Towards an asymmetric synthesis of the bacterial peptide deformylase (PDF) inhibitor fumimycin†‡

Caroline E. Hartmann,[a] Patrick J. Gross,[a] Martin Nieger[b] and Stefan Bräse*[a]

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Studies towards the synthesis of the bacterial peptide deformylase (PDF) inhibitor fumimycin are reported. The synthetic approach features an organocatalytic access to the α,α-disubstituted amino acid unit and results in the synthesis of an advanced intermediate which already contains all functionalities of fumimycin.

In the course of screening for new bacterial peptide deformylase (PDF) inhibitor lead structures, fumimycin (**1**)[1] was isolated from the fermentation broth of *Aspergillus fumisynnematus* F746.[2] Structurally it is related to sorbicillactones A and B (**2**) from *Penicillium chrysogenum*.[3] These also possess a skeleton with a six-membered ring fused with the similar five-membered lactone and an α,α-disubstituted amino acid moiety linked to a fumaric acid residue. Besides exhibiting antibacterial activity against *S. aureus*, MRSA (methicillin resistant *S. aureus*) and QRSA (quinolone-resistant *S. aureus*), compound **1** (Fig. 1) shows promising inhibitory activity towards *S. aureus* PDF with an IC_{50} of 4.1 μM. As the emergence of bacterial resistance to all known classes of antibiotics is a serious hazard to humans, the search for new antibiotics with novel modes of action is of utmost urgency.

A field that has attracted more and more attention lately is the bacterial PDF (EC 3.5.1.31) as a potential target.[4] Peptide deformylase is an enzyme that catalyzes the removal of the formyl group at the *N*-terminus of bacterial proteins and is on the other hand not required in the mammalian cells. Although PDF inhibitors offer access to a new area of antibacterial agents,[3a,5] few PDF inhibitors have been reported so far.[6] Hence, from this starting point, **1** could be an interesting lead structure for future structural optimizations.[7,8]

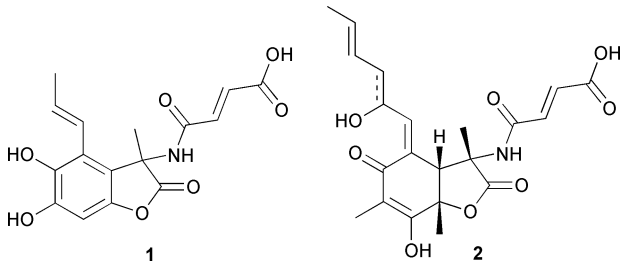

Fig. 1 Fumimycin (**1**) and sorbillactone A/B (**2**) (unsaturated/saturated).

We became interested in fumimycin through the α,α-disubstituted amino acid precursor unit,[9] as such building blocks have been the focus of our research for quite some time. Therefore we turned our attention to the application of different methodologies to forming this crucial stereogenic centre since fumimycin was isolated as a non racemic mixture with unknown absolute configuration.

Considering a strategy for the construction of the key structure, we envisioned an organocatalytic approach to the stereogenic centre (Scheme 1).

Claisen-rearrangement of the allylic substituent and exchange of the amide side group followed by a ring opening of the lactone would lead to our central product **4**. Subsequently, the *N*-electrophile, which can be introduced *via* an organocatalytic reaction, is disconnected to afford **5** which is synthesized from **6** in a Wittig reaction.

Our synthesis began with a Baeyer–Villiger type oxidation (Dakin reaction)[10] of commercially available 2,4-dimethoxybenzaldehyde (**8**) into the corresponding phenol **10** (Scheme 2), which could then be etherified into **12** with a yield of 83%.[11] Acylation of the aromatic ring using the mixed anhydride formed by trifluoroacetic acid anhydride and acetic acid gave rise to the acetophenone **14** in 74% yield.[12] To overcome the drawbacks of this route that lie in the harsh conditions necessary to deprotect the hydroxyl groups, we also tested a protection group other than methyl ether. Starting from 2,4-dihydroxybenzaldehyde, the hydroxyl groups were protected with *tert*-butyl-diphenylsilyl-chloride (TBDPSCl) to furnish **9** in 87% yield. Oxidation of the aldehyde to **11** proceeded smoothly, but successive treatment with allylbromide produced only traces of **13**, which is probably due to a migration of the protective groups throughout the molecule under

[a]*Institut für Organische Chemie, Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6, 76131, Karlsruhe, Germany. E-mail: stefan.braese@kit.edu; Fax: +49 721 608 8581; Tel: +49 721 608 2903*
[b]*Laboratory of Inorganic Chemistry, University of Helsinki, 00014, Helsinki, Finland*

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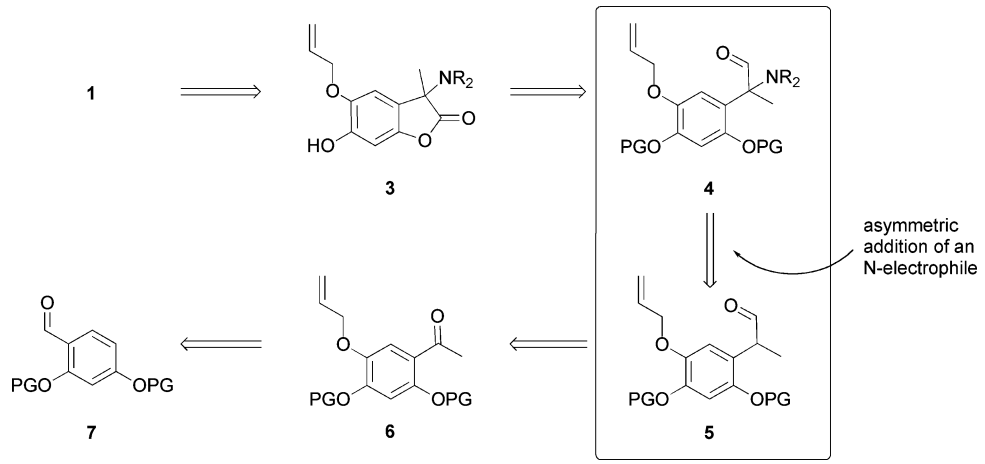
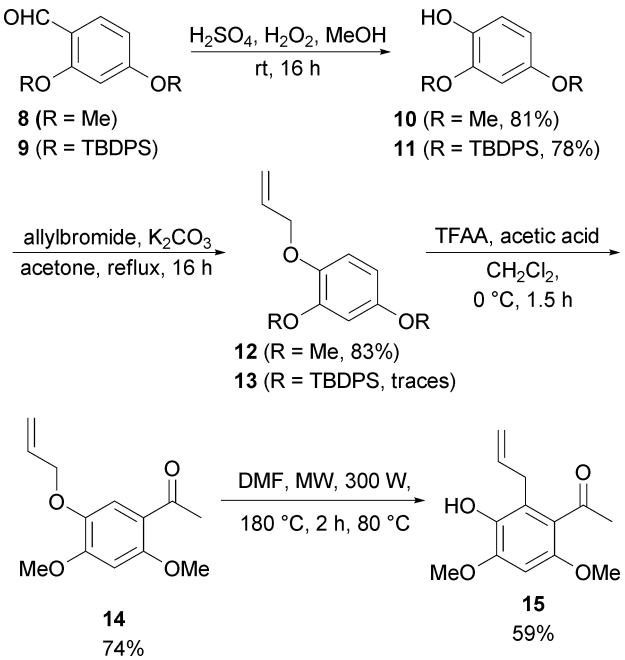
‡ Crystal structure determination
The single-crystal X-ray diffraction study was carried out on a Nonius Kappa-CCD diffractometer at 123(2) K using Mo-Kα radiation (λ = 0.71073 Å). Direct Methods (SHELXS-97)[24a] were used for structure solution and refinement was carried out using SHELXL-97[24a] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). The absolute structure of **21** could not be determined reliably by refinement of Flack's *x*-parameter (x = 0.2(7)),[24b] but using Bayesian statistics on Bijvoet differences the absolute configuration at C2 was determined as (C2:S) (FLEQ = 0.05(40)).[24c]
21: colourless, $C_{20}H_{28}N_2O_8$, M = 424.44, crystal size 0.40 × 0.25 × 0.15 mm, orthorhombic, space group $P2_12_12_1$ (No. 19): a = 8.681(1) Å, b = 9.784(1) Å, c = 24.875(3) Å, V = 2112.8(4) Å^3, Z = 4, ρ(calc) = 1.334 Mg m^{-3}, $F(000)$ = 904, μ = 0.103 mm^{-1}, 16621 reflexes ($2\theta_{max}$ = 55°), 4774 unique [R_{int} = 0.051], 276 parameters, 1 restraint, $R1$ ($I > 2\sigma(I)$) = 0.036, $wR2$ (*all data*) = 0.087, GOOF = 1.07, largest diff. peak and hole 0.212/−0.244 e Å^{-3}. CCDC 738983.



Scheme 1 Retrosynthetic analysis with the planned key step highlighted.

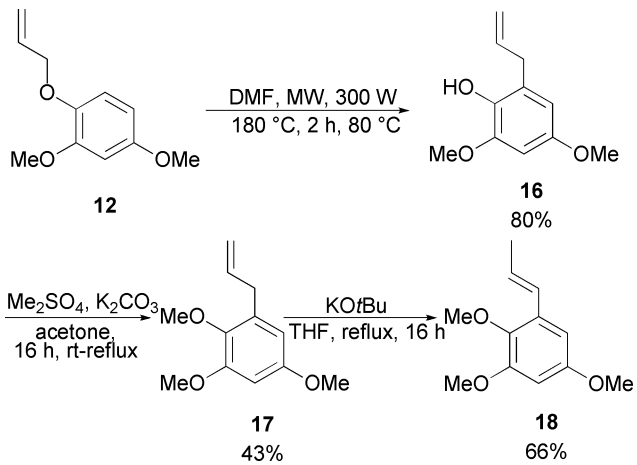


Scheme 2 Synthesis of the acetophenone **14**.

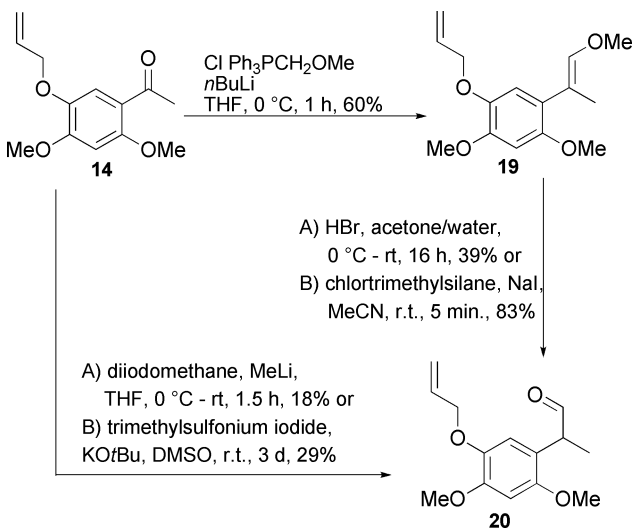
the reaction conditions. Even under varied reaction conditions, an improvement of the yield was not possible.

Compound **12** was used as a model system, and was submitted to microwave irradiation and underwent a Claisen rearrangement within 2 h to give **16** in 80% yield (Scheme 3).[13] In a further step, the isomerization of this compound was also tested. First, the free phenol **16** was protected using dimethylsulfate in 43% yield, then 2,4-dimethoxy-6-allylanisole (**17**) in THF was heated to reflux for 16 h in the presence of potassium-*tert*-butoxide. This procedure furnished 1,2,4-trimethoxy-6-propenylbenzene (**18**) in 66% yield with the thermodynamically more stable *E*-isomer being the only product. For practical reasons, though, **14** was used as a starting point for further studies.

The preparation of the starting material for our key step began with a Wittig reaction with methoxymethyl(triphenyl)-phosphonium chloride at −78 °C (Scheme 4). Unfortunately, the electron-rich acetophenone did not react under these conditions.



Scheme 3 Model study starting from **12**.

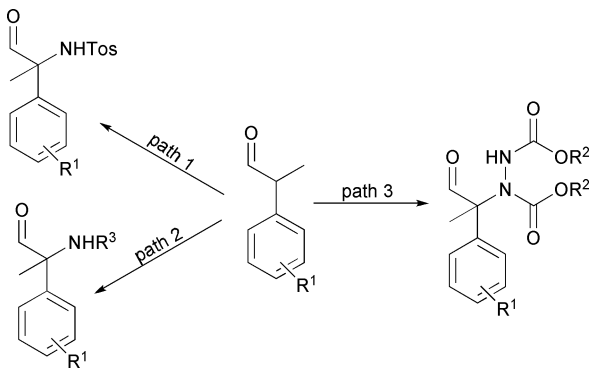


Scheme 4 Generation of the aldehyde **20** through four different routes.

Simply by changing the reaction temperature to 0 °C, however, **19** could be isolated in 60% as a *E*/*Z*-mixture of 1 : 1.36.

Cleavage of the enol ether under acetic conditions[14] resulted in formation of the desired product **20** in 39% yield. Using an improved procedure of Cohen and co-workers under mild conditions, treatment of the starting material with chlorotrimethylsilane/NaI for 5 min at rt furnished 83% of the aldehyde **20**.[15] Alternatively, we performed an epoxidation of **14** and Meinwald rearrangement to **20**. As a fortuitous outcome, the intermediate epoxide opened to the designated aldehyde **20** directly without addition of accessory Lewis acid.[16] Nevertheless, with this direct method the yields remained lower (at best 18% with diiodomethane[17] and 29% with trimethylsulfonium iodide,[18] no reaction at all with trimethylsulfoxonium iodide), thus the synthesis of **20** was most efficiently achieved when using Wittig-reaction and subsequent cleavage rather than by use of the one-pot procedure.

We then turned our attention towards the main topic of our study. The direct, catalytic α-amination of α-substituted carbonyl compounds with either sulfonamides (Scheme 5, path 1 and 2) or azodicarboxylates (path 3) as nitrogen sources represents one of the simplest procedures for construction of the stereogenic centre attached to a nitrogen atom. The first procedure we followed was the addition of chloramine-T to our substrate (path 1). Following a previously developed procedure,[19] aldehyde **20** was exposed to 1.5 eq chloramine-T and 5 mol% L-proline in acetonitrile at rt for 16 h. On TLC, though, only starting material and the sulfonamide as the byproduct of the reagent could be observed. Even when the amount of catalyst was increased to 1.0 eq. and the temperature was raised to 60 °C, the reaction mixture remained the same. This is however probably explicable by the higher substitution pattern with three electron-donating groups on the aromatic backbone. In our earlier work, we found that with 2 mol% catalyst and either an un- or fluorine-substituted phenylic backbone, the reaction proceeded well (83%), whereas with a methoxy substituent a drop in yield was observed (71% in 4-position and 74% in 3-position).[19]



Scheme 5 Addition of *N*-electrophiles to aldehydes.

Employing a different *N*-electrophile (Scheme 5, path 2, in the case of tosylazide same product as from path 1 was isolated), conversion of **20** with 1.2 eq. tosylazide and 1.0 eq. L-proline in ethanol at rt for 3 d was attempted,[20] but again no reaction was observed.

Path 3 comprises the attack of azodicarboxylates to α-substituted aldehydes.[9,21] In compliance with previously published results, **20** was stirred with 1.5 eq diethyl azodicarboxylate and 50 mol% L-proline in acetonitrile at 60 °C for 16 h as a test reaction (Table 1, Entry 1).[22] Pleasingly, 48% of the amidated product **21** could be isolated. Most likely the low yield results

Table 1 Selected data of the optimization of the addition of azodicarboxylates to aldehyde **20**[a]

20

21 (R = ethyl)
22 (R = benzyl)
23 (R = *tert*-butyl)

Entry	Reagent	eq. L-proline	Temp./°C	Time/h	Yield (%)	*Ee* (%)
1	DEAD	0.5	60	16	48	38
2	DEAD	1.0	60	16	50	35
3	DEAD	2.0	60	16	80	47
4	DEAD	0.5	80	16	41	44
5	DEAD	0.5	rt	120	72[b]	8
6	DEAD	0.5	60	1	47[c]	33
7	DEAD	1.0	60	1	42[c]	34
8	DBAD	1.0	60	16	45	26
9	DBAD	2.0	60	16	81	23
10	DtBAD	2.0	60	16	71	60

[a] Solvent: acetonitrile. [b] Solvent: 1,4-dioxane. [c] Application of constant microwave power of a max. of 200 W.

from electronic effects of the substrate. In an earlier work[23] it had been shown that a drop of yield from 87% to 63% was observed when switching from one to two methoxy-substituents. In our case, with a system bearing three electron-pushing groups, this effect should be obviously even more distinctive. In order to overcome this handicap, the catalyst amount was first raised to 1.0 and in the next step to 2.0 equivalents (Table 1, Entries 2 and 3). Gratifyingly, in the latter case, 80% of the amidated product could be obtained. The enantioselectivity, however, remained the same for 0.5 and 1.0 equivalent of catalyst; only with 2.0 eq. of catalyst an *ee* of 47% was reached. Heating the reaction mixture even more to 80 °C with 0.5 eq of L-proline had no positive influence on the reaction outcome as the yield remained in the same range as at a lower temperature with just a slightly higher *ee* of 44% (Table 1, Entry 4 compared to Entry 1). We also performed the reaction at room temperature within 5 d using 1,4-dioxane as a solvent (Entry 5). This combination gave the best results in the case of hydratropaldehyde with 87% conversion and 67% *ee*. In our case, an increased yield of 72% was observed, but the enantioselectivity decreased significantly to 8% *ee*. In this case the catalyst probably functions more as a sub-stoichiometric base rather than in a true catalytic way.

The reaction was also tested using microwave heating, however with disappointing results (Table 1, Entries 6 and 7). Contrary to our previously published findings,[22] neither the yield nor enantioselectivity could be improved. The structure of **21** is presented in Fig. 2. Besides diethyl azodicarboxylate, dibenzyl (DBAD) and di-*tert*-butyl (D*t*BAD) azodicarboxylates could also be utilized as nitrogen-transfer reagents (Entries 8–10). For the dibenzyl compound, the yields display the same trend as with the ethyl ester, the enantioselectivities on the other hand being lower than with the ethyl residue (Table 1, Entries 8 and 9). Surprisingly, when changing from dibenyzl- to di-*tert*-butylazocompound, stereoselectivity rose significantly to 60% with the yield dropping only slightly to 71% (Table 1, Entry 10).

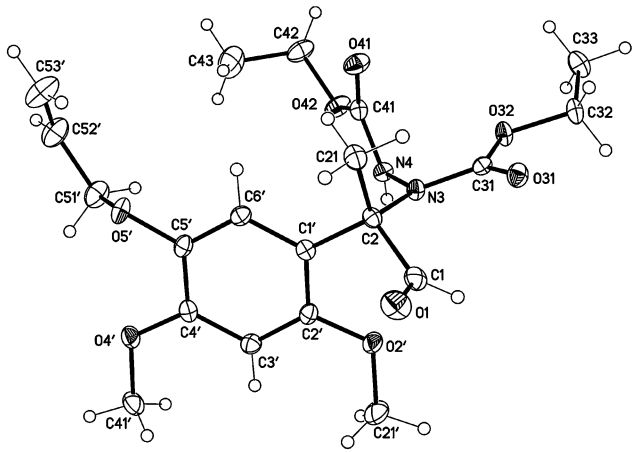
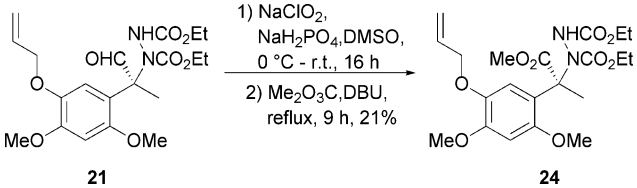


Fig. 2 Molecular structure of **21** (displacement parameters are drawn at 50% probability level).

Oxidation of the aldehyde **21** and subsequent esterification of the free carboxylic acid with dimethylcarbonate and DBU furnished **24** in 21% yield over two steps (Scheme 6).



21 **24**

Scheme 6 Mild oxidation and esterification of **21**.

Conclusions

In conclusion, we prepared an advanced arene precursor of the fungal natural product fumimycin using a Claisen rearrangement and an asymmetric organocatalytic amination reaction. We are now exploring this method for the total synthesis of fumimycin.

Acknowledgements

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