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Synthesis of Methoxyfumimycin with 1,2-Addition to Ketimines

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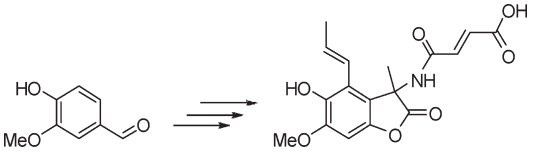

The synthesis of (±)-methoxyfumimycin, a potential new bacterial peptide deformylase (PDF) inhibitor, is reported. To generate the stereogenic fully substituted carbon, the key step is a 1,2-addition of a methyl Grignard reagent to a ketimine. The overall synthetic strategy involves a Dakin oxidation of a vanillin derivative, Friedel−Crafts acylation, Claisen rearrangement, lactonization, and rhodium-catalyzed olefin isomerization.

Due to bacterial resistance to common classes of antibiotics, a continuing discovery of antibiotics with new modes of action is critical.[1] One target of special interest is the bacterial peptide deformylase (PDF),[2] a metalloenzyme catalyzing the removal of the formyl group at the N-terminus of bacterial proteins. In the course of screening for PDF inhibitors, fumimycin[3,4] (**1**, Figure 1) was isolated from cultures of the mildew *Aspergillus fumisynnematus* F746.[5] Fumimycin exhibits potent inhibition of *Staphylococcus aureus* PDF with an IC_{50} of 4.1 μM and also shows activity against methicillin-resistant *S. aureus* (MRSA) and quinoline-resistant *S. aureus* (QRSA). PDF is required for bacterial development, but is not essential in mammals. Therefore PDF-inhibitors like fumimycin and structurally related analogues like methoxyfumimycin might lead to novel broad-spectrum antibacterial agents.[6]

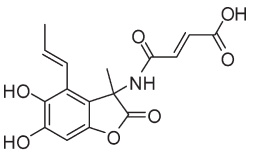

FIGURE 1. Fumimycin, a potential lead to antibacterial agents.

The structure of fumimycin was determined by ESI-MS, IR, and two-dimensional NMR spectroscopy. The absolute configuration is not yet known. Due to its fully substituted stereogenic center, fumimycin is a challenging synthetic target. So far no synthesis has been reported.[7]

Due to our longstanding interest in constructing α-trisubstituted amines[8] we became interested in the synthesis of methoxyfumimycin (**2**). We decided first to synthesize methoxyfumimycin to elucidate the structure activity relationship. Will the substitution of a methoxy group for a hydroxyl group affect the PDF-inhibition ability?

To build up the stereogenic center, we decided to use a 1,2-addition of organometallic reagents to ketimines. Simultaneously we also pursued an organocatalytic approach via electrophilic amination.[9]

Our retrosynthetic strategy employing alkylation of ketimine **4** as the key step is outlined in Scheme 1. Foremost, we intended to complete the racemic synthesis by using Grignard reagents for the 1,2-addition to **4**. For an asymmetric synthesis, we envision the use of an enantioselective addition of methyl zinc reagents that is currently under investigation in our laboratories.[10] Methoxyfumimycin (**2**) derives from amine **3** through amidation, lactonization, Claisen rearrangement, and olefin isomerization. The precursor for amine **3**, the ketimine **4**, can be built via Friedel−Crafts acylation, Dakin oxidation, and allylation by employing vanillin (**7**) as readily available starting material.

We began the synthesis with a sequence of allylation/oxidative degradation (Scheme 2). To install the third oxygen group at the aromatic core, vanillin (**7**) was converted with

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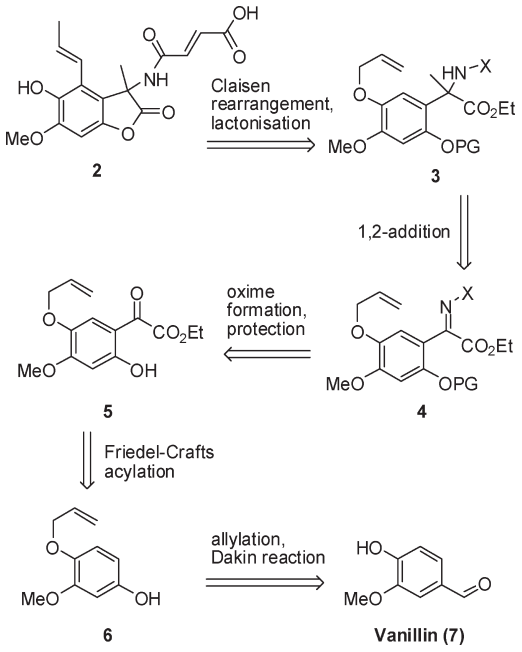
SCHEME 1. Retrosynthetic Analysis for Methoxyfumimycin (2)



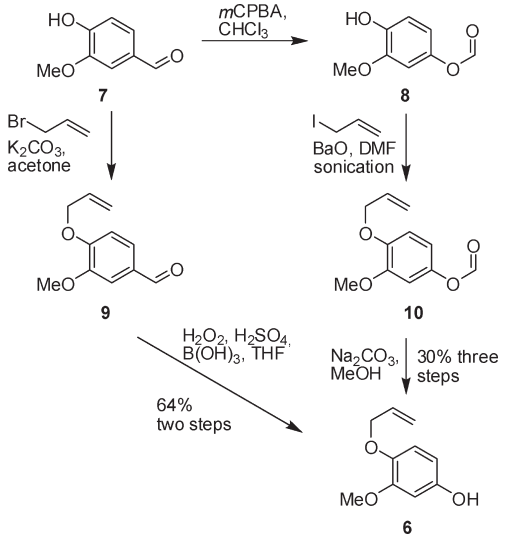
*m*CPBA in a Dakin oxidation. Thus the new hydroxy group was obtained protected as formate ester. We planned to allylate the free phenol group of **8** under mild conditions to furnish **10**, followed by cleaving the ester function in basic methanol. Various conditions were tested for the allylation of **8**, but due to the instability of the formate ester, the best conditions (allyl iodide, BaO, DMF) generated an unacceptable yield of **6**.[11]

Therefore we changed the reaction order: Allylation of vanillin (**7**) gave **9** in quantitative yield. Oxidation of the aldehyde was accomplished without epoxidation of the olefinic side chain, using acidic hydrogen peroxide, and the best results were obtained following a procedure[12] employing boric acid as an additive.

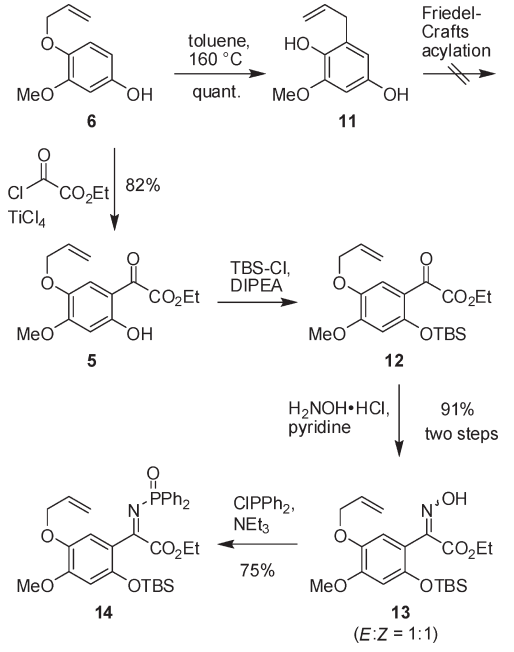
Claisen rearrangement of allyl ether **6** smoothly provided **11** (Scheme 3),[13] but subsequent acylation was not successful, presumably because of steric hindrance. Friedel−Crafts acylation of the unhindered phenol **6** with ethyl oxalyl chloride gave ester **5** as a single regioisomer.

Protection of the phenol with a *tert*-butylsilyl group (TBS) and condensation of the keto function with hydroxylamine furnished oxime **13** as 1:1 mixture of *E* and *Z* diastereomers. To enable a 1,2-addition to the N=C function, the electron-withdrawing group *N*-diphenylphosphinoyl (dpp) was installed.[14] This reaction starts with an N−O−P formation, presumably followed by a radical fragmentation/combination mechanism.[15] Conversion of the *E*/*Z* mixture of **13** led

SCHEME 2. Synthesis of Phenol 6 via Allylation and Dakin Oxidation



SCHEME 3. Sequence To Yield Ketimine 14



to a single diastereomer **14**,[16] which was identified by crystal structure as the *Z*-product.[17]

The best results for the 1,2-addition to imine **14** were achieved with methyl magnesium bromide in a nonpolar solvent, establishing the fully substituted center of methoxyfumimycin (Scheme 4). As a next step, we intended to induce a Claisen rearrangement at high temperature. Surprisingly,

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(14) (a) Steinig, A. G.; Spero, D. M. *Org. Prep. Proced. Int.* **2000**, *32*, 205–234. (b) Ferraris, D. *Tetrahedron* **2007**, *63*, 9581–9597. (c) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888.
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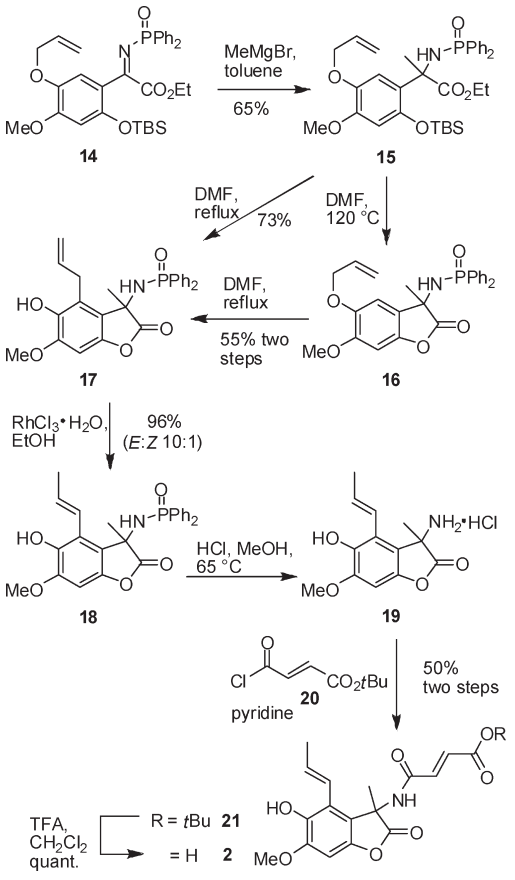
(16) It is reported that *N*-diphenylphosphinoyl ketimines exist in a very fast equilibrium between *E*- and *Z*-isomers: Masumoto, S.; Usuada, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635.
(17) Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 743652 (**14**) and no. CCDC 743653 (**18**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (fax: int.code + (1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

SCHEME 4. Final Assembly of Methoxyfumimycin 2



heating of **15** in dry DMF at 120 °C first led to the formation of the lactone ring. Presumably, the required deprotection of the TBS group is facilitated by an intramolecular attack of the nitrogen via a six-membered ring.

Further heating of the lactone **16** at 153 °C finally led to a rearrangement of the allyl ether to the desired product **17**. A one-pot synthesis involving lactonization−Claisen rearrangement proved to be advantageous, giving **17** in a overall 73% yield, and we were gratified that this sequence avoided an extra TBS-deprotection step. Isomerization of the terminal double bond was achieved under mild conditions by transition metal catalysis. Treatment of **17** with $PdCl_2(PhCN)_2$ in CH_2Cl_2 at 40 °C[18] gave **18** in good yield, but with a poor *E*:*Z* ratio of 4:1. Better results were obtained employing $RhCl_3 \cdot H_2O$ in ethanol,[19] which gave an *E*:*Z* ratio of 10:1. The structure of **18** was validated by crystal structure. The cleavage of the diphenylphosphinoyl group to the ammonium salt **19** proved to be challenging. In acidic methanol deprotection took place, but decomposition also was observed. The conversion was optimized by NMR analysis of the reaction mixture (DCl in CD_3OD). Best results were achieved at 65 °C for 3 h.

After various optimizations, direct conversion of **19** with *tert*-butyl protected acid chloride **20** gave the amide **21** in 50% yield over two steps. This method avoids isolation of the free amine.

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Final deprotection of the *tert*-butyl ester **21** to the acid was simply achieved by treatment with TFA, furnishing methoxyfumimycin (**2**) in quantitative yield. All ^1H and ^{13}C NMR data of **2** match quite well with the respective data of fumimycin (**1**).

We tried to deprotect the methyl ether in **2** to the free phenol group at various stages of the synthesis, but the isolation and further conversion of the catechol products were difficult, presumably because of their instability. Further studies to complete the (asymmetric) synthesis[10] of fumimycin as well as the elucidation of the pharmacophore are currently in progress in our laboratories and will be reported in due course.

In summary, we have developed a concise route to methoxyfumimycin (**2**) that involves generation of a hydroxyl group via Dakin oxidation. Further carbon atoms for the scaffold were introduced by allylation and Friedel−Crafts acylation. A key step for the formation of the stereogenic fully substituted carbon is a 1,2-addition to a ketimine. Tandem Claisen rearrangement−lactonization and subsequent isomerization established the olefinic side chain. Amidation and acid deprotection finally accomplished the first synthesis of (±)-methoxyfumimycin.

Experimental Section

***E*)-3-(3-Carboxyacrylamido)-5-hydroxy-6-methoxy-3-methyl-3*H*-benzofuran-2-one (Methoxyfumimycin) (2).** A solution of **21** (2.9 mg, 8.2 μmol) in CH_2Cl_2 (0.60 mL) was cooled to 0 °C and treated with trifluoroacetic acid (0.30 mL). After 1.5 h of stirring, the reaction was allowed to reach rt. After 1 h the solvent was removed under reduced pressure without warming to afford the acid **2** as a brown film (2.5 mg, quant.). ^1H NMR (500 MHz, CD_3OD) δ 1.67 (s, 3H), 1.91 (d, J = 5.8 Hz, 3H), 3.89 (s, 3H), 6.40 (d, J = 15.6 Hz, 1H), 6.59 (d, J = 15.4 Hz, 1H), 6.73 (s, 1H), 6.74 (m, 1H), 6.99 (d, J = 15.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.8, 23.4, 57.1, 59.6, 95.0, 118.2, 122.1, 123.1, 132.8, 134.7, 135.6, 143.0, 147.30, 149.8, 165.1, 168.1, 178.1; IR (KBr) ν^{-1} 3302, 1806, 1665, 1439, 1153, 1032, 924 cm^{-1}; MS (EI), *m*/*z* (%) 347 (72) [M^+], 281 (24), 205 (34); HRMS (EI) calcd for $C_{17}H_{17}NO_7$ 347.1005, found 347.1002.

Ethyl 2-[5-Allyloxy-2-(*tert*-butyldimethylsilanyloxy)-4-methoxyphenyl]-2-diphenylphosphinoylaminopropionate (15). A solution of **14** (10.67 g, 17.97 mmol, 1.00 equiv) in toluene (240 mL) was cooled to −78 °C. MeMgBr (3 M in Et_2O, 13.4 mL, 35.9 mmol, 2.00 equiv) was added dropwise. After 3 h of stirring, sat. $KHSO_4$ 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 **15** as highly viscous brown oil (7.11 g, 65%). ^1H NMR (400 MHz, acetone-d_6) 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 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) 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); IR (KBr) ν^{-1} 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) calcd for $C_{33}H_{44}NO_6$-SiP 609.2676, found 609.2673.

3-Diphenylphosphinoylamino-5-hydroxy-6-methoxy-3-methyl-4-[(*E*)-propenyl]-3*H*-benzofuran-2-one (18). A mixture of **17** (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 filtrated through a 3 cm pad of Celite. The fitrate was concentrated under reduced pressure. Flash chromatography (cyclohexane:EtOAc 3:2 + 5% MeOH → 3:2 + 10% MeOH) afforded the lactone **18** as light brown solid (*E*:*Z* 10:1, 288 mg, 96%; an analytical portion was recrystallized from hexane/$CHCl_3$ to furnish pure *E* product). Mp 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 (m); ^{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; IR (KBr) ν^{-1} 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) calcd for $C_{25}H_{24}NO_5P$ 449.1392, found 449.1400.

(*E*)-3-(4-*tert*-Butoxy-4-oxobut-2-enamido)-5-hydroxy-6-methoxy-3-methyl-3*H*-benzofuran-2-one (21). A solution of **18** (110 mg, 0.245 mmol) in HCl in MeOH (0.5 M, 2.0 mL) was heated to 65 °C for 4 h. The solvent was removed under reduced pressure, then the residue was diluted with CH_2Cl_2 (1.0 mL) and pyridine (0.20 mL, 0.19 g, 2.5 mmol, 10 equiv) and cooled to 0 °C. A solution of (*E*)-*tert*-butyl-4-chloro-4-oxobut-2-enoate (0.32 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. After 2 h of stirring, the mixture was diluted with cold water (10 mL). The phases were separated; the aqueous layer was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (cyclohexane:EtOAc 5:2 → 2:1) afforded the amide **21** as a light brown solid (49.0 mg, 50%). Mp 203−205 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.47 (s, 9H), 1.71 (s, 3H), 1.87 (dd, J = 6.6, 1.6 Hz, 3H), 3.90 (s, 3H), 6.52 (d, J = 15.5 Hz, 1H), 6.57 (dq, J = 15.8, 1.6 Hz, 1H), 6.75 (s, 1H), 6.62 (dq, J = 15.8, 6.7 Hz, 1H), 6.95 (d, J = 15.5 Hz, 1H), 7.59 (b. S, 1H), 8.86 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.8, 24.6, 29.1, 57.9, 59.8, 82.9, 95.7, 119.1, 122.1, 124.0, 134.2, 134.9, 135.9, 143.2, 147.8, 149.7, 164.2, 165.9, 177.5; IR (KBr) ν^{-1} 3466, 2979, 2850, 2472, 1811, 1626, 1370, 1155, 973 cm^{-1}; MS (EI), m/z (%) 493 (14) [M^+], 232 (14); HRMS (EI) calcd for $C_{21}H_{25}NO_7$ 403.1631, found 403.1635.

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Supporting Information Available: General information, ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic data for **14** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.