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The Total Synthesis of (±)-Fumimycin

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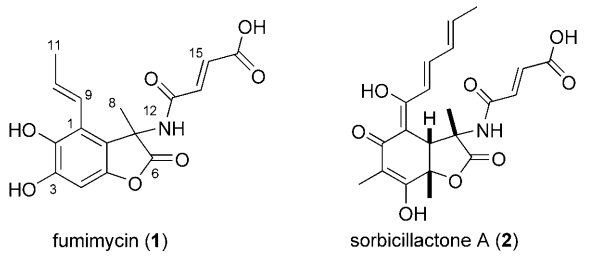
Abstract: The antibiotic agent fumimycin has been synthesized for the first time. This natural product was found to inhibit the bacterial peptide deformylase and may represent a lead structure to a class of novel antibacterials. Our synthetic strategy towards fumimycin involved the following steps: Dakin oxidation of an aldehyde functionality, conversion of an oxime through radical fragmentation to form an *N*-diphenylphosphoryl group, construction of an α-trisubstituted amine by 1,2-addition to a ketimine, a Claisen rearrangement with subsequent transition-metal-catalyzed olefin isomerization to install a propenyl chain and final amidation.

Keywords: amines · fumimycin · inhibitors · natural products · total synthesis

Introduction

In 2007, Kim and co-workers reported the structural determination and the biological activity of fumimycin (**1**).[1] It was isolated from the fermentation broth of *Aspergillus fumisynnematus* F746, a fungus that was collected from a Korean soil sample. The mycotoxin[2] fumimycin displayed high activity in a screening of peptide deformylase (PDF) inhibition. Peptide deformylase,[3] a member of a unique subclass of metalloenzymes, catalyzes the removal of the formyl group at the *N*-terminus of bacterial proteins. This mechanism is essential for prokaryotic growth, but not for mammalian cells. The screening for PDF inhibitors thus allows identification of selective mechanism-based antibacterial agents, which are potentially non-toxic. Several studies have shown that PDF inhibitors act as broad-spectrum antibacterial agents.[4] Fumimycin showed inhibition of *Staphylococcus aureus* PDF, specifically two methicillin-resistant *S. aureus* (MRSA) strains and two quinolone-resistant *S. aureus* (QRSA) strains, with an IC_{50} value of 4.1 μM. Therefore, fumimycin may represent a lead structure to a class of novel antibacterials.[5]

Based on HRMS and NMR spectroscopy studies (^1H, ^{13}C, COSY, DEPT, HMQC spectra), the structure of fumimycin was proposed to be an alanine unit linked to a phenyl group at the α-carbon, possessing both lactone and amide moiety (Scheme 1). Structurally, fumimycin is related to sorbicillactone A (**2**),[6] a sponge-derived natural product possessing antileukemic activity. They both possess a six-membered ring fused to a five-membered lactone as skeleton and have an α-trisubstituted amine linked to a fumaric acid moiety. Fumimycin shows optical activity, but its absolute configuration is as yet unknown.



Scheme 1. Fumimycin (**1**) and structurally related sorbicillactone A (**2**).

Despite the interest in new antibacterials,[7] no synthesis of fumimycin has been achieved so far. The significant biological properties and the distinctive structural features of this natural compound prompted us to approach the synthesis of fumimycin. We have previously reported methods for the asymmetric construction of α-trisubstituted amines[8] and our preliminary results towards a derivative of fumimycin.[9] Since we were not able to convert this material into fumimycin itself, we explored systematically alternatives to synthesize the natural product. Herein, we describe our various

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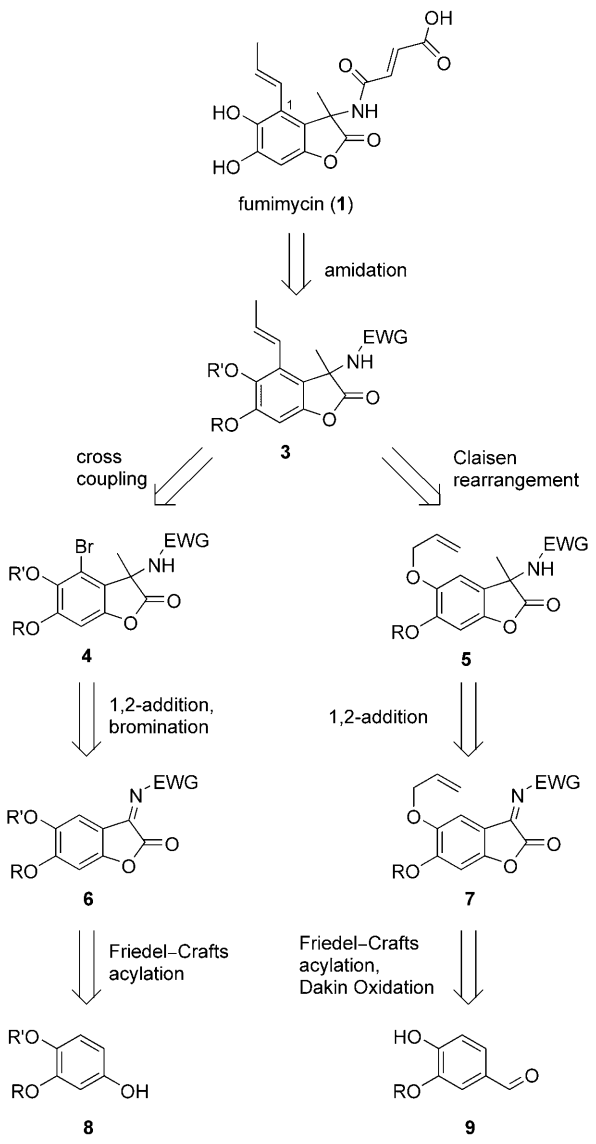
strategies towards (±)-fumimycin and the 18step sequence, accomplishing the first total synthesis.

Results and Discussion

Synthetic plan: Fumimycin (**1**) is a highly polar compound with a carboxylic acid group and two phenol groups. To simplify synthetic handling, we decided to deprotect these functionalities at the very end of the synthesis. We intended to introduce the fumaric acid side chain by amidation of an α-trisubstituted amine, which derives from **3** through *N*-deprotection (Scheme 2).

The 1-propenyl side chain at C1 could be installed by a palladium-catalyzed cross-coupling of aryl bromide **4** with 1-propene boronic acid[10] or (trialkyl)-1-propenyl stannane[11] (left pathway). Alternatively, we planned a two-step sequence involving a Claisen rearrangement and subsequent olefin isomerization, by using allyl ether **5** (right pathway). Key steps in both pathways are the construction of the α-trisubstituted amine through the 1,2-addition of a methyl Grignard reagent to ketimines **6** and **7**, respectively.[12] To improve the reactivity of the ketimines, we postulated that an electron withdrawing group at the nitrogen atom had to be installed. In the left pathway, selective bromination of the aromatic core is necessary. Both pathways include Friedel–Crafts acylation with an oxalyl derivative and lactonization. Starting materials for these synthetic routes are the bis-protected phenol **8** and *para*-hydroxy benzaldehyde (**9**), which would be allylated and oxidized prior to acylation.

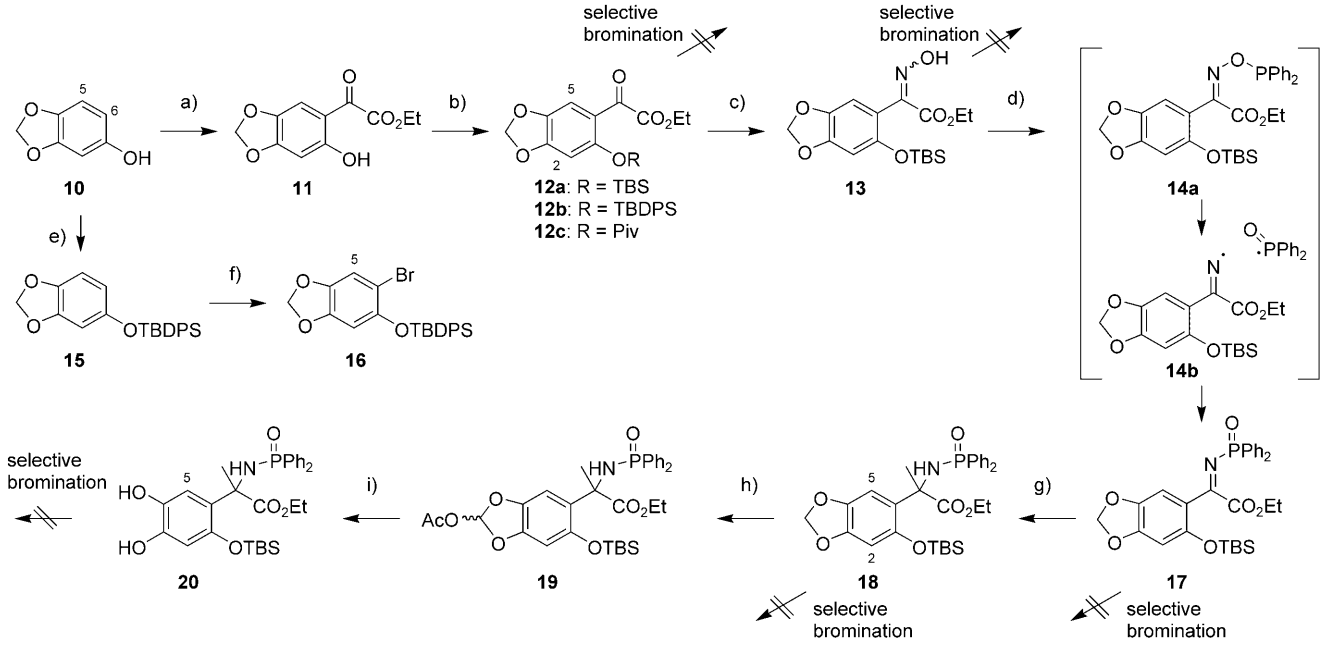


Scheme 2. Planned synthetic pathways towards **1**.

Approach by bromination: We first pursued the synthetic pathway through the bromination/cross-coupling sequence (Scheme 3), starting from sesamol (**10**). We hoped to achieve selective bromination at C5 of one of the intermediate compounds of the sequence. To that end, we tried to block the C2- and C6-position of **10** by silylation of the hydroxyl group, installing the very bulky *tert*-butyldiphenylsilyl group (TBDPS), to form **15**. Subsequent reaction of **15** with *N*-bromosuccinimide (NBS) gave exclusively the undesired 6-bromo compound. Unfortunately, the same regioselectivity was observed when a lithiation/bromination process was employed.[13] To overcome this obstacle we decided to use the reactivity at the C6 position of **10** in a Friedel–Crafts acylation with ethyl oxalyl chloride to produce **11**. The phenol group of **11** was again protected with bulky groups (**12a**: *tert*-butyldimethylsilyl (TBS), **12b**: TBDPS, **12c**: pivaloyl) and bromination was performed. In all cases, only bromination at C2 was observed, indicating that the electronic effects for the aromatic substitution dominated over steric factors.

All attempts to achieve direct condensation of ketone **12a** with phosphonamide[14] to form **17** gave only unsatisfying yields; therefore we used a more reliable two-step procedure. Ketone **12a** was converted with hydroxylamine to the oxime **13** in 96% yield (*E*/*Z* 1:1), followed by transformation to the ketimine **17**. This reaction proceeds via the unstable intermediate **14a**.[15] At elevated temperature, homolytic cleavage of the N–O bond forms the radical **14b** and the phosphorous-centered radical, the recombination of which forms the diphenylphosphoryl group in **17**. Neither **13** nor **17** could be brominated. Attempted palladium-catalyzed C–H activation approaches were also unsuccessful.[16]

Due to the presence of the phosphoryl group, the ketimine functionality in **17** is eletrophilic enough to react readily with methylmagnesium chloride to form the α-trisubstituted amine **18** in 65% yield. Deprotection of the two dioxolane oxygen atoms required a two-step sequence: oxidation of **18** by using $Pb(OAc)_4$[17] to form the *ortho*-ester **19** through a radical mechanism (as 1:1 mixture of diastereomers), followed by an acidic cleavage under mild conditions to give catechol **20** in only moderate yields. To our disappointment, all attempts at the halogenation of **20** failed. We also considered allylation of the 4-hydroxyl group to install



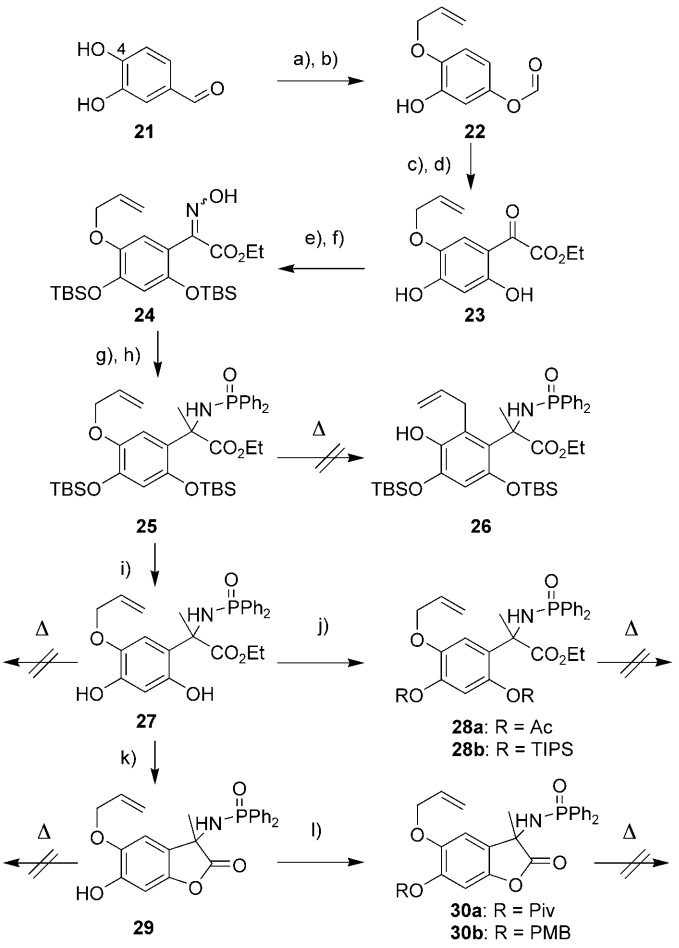
Scheme 3. Attempts at selective bromination: a) $ClCOCO_2Et$, $AlCl_3$, CH_2Cl_2, 0°C, 90%; b) for **12a**: TBSCl, *i*Pr_2NEt, CH_2Cl_2, RT, 95%; for **12b**: TBDPSCl, *i*Pr_2NEt, CH_2Cl_2, RT, quant, for **12c**: PivCl, Et_3N, CH_2Cl_2, RT, 89%; c) $H_2NOH{\cdot}HCl$, pyridine, EtOH, reflux, 96%; d) $ClPPh_2$, Et_3N, *n*-hexane/CH_2Cl_2 1:1, −50°C, 70%; e) TBDPSCl, *i*Pr_2NEt, CH_2Cl_2, RT, 99%; f) NBS, CH_3CN, 60°C; or *s*BuLi THF/*n*-hexane 2:1, −78°C, Br_2; g) MeMgCl, toluene, 0°C, 65%; h) $Pb(OAc)_4$, benzene, 80°C; i) AcOH, MeOH, 60°C, 61% over two steps.

the desired olefinic side chain through a Claisen rearrangement, but selective allylation could not be accomplished. Due to the problems with reactivity and selectivity we decided to turn our attention to the synthetic pathway through the Claisen rearrangement.

Approach by Claisen rearrangement starting from catechol 21: For this route we started with the regioselective allylation of the *para*-hydroxyl group in **21** (Scheme 4). Oxidation of the aldehyde took place without epoxidation of the allylic group and was best accomplished with oxone to yield the unstable formate ester **22**, which was hydrolyzed with a methanolic $NaHCO_3$ solution.[18] The highest yield for the following Friedel–Crafts acylation was achieved by using $TiCl_4$ at −15°C to give **23**. Protection of both hydroxyl groups and oxime formation gave **24** in high yields. Installation of a diphenylphosphoryl group and subsequent methyl Grignard addition was carried out as described above and gave rise to α-trisubstituted amine **25**. Heating of **25** led to decomposition instead of the Claisen rearrangement, most likely due to the thermal instability of the TBS groups. Therefore we cleaved the TBS group using tetrabutylammonium fluoride (TBAF) to form the diol **27**. Heating of **27** gave complex mixtures through partial lactonization. To avoid this side reaction, both phenol groups were protected. Unfortunately, neither the bis-acetate **28a** nor the bis-triisopropylsilyl (TIPS) ether **28b** underwent the [3,3] rearrangement. Conversion of **27** through acid catalysis with *para*-toluenesulfonic acid (PTSA) gave lactone **29**, which again decomposed when heated.

We reasoned that the Claisen rearrangement product with the free hydroxyl groups might be unstable under the high temperature conditions. Hence, we tested protecting groups again, but neither pivaloyl ester **30a** nor *para*-methoxy benzyl (PMB) ether **30b** could be converted into the desired product. We tested solvents with different polarities, the use of Lewis acid catalysts, microwave conditions and high pressure in a sealed tube for the Claisen rearrangement, all without success. Considering the lack of reactivity, we reasoned that this system is especially sensitive to steric hindrance. Adjacent to the allyl ether, even groups with moderate bulkiness prevent the formation of the favorable chair-like transition state for the [3,3] rearrangement. Consequently, we decided to use the small methyl group as protecting group.

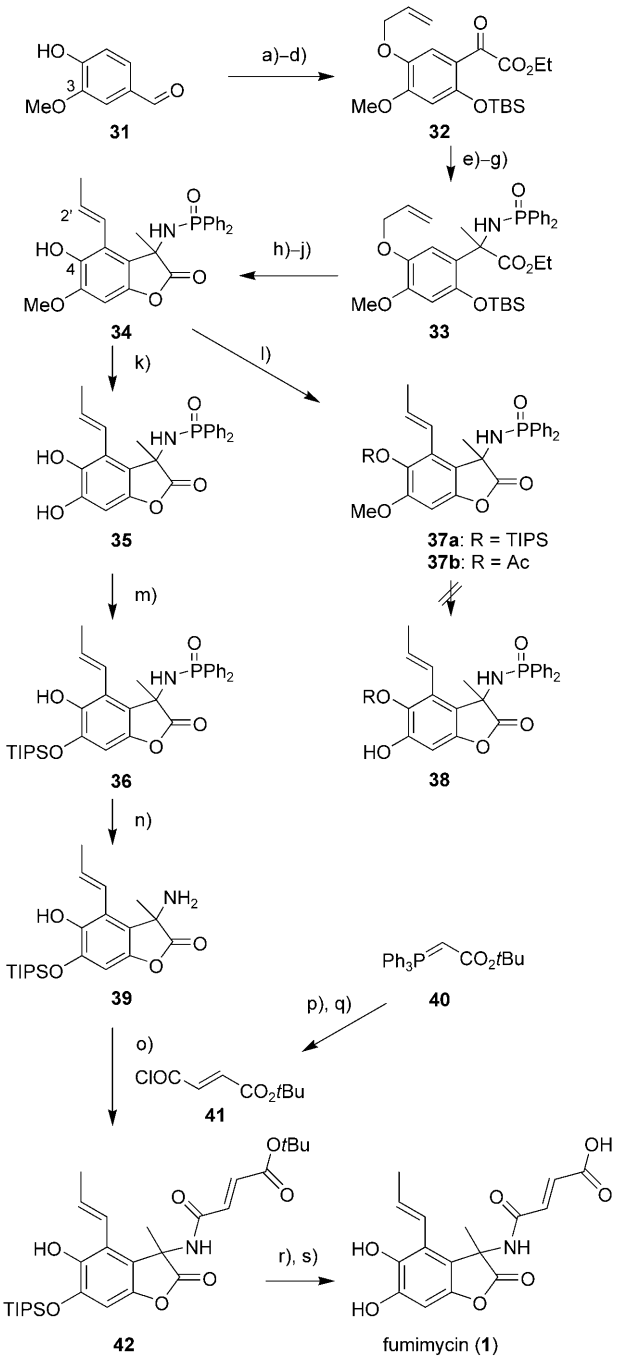
Approach by Claisen rearrangement starting from vanillin (31): For this synthetic pathway (Scheme 5, for intermediate structures, see Scheme 6 in the Experimental Section), vanillin (**31**) could be employed as an inexpensive starting material. At the beginning of this route, the same steps as discussed in Scheme 4 were utilized. Vanillin (**31**) was allylated, then subjected to a Dakin oxidation by using $H_2O_2/B(OH)_3/H_2SO_4$,[19] under which conditions the initially formed formate ester was directly hydrolysed. Friedel–Crafts acylation and silylation gave ketone **32** in good yield. As described above, the procedure for oxime formation, diphenylphosphoryl formation and 1,2-addition gave amine **33**, which we hoped would undergo Claisen rearrangement. Heating of **33** in DMF to 120°C lead to lactonization, enabled through the thermal instability of the TBS ether under these conditions. Further heating to reflux finally gave rise to the desired



Scheme 4. Synthetic route starting with selective allylation of catechol **21**, attempts for Claisen rearrangement: a) allyl bromide, Na_2CO_3, DMF, 35 °C, 65 %; b) oxone, DMF, RT; c) $NaHCO_3$, MeOH, H_2O, RT, 75 % over two steps; d) $ClCOCO_2Et$, $TiCl_4$, CH_2Cl_2, −15 °C, 73 %; e) TBSCl, iPr_2NEt, CH_2Cl_2, RT, 81 %; f) $H_2NOH{\cdot}HCl$, pyridine, EtOH, reflux, 98 %; g) $ClPPh_2$, Et_3N, THF, −50 °C, 61 %; h) MeMgBr, toluene, −78 °C, 73 %; i) TBAF, AcOH, THF, 0 °C→RT, 73 %; j) for **28a**: AcCl, Et_3N, CH_2Cl_2, RT, 73 %; for **28b**: TIPSCl, iPr_2NEt, DMAP, CH_2Cl_2, RT, 83 %; k) PTSA, toluene, reflux, 49 %; l) for **30a**: PivCl, Et_3N, DMAP, CH_2Cl_2, RT, 80 %; for **30b**: PMBCl, K_2CO_3, DMF, 65 °C, 48 %. DMAP = 4-dimethylaminopyridine.

[3,3] rearrangement. Subsequent isomerization of the terminal double bond to provide olefin **34** was accomplished under rhodium catalysis[20] in excellent yield (*trans*/*cis* 10:1). Undesired *cis*-**34** could be separated from *trans*-**34** through column chromatography with 10 % $AgNO_3$.[21]

Our initial plan was to protect the newly generated phenol group with subsequent cleavage of the methyl ether, avoiding the generation of the free catechol group. But demethylation of the silylether **37a** was unsuccessful due to the hindrance of the adjacent TIPS group. We synthesized acetate **37b** and subjected it to demethylation conditions employing MgI_2,[22] hoping that the acetate might coordinate to the metal and facilitate the reaction. Disappointingly, again only decomposition could be observed. We did not succeed in the demethylation of **34** before screening a multi-



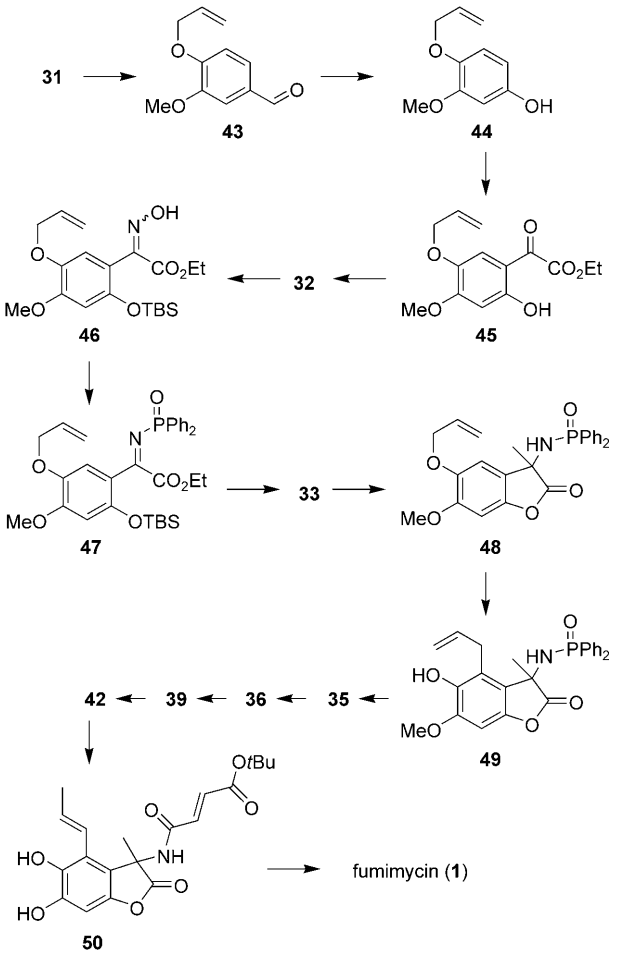
Scheme 5. Total synthesis of fumimycin (**1**): a) allyl bromide, K_2CO_3, acetone, reflux, 85 %; b) H_2O_2, $B(OH)_3$, H_2SO_4, THF, 30 °C, 81 %; c) $ClCOCO_2Et$, $TiCl_4$, CH_2Cl_2, −15 °C, 82 %; d) TBSCl, iPr_2NEt, CH_2Cl_2, RT; e) $H_2NOH{\cdot}HCl$, pyridine, EtOH, reflux, 91 % over two steps; f) $ClPPh_2$, Et_3N, THF, −50 °C, 74 %; g) MeMgBr, toluene, −78 °C, 65 %; h) DMF, 120 °C; i) DMF, reflux, 55 % over two steps; j) $RhCl_3{\cdot}H_2O$, EtOH, 45 °C, 96 % (*trans*/*cis* 10:1); k) BI_3, CH_2Cl_2, −20 °C, 90 %; l) for **37a**: TIPSCl, iPr_2NEt, DMAP, CH_2Cl_2, RT, 64 %; for **37b**: AcCl, Et_3N, DMAP, CH_2Cl_2, RT, 89 %; m) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −15 °C→RT, 83 %; n) HCl, MeOH, 55 °C; o) **41**, pyridine, CH_2Cl_2, 0 °C→RT, 24 % over two steps; p) $CHOCO_2H{\cdot}H_2O$, THF, RT, 60 %; q) oxalyl chloride, DMF, CH_2Cl_2, 0 °C→RT, quant; r) TBAF, AcOH, THF, RT, 93 %; s) TFA, CH_2Cl_2, 0 °C→RT, quant.

tude of deprotection conditions. One problem was the cyclization of the 4-hydroxyl function with the sp^2 carbon at 2′.[23] With boron triiodide[24] this side reaction could be suppressed, giving the desired diol **35** in 90% yield, which was then selectively monosilylated to form **36**, employing triisopropylsilyl triflate and 2,6-lutidine. Deprotection of the nitrogen in the presence of the silyl group required carefully chosen acidic conditions. The crude product was directly used in the next step, avoiding the isolation of the free amine. For the amidation of **39**, acid chloride **41** was employed, derived from phosphoranylidene **40**.[25] The reaction sequence gave amide **42** only in low yield, which was then subjected to desilylation with TBAF/AcOH. As the last step of the sequence, the cleavage of the *tert*-butyl ester was achieved with trifluoroacetic acid, yielding (±)-fumimycin (**1**) in quantitative yield.

The NMR spectral data, as well as the HRMS and IR data are consistent with those for the natural (−)-fumimycin.

Conclusion

In summary, three synthetic pathways towards the synthesis of fumimycin have been pursued. Ultimately, a pathway starting from vanillin (**31**) and employing a Claisen rearrangement culminated in the synthesis of (±)-fumimycin (**1**) in 18 steps (16-step longest linear sequence, 2.2% overall yield). We have reported the first total synthesis of this natural product possessing highly interesting biological properties.



Scheme 6. Overview of further structures in the synthesis towards Fumimycin.

Experimental Section

4-Allyloxy-3-methoxybenzaldehyde (43): Allylbromide (0.69 mL, 0.95 g, 7.9 mmol, 1.2 equiv) was added to a suspension of vanillin (**31**) (1.00 g, 6.57 mmol, 1.00 equiv) and K_2CO_3 (1.82 g, 13.1 mmol, 2.00 equiv) in acetone (10 mL). The mixture was heated to reflux for 6 h. After filtration, the filtrate was concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1→3:1) afforded the allylether **43** as a colorless oil (1.07 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3H), 4.70 (dm, J = 5.4 Hz, 2H), 5.34 (dq, J = 10.5, 1.2 Hz, 1H), 5.44 (dq, J = 17.3, 1.4 Hz, 1H), 6.08 (ddt, J = 17.3, 10.5, 5.3 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 7.42 (brs, 1H), 7.43 (dd, J = 7.5, 1.9 Hz, 1H), 9.85 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 69.6, 109.2, 111.8, 118.6, 126.4, 130.0, 132.1, 149.7, 153.3, 190.7 ppm; IR (KBr): $\tilde{\nu}$ = 3080, 2938, 2728, 1586, 1268, 1136, 935, 810, 732 cm^{-1}; MS (EI): m/z (%): 192 (100) [M^+], 152 (69) [$C_8H_7O_3^+$]. HRMS (EI): m/z: calcd for $C_{11}H_{12}O_3$: 192.0786; found 192.0790.

4-Allyloxy-3-methoxyphenol (44): Boric acid (3.22 g, 52.0 mmol, 5.00 equiv) was suspended in THF (30 mL), H_2O_2 (30% in H_2O, 3.4 mL), and H_2SO_4 (1.5 mL). After stirring for 30 min, **43** (2.00 g, 10.4 mmol, 1.00 equiv) was added as a solution in THF (10 mL) within 15 min. After additional stirring for 5 h, the mixture was filtered. The filtrate was neutralized by addition of sat. aqueous $NaHCO_3$ solution (100 mL); the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1→3:1) afforded the phenol **44** as a brown oil (1.48 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 4.52 (dm, J = 5.6 Hz, 2H), 5.12 (brs, 1H), 5.25 (dq, J = 10.4, 1.3 Hz, 1H), 5.36 (dq, J = 17.3, 1.5 Hz, 1H), 6.08 (ddt, J = 17.3, 10.5, 5.6 Hz, 1H), 6.31 (dd, J = 8.6, 2.8 Hz, 1H), 6.46 (d, J = 2.8 Hz, 1H), 6.75 ppm (dd, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.8, 71.1, 100.7, 105.9, 115.5, 117.8, 133.7, 141.9, 150.5, 150.6 ppm; IR (KBr): $\tilde{\nu}$ = 3360, 2940, 2603, 1607, 1455, 1217, 952, 722 cm^{-1}; MS (EI): m/z (%): 180 (44) [M^+], 139 (100) [$C_7H_7O_3^+$]; HRMS (EI): m/z: calcd for $C_{10}H_{12}O_3$: 180.0786; found 180.0786.

Ethyl (5-allyloxy-2-hydroxy-4-methoxyphenyl)oxoacetate (45): A solution of **44** (100 mg, 0.550 mmol, 1.00 equiv) and ethyl oxalyl chloride (0.074 mL, 91 mg, 0.67 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was cooled to −15 °C. $TiCl_4$ (1.0 M in CH_2Cl_2, 0.67 mL, 0.67 mmol, 1.2 equiv) was added over 20 min. After additional stirring for 40 min, the mixture was poured into ice-cooled 1 M HCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (4×15 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) afforded the phenol **45** as a yellow solid (126 mg, 82%). M.p. 56–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3H), 3.94 (s, 3H), 4.44 (q, J = 7.1 Hz, 2H), 4.54 (dt, J = 5.6, 1.4 Hz, 2H), 5.32 (dq, J = 10.5, 1.3 Hz, 1H), 5.41 (dq, J = 17.2, 1.5 Hz, 1H), 6.05 (ddt, J = 17.2, 10.5, 5.5 Hz, 1H), 6.49 (s, 1H), 7.25 (s, 1H), 11.80 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 56.4, 62.5, 70.6, 100.5, 108.4, 114.4, 118.6, 132.8, 141.4, 159.2, 162.6, 162.7, 187.2 ppm; IR (KBr): $\tilde{\nu}$ = 3089, 2912, 1725, 1511, 1201, 1007, 953, 757 cm^{-1}; MS (FAB): m/z (%): 281 (83)

[M^+], 239 (46) [$C_{11}H_{11}O_6^+$], 207 (88), [$C_{11}H_{11}O_4^+$], 165 (36), [$C_8H_5O_4^+$]; HRMS (FAB$^+$) m/z: calcd for $C_{14}H_{17}O_6$: 281.1025; found 281.1023.

Ethyl (5-allyloxy-2 *tert*-butyldimethylsilanyloxy-4-methoxyphenyl)oxo-acetate (32): A solution of **45** (11.57 g, 41.29 mmol, 1.00 equiv) and *tert*-butyldimethylchlorosilane (8.08 g, 53.7 mmol, 1.30 equiv) in CH_2Cl_2 (20 mL) was cooled to 0 °C. iPr$_2$NEt (11 mL, 8.0 g, 62 mmol, 1.5 equiv) was added within 5 min. The mixture was stirred at 0 °C for 4 h, followed by stirring at RT for 1 d. The reaction was quenched by addition of H_2O (300 mL), the aqueous layer was extracted with EtOAc (4×250 mL). The combined organic extracts were washed with H_2O (300 mL) and brine (300 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 7:1→4:1) afforded the silylether **32** as a yellow oil (15.42 g, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.28 (s, 6H), 0.96 (s, 9H), 1.35 (t, J = 7.2 Hz, 3H), 3.87 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 4.57 (dt, J = 4.6, 1.4 Hz, 2H), 5.29 (dq, J = 10.5, 1.4 Hz, 1H), 5.43 (dq, J = 17.2, 1.4 Hz, 1H), 6.06 (ddt, J = 17.2, 10.5, 5.5 Hz, 1H), 6.39 (s, 1H), 7.27 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −3.8, 13.9, 19.0, 26.1, 56.0, 61.7, 70.1, 103.3, 113.4, 116.4, 118.5, 132.7, 142.8, 153.5, 155.8, 165.0, 185.6 ppm; IR (KBr): $\tilde{\nu}$ = 3083, 2932, 1744, 1605, 1511, 1366, 1221, 1019, 886, 788 cm^{-1}; MS (EI): m/z (%): 394 (3) [M^+], 337 (100) [$C_{16}H_{21}O_6Si^+$], 321 (18) [$C_{17}H_{25}O_4Si^+$]. HRMS (EI): m/z: calcd for $C_{20}H_{30}O_6Si$: 394.1812; found 394.1809.

Ethyl [5-allyloxy-2-(*tert*-butyldimethylsilanyloxy)-4-methoxyphenyl]-(hydroxy imino) acetate (46): A mixture of **32** (20.82 g, 52.77 mmol, 1.00 equiv), hydroxylamine hydrochloride (7.33 g, 106 mmol, 2.00 equiv), EtOH (175 mL), and pyridine (41 mL, 40 g, 510 mmol, 9.7 equiv) was heated to reflux for 70 min. The reaction was diluted with H_2O (300 mL) and extracted with EtOAc (4×250 mL). The combined organic extracts were washed with H_2O (200 mL) and brine (200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:1→3:1) afforded the oxime **46** as 1:1 mixture of separable *E*/*Z* isomers as a yellow oil (20.67 g, 96 %). Isomer **13a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6H), 0.93 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 3.83 (s, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.54 (dt, J = 5.5, 1.4 Hz, 2H), 5.26 (dq, J = 10.4, 1.4 Hz, 1H), 5.38 (dq, J = 17.3, 1.4 Hz, 1H), 6.05 (ddt, J = 17.3, 10.4, 5.5 Hz, 1H), 6.39 (s, 1H), 6.95 (s, 1H), 10.51 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.1, 14.0, 18.4, 25.8, 55.8, 61.7, 70.4, 104.2, 114.2, 114.7, 118.1, 133.2, 142.5, 148.3, 148.6, 151.4, 162.8 ppm; IR (KBr): $\tilde{\nu}$ = 3436, 2931, 1737, 1512, 1414, 1260, 1154, 1050, 944, 784 cm^{-1}; Isomer **13b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 6H), 0.92 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 3.84 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 4.53 (dt, J = 5.6, 1.4 Hz, 2H), 5.25 (dq, J = 10.5, 1.4 Hz, 1H), 5.38 (dq, J = 17.2, 1.4 Hz, 1H), 6.07 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 6.43 (s, 1H), 6.84 (s, 1H), 9.64 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.5, 14.0, 18.0, 25.6, 55.8, 61.8, 70.6, 104.0, 112.0, 115.2, 118.0, 133.3, 142.1, 147.8, 148.7, 151.3, 163.3 ppm; IR (KBr): $\tilde{\nu}$ = 3406, 2931, 1728, 1510, 1411, 1261, 1147, 993, 838 cm^{-1}; mixture of isomers: MS (EI): m/z (%): 409 (54) [M^+], 368 (46) [$C_{17}H_{26}NO_6Si^+$], 352 (100) [$C_{16}H_{22}NO_6Si^+$]; HRMS (EI): m/z: calcd for $C_{20}H_{31}NO_6Si$: 409.1921; found 409.1921.

Ethyl [5-allyloxy-2-(*tert*-butyldimethylsilanyloxy)-4-methoxyphenyl]-(diphenyl phosphorylimino) acetate (47): A solution of **46** (1:1 mixture of *E*/*Z* isomers, 7.55 g, 18.4 mmol, 1.00 equiv) in THF (40 mL) and Et$_3$N (2.6 mL, 1.9 g, 18 mmol, 1.0 equiv) was cooled to −50 °C (acetonitrile/dry ice bath). Chlorodiphenylphosphine (3.4 mL, 4.1 g, 18 mmol, 1.0 equiv) was added as a solution in THF (8.0 mL) within 15 min. The dry ice was removed from the cool bath and the reaction was allowed to warm slowly. After 4 h H_2O (150 mL) was added, the mixture was extracted with EtOAc (4×100 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1→1:1) afforded the ketimine **47** as an orange oil (8.10 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.26 (s, 6H), 0.91 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 3.86 (s, 3H), 4.38 (q, J = 7.2 Hz, 2H), 4.60 (dt, J = 5.5, 1.4 Hz, 2H), 5.29 (dq, J = 10.5, 1.4 Hz, 1H), 5.38 (dq, J = 17.3, 1.4 Hz, 1H), 6.06 (ddt, J = 17.3, 10.5, 5.5 Hz, 1H), 6.39 (s, 1H), 7.40–7.50 (m, 6H), 7.52 (s, 1H), 7.80–8.00 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −3.6, 13.7, 19.2, 26.3, 56.0, 62.4, 70.4, 103.4, 114.4, 117.8 (d, J_P = 10.5 Hz), 118.3, 128.3 (d, J_P = 12.8 Hz), 131.4 (d, J_P = 2.5 Hz), 131.7 (J_P = 9.3 Hz), 133.3, 134.0 (d, J_P = 133.9 Hz), 142.8, 152.9, 155.2, 165.0 (d, J_P = 15.5 Hz), 169.0 ppm (d, J_P = 7.6 Hz); IR (KBr): $\tilde{\nu}$ = 3438, 3059, 2929, 2645, 1591, 1370, 1216, 983, 841 cm^{-1}; MS (EI): m/z (%): 552 (6) [M^+], 552 (22) [$C_{29}H_{35}NO_6PSi^+$], 536 (72) [$C_{28}H_{31}NO_6SiP^+$], 201 (100); HRMS (EI): m/z: calcd for $C_{32}H_{40}NO_6SiP$: 593.2363; found 593.2365.

Ethyl 2-[5-allyloxy-2-(*tert*-butyldimethylsilanyloxy)-4-methoxyphenyl]-2-diphenylphosphinoylamino-propionate (33): A solution of **47** (10.67 g, 17.97 mmol, 1.00 equiv) in toluene (240 mL) was cooled to −78 °C. MeMgBr (3 M in Et$_2$O, 12 mL, 36 mmol, 2.0 equiv) was added dropwise. After stirring for 3 h sat. aqueous $KHSO_4$ solution (600 mL) was added. The phases were separated; the aqueous layer was extracted with EtOAc (3×150 mL). The combined organic extracts were washed with brine (130 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1→2:3) afforded the amine **33** as a highly viscous brown oil (7.11 g, 65 %). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 0.24 (s, 3H), 0.33 (s, 3H), 0.94 (s, 9H), 1.14 (t, J = 7.1 Hz, 3H), 1.83 (s, 3H), 3.79 (s, 3H), 4.06 (dq, J = 10.8, 7.1 Hz, 1H), 4.24 (dq, J = 10.8, 7.1 Hz, 1H), 4.38 (m$_c$, 2H), 5.20 (dq, J = 10.5, 1.5 Hz, 1H), 5.39 (dq, J = 17.3, 1.5 Hz, 1H), 6.04 (ddt, J = 17.3, 10.5, 5.3 Hz, 1H), 6.45 (s, 1H), 6.88 (s, 1H), 7.28–7.34 (m, 2H), 7.40–7.56 (m, 4H), 7.62–7.70 (m, 2H), 7.90–7.96 ppm (m, 2H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = −2.6, 15.3, 20.3, 25.8 (d, J_P = 4.1 Hz), 27.6, 57.3, 62.4, 63.1, 72.4, 105.5, 116.5, 118.0, 126.4, 129.9 (d, J_P = 12.7 Hz), 130.2 (d, J_P = 12.5 Hz), 133.0 (d, J_P = 2.6 Hz), 133.4 (d, J_P = 2.8 Hz), 133.5 (J_P = 9.5 Hz), 133.7 (J_P = 9.5 Hz), 136.1 (d, J_P = 129.4 Hz), 136.5, 137.1 (d, J_P = 131.9 Hz), 143.5, 159.1, 151.5, 176.4 (d, J_P = 8.7 Hz) ppm; IR (KBr): $\tilde{\nu}$ = 3335, 2932, 1735, 1611, 1510, 1391, 1245, 1123, 913, 839 cm^{-1}; MS (EI): m/z (%): 609 (16) [M^+], 568 (52) [$C_{30}H_{39}NO_6PSi^+$], 552 (100) [$C_{29}H_{35}NO_6SiP^+$], 536 (78); HRMS (EI): m/z: calcd for $C_{33}H_{44}NO_6SiP$: 609.2676; found 609.2673.

5-Allyloxy-3-diphenylphosphinoylamino-6-methoxy-3-methyl-3*H*-benzofuran-2-one (48): A solution of **33** (505 mg, 0.828 mmol) in DMF (5.0 mL) was heated to 120 °C for 19 h. The solvent was removed under reduced pressure. The lactone **48** was obtained as a brown solid and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 3H), 3.77 (s, 3H), 4.43 (m$_c$, 2H), 5.28 (dq, J = 10.6, 1.4 Hz, 1H), 5.41 (dq, J = 17.3, 1.4 Hz, 1H), 6.06 (ddt, J = 17.3, 10.6, 5.5 Hz, 1H), 6.35 (s, 1H), 7.06 (s, 1H), 7.28–7.58 (m, 8H), 7.82–7.90 ppm (m, 2H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 27.7 (d, J_P = 5.2 Hz), 56.2, 59.0, 70.5, 95.8, 111.2, 118.0 (d, J_P = 2.0 Hz), 118.2, 128.3 (d, J_P = 12.9 Hz), 128.5 (d, J_P = 12.7 Hz), 131.4 (J_P = 10.1 Hz), 131.6 (d, J_P = 128.7 Hz), 131.6 (d, J_P = 2.5 Hz), 131.9 (J_P = 9.7 Hz), 132.1 (d, J_P = 2.7 Hz), 132.7 (d, J_P = 130.2 Hz), 133.0, 144.9, 146.7, 151.1, 179.0 ppm (d, J_P = 4.2 Hz); IR (KBr): $\tilde{\nu}$ = 3079, 2843, 1628, 1439, 1190, 1034, 856 cm^{-1}; MS (EI): m/z (%): 449 (36) [M^+], 408 (3) [$C_{22}H_{19}NO_5P^+$], 380 (100); HRMS (EI): m/z: calcd for $C_{25}H_{24}NO_5P$: 449.1392; found 449.1394.

4-Allyl-3-diphenylphosphinoylamino-5-hydroxy-6-methoxy-3-methyl-3*H*-benzo-furan-2-one (49): A solution of crude **48** (1.70 g, 2.79 mmol) in DMF (75 mL) was heated to reflux for 39 h. The solvent was removed under reduced pressure; the residue was dissolved in EtOAc (200 mL). The mixture was washed with half-saturated aqueous NaCl solution (3× 175 mL) and with brine (175 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1 + 5 % MeOH) afforded the lactone **49** as a brown solid (920 mg, 55 % over two steps). M.p. 200–202 °C; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.70 (s, 3H), 3.18 (dm, J = 15.3 Hz, 1H), 3.55 (ddm, J = 15.3, 7.1 Hz, 1H), 3.86 (s, 3H), 4.89 (dddd, J = 10.3, 3×1.5 Hz, 1H), 4.89 (dddd, J = 17.2, 3× 1.6 Hz, 1H), 5.55 (d, 9.3 Hz), 5.95 (dddd, J = 17.2, 10.3, 7.1, 5.0 Hz, 1H), 6.58 (s, 1H), 7.21 (s, 1H), 7.36–7.44 (m, 4H), 7.46–7.54 (m, 2H), 7.72–7.80 ppm (m, 4H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 27.5 (d, J_P = 8.0 Hz), 30.7, 57.7, 61.1 (d, J_P = 6.4 Hz), 95.7, 116.2, 120.6, 125.8, 129.8 (d, J_P = 12.9 Hz), 130.0 (d, J_P = 12.8 Hz), 133.4, 133.5 (J_P = 10.3 Hz), 133.6, 133.8 (J_P = 9.9 Hz), 134.8 (d, J_P = 129.3 Hz), 135.0 (d, J_P = 125.7 Hz), 138.5, 143.0, 147.4, 149.9, 180.8 ppm; IR (KBr): $\tilde{\nu}$ = 3441, 2932, 2468, 1636, 1358, 1188, 1027, 943, 822 cm^{-1}; MS (EI): m/z (%): 449 (18) [M^+], 232 (22), 218 (100), 201 (84); HRMS (EI): m/z: calcd for $C_{25}H_{24}NO_5P$: 449.1392; found 449.1395.

3-Diphenylphosphinoylamino-5-hydroxy-6-methoxy-3-methyl-4-[(*E*)-propenyl]-3*H*-benzofuran-2-one (34): A mixture of **49** (299 mg, 0.666 mmol,

1.00 equiv) and rhodium(III)chloride hydrate (12.8 mg, 33.3 μmol, 0.050 equiv) in EtOH (9.0 mL) was heated to 45 °C. After 4 h, the reaction was allowed to cool to RT and filtered through a 3 cm pad of celite. The filtrate was concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:2+5% MeOH→3:2+10% MeOH) afforded the lactone **34** as a light brown solid (*E*/*Z* 10:1, 288 mg, 96%; an analytical portion was separated by flash chromatography on silica gel with 10% $AgNO_3$ to give pure *E* product). M.p. 199–200 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 1.70 (d, J = 1.4 Hz, 3H), 1.82 (dd, J = 6.6, 1.5 Hz, 3H), 3.85 (s, 3H), 6.47 (dq, J = 15.8, 1.5 Hz, 1H), 6.52 (s, 1H), 6.62 (dq, J = 15.8, 6.6 Hz, 1H), 7.31–7.37 (m, 2H), 7.41–7.48 (m, 3H), 7.52–7.60 (m, 3H), 7.68–7.74 ppm (m, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ = 20.0, 26.4 (d, J_P = 9.3 Hz), 57.0, 60.4, 94.8, 118.7, 122.8, 124.2, 129.0 (d, J_P = 13.1 Hz), 129.4 (d, J_P = 13.1 Hz), 132.9 (d, J_P = 130.6 Hz), 133.0 (d, J_P = 2.5 Hz), 133.0 (J_P = 10.5 Hz), 133.1 (J_P = 10.4 Hz), 133.4, 133.6, 133.8 (d, J_P = 126.1 Hz), 142.9, 146.5, 150.0, 181.0 ppm; IR (KBr): $\tilde{\nu}$ = 3487, 3242, 2975, 2848, 1631, 1469, 1314, 1174, 1038, 924 cm^{-1}; MS (EI): *m*/*z* (%): 449 (24) [M^+], 406 (14), 218 (68), 201 (100); HRMS (EI): *m*/*z*: calcd for $C_{25}H_{24}NO_5P$: 449.1392; found 449.1400.

5,6-Dihydroxy-3-diphenylphosphinoylamino-3-methyl-4-((*E*)-propenyl)-3*H*-benzofuran-2-one (35): A solution of BI_3 (1.10 g, 2.81 mmol, 2.50 equiv) in CH_2Cl_2 (8.0 mL) was slowly added at −20 °C to a suspension of **34** (506 mg, 1.13 mmol) in CH_2Cl_2 (10 mL). After 50 min, the reaction was poured into ice-cooled $Na_2S_2O_3$ solution (60 mL). The resulting mixture was extracted with EtOAc (4×60 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), followed by drying over Na_2SO_4. Removal of the solvent and column chromatography (cyclohexane/EtOAc 3:2+5% MeOH) afforded **35** as a light brown solid (440 mg, 90%). M.p. 136 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 1.77 (s, 3H,), 1.80 (d, J = 3.9 Hz, 3H), 6.68 (d, J = 11.0 Hz, 1H), 6.64–6.60 (m, 2H), 6.64 (s, 1H), 6.97 (s, 1H), 7.32–7.38 (m, 2H), 7.44–7.54 (m, 3H), 7.56–7.68 (m, 3H), 7.80–7.88 (m, 2H), 9.87 ppm (s, 1H);^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 20.8, 27.2 (d, J_P = 9.1 Hz), 61.1 (d, J_P = 2.0 Hz), 99.1, 117.8, 123.3, 125.1, 129.7 (d, J_P = 13.2 Hz), 130.2 (d, J_P = 12.6 Hz), 133.5 (d, J_P = 10.6 Hz), 133.5 (d, J_P = 2.9 Hz), 133.7 (d, J_P = 10.4 Hz), 133.8 (d, J_P = 129.3 Hz), 134.0 (d, J_P = 2.5 Hz), 134.5, 135.1 (d, J_P = 124.7 Hz), 142.4, 147.4, 147.9, 181.9 ppm. IR (ATR): $\tilde{\nu}$ = 2980, 1790, 1628, 1437, 1174, 1145, 1026, 918 cm^{-1}. MS (FAB): *m*/*z* (%): 436 (52) [(M+H)$^+$], 218 (96), 201 (58), 154 (100), 133 (90); HRMS (FAB): *m*/*z*: calcd for $C_{24}H_{23}NO_5P$ [M+H]: 436.1314; found 436.1312.

3-Diphenylphosphinoylamino-5-hydroxy-3-methyl-4-((*E*)-propenyl)-6-triisopropylsilanyloxy-3*H*-benzofuran-2-one (36): 2,6-Lutidine (0.11 mL, 99 mg, 0.93 mmol, 5.0 equiv) and TIPSOTf (0.11 mL, 0.13 g, 0.43 mmol, 2.3 equiv) were added to a suspension of **35** (80.6 mg, 0.185 mmol) in CH_2Cl_2 (3.0 mL) at −15 °C. The mixture was slowly allowed to warm to RT and stirred for 9 h. The reaction was quenched with water (30 mL), and the resulting mixture was extracted with EtOAc (4×10 mL). The combined organic layers were washed with water (2×30 mL) and brine (30 mL), followed by drying over Na_2SO_4. Removal of the solvent and column chromatography (cyclohexane/EtOAc 3:2→1:1) afforded **36** (91.0 mg, 83%) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, J = 7.4 Hz, 9H), 1.13 (d, J = 7.4 Hz, 9H), 1.33 (sept, J = 7.4 Hz, 3H), 1.73 (s, 3H), 1.91 (d, J = 5.4 Hz, 3H), 3.62 (d, J = 6.0 Hz, 1H), 5.84 (s, 1H), 6.35 (s, 1H), 6.58–6.63 (m, 2H), 7.30–7.46 (m, 6H), 7.68–7.82 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 17.9, 17.9, 19.8, 25.8 (d, J_P = 8.3 Hz), 59.2 (d, J = 2.3 Hz), 98.9, 116.8, 121.8, 127.8, 127.9 (d, J_P = 13.0 Hz), 128.4 (d, J_P = 12.6 Hz), 131.4 (d, J_P = 10.1 Hz), 131.7 (d, J_P = 2.8 Hz), 131.7 (d, J_P = 131.7 Hz), 132.0 (d, J_P = 2.8 Hz), 132.3 (d, J_P = 125.0 Hz), 132.4 (d, J_P = 10.0 Hz), 133.2, 142.0, 143.5, 145.2, 178.8 ppm; IR (KBr): $\tilde{\nu}$ = 2932, 1740, 1559, 1388, 1252, 1168, 1123, 1021 cm^{-1}; MS (FAB): *m*/*z* (%): 592 (18) [(M+H)$^+$], 375 (20) [$C_{21}H_{31}O_4Si^+$], 331 (66), 218 (100), 201 (92); HRMS (FAB): *m*/*z* calcd for $C_{33}H_{43}NO_5SiP$ [M+H]: 592.2648; found 592.2646.

(*E*)-3-(4-*tert*-Butoxy-4-oxobut-2-enamido)-5-hydroxy-3-methyl-6-triisopropylsilanyloxy-3*H*-benzofuran-2-one (42): Compound **36** (65.0 mg, 0.149 mmol) was dissolved in HCl (0.5 M in MeOH, 2.0 mL) and heated to 55 °C. After 3.5 h the solvent was removed in vacuo. The residue was suspended in CH_2Cl_2 (1.0 mL) and cooled to 0 °C. Pyridine (0.12 mL, 0.12 g, 1.5 mmol, 10 equiv) and a solution of the acid chloride **41** (0.32 mmol, 1.3 equiv) in CH_2Cl_2 (0.70 mL) were added dropwise. After 1 h, the mixture was allowed to warm to RT, followed by stirring for another 2 h. The reaction was quenched with water (20 mL), and the resulting mixture was extracted with EtOAc (4×15 mL). The combined organic layers were washed with water (4×20 mL) and brine (20 mL), followed by drying over Na_2SO_4. Removal of the solvent and column chromatography (cyclohexane/EtOAc 5:1→2:1) afforded **42** as a light brown oil (19.4 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, J = 7.4 Hz, 9H), 1.12 (d, J = 7.4 Hz, 9H), 1.34 (sept, J = 7.4 Hz, 3H), 1.48 (s, 9H), 1.73 (s, 3H), 1.91 (dd, J = 6.7, 1.7 Hz, 3H), 5.93 (s, 1H), 6.33 (dq, J = 15.8, 1.7 Hz, 1H), 6.58 (s, 1H), 6.67 (d, J = 15.4 Hz, 1H), 6.70 (dq, J = 15.8, 6.7 Hz, 1H), 6.85 (d, J = 15.4 Hz, 1H), 7.03 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 17.9, 19.8, 23.4, 28.0, 58.3, 82.0, 99.4, 117.1, 120.4, 121.4, 133.1, 134.0, 134.1, 142.3, 143.2, 145.7, 162.8, 164.7, 176.1 ppm; IR (KBr): $\tilde{\nu}$ = 1811, 1719, 1510, 1369, 1279, 1062, 975, 923, 883 cm^{-1}; MS (FAB): *m*/*z* (%): 545 (6) [(M+H)$^+$], 375 (26) [$C_{21}H_{31}O_4Si^+$], 331 (100), 303 (10), 133 (14); HRMS (FAB): *m*/*z*: calcd for $C_{29}H_{43}NO_7Si$ (M+H): 545.2809; found 545.2812.

5,6-Dihydroxy-(*E*)-3-(4-*tert*-butoxy-4-oxobut-2-enamido)-3-methyl-6-triisopropylsilanyloxy-3*H*-benzofuran-2-one (50): AcOH (0.016 mL, 0.017 g, 0.28 mmol, 5.0 equiv) and TBAF (1 M in THF, 0.072 mL, 0.072 mmol, 1.3 equiv) were added to a solution of **42** (30.3 mg, 0.0555 mmol) in THF (0.70 mL). After stirring for 2 h, water (20 mL) was added. The resulting mixture was extracted with Et_2O (4×10 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. Removal of the solvent and column chromatography (cyclohexane/EtOAc 3:1 +10% MeOH→2:1 +10% MeOH) afforded **50** (20.2 mg, 93%) as a brown oil. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.49 (s, 9H), 1.65 (s, 3H), 1.91 (dd, J = 6.6, J = 1.6 Hz, 3H), 6.49 (dq, J = 15.8, 1.6 Hz, 1H), 6.49 (s, 1H), 6.52 (d, J = 15.5 Hz, 1H), 6.68 (dq, J = 15.8, 6.6 Hz, 1H), 6.93 ppm (d, J = 15.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 19.8, 23.5, 28.2, 59.5, 83.0, 97.7, 117.0, 122.7, 123.3, 133.9, 134.4, 134.9, 141.9, 147.3, 147.4, 165.0, 165.8, 178.2 ppm; IR (KBr): $\tilde{\nu}$ = 2934, 1741, 1619, 1474, 1252, 1167, 1106, 1021, 878 cm^{-1}; MS (FAB): *m*/*z* (%): 390 (38) [(M+H)$^+$], 333 (22) [$C_{16}H_{15}NO_7^+$], 219 (100) [$C_{12}H_{11}O_4^+$], 133 (36); HRMS (FAB): *m*/*z*: calcd for $C_{20}H_{24}NO_7$ (M+H): 390.1553; found 390.1550.

(*E*)-3-[5,6-Dihydroxy-3-methyl-2-oxo-4-((*E*)-propenyl)-2,3-dihydro-benzofuran-3-ylcarbamoyl]-acrylic acid (Fumimycin (1)): Compound **50** (8.7 mg, 0.022 mmol) was dissolved in CH_2Cl_2 (0.60 mL), cooled to 0 °C and treated with trifluoroacetic acid (0.30 mL). After 4 h, the solvent was removed at RT under reduced pressure to yield **1** as a brown solid (7.4 mg, quant). ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD 1.00:1.00): δ = 1.38 (s, 3H), 1.62 (dd, J = 6.4, 1.5 Hz, 3H), 6.08 (dq, J = 15.8, 1.5 Hz, 1H), 6.23 (s, 1H), 6.34 (d, J = 15.5 Hz, 1H), 6.36 (dq, J = 15.8, 6.4 Hz, 1H), 6.69 ppm (d, J = 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD 1.00:1.00): δ = 19.2, 22.6, 58.4, 96.8, 115.9, 121.4, 122.0, 131.7, 133.5, 134.7, 140.6, 145.9, 146.1, 163.8, 167.3, 177.4 ppm; IR (ATR): $\tilde{\nu}$ = 3300, 2922, 1800, 1708, 1645, 1436, 1319, 1261, 1149, 1080, 970, 920 cm^{-1}; MS (EI): *m*/*z* (%): 333 (2) [M^+], 281 (2), 218 [$C_{12}H_{10}O_4^+$] (10), 142 (12), 99 (16), 44 (100); HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}NO_7$: 333.0849; found 333.0847.

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