotation the amide bond at room temperature most of the compounds existed in solution ($CDCl_3$) in two conformers (mixture of *trans–cis* amide rotameres), only data for the predominant conformer and relevant absorption are given. All mass spectra are fast atom bombardment (FAB) spectra (matrix: nitrobenzylic alcohol) and was recorded on a VG 70-SE instrument (VG Analytical) operating at 8 kV accelerating voltage. All reactions were monitored by thin-layer chromatography performed by use of silica gel F254 plates (Merck). Visualisation was performed with a solution of molybdato-phosphoric acid (20% in EtOH/H_2O, 3:1) followed by heating to 150°C or UV. Column chromatography was carried out on silica gel 60 (40–63 μm, Merck) using pressures up to 5 bars with the indicated solvent system. Tetrahydrofuran (THF) was obtained dry by distillation from $LiAlH_4$; all other solvents were dried by storing over 3- or 4-Å molecular sieves.

33-(*tert*-Butyldimethylsilyl)-22-dihydro-22-(methoxycarbonyl)methyl-ascomycin (6). A solution of 33-*O*-TBDMS-ascomycin **5** (1.36 g, 1.5 mmol) in CH_2Cl_2 (2 ml) was treated with boron trifluoride etherate (496 mg, 3.5 mmol) at −78°C under argon atmosphere. After 10 min, 1-*tert*-butyldimethylsilyloxy-1-methoxy-ethene (500 mg, 2.7 mmol) was added by drops, the mixture was warmed to −30°C and stirred for 3 h. The mixture was neutralised with sat. aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue (toluene/ethyl acetate 5:1) gave 529 mg (36%) of **6**. ^{1}H NMR ($CDCl_3$): δ 5.34 (s, H-26), 5.0 (d, J=9 Hz, H-29), 4.79 (d, J=10.4 Hz, H-20), 4.45 (br, d, J=10 Hz, H_e-6), 4.43 (s, 10-OH), 4.35 (d, J=1 Hz, H-22), 4.32 (d, J=4.1 Hz, H-2), 4.1 (dd, J_1=3.4 Hz, J_2=10.9 Hz, H-24), 3.76 (s, $COOCH_3$), 3.55 (d, J=9.3 Hz, H-15), 3.49 (d, J=9.7 Hz, H-14), 2.95 (m, H-32), 2.63, 2.39 (AB, J=17.5 Hz, CH_2COO), 1.85 (m, H-25), 1.66 (d, J=1 Hz, $28CH_3$), 1.44 (s, $19CH_3$), 0.77 (t, J=7.4 Hz, H-40), 0.07, 0.06 (2s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 195.9 (C-9), 173.9 ($COOCH_3$), 168.3 (C-11), 164.8 (C-8), 136.9 (C-19), 133.3 (C-28), 128.3,128.0 (C-20, C-29), 97.3 (C-10), 84.2 (C-32), 76.2 (C-22), 75.3, 74.1 (C-13, C-14, C-15), 74.7 (C-26), 73.9 (C-33), 71.8 (C-24), 58.1, 56.6, 56.2 ($3OCH_3$), 57.3 (C-2), 52.0 ($COOCH_3$), 50.8 (C-18), 48.5 (C-21), 45.3 (CH_2COO), 39.2 (C-6), 38.9 (C-23), 36.9 (C-31), 34.9, 34.7 (C-11, C-30), 33.8 (C-12, C-16), 32.0 (C-34), 31.0 (C-35), 27.7 (C-3, C-17), 25.8 ($SiC(CH_3)_3$), 24.7 (C-5), 23.5 (C-39), 22.0 (C-4), 21.3 ($17CH_3$), 16.3 ($11CH_3$), 15.9 ($19CH_3$), 14.8 ($28CH_3$), 13.3 (C-40), 9.5 ($25CH_3$), −4.5, −4.7 ($Si(CH_3)_2$). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{52}H_{89}NO_{14}SiLi$ *m/e* 986, found 986.

22-Dihydro-24-deoxy-(22b-oxo-tetrahydropyrano[22,24-*b,c*])-ascomycin (7). A solution of **6** (55 mg, 0.03 mmol) in acetonitrile (1 ml) was treated with 0.5 ml 1N HCl at rt for 1 h. The mixture was neutralised with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was successively washed with water and brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product purified by chromatography (hexane/ethyl acetate 1:3) gave **7** 31 mg (64%). ^{1}H NMR ($CDCl_3$): two conformers (2:1), signals of the major conformer: δ 5.21 (d, 2 Hz, H-26), 4.97 (d, J=9 Hz, H-29), 4.92 (d, J=10.2 Hz, H-20), 4.88 (d, J=4.9 Hz, H-2), 4.63 (ddd, J_1=2.3 Hz, J_2=11 Hz, J_3=13 Hz, H-24), 4.16 (s, OH), 3.75 (dd, J_1=2.5 Hz, J_2=9.5 Hz, H-14), 3.59 (m, H-15), 3.16 (s, OH), 3.02 (ddd, J_1=4.3 Hz, J_2=8 Hz, J_3=13 Hz, H-32), 2.65 and 2.55 (AB, J_{AB}=17 Hz, CH_2COO), 1.71 (m, H-23). ^{13}C NMR ($CDCl_3$): δ 196.0 (C-9), 171.7 (COO-lactone), 169.2 (C-1), 165.7 (C-8), 137.2 (C-19), 130.4 (C-28), 128.8 (C-29), 124.4 (C-20), 98.6 (C-10), 84.1 (C-32), 78.6 (C-24), 76.2 (C-15), 76.1 (C-26), 73.5 (C-33), 73.0 (C-13), 72.6 (C-14), 72.1 (C-22), 56.8 ($15\text{-}OCH_3$), 56.6 ($32\text{-}OCH_3$) 56.2 ($13OCH_3$), 52.3 (C-2), 50.1 (C-21), 49.4 (C-18), 43.9 (C-6), 39.3 (C-25), 39.1 (CH_2COO), 38.1 (C-11), 37.3 (C-23) 34.8 (C-30, C-31), 33.8 (C-16), 32.4 (C-12), 32.7, 31.2 (C-34), 30.7 (C-35), 25.9 (C-3, C-17), 24.2 (C-5), 23.8 (C-39), 20.7 (C-4), 20.1 ($17CH_3$), 16.1 ($11CH_3$), 15.6 ($19CH_3$), 14.3 ($28CH_3$), 12.4 (C-40), 10.5 ($25CH_3$). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{45}H_{71}NO_{13}Li$ *m/e* 840, found 840.

22-Deoxo-24-deoxy-(22b-oxo-22,22a-dihydro-pyrano-[22,24-*b,c*])-ascomycin (8). A solution of **7** (90 mg, 0.1 mmol) in toluene (1.5 ml) was treated with *p*-toluenesulfonic acid (3 mg) and heated at 60°C for 16 h. Purification of the mixture by chromatography (hexane/ethyl acetate 1:2→1:4) afforded 10 mg **8** (12%) as a colourless foam. ^{1}H NMR ($CDCl_3$): two conformers (4:5), signals of the major conformer: δ 5.79 (s, C=C*H*–COO), 5.24 (s, H-26), 5.09 (d, J=8.9 Hz, H-29), 4.98 (d, J=4.2 Hz, H-2), 4.93 (d, J=9 Hz, H-20), 4.18 (m, H-24), 3.88 (dd, J_1=2.5 Hz, J_2=9.5 Hz, H-14), 3.01 (m, H-23). ^{13}C NMR ($CDCl_3$): δ 168.7 (COO-lactone), 165.4 (C-1), 164.3 (C-8), 138.7 (C-19), 131.8 (C-28), 129.6 (C-29), 125.3 (C-20), 114.2 (C=*C*H–COO), 98.6 (C-10), 84.1 (C-32), 79.1 (C-24), 76.4 (C-15), 75.3 (C-26), 73.6 (C-13, C-33), 72.4 (C-14), 72.0 (C-14), 72.0 (C-22), 56.7, 56.5, 56.3 ($3OCH_3$), 52.6 (C-2).

33-(*tert*-Butyldimethylsilyl)-$\Delta^{23,24}$-22-dihydro-22-(methoxycarbonyl)methyl-ascomycin (10) and 33,22-bis(*tert*-butyldimethylsilyl)-$\Delta^{23,24}$-22-dihydro-22-(methoxycarbonyl)methyl-ascomycin (12)

According to the procedure as described for **6**, prepared from **9** (176 mg, 0.2 mmol), boron trifluoride etherate (85 mg, 0.6 mmol) and 1-*tert*-butyldimethylsilyloxy-1-methoxy-ethene (279 mg, 1.5 mmol) in CH_2Cl_2 (2 ml). Purification of the crude product by chromatography (hexane/ethyl acetate 6:1→4:1) gave 57 mg (30%) **10** along 39 mg of **12** (18%) as colourless foam.

Compound 10. ^{1}H NMR ($CDCl_3$): δ 5.57 (d, J=16 Hz, H-23), 5.25 (dd, J_1=8.5 Hz, J_2=16 Hz, H-24), 5.09 (s, H-26), 5.01 (d, J=9.1 Hz, H-29), 4.94 (d, J=1.5 Hz, 10-OH), 4.76 (br, d, J=4.5 Hz, H-20), 4.67 (d, J=10.4 Hz, H-2), 4,41 (br, d, J=14.6 Hz, H_e-6), 4.16 (s, OH), 3.76 (COOMe), 2.64 (s, $COCH_2$), 0.9 (s, $SiC(CH_3)_3$), 0.08 and 0.07 (2s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 196.7 (C-9), 174.0

(*C*OOMe), 169.0 (C-1), 165.6 (C-8), 136.2, 132.5, 131.7,130.6 (C-19, C-23, C-24, C-28), 129.6, 128,6 (C-20, C-29), 96.9 (C-10), 84.2 (C-32), 79.4 (C-22), 75,3, 75.2 (C-15, C-13,), 75.0 (C-26), 74.0 (C-14), 73.5 (C-33), 58.12, 57.0 ($3OCH_3$), 52.0 (C-2), 50.8 ($COOCH_3$), 42.2 (CH_2COO), 25.8 ($SiC(CH_3)_3$), −4.5, −4.7 ($Si(CH_3)_2$).

Compound 12. ^{1}H NMR ($CDCl_3$): δ 5.64 (d, J=16 Hz, H-23), 5.52 (d, J=1.5 Hz, 10-OH), 5.08 (s, H-26), 5.00 (m, H-29 and H-2), 4.98 (dd, J_1=8.9 Hz, J_2=16 Hz, H-24), 4.57 (d, J=10.7 Hz, H-20), 4.43 (br, d, J=10.4 Hz, H_e-6), 3.70 (COOMe), 2.76 and 2.70 ($J_{a,b}$=16.4 Hz, $COCH_2$), 0.08–0.065 (4s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 197.0 (C-9), 172.0 (*C*OOMe), 169.2 (C-1), 166.0 (C-8), 136.2,134.4, 130.7, 130.2 (C-19, C-23, C-24, C-28), 129.5, 128.7 (C-20, C-29), 96.9 (C-10), 84.2 (C-32), 79.0 (C-22), 75.0 (C-26), 73.5 (C-33), 55.8 (C-2), 51.5 ($COOCH_3$), 42.4 (CH_2COO), 26.0 ($SiC(CH_3)_3$), −1.6,-2.6, −4.5, −4.7 ($Si(CH_3)_2$). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{58}H_{101}NO_{13}Si_2Li$ *m/e* 1082, found 1082.

$\Delta^{23,24}$-22-Dihydro-22-(methoxycarbonyl)methyl-ascomycin (11). According to the procedure as described for **7**, a mixture of **10** (55 mg, 0.06 mmol) and 0.5 ml of 1 N HCl in acetonitrile (1 ml) was stirred for 1 h, and then worked up. The residue was purified by chromatography (hexane/ethyl acetate 1:5) to give 39 mg (82%) **11** as colourless foam. ^{1}H NMR ($CDCl_3$): δ 5.56 (d, J=16.1 Hz, H-23), 5.29 (dd, J_1=8.5 Hz, J_2=16.1 Hz, H-24), 5.12 (br, d, J=8.2 Hz, H-26), 5.06 (d, J=9.1 Hz, H-29), 4.91 (d, J=1 Hz, 10-OH), 4.76 (d, J=4.8 Hz, H-2), 4.69 (d, J=10.4 Hz, H-20), 4.43 (br, d, J=10.5 Hz, H_e-6), 4.17 (s, OH), 3.75 (s, $COOCH_3$), 3.61 (dd, J_1=2.1 Hz, J_2=9.6 Hz, H-15), 3.56 (d, J=9.6 Hz, H-14), 2.65 (d, J=1.3 Hz, $COCH_2$), 1.66 (s, $18CH_3$), 1.51 (s, $19CH_3$), 1.04 (d, J=6.3 Hz, $11CH_3$), 1.01 (d, J=6.5 Hz, $17CH_3$), 0.92 (d, J=7 Hz, $25CH_3$), 0.76 (t, J=7.5 Hz, H-40). ^{13}C NMR ($CDCl_3$): δ 196.6 (C-9), 173.9 ($COOCH_3$), 169.0 (C-1), 165.5 (C-8), 136.3 (C19), 132.6 (C-23), 131.6 (C-24), 131.0 (C-28), 129.6 (C-29), 128.6 (C20), 97.0 (C-10), 84.2 (C-32), 79,5 (C-26), 75.5 (C-22), 75.0 (C-15), 74.0 (C-33), 73.8 (C-13), 73.6 (C-14), 57.0, 56.6 ($2OCH_3$), 56.1 (C-2 and OCH_3), 52.0 ($COOCH_3$), 50.7 (C-18), 49.1 (C-21), 42.3 (CH_2COO), 39.0 (C-6), 38.2 (C-25), 34.9 (C-30, C-31), 34.7 (C-16), 34.5 (C-11), 32.3 (C-12), 31.2 (C-34), 30.6 (C-35), 28.1 (C-12), 27.8 (C-3), 24.4 (C-5), 22.2 (C-39), 21.4 (C-4), 21.1 ($17CH_3$), 16.5, 16.4 ($11CH_3$, $15CH_3$, $19CH_3$), 14.8 ($28CH_3$), 13.8 ($25CH_3$), 12.2 (C-40). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{46}H_{73}NO_{13}Li$ *m/e* 854, found 854.

Reaction with lithium perchlorate

A mixture of **9** (444 mg, 0.5 mmol) and 1-*tert*-butyldimethylsilyloxy-1-methoxy-ethene (242 mg, 1.3 mmol) in anhydrous CH_2Cl_2 (5 ml) was treated with lithium perchlorate (1.7 mg 0.016 mmol). After stirring at rt for 30 min, the mixture was diluted with saturated aqueous $NaHCO_3$ solution and ethylacetate. The organic layer was washed with water and brine, dried over $MgSO_4$ and concertrated in vacuo. Upon chromatography of the residue (hexane/ethyl acetate 6:1→4:1) 90 mg **13a** (16.6%) and 154 mg **13b** (29%) were obtained along 89 mg **12** (16%).

Compound 13a. ^{1}H NMR ($CDCl_3$): two conformers (1:1), due to complicated overlapping, signals of both conformers: δ 4.25 and 4.24 (d, J=10.5 Hz, H-23), 3.98 (s, OH), 3.79 and 3.78 (dd, J_1=1 Hz, J_2=9.5 Hz, H-14), 3.64 and 3.62 (s, $COOCH_3$), 2.94 (m, H-21), 2.43 (m, H-24), 2.55 (dd, J_1=3.5 Hz, J_2=13.6 Hz, CH_2COO) and 2.17 (dd, J_1=10 Hz, J_2=13.6 Hz, CH_2COO). ^{13}C NMR ($CDCl_3$): δ 195.9 (C-9), 172.9, 172.6 ($COOCH_3$), 170.1, 169.5 (C-1), 164.2, 163.5 (C-8), 154.2, 153.8 (C-22), 133.7, 132.9 (C-19), 131.6 (C-28), 130.2, 129.6 (C-29), 127.2, 126.8 (C-20), 109.4, 108.6 (C-23), 99.4, 98.2 (C-10), 84.4, 84.2 (C-32), 77.7 (C-15), 75.5, 75.4, 75.3 (C-13, C-33), 73.6 (C-14), 72.9, 72.0 (C-26), 57.9, 57.7, 56.9, 56.7, 56.4, 56.2,($3OCH_3$), 56.3, 53.5 (C-2), 51.5, 51.3 ($COOCH_3$), 49.6, 49.4 (C-18). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{58}H_{101}NO_{13}SiLi$ *m/e* 1082, found 1082.

Compound 13b. ^{1}H NMR ($CDCl_3$): δ 5.21 (d, J=8 Hz, H-29), 5.20 (d, J=4.9 Hz, H-2), 5.06 (d, J=8 Hz, H-20), 4.98 (d, J=8.7 Hz, H-26), 4.51 (d, J=7.4 Hz, H-23), 3.79 (dd, J_1=2.7 Hz, J_2=9.6 Hz, H-14), 3.63 (s, $COOCH_3$), 3.17 (dt, J_1=3.3 Hz, J_2=13 Hz, H_a-6), 2.86 (m, H-24), 2.74 (m, H-21), 2.59 (dd, J_1=4.1 Hz, J_2=15.7 Hz, CH_2COO), 2.25 (dd, J_1=11.2 Hz, J_2=15.7 Hz, CH_2COO), 2.03 (ddd, J_1=2.4 Hz, J_2=8.7 Hz, J_3=7 Hz, H-25), 0.89 ($SiC(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 195.6 (C-9), 173.0 ($COOCH_3$), 169.0 (C-1), 166.5 (C-8), 155.4 (C-22), 136.6 (C-19), 134.2 (C-29), 131.9 (C-28), 127.8 (C-20), 104.2 (C-23), 98.2 (C-10), 84.2 (C-32), 82.7 (C-15), 77.5, (C-26), 75.0 (C-33), 74.0 (C-13, C-14), 57.8, 57.3, 56.0 ($3OCH_3$), 51.8 ($COOCH_3$), 51.2 (C-2). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{58}H_{101}NO_{13}SiLi$ *m/e* 1082, found 1082.

24-Deoxy-24-(methoxycarbonyl)methyl-ascomycin (14). A solution of **13a** (110 mg, 0.1 mmol) in acetonitrile (2 ml) was treated with 40% aqueous HF solution (20 μl) at rt for 45 min. The mixture was neutralised with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3×5 ml). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography (hexane/ethyl acetate 1:2) yielded 53 mg (63%) **14** as a colourless foam.

According to the procedure above, a solution of **13b** (125 mg, 0.12 mmol) in acetonitrile (2 ml) was treated with 40% aqueous HF (20 μl) for 45 min and then worked up. Purification by chromatography afforded **14** 61 mg (62%). ^{1}H NMR ($CDCl_3$): two conformers (5:4), signals of the major conformer: δ 5.17 (s, H-26), 4.98 (m, H-20, H-29), 4.45 (t, J=3.7 Hz, H-2), 4.40 (d, br, J=10.7 Hz, H_{eq}-6), 3.82 (dd, J_1=2.4 Hz, J_2=9.5 Hz, H-14), 3.67 ($COOCH_3$), 3.01 (ddd, J_1=4.5 Hz, J_2=9 Hz, J_3=11.5 Hz, H-32). ^{13}C NMR ($CDCl_3$): δ 212.3 (C-22), 196.4 (C-9), 173.1 ($COOCH_3$), 169.4 (C-1), 165.6 (C-8), 138.7 (C-19), 131.6 (C-28), 128.7 (C-29), 123.7 (C-20), 98.0 (C-10), 84.2 (C-32), 79.8 (C-26), 75.9, 74.1 (C-13, C-15), 73.5 (C-33), 73.4 (C-14), 56.3 (C-2) 55.6 (C-21), 51.5 ($COOCH_3$), 48.5 (C-18), 40.0 (CH_2COO), 40.0 (C-6), 36.5 (C-25), 34.9 (C-31), 33.3 (C-16), 32.5 (C-12), 31.2 (C-34), 30.6 (C-35), 27.7 (C-17), 26.3 (C-3), 25.1 (C-39), 24.3 (C-5), 21.2 (C-4). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{46}H_{73}NO_{13}Li$ *m/e* 854, found 854.

Reactions with trietylsilane

33-(*tert*-Butyldimethylsilyl)-24-deoxy-22-dihydro-22-triethylsilyl enol ether ascomycin (15). A solution of **9** (500 mg, 0.563 mmol) and triethylsilane (561 mg, 5.6 mmol) in anhydrous benzene (86 ml) was treated with tris(triphenylphosphine)chlororhodium (32 mg, 0.034 mmol) under argon atmosphere at rt. After stirring for 24 h, the reaction mixture was concentrated in vacuo. Chromatography of the residue (hexane/ethyl acetate 8:1→3:1) gave 308 mg (55%) of **15** as colourless foam along 84 mg (17%) of 33-TBDMS-24-deoxy-ascomycin (**17**).

Compound 15. ^{1}H NMR ($CDCl_3$): isomers (5:2), signals of the major conformer: δ 5.15 (d, J=5.8 Hz, H-2), 5.11 (d, J=10 Hz, H-20), 4.99 (d, J=6 Hz, H-26), 4.7 (s, 10-OH), 4.5 (t, J=7 Hz, H-23), 3.85 (dd, J_1=3.2 Hz, J_2=9.5 Hz, H-14), 3.24 (m, H_e-6), 2.9 (m, H-32), 2.76 (m, H-21), 0.9 (s, $SiC(CH_3)_3$), 0.67 (m, $Si(CH_2CH_3)$, 0.59 ($Si(CH_2CH_3)$), 0.08, 0.06 (s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 195.7 (C-9), 169.2 (C-1), 166.2 (C-8), 154.0 (C-22), 135.8 (C-19), 131.6,131.4 (C-28, C-29), 128.2 (C-20), 103.7 (C-23), 98.3 (C-10), 84.2 (C-32), 78.1 (C-26), 75.2, (C-33, C-15), 74.1 (C-13), 52.1 (C-2) 48.3 (C-18), 46.0 (C-21), 44.0 (C-6), 25.8 ($SiC(CH_3)_3$), 5.8 ($SiCH_2CH_3$), −4.5, −4.7 ($Si(CH_3)_2$). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{55}H_{97}NO_{11}Si_2Li$ *m/e* 1010, found 1010.

To a solution of **9** (5 g, 5.63 mmol) and triethylsilane (5.61 g, 56 mmol) in benzene (65 ml) was added tris(triphenylphosphine)chlororhodium (320 mg, 0.34 mmol) and refluxed for 1 h. The mixture was filtered trough a pad of Celite and the solvent was removed in vacuo. The crude product was purified by multiple chromatography (toluene /ethylacetate 15:1→4:1) gave 1.4 g (25%) of **16** and 825 mg (15%) of **15**.

Compound 16. ^{1}H NMR ($CDCl_3$): δ 5.11 (s, H-26), 4.95 (br, d, J=9 Hz, H-29), 4.68, 4.61 (2s, H-38), 4.52 (br, H-2), 4.41 (d, J=16 Hz, H_e-6), 4.32 (dd, J_1=2.8 Hz, J_2=10.2 Hz, H-23), 3.79 (dd, J_1=1.7 Hz, J_2=10.5 Hz, H-14), 3.65 (m, H-15). ^{13}C NMR ($CDCl_3$): δ 196.4 (C-9), 169.3 (C-1), 164.8 (C-8), 151.9 (C-22), 145.2 (C-19), 131.1 (C-28), 128.0 (C-29), 113.5 (C-38), 104.7 (C-19), 97.2 (C-10), 84.3 (C-32), 80.5 (C-26), 75.2 (C-15, C-33), 73.2 (C-13), 72.5 (C-14), 58.0, 57.1, 56.2 ($3OCH_3$), 56.1 (C-2), 48.8 (C-18), 39.5 (C-21), 38.9 (C-6), 37.9 (C-20), 36.7 (C-35), 36.5 (C-16), 35.7 (C-25), 34.9, 34.8 (C-11,C-30), 33.8 (C-34), 32.5 (C-12), 31.6 (C-24), 31.0 (C-31), 27.5 (C-3), 27.0 (C-39), 25.9 ($Si(CH_3)_2$), 25.4 (C-17), 24.2 (C-5), 20.9 (C-4), 17.2 ($17CH_3$), 16.0 ($11CH_3$), 14.6 ($C\text{-}28CH_3$), 11.9 (C-40), 10.7 ($25CH_3$), 6.8, 5.3 ($SiCH_2CH_3$), −4.5, −4.7 ($Si(CH_3)_2$). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{55}H_{97}NO_{11}Si_2Li$ *m/e* 1010, found 1010.

33-(*tert*-Butyldimethylsilyl)-24-deoxy-23-(1-hydroxy-1-phenyl-methyl)-ascomycin (18). To a solution of **15** (100 mg, 0.1 mmol) in CH_2Cl_2 (3 ml) were added a drop of boron triflouride etherate and benzaldehyde (110 mg, 2 mmol) at −78°C under argon atmosphere. After stirring for 30 min the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted (3×10 ml) with CH_2Cl_2. The combined organic layers were subsequently washed with water and brine, dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography (hexane/ethyl acetate 4:1→3:1) supplied 28 mg (28%) of **18**. ^{1}H NMR ($CDCl_3$): δ 7.36–7.26 (m, C_6H_5), 5.21 (d, br, J=9 Hz, H-29), 4.81 (d, J=10 Hz, H-26), 4.67 (d, J=7 Hz, ($CHOHC_6H_5$), 4.43 (d, J=10.5 Hz, H-20), 4.42 (d, J=5 Hz, H-2), 4.36 (m, H_e-6), 4.19 (s,10OH), 3.84 (dd, J_1=2.2 Hz, J_2=9.6 Hz, H-14), 3.6 (m, H-15), 3.51 (m, H-13), 2.62 (d, J=2 Hz, $CHOHC_6H_5$), 0.9 ($SiC(CH_3)_3$), 0.04 (s $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 215 (C-22), 196.9 (C-9), 169.1 (C-1), 164.6 (C-8), 141.6, 128.5, 128.0, 126.4 (C_6H_5), 138.7 (C-19), 136.0 (C-29), 130.7 (C-28), 123.4 (C-20), 97.7 (C-10), 85.6 (C-26), 84.1 (C-32), 75.5 (C-15), 75.2 (C-33), 74,2 ($CHOHC_6H_5$), 73.4 (C-13), 72.7 (C-14), 58.9 (C-23), 57.9, 57.1, 56.3 ($3OCH_3$), 56.6 (C-21), 55.9 (C-2), 49.9 (C-18), 38.9 (C-6), 36.3 (C-16), 36.12 (C-31), 34.9 (C-30), 34.8 (C-11), 33.9 (C-34), 32.6 (C-12), 30.5 (C-35), 30.2 (C-24), 28.2 (C-3), 25.9 ($SiC(CH_3)_3$), 24.8 (C-17), 24.0 (C-5), 23.6 (C-39), 20.2 (C-4), 18.7 ($17CH_3$), 17.3 ($25CH_3$), 15.9 ($11CH_3$), 15.2 ($19CH_3$), 11.3 (C-40), 10.9 ($28CH_3$), −4.4, −4.7 ($Si(CH_3)_2$).

24-Deoxy-23-(1-hydroxy-1-phenyl-methyl)-ascomycin (19). Deprotection of compound **18** was carried out as described for **14**. A solution of **18** (66 mg, 0.06 mmol) in acetonitrile (1 ml) was treated 40% aqueous HF (10 μl). Purification by chromatography (hexane/ethyl acetate 1:2→1:3) supplied 37 mg (70%) of **19** as a colourless foam. ^{1}H NMR ($CDCl_3$): δ 7.36–7.26 (m, C_6H_5), 5.22 (d, br, J=9 Hz, H-29), 4.81 (d, J=10 Hz, H-26), 4.65 (d, J=7 Hz, ($CHOHC_6H_5$), 4.61 (d, br, J=10.5 Hz, H-20), 4.42 (d, J=5 Hz, H-2), 4.38 (dd, J_1=4.2 Hz, J_2=13.5 Hz, H_e-6), 4.19 (s,10OH), 3.85 (dd, J_1=2.2 Hz, J_2=9.6 Hz, H-14), 3.6 (m, H-15), 3.51 (dt, J_1=4.6 Hz, J_2=9.6 Hz, H-13), 2.72 (d, br, J=9.8 Hz, OH). ^{13}C NMR ($CDCl_3$): δ 214.7 (C-22), 196.9 (C-9), 164.6 (C-8), 141.7, 128.5, 128.0, 126.4 (C_6H_5-), 138.7 (C-19), 135.5 (C-29), 131.0 (C-28), 123.5 (C-20), 97.7 (C-10), 85.7 (C-26), 84.1 (C-32), 75.5 (C-15), 74.3 ($CHOHC_6H_5$), 73.5 (C-13, C-33), 72.7 (C-14), 58.9 (C-23), 30.4 (C-24). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{50}H_{75}NO_{12}Li$ *m/e* 881, found 881.

33-(*tert*-Butyldimethylsilyl)-24-deoxy-23-(1-hydroxy-ethyl)-ascomycin (20). Compound **20** was prepared from **15** (150 mg, 0.15 mmol) and acetaldehyde (33 mg, 0.75 mmol) according to the procedure as described for **18**. Purification of the crude product by chromatography (hexane/ethyl acetate 3:1) provided 60 mg (43%) **20.** ^{1}H NMR ($CDCl_3$): δ 5.26 (d, J=7.7 Hz, H-29), 4.87 (d, J=9.8 Hz, H-26), 4.73 (d, br J=10 Hz, H-20), 4.45 (d, J=5.4 Hz, H-2), 4.40 (d, br, J=9.6 Hz, H_e-6), 4.21 (s, 10OH), 3.89 (m, $CHOHCH_3$), 3.86 (dd, J_1=2.3 Hz, J_2=9.6 Hz, H-14), 3.63 (m, H-15), 2.93 (ddd, J_1=4.5 Hz, J_2=8.5 Hz, J_3=11 Hz, H-32), 2.69 (ddd, J_1=1.8 Hz, J_2=3.8 Hz, J_3=11.2 Hz, H-23), 2.4 (d, J=2 Hz, OH) 2.33 (m, H-11), 1.18 (d, J=6.5 Hz, $CHOHCH_3$), 0.97 (d, J=7 Hz, $11CH_3$). ^{13}C NMR ($CDCl_3$): δ 215.9 (C-22), 197.0 (C-9), 169.2 (C-1), 164.6 (C-8), 138.7 (C-19), 136.0 (C-29), 130.71 (C-28), 123.4 (C-20), 97.7 (C-10), 85.8 (C-26), 84.1 (C-32), 75.5 (C-15), 75.1 (C-33), 73.4 (C-13), 72.8 (C-14), 67.6 ($CHOHCH_3$), 57.8, 56.8, 56.26 ($3OCH_3$), 57.3 (C-23), 56.6 (C-21), 56.0 (C-2), 49.9 (C-18), 36.9 (C-6), 36.3 (C-16), 36.1 (C-31), 34.9 (C-30). 34.7 (C-11),

33.8 (C-25, C-34), 32.6 (C-12), 30.5 (C-35), 29.3 (C-24), 28.1 (C-3), 25.9 ($Si(CH_3)_3$), 25.0 (C-17), 24.3 (C-5), 23.9 (C-39), 20.5 ($CHOHCH_3$), 20.4 (C-4), 18.8 ($17CH_3$), 17.5 ($25CH_3$), 16.0 ($11CH_3$), 15.2 ($19CH_3$), 11.6 (C-40), 10.9 ($28CH_3$), −45, −4.7 ($Si(CH_3)_2$).

24-Deoxy-23-(1-hydroxy-ethyl)-ascomycin (21). Deprotection of compound **20** was carried out as described for **14**. Compound **20** (60 mg, 0.06 mmol) was treated in acetonitrile (1 ml) with 40% aqueous HF (10 μl) for 1.5 h. Purification by chromatography (hexane/ethyl acetate 1:4) supplied 35 mg (67%) of **21** as a colourless foam. ^{1}H NMR ($CDCl_3$): δ 4.87 (d, J=9.8 Hz, H-26), 4.73 (d, br J=10 Hz, H-20), 4.45 (d, J=5.4 Hz, H-2), 4.40 (dd, br, J=9.6 Hz, H_e-6), 3.89–3,82 (m, C*H*OHCH$_3$, H-14), 3.63 (m, H-15), 2.71 (m, H-23), 1.18 (d, J=6.5 Hz, CHOHC*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 215.9 (C-22), 197.0 (C9), 169.2 (C-1), 164.6 (C-8), 138.7 (C-19), 136.0 (C-29), 131.0 (C-28), 123.4 (C-20), 97.7 (C-10), 85.7 (C-26), 84.1 (C-32), 75.5 (C-15), 73.8 (C-33), 73.4 (C-13), 72.8 (C-14), 67.7 (*C*HOHCH$_3$). FABMS: Calcd $(M+Li)^+$ Calcd for $C_{45}H_{73}NO_{12}Li$ *m/e* 826, found 826.

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