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Natural Product Synthesis

4,5-Disubstituted *N*-Methylimidazoles as Versatile Building Blocks for Defined Side-Chain Introduction[‡]

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Abstract: Fungerin is a 1,4,5-trisubstituted imidazole natural product characterised by a broad spectrum of antifungal activities. We planned to develop flexible strategies to access to such compounds. Imidazoles bearing suitable anchor groups at C-4 and C-5 allow the introduction of various substituted side-chains, generating libraries of fungerin derivatives for biological tests. Starting from commercially available reactants, two *N*-methyl 4,5-substituted imidazole core units were synthesised. Derivatives of type 1 contained two orthogonally protected C-1 anchors. Selective side-chain introduction was achieved through a sequence of Grignard coupling at C-5 to replace a tosylate and a Horner olefination through an aldehyde attached to C-4. Two target fungerin derivatives were synthesised. Since the organometallic substitution of the C-5-CH_2-positioned leaving group proved to suffer from limitations concerning potential competing side-reactions, a type 2 imidazole core was built up. These structures had a halogen centre at C-4 and a hydroxyethyl anchor at C-5. Now, selective side-chain introduction allowed us to use Julia olefination to form the allyl side-chain at C-5 and Heck reactions to introduce the C-4 acryl substituents. Eight derivatives, including fungerin, were synthesised by this latter strategy, without producing any regioisomers. The second approach had the advantage that various side-chains could be coupled at C-4 and C-5 in two final steps. Thus, this strategy represents a versatile way to build up libraries of fungerin derivatives for biological testing.

Introduction

Defined 1,4,5-trisubstituted imidazoles are best known as natural products and pharmaceutically important compounds.[1] The strategy of choice for the efficient synthesis of such heterocycles has often involved the generation of a 4,5-disubstituted imidazole **a** as a key intermediate and a final regioselective N-1 functionalisation (→ **b**). In various publications, highly regioselective syntheses have been reported (**a** → **b-1**).[1f,2] However, the avoidance of the production of regioisomeric mixtures (**a** → **b-1** + **b-2**) remains a challenge; in various cases, the substitution pattern of reactant **a** was found to be crucial to the selectivity of the final *N*-alkylations (Figure 1).[3]

An alternative strategy involves the use of suitably substituted α-*N*-alkyl aminoketones **e** as reactants. Starting from a sarcosine-derived central building block **c**, two sequential C–C couplings (via **d**) gave the key intermediate **e**.[4] Bredereck,[5] Marckwald,[6] and related imidazole cyclisations[7] delivered the target heterocycles **b-1** with complete chemo- and regioselectivity. Despite the flexibility of this sequence, the harsh reaction conditions used for the cyclisations (**e** → **b-1**) resulted in moderate overall yields for compounds containing sensitive side-chains (e.g., prenyl).[4] To overcome this drawback, the C–C couplings and imidazole formation should be carried out in the reverse order. In this context, reactants **c** should undergo suitable cyclisation reactions to give key imidazoles **f** with defined anchoring groups for chain elongation. Finally, two subsequent C–C couplings should enable the introduction of various side-chains (via **g**, including sensitive groups) to give the product imidazoles **b-1** with complete chemo- and regioselectivity. It should be pointed out that the introduction of the side-chains at such a late stage potentially allows the synthesis of natural products like fungerin (**1a**), or a variety of analogues, in a few steps without changing the strategy (Figure 1).

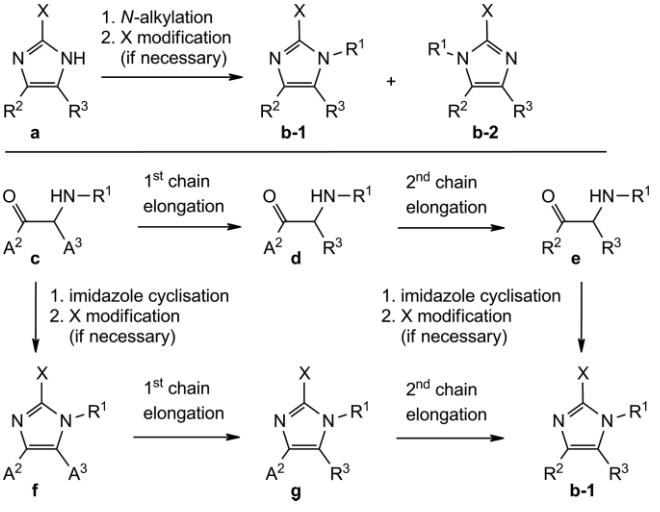

Figure 1. Syntheses of 1-*N*-alkyl 4,5-disubstituted imidazoles [X = H, halogen, SR, NR_2; R^x = (product) side-chain; A^x = anchor group for chain elongation].

[‡] Synthesis of Fungerin and Analogues II. Part I: Ref.[4]

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Multiple fungal infestations caused by *Colletotrichum lagenarium*, *Alternaria mali*, *Pyricularia oryzae*, *Aphanomyces cochlioides* and *Phytophthora sojae* are connected with serious crop loss and economic damage every year.[8] The permanent need for new antifungal compounds is clear. In 1994 and 1996, A. Visconti and Y. Kato reported the isolation and structure elucidation of new imidazole alkaloids from *Fusarium tricinctum* and *Fusarium sp.* that show promising fungicidal, cytotoxic and anticholinergic properties.[9] Ohmura found that fungerin (**1a**) inhibits the polymerisation of microtubules, interrupting the cell cycle in the M-phase.[10] Fungerin (**1a**) and hydroxyfungerins **2** have now been isolated from several fungal sources.[11]

A first total synthesis of fungerin (**1a**) was published in 1998 by Benhida et al. This synthesis involves a strategy of regioselective alkylation of the imidazole core **a-1** (Figure 2).[12] Recently, we described a new attempt involving an alkylation–cyclisation strategy as shown in Figures 1 and 2. Starting from *N*-Boc sarcosine methyl ester **c-1** (Boc = *tert*-butoxycarbonyl), enolate prenylation (→ **d-1**) and vinyllithium addition to an intermediate Weinreb amide delivered α-*N*-methyl aminoketones **e-1**, which finally underwent Marckwald cyclisation and sulfur removal (X = SH → X = H) to give fungerin (**1a**) with a moderate yield in the imidazole-forming step. Furthermore, a phenyl analogue of fungerin (**1a**) was synthesised in a significantly higher yield by using the same strategy (Figure 2).[4]

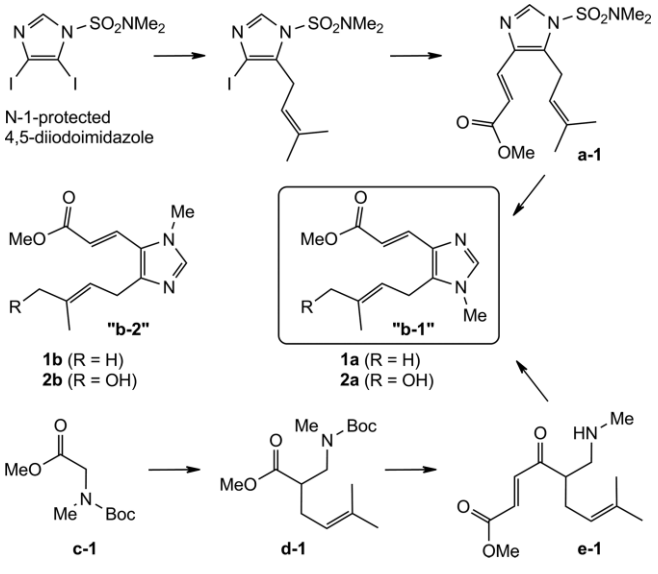
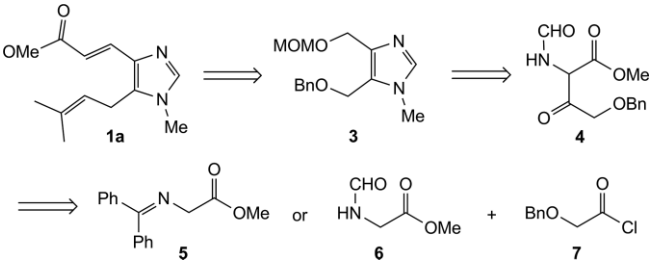


Figure 2. Fungerins [fungerin (**1a**), visoltricin (**1b**) ("**b-2**") – originally published structure (wrong regioisomer), revision by J. Rieder[11c]], hydroxyfungerin A (**2a**) and hydroxyfungerin B (**2b**). Syntheses of fungerin (**1a**) ("**b-1**"): from protected 4,5-diiodoimidazole according to Benhida, and from *N*-Boc sarcosine methyl ester **c-1** according to Przybyla.

Results and Discussion

For increased flexibility around the introduction of C-4 and C-5 side-chains, a key imidazole intermediate incorporating suitable anchoring groups that could be used for late stage C–C coupling processes should be synthesised. An orthogonally protected 4,5-bis(hydroxymethyl)-1-methylimidazole **3** was chosen as a suitable key intermediate. We anticipated that this intermediate would allow the introduction of the side-chains through olefinations (e.g., Horner reaction after oxidation) and Grignard reactions (after activation). Imidazole **3** should be generated from β-keto ester **4** through a Brederek-type cyclisation. Keto ester **4** has to be synthesised by Claisen-type condensations from *N*-(diphenylmethylene)glycine methyl ester (**5**) or *N*-formylglycine methyl ester (**6**), together with benzyloxyacetyl chloride (**7**) using one-pot procedures (Scheme 1).



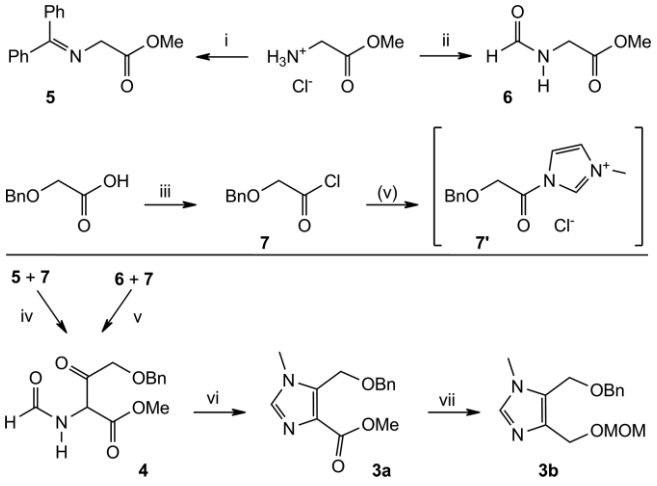
Scheme 1. Retrosynthesis of fungerin derivatives via the orthogonally protected 4,5-bis(hydroxymethyl)-1-methylimidazole **3**.

The synthesis began with the assembly of the building blocks for β-keto ester generation following literature procedures. Benzyloxyacetyl chloride (**7**) was obtained from benzyloxyacetic acid (Williamson etherification from chloroacetic acid) by $SOCl_2$ activation.[13] *N*-(Diphenylmethylene)glycine methyl ester (**5**) was obtained from glycine methyl ester hydrochloride by condensation with benzophenone.[14] Alternatively, glycine methyl ester hydrochloride was treated with trimethyl orthoformate and *p*TsOH/trimethylamine to give *N*-formylglycine methyl ester (**6**) in 60 % yield.[15]

In a first attempt to synthesise β-keto ester **4**, we used a modification of a one-pot procedure published by G. Haberhauer et al.[16] Imino ester **5** was deprotonated with KO*t*Bu in THF at –60 °C, and the resulting enolate was then treated with acid chloride **7**. The reaction was quenched with HCl (1 M aq.) to cleave the azomethine unit, and the crude hydrochloride was immediately treated with an excess of *O*-formyl acetate to give the product *N*-formyl benzyloxy acetoacetate in low to moderate yield (20–40 %), even though a wide variety of reaction conditions were tested.

Since the Claisen condensation under basic conditions gave disappointing results, a switch to a Lewis-acid-mediated alternative in analogy to a procedure published by Y. Tanabe was investigated.[17] Condensation of benzyloxyacetyl chloride (**7**), glycine derivative **6** and *N*-methylimidazole (forming imidazolium salt **7′** as a reactive intermediate) with $TiCl_4$ and tributylamine in CH_2Cl_2 at –45 °C gave β-keto ester **4** in 62 % yield (Scheme 2).

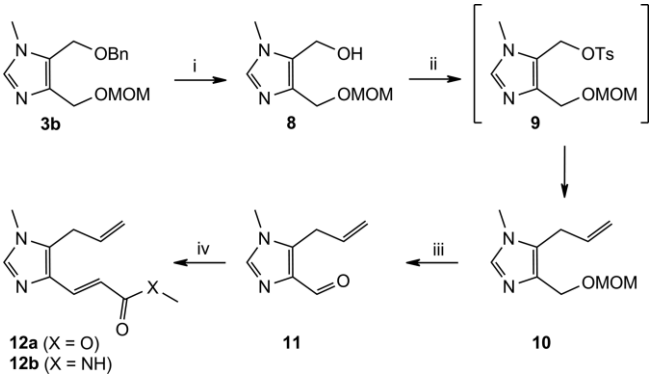
Imidazole ring closure was achieved by heating β-keto ester **4** with methylamine and TFA (trifluoroacetic acid) in refluxing xylenes under microwave irradiation to give *N*-methylimidazole 4-carboxylic ester **3a** in 59 % yield as the first key compound bearing suitably functionalised anchoring groups at C-4 and C-5.[16b] DIBAL-H (diisobutylaluminium hydride) reduction smoothly delivered the corresponding alcohol in 97 % yield.[3b,18] The final protection of the OH group as a MOM



Scheme 2. Synthesis of orthogonally protected 4,5-bis(hydroxymethyl)-1-methylimidazoles **3**. Conditions. i) $Ph_2C{=}O$, iPr_2NEt, *p*TsOH, PhMe, reflux, Dean–Stark, 8 h, 68 %. ii) *p*TsOH, $HC(OMe)_3$, reflux, 2 h; then Et_3N, reflux, 14 h, 60 %. iii) $SOCl_2$, reflux, 2 h, 92 %. iv) 1. **5**, *t*BuOK, THF, –60 °C, 30 min; then **7**, –60 °C to 23 °C, 6 h; then HCl (2 M aq.), 23 °C, 1 h; 2. AcOCHO, HCO_2Na, 23 °C, 14 h, 29 % yield of **4**. v) **6**, *N*-methylimidazole, CH_2Cl_2; then **7**, –45 °C, 30 min; then $TiCl_4$, Bu_3N, –45 °C, 30 min, 62 % yield of **4**. vi) $MeNH_2$ (33 % in EtOH), TFA, xylenes, microwave (300 W), 30 min, 59 %. vii) 1. DIBAL-H, THF, 0 °C, 2 h, 97 %; 2. NaHMDS, THF, 0 °C, 15 min; then MOMCl, 0 °C, 1 h; then 23 °C, 14 h, 83 %.

(methoxymethyl) ether required special conditions. Standard MOM ether formation using MOMCl and either trimethylamine or diisopropylethylamine delivered only imidazolium salts. This indicates that alkylation of the nucleophilic imidazole N-3 centre was preferred. The reactivity of the hydroxy group could be enhanced by deprotonation with NaHMDS (sodium hexamethyldisilazide).[19] Now, selective *O*-alkylation gave the second key imidazole **3b** in 83 % yield (80.5 % over two steps) on a 10 g scale. We anticipated that this latter imidazole **3b** could be used for the introduction of C-5 side-chains through various organometallic transformations (Scheme 2).

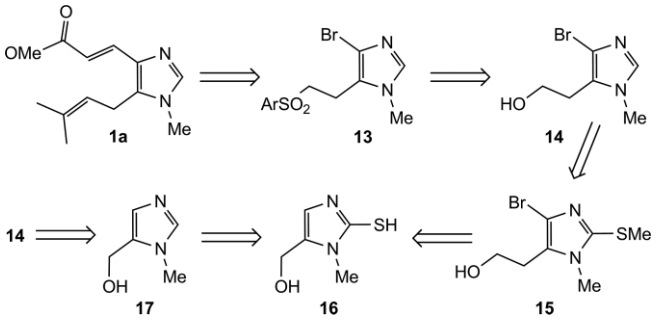
Elongation of the C-5 side-chain first required removal of the benzyl ether group of **3b**. Various attempts using hydrogen in the presence of palladium catalysts failed, even though a wide variety of catalysts, hydrogen pressures and solvents were tested.[20] Finally, Birch reduction was found to be the best choice. Treatment of benzyl ether **3b** with sodium in THF and liquid NH_3 gave the product alcohol **8** in 86 % yield.[21] In preparing for Grignard and Schlosser–Fouquet couplings, the OH group of imidazole **8** had to be activated as a leaving group. Chemoselective *O*-acylation was achieved through initial deprotonation using *n*BuLi in THF. Subsequent treatment of the alcoholate with *p*TsCl at low temperatures gave intermediate tosylate **9**. Small-scale couplings using vinylmagnesium bromide and CuBr gave 5-allylimidazole derivative **10** in up to 62 % yield. Unfortunately, all attempts to develop this procedure into a reliable and robust chain-elongation process failed. Despite extensive variation of the leaving group (halides, sulfonates, phosphates, carbonates/carbamates and esters), copper salts (and further additives), vinyl building blocks, solvents and temperatures, no progress was made.[22] In various runs, the handling of the leaving-group-containing intermediate, such as tosylate **9**, was found to be crucial. Competing oligomerisation took place through attack on the benzylic position by the nucleophilic N-3 nitrogen centre of a second imidazole; this delivered imidazolium salts, which then formed unreactive and insoluble precipitates. Overall, only a small quantity of 5-allylimidazole **10** could be assembled for further transformation (Scheme 3).



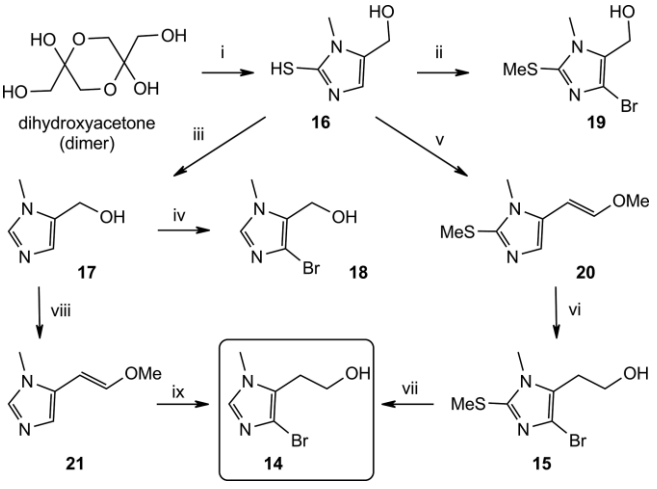
Scheme 3. Synthesis of fungerin derivatives **12**. Conditions: i) Na, THF/NH_3(l), –50 °C, 30 min, 86 %. ii) *n*BuLi, THF, 0 °C, 30 min; then *p*TsCl, –78 °C to –40 °C, 1 h; then vinylMgBr/CuBr in THF, –40 °C to 23 °C, 12 h, 62 %. iii) 1. HCl (6 M aq.), MeOH, 23 °C, 12 h, 86 %; 2. MnO_2, $CHCl_3$, reflux, 1 h, 95 %. iv) $(MeO)_2P(O)CH_2CO_2Me$, NaHMDS, THF, 0 °C, 1 h; then **11** in THF, 0 °C to 23 °C, 14 h, 90 % yield of **12a**; or $(MeO)_2P(O)CH_2C(O)NHMe$, NaHMDS, THF, 0 °C, 1 h; then **11** in THF, 0 °C to 23 °C, 14 h, 85 % yield of **12b**.

In contrast to the troublesome introduction of the C-5 side-chain, the next steps gave satisfactory results. Starting from imidazole **10**, removal of the MOM group using aq. HCl in MeOH and subsequent Braunstein oxidation (MnO_2) smoothly gave 4-formylimidazole **11** in ca. 82 % yield over two steps. Finally, standard Horner olefination using trimethyl phosphonoacetate (sodium salt) or the corresponding phosphonoamide allowed us to complete the syntheses of the fungerin derivatives. Ester **12a** was isolated in 90 % yield and amide **12b** in 85 % yield.[23] However, the unsatisfactory results for the C-5 chain elongation necessitated the development of an alternative more robust and more reliable strategy (Scheme 3).

Since the instability of an activated benzyl derivative such as tosylate **9** was regarded as the major obstacle for the first strategy, such an intermediate had to be avoided. Therefore, 4-bromo-5-hydroxyethyl-1-methylimidazole (**14**) was chosen as the key intermediate. This compound should allow the assembly of the C-5 allyl system after the conversion of the OH group into a sulfonyl substituent (→ **13**) for Julia olefination. The final C-4 side-chain should be introduced by a Heck reaction or suitable palladium-catalysed cross-coupling processes. For the chemoselective/regiospecific synthesis of key imidazole **14**, short reaction sequences starting from known 2-mercapto-5-hydroxymethylimidazole **16** seemed reasonable. On the one hand, protection of the thiol, oxidation, C-1 chain elongation through a Wittig-type olefination and C-4 bromination should deliver imidazole 2-thiomethyl ether **15**. A final reductive sulfur removal should lead to key imidazole **14**. On the other hand, a sequence was planned starting with removal of the sulfur to give known 5-hydroxmethylimidazole **17**. C-5 side-chain assembly would follow the removal of the 2-mercapto group, but the subsequent regioselective C-4 bromination aiming for key imidazole **14** would potentially require carefully optimised conditions to avoid competing C-2 bromination (Scheme 4).



Scheme 4. Retrosynthesis of fungerin derivatives via 4-bromo-5-(hydroxyethyl)-1-methylimidazole (**14**).



Scheme 5. Synthesis of 4-bromo-5-(hydroxyethyl)-1-methylimidazole (**14**). Conditions: i) KSCN, $MeNH_2$•HCl, *n*BuOH, AcOH, 23 °C, 3 d, 73 %. ii) 1. MeI, K_2CO_3, MeOH, 23 °C, 2 h, 73 %; 2. NBS, DMF, 0 °C to 23 °C, 2 h, 8 %. iii) $NaNO_2$, HNO_3 (2.4 M aq.), 0 °C to 23 °C, 14 h, 79 %. iv) NBS, DMF, 0 °C to 23 °C, 2 h, 4 %. v) 1. MeI, K_2CO_3, MeOH, 23 °C, 2 h, 73 %; 2. MnO_2, $CHCl_3$, reflux, 6 h, 98 %; 3. $[MeOCH_2PPh_3]^+Cl^-$/NaHMDS, THF, 0 °C to 23 °C, 3 h; then aldehyde, THF, 0 °C to 23 °C 14 h, 73 %. vi) 1. HCl (6 M aq.), 23 °C, 2 h; 2. $NaBH_4$, MeOH, 23 °C, 1 h, 83 %; 3. NBS, DMF, 0 °C to 23 °C, 2 h, 84 %. vii) Raney Ni, EtOH, 23 °C to reflux, 1.5 h, 90 %. viii) 1. MnO_2, $CHCl_3$, reflux, 6 h, 98 %; 2. $[MeOCH_2PPh_3]^+Cl^-$/NaHMDS, THF, 0 °C to 23 °C, 3 h; then aldehyde, THF, 0 °C to 23 °C 14 h, 90 %. ix) 1. HCl (6 M aq.), 23 °C, 2 h; 2. $NaBH_4$, MeOH, 23 °C, 1 h, 82 %; 3. NBS, DMF, 0 °C to 23 °C, 2 h, 79 % (+ 2-bromo analogue 8 %).

The generation of 2-mercapto-5-hydroxymethylimidazole **16** was easily achieved through a Marckwald cyclisation involving dihydroxyacetone dimer and KSCN, as published by H. Rapoport et al.[24] Product **16** was obtained in 73 % yield on a 100 g scale. Sulfur removal using Raney nickel in EtOH succeeded, delivering known hydroxymethylimidazole **17** in 58 % yield.[25] However, an alternative approach using $NaNO_2$ and HNO_3, following the Rapoport[24] procedure, gave imidazole **17** in an optimised 79 % yield.[26]

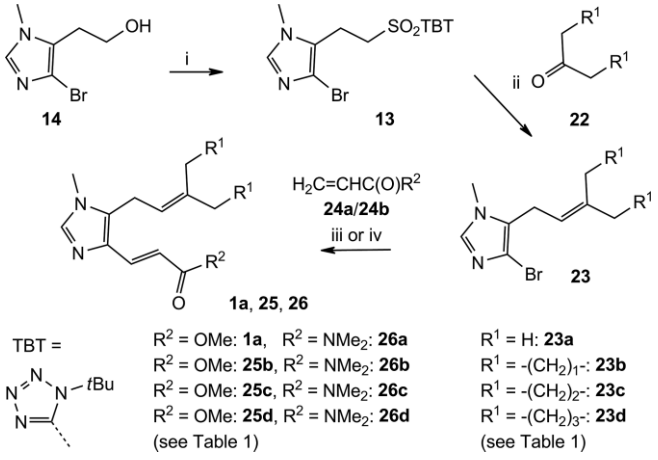
With the aim of avoiding the formation of any mixtures of C-2 and C-4 regioisomers upon bromination of the imidazole core, a first synthesis of key imidazole **14** was started keeping the C-2 sulfur protection in place. After initial thioether formation (MeI/K_2CO_3, 73 % yield) according to J. Lee,[27] C-4 bromination was carried out, adapting a procedure using NBS (*N*-bromosuccinimide) in DMF.[28] A disappointing 8 % yield of bromoimidazole **19** was achieved. Presumably, an efficient competing bromination–deformylation cascade as observed by Y. Shi for a related reaction with NCS (*N*-chlorosuccinimide) prevented a higher yield of the desired product.[29] Consequentially, C-5 chain elongation had to be carried out first (Scheme 5).

Starting from the 2-thiomethylimidazole intermediate, oxidation with MnO_2 (98 %) and subsequent methoxymethylene Wittig olefination gave vinyl ether **20** in 73 % yield as a nearly 1:1 *E*/*Z* mixture. Then, cleavage of the enol ether upon treatment with HCl (6 M aq.) delivered the intermediate imidazole-5-acetaldehyde. This was immediately reduced with $NaBH_4$ in MeOH to give the imidazole bearing a C-5 2-hydroxyethyl side-chain in 83 % yield. In contrast to the imidazole containing the C-5 hydroxymethyl side-chain, this homologue underwent smooth C-4 bromination upon reaction with NBS/DMF. 4-Bromoimidazole **15** was isolated with 84 % yield.[30] Finally, sulfur removal with Raney nickel successfully gave key imidazole **14** in 90 % yield. Overall, this sequence required eight steps (from dihydroxyacetone), and delivered key imidazole **14** in 24 % yield.

The alternative synthesis started from 5-hydroxymethylimidazole **17**. Similarly to the sequence described above, early bromine introduction gave a mixture of products. The desired 4-bromoimidazole **18** was formed as a minor product in only 4 % yield.[29] In contrast, the reaction cascade in which the C-5 chain elongation was run first proved successful. Imidazole **17** was subjected to MnO_2 oxidation and methoxymethylene Wittig olefination to give enol ether **21** in ca. 88 % yield (over two steps, *E*/*Z* mixture). The subsequent cascade of vinyl ether cleavage (HCl, 6 N aq.) and aldehyde reduction ($NaBH_4$/MeOH) delivered the 5-hydroxyethylimidazole derivative (82 % yield over two steps). Carefully optimised C-4 bromination allowed us to complete the synthesis of key imidazole **14** in 79 % yield. The corresponding 2-bromo regioisomer **14a** was formed as a minor product (8 % yield).[31] Overall, this sequence required seven steps (from dihydroxyacetone), and delivered key imidazole **14** in 33 % yield (Scheme 5).

The endgame of the syntheses of the fungerin derivatives required a suitable activation of the hydroxyethyl side-chain of key intermediate **14**. Since Julia–Kociensky olefinations reliably and flexibly allow the introduction of double bonds, 1-*tert*-butyl-5-mercaptotetrazole (TBTSH) was introduced by means of a Mitsunobu reaction [DIAD (diisopropyl azodicarboxylate), PPh_3].[32] Subsequent oxidation with H_2O_2/ammonium molybdate gave key sulfone **13** in ca. 75 % yield (over two steps).[33]

Then, Julia–Kociensky olefinations were run using symmetrical ketones **22** to avoid the formation of *E*/*Z* isomers.[34] After deprotonation of sulfone **13** with LiHMDS in THF at –60 °C, addition of acetone **22a** (R^1 = H) or standard cycloalkanones **22b**–**22d** [R^1 = -$(CH_2)_{1-3}$-] gave 4-bromo-substituted 5-allylimidazole derivatives **23** in 77–85 % yield after careful purification by preparative HPLC. It should be pointed out that the 5-allyl double bond did not suffer from any isomerisation during the formation of the vinylimidazole derivatives.[35] (Scheme 6, Table 1).



Scheme 6. Synthesis of fungerin derivatives **1a**, **25** and **26**. Conditions: i) 1. TBTSH, PPh_3, DIAD, THF, 0 °C to 23 °C, 2.5 h, 92 %; 2. HCl (1 M aq.), EtOH (pH 6), then $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2 (35 % in H_2O), 0 °C to 23 °C, 14 h, 82 %. ii) LiHMDS, THF, –60 °C, 1 h; then ketone **22** (Table 1), –60 °C to 23 °C, 14 h, 77–89 % yield of **23** (Table 1). iii) methyl propenoate **24a** (R^2 = OMe), K_2CO_3, $Pd(OAc)_2$, $P(Tol)_3$, DMF, 120 °C, sealed tube, 14 h, 25–33 % yield of **1a** and **25** (Table 1). iv) *N,N*-dimethylamino propenoate **24b** (R^2 = NMe_2), K_2CO_3, $Pd(OAc)_2$, $P(Tol)_3$, DMF, 120 °C, sealed tube, 14 h, 22–31 % yield of **26** (Table 1).

Table 1. Results of Julia–Kociensky olefination and Heck reaction.

Entry	Product	R^1 [a]	Yield [%]	Product	R^2	Yield [%]
1	**23a**	H	86	**1a**[b]	OMe	27
2				**26a**[c]	NMe_2	29
3	**23b**	-$(CH_2)_1$-	89	**25b**[b]	OMe	25
4				**26b**[c]	NMe_2	31
5	**23c**	-$(CH_2)_2$-	77	**25c**[b]	OMe	29
6				**26c**[c]	NMe_2	22
7	**23d**	-$(CH_2)_3$-	85	**25d**[b]	OMe	33
8				**26d**[c]	NMe_2	27

[a] Substitution pattern in ketones **22**, bromoimidazoles **23** and fungerin derivatives **1a**, **25** and **26**. [b] Heck reaction product with methyl propenoate **24a** (R^2 = OMe). [c] Heck reaction product with *N,N*-dimethylamino propenoate **24b** (R^2 = NMe_2).

With a set of four 4-bromo-5-allylimidazoles **23** in hand, the final C-4 side-chains were introduced through Heck couplings with acrylic acid derivatives **24**.[36] An analysis of the literature revealed that Heck reactions of non-acceptor-substituted 4-haloimidazoles have hardly been described. Other than the original Benhida fungerin synthesis using the 4-iodo analogue of **23a**,[12] preferentially monosubstituted 4-halo-5*H*-imidazoles were successfully converted into 4-alkenyl derivatives.[37] Furthermore, Langer reported multiple high-yielding Heck reactions using 2,4,5-trihaloimidazoles as starting materials.[38] In our hands, the 4-bromoimidazole derivatives **23** proved to react sluggishly. Despite some variation of the reaction conditions (temperature, pressure, catalyst, etc.) the yields of product esters **1a** and **25** as well as amides **26** remained around 30 %. However, enough material for initial phytological tests had been produced. Therefore, extensive optimisation would seem to be more reasonable after biological evaluation of the target compounds and identification of the most promising structures.

Conclusions

1,4,5-Trisubstituted imidazoles such as the natural product fungerin are known to be biologically active compounds, characterised by a wide range of antifungal, cytotoxic and anticholinergic properties. Focussing on flexible chemo- and regioselective syntheses, N-1-alkylation of 4,5-difunctionalised imidazole derivatives was applied successfully (e.g., fungerin synthesis according Benhida[12]). However, the regioselectivity was found to be always dependent on the substitution pattern of the particular reactant. An alternative attempt excluding the N-1/N-3-alkylation selectivity problem incorporated the synthesis of a defined α-aminoketone. But the harsh conditions of the final imidazole-ring formation were found to be unfavourable for sensitive products. Consequentially, *N*-alkylimidazoles bearing suitably substituted anchor groups at C-4 and C-5 were chosen as useful starting materials.

The first type of N-1-methylimidazole key compounds incorporated orthogonally protected C-1 anchors attached to C-4 and C-5. Starting from glycine and benzyloxyacetic acid derivatives, Claisen-type ester condensation delivered α-amino β-keto ester **4** (10 g scale, using literature procedures if useful). Imidazole-ring closure gave imidazole 4-carboxylic ester **3a** (20–37 % over two steps). Orthogonally protected 4,5-bis(hydroxymethyl)imidazole **3b** was built up using a three-step sequence (47.5 % yield). For the synthesis of fungerin-type products, chain elongation to complete the C-5 allyl substitution pattern required organometallic coupling processes. After deprotection and activation of the C-5 CH_2OH group as a tosylate, Grignard alkenylation gave the C-5 allylimidazole in up to 62 % yield (small scale). Unfortunately, this reaction proved not to be robust, because of the formation of various (insoluble and unreactive) side-products. However, 5-allylimidazole **10** underwent smooth C-4 hydroxymethyl group deprotection, oxidation and Horner olefination to give the target fungerin-type derivatives in 39 % yield (over five steps from imidazole **3b**). Overall, five steps were required to generate the key imidazole compound **3b** (ca. 18 % yield), and five further steps (39 % yield) completed the synthesis of the selectively substituted fungerin derivatives.

With the aim of avoiding potential side-reactions involving acceptor -substituted CH_2 groups at C-5, 4-bromo-5-hydroxyethyl-1-methylimidazole (**14**) was chosen as the key compound for the selective introduction of side-chains. Starting from dihydroxyacetone, two sequences for the synthesis of imidazole **14** were developed, incorporating literature procedures in the initial steps. Since the initial Marckwald imidazole cyclisation according Rapoport[24] delivered a 2-mercaptoimidazole **16**, the sulfur was used as a C-2 protective group. Furthermore, bromination of 5-hydroxymethylimidazoles caused, for example, deformylations as competing processes (low yield). Thus, chain elongation by oxidation, C-1 Wittig olefination, enol ether cleavage and reduction had to be carried out first. Then, selective C-4 bromination and C-2 sulfur removal delivered the key imidazole **14** in 24 % overall yield (over eight steps). Alternatively, the sulfur of the Rapoport product **16** was removed first (→ **17**). The analogous sequence for chain extension smoothly delivered the 5-hydroxyethylimidazole, and carefully optimised

conditions allowed the preferred C-4 bromination to take place in high yield. However, separation of the minor 2-bromo product required preparative HPLC. The synthesis of key intermediate **14** required seven steps, which gave an overall yield of 33 %. Comparing the two approaches, the latter is characterised by a higher overall yield (33 vs. 24 %), but the former does not require HPLC separation.

Starting from key imidazole **14**, two high-yielding transformations prepare for a Julia–Kociensky olefination (→ **13**). A subsequent olefination allows the establishment of olefins, as demonstrated by four examples (77–89 % yield). A Heck-type process is a simple way to introduce acrylic acid derivatives, so a series of reactions was run to generate fungerin (**1a**) and several derivatives **25** and **26**. Focussing on improving the flexibility of the synthesis, optimisation of the final steps of these transformations should be carried out after identification of the biologically interesting compounds. In summary, nine-to-ten-step sequences allow the synthesis of 1,4,5-trisubstituted imidazoles such as **14** and **13** as key intermediates (25 % yield overall, up to 10 g scale). Two final side-chain introductions complete the syntheses of the fungerin derivatives. It should be pointed out that the number of accessible imidazole substitution patterns might be extended, and the syntheses might be optimised, by replacing the Julia reaction by alternative olefination methods, and the Heck reaction by various other cross-coupling[39] or umpolung reactions. The synthesis of libraries of fungerin derivatives for extensive biological testing will now be started.

Experimental Section

General Remarks: Reaction solvents were dried by standard procedures before use when necessary. All reactions including moisture- or air-sensitive reagents were carried out under an argon atmosphere. ^{1}H, ^{13}C, and 2D (COSY, HSQC, HMBC, NOESY) NMR spectra were recorded at room temperature with a Bruker ARX400 or AV400 spectrometer in $CDCl_3$, using the signal of residual $CHCl_3$ as an internal standard. Additional signals from the amide's rotamers are given in square brackets. IR spectra were recorded with a Jasco FTIR-400 plus spectrometer. High-resolution mass spectra (HRMS) were recorded with a Waters Q-Tof Ultima 3 Micromass spectrometer. Column chromatography was carried out on MN silica gel 60M from Macherey–Nagel (grain size: 0.040–0.063 mm). The progress of reactions was monitored by thin-layer chromatography (TLC), carried out on aluminum sheets precoated with silica gel 60 F254 silica gel from Merck. HPLC: t_R = peak retention time, k = retention factor = $(t_R - t_0)/t_0$.

Methyl 4-Benzyloxy-2-*N*-formylamido-3-oxobutyrate (4) from Methyl *N*-Formylglycinate (6):[17] Methyl *N*-formylglycinate (**6**; 1.17 g, 9.99 mmol) and *N*-methylimidazole (0.82 g, 0.12 mol) were dissolved in dry CH_2Cl_2 (200 mL), and the solution was cooled to –45 °C. Benzyloxyacetyl chloride (1.85 g, 10.02 mmol) was added dropwise, and the reaction mixture was stirred at –45 °C for 30 min. Then, $TiCl_4$ (6.64 g, 35 mmol) and tri-*n*-butylamine (7.41 g, 40 mmol) were added, and a deep-black-coloured mixture resulted. The mixture was stirred at –45 °C for a further 30 min. The reaction was quenched with H_2O (50 mL), and the mixture was stirred for 1 min at low temperature, then the organic layer was poured over a mixture of Na_2SO_4 and small amounts of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layers were dried (Na_2SO_4). The solid residues were removed by filtration, and the solvent was removed in vacuo. The oily residue was purified by column chromatography (silica gel, gradient 10–50 % EtOAc in petroleum ether) to give keto ester **4** (1.65 g, 6.21 mmol, 62 %) as a yellow oil. R_f = 0.58 (100 % EtOAc) Ninhydrin/UV. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.20 (m, 1 H, 11-H), 7.42–7.28 (m, 5 H, 7-H/8-H/9-H), 6.83 (s, 1 H, -NH), 5.46 (dd, J = 6.9, 0.9 Hz, 1 H, 2-H), 4.59 (d, J = 1.8 Hz, 2 H, 5-H), 4.40 (d, J = 3.5 Hz, 2 H, 4-H), 3.76 (s, 3 H, 10-H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 199.4 (C-3), 166.6 (C-1), 160.9 (C-11), 137.6 (C-6), 129.0 (C-8), 128.6 (C-9), 128.5 (C-7), 74.3 (C-4), 74.0 (C-5), 58.2 (C-2), 54.0 (C-10) ppm. IR: $\tilde{\nu}$ = 3327 (br), 3060 (w), 3032 (w), 2955 (w), 2880 (w), 1734 (s), 1671 (s), 1496 (m), 1436 (m), 1385 (m), 1332 (w), 1369 (s), 1207 (s), 1103 (s), 1026 (m), 914 (w), 742 (s), 699 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}NO_5{}^{23}Na$ [M + Na]$^+$ 288.0848; found 288.0858.

1-Methyl-5-benzyloxymethylimidazole 4-Carboxylic Acid Methyl Ester (3a): A stirred solution of formamide (1.0 g, 3.77 mmol) in xylenes (70 mL) was treated with methylamine (33 wt.-% in EtOH; 1.41 mL, 11.31 mmol) followed by trifluoroacetic acid (0.90 mL, 11.69 mmol). The reaction mixture was irradiated in a microwave reactor (300 W) under reflux for 30 min with vigorous stirring. The mixture was cooled, and EtOAc (50 mL) was added. The organic phase was extracted with $NaHCO_3$ (10 % aq.; 50 mL) and H_2O (50 mL). The aqueous layers were reextracted with EtOAc (30 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, 100 % EtOAc) to give **3a** (0.58 g, 2.23 mmol, 59 %) as a white solid, m.p. 75–82 °C. R_f = 0.33 (50 % acetone in EtOAc) Schlittler stain. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, 2-H), 7.37–7.28 (m, 5 H, 10-H/11-H/12-H), 4.99 (s, 2 H, 7-H), 4.53 (s, 2 H, 8-H), 3.88 (s, 3 H, 6-H), 3.69 (s, 3 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (C-5), 138.4 (C-2), 137.6 (C-9), 134.4 (C-4), 131.7 (C-3), 128.4 (C-11), 127.8 (C-10, C-12), 72.2 (C-8), 60.5 (C-7), 51.7 (C-6), 32.1 (C-1) ppm. IR: $\tilde{\nu}$ = 3028 (w), 2949 (w), 2855 (w), 1707 (s), 1565 (w), 1513 (m), 1437 (m), 1368 (m), 1329 (m), 1253 (s), 1200 (s), 1162 (s), 1062 (s), 939 (w), 793 (w), 742 (m), 700 (m), 666 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{16}N_2O_3{}^{23}Na$ [M + Na]$^+$ 283.1059; found 283.1049.

1-Methyl-4-hydroxymethyl-5-benzyloxymethylimidazole: A stirred solution of ester **3a** (13.0 g, 49.94 mmol) in dry THF (200 mL) was treated dropwise with DIBAL-H (1 M in hexanes; 109.87 mL, 109.87 mmol) at 0 °C. The mixture was stirred for 2 h, and over this period, the temperature was allowed to reach 23 °C. The reaction was stopped by the dropwise addition of MeOH at 0 °C. The resulting precipitate was dissolved by the addition of NaOH (2 M aq.). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases were dried (Na_2SO_4) and the solvents were removed in vacuo. The residue was purified by column chromatography (silica gel, 100 % acetone) to give 1-methyl-4-hydroxymethyl-5-benzyloxymethylimidazole (9.30 g, 48.65 mmol, 97 %). For data, see the Supporting Information.

1-Methyl-4-methoxymethyloxymethyl-5-benzyloxymethylimidazole (3b): NaHMDS (2 M in THF; 2.84 mL, 5.69 mL) was added dropwise to a stirred solution of 1-methyl-4-hydroxymethyl-5-benzyloxymethylimidazole (1.1 g, 4.74 mmol) in dry THF (20 mL) at 0 °C. After 15 min, MOMCl (0.38 mL, 4.98 mmol) was added dropwise at 0 °C. The mixture was stirred for a further 1 h at 0 °C, and then at 23 °C overnight. The reaction was quenched by addition of some drops of NaOH (4 M aq.), and the mixture was stirred for 10 min. Then, the solvents were removed by vacuum distillation. The residue was dissolved in CH_2Cl_2, and the solution was washed with H_2O. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chroma-

tography (silica gel, 100 % acetone) to give benzyl ether **3b** (1.09 g, 3.94 mmol, 83 %) as an oil, which solidified upon storage in a fridge, m.p. 32–35 °C. R_f = 0.18 (50 % acetone in EtOAc) Schlittler stain. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 1 H, 2-H), 7.34–7.23 (m, 5 H, 11-H/12-H/13-H), 4.63 (s, 2 H, 6-H), 4.53 (s, 2 H, 9-H), 4.48 (s, 2 H, 8-H), 4.46 (s, 2 H, 5-H), 3.58 (s, 3 H, 1-H), 3.33 (s, 3 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (C-2), 137.9 (C-3), 137.7 (C-10), 128.5 (C-12), 127.8 (C-11 and C-13), 126.3 (C-4), 95.5 (C-6), 71.6 (C-9), 61.8 (C-5), 59.8 (C-8), 55.2 (C-7), 31.7 (C-1) ppm. IR: $\tilde{\nu}$ = 3029 (w), 2930 (w), 2879 (w), 1506 (m), 1146 (m), 1095 (m), 1064 (s), 1029 (s), 916 (m), 739 (m), 699 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_3{}^{23}$Na $[M + Na]^+$ 299.1372; found 299.1383.

1-Methyl-4-methoxymethyloxymethyl-5-hydroxymethylimidazole (8): A solution of benzyl ether **3b** (10.81 g, 39.13 mmol) in dry THF (150 mL) was added to liquid NH_3 (150 mL) at –55 °C. At the same temperature, sodium pellets were added portionwise with vigorous stirring until a blue-coloured reaction mixture remained. The mixture was stirred for a further 1 h, then an excess of aq. NH_4Cl was added dropwise until the blue colour disappeared to give a colourless solution. The mixture was warmed to 23 °C, and the remaining solvents were removed by vacuum distillation. The residue was extracted with CH_2Cl_2 (3 × 50 mL), and the solvent was removed by distillation. The residue was purified by column chromatography (silica gel, 100 % acetone) to gove MOM ether **8** (6.25 g, 33.56 mmol, 86 %) as a white solid, m.p. 91–95 °C. R_f = 0.18 (100 % acetone) Schlittler stain. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1 H, 2-H), 4.52 (s, 4 H, 5-H and 8-H), 3.67 (s, 2 H, 6-H), 3.42 (s, 3 H, 7-H), 3.36 (s, 3 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5 (C-2), 135.4 (C-3), 130.1 (C-4), 94.7 (C-6), 61.2 (C-5), 55.0 (C-8), 52.0 (C-7), 31.5 (C-1) ppm. IR: $\tilde{\nu}$ = 3305 (bs), 3112 (w), 2946 (w), 2886 (w), 1511 (m), 1147 (m), 1101 (m), 1035 (s), 916 (w) cm^{-1}. HRMS (ESI): calcd. for $C_8H_{15}N_2O_3$ $[M + H]^+$ 187.1083; found 187.1090.

1-Methyl-4-methoxymethyloxymethyl-5-(2-propenyl)-imidazole (10): Alcohol **8** (0.20 g, 1.07 mmol) was dissolved in dry THF (50 mL, ultrasonication), and then the solution was cooled to 0 °C. *n*BuLi (1.6 M in hexanes; 0.74 mL, 1.18 mmol) was added dropwise, resulting a cloudy solution. The mixture was stirred for 30 min at 0 °C, then the resulting suspension was cooled to –78 °C, and a solution of *p*TsCl (0.25 g, 1.29 mmol) in dry THF (5 mL) was added dropwise. The temperature was slowly raised to –40 °C until a clear solution remained. Then, the solution was cooled to –78 °C.

Cuprate reagent:[10] Vinylmagnesium bromide (0.7 M in THF; 7.67 mL, 5.37 mmol) was added dropwise to CuBr (0.15 g, 1.07 mmol) in dry THF (20 mL) at –20 °C. The resulting black coloured mixture was stirred for a further 30 min at 0 °C.

The freshly prepared cuprate solution was added to the tosylate solution by Teflon cannula. The resulting black mixture was stirred overnight, and during this time, the temperature reached 23 °C. The mixture was quenched with $NaHCO_3$ (5 % aq.), and the solid residues were removed by filtration. The solvents of the filtrate were removed by vacuum distillation. The resulting residue was extracted with CH_2Cl_2 (3 × 30 mL, ultrasonication), the organic layers were filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, gradient 0–100 % acetone in EtOAc) to give 5-allylimidazole **10** (0.131 g, 0.668 mmol, 62 %) as a clear oil oil. R_f = 0.25 (100 % acetone) Schlittler stain. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1 H, 2-H), 5.81 (ddt, J = 17.0, 10.1, 5.7 Hz, 1 H, 9-H), 5.05 (ddd, J = 10.1, 3.1, 1.5 Hz, 1 H, 10-H *cis*), 4.92 (ddd, J = 17.1, 3.3, 1.7 Hz, 1 H, 10-H *trans*), 4.64 (s, 2 H, 5-H), 4.46 (s, 2 H, 6-H), 3.49 (s, 3 H, 7-H), 3.38–3.35 (m, 5 H, 8-H/1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1 (C-2), 135.1 (C-3), 134.4 (C-9), 127.5 (C-4), 116.4 (C-10), 95.3 (C-6), 61.8 (C-5), 55.2 (C-7), 31.5 (C-1), 27.2 (C-8) ppm. IR: $\tilde{\nu}$ = 3084 (w), 2929 (w), 2880 (w), 1505 (m), 1145 (m), 1097 (m), 1029 (s), 915 (m), 808 (w), 639 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}N_2O_2{}^{23}$Na $[M + Na]^+$ 219.1109; found 219.1116.

1-Methyl-4-hydroxymethyl-5-(2-propenyl)-imidazole: Allylimidazole **10** (0.26 g, 1.31 mmol) in MeOH (10 mL) was treated with conc. aq. HCl (1 mL) at 0 °C with stirring. The mixture was stirred at 23 °C overnight, then solid $NaHCO_3$ was added until a pH of >7 was reached. The solvents were removed by vacuum distillation, and the residue was extracted with CH_2Cl_2 (3 × 15 mL). Then, the solvent of the organic layer was removed by distillation, and the residue was purified by column chromatography (silica gel, gradient 0–10 % MeOH in acetone) to give the hydroxymethylimidazole (0.17 g, 1.12 mmol, 86 %). For data, see the Supporting Information.

1-Methyl-4-formyl-5-(2-propenyl)-imidazole (11): MnO_2 (0.68 g, 7.87 mmol) was added to 1-methyl-4-hydroxymethyl-5-(2-propenyl)-imidazole (0.17 g, 1.12 mmol) in $CHCl_3$ (30 mL). The mixture was heated at reflux until TLC indicated the complete consumption of the hydroxymethylimidazole (ca. 1 h). The hot mixture was filtered through a plug of Celite (careful washing with hot $CHCl_3$), and the filtrate solvent was removed in vacuo. The resulting residue was purified by column chromatography (silica gel, gradient 0–50 % acetone in EtOAc)to give aldehyde **11** (0.16 g, 1.07 mmol, 95 %) as a colourless oil. For data, see the Supporting Information.

3-[1-Methyl-5-(2-propenyl)-1*H*-imidazol-4-yl]-2*E*-propenoic Acid Methyl Ester (12a): NaHMDS (2 M in THF; 0.3 mL, 0.6 mmol) was added to trimethyl phosphonoacetate (0.12 g, 0.67 mmol) in dry THF (10 mL) at 0 °C with stirring. After ca. 1 h of deprotonation time, a solution of aldehyde **11** (0.05 g, 0.33 mmol) in dry THF (5 mL) was added dropwise, and the mixture was stirred at 0 °C for 1 h and then at 23 °C overnight. The reaction was quenched by the addition of some drops of saturated aq. NH_4Cl, and the solvents were removed in vacuo. The residue was dissolved in a mixture of CH_2Cl_2 (10 mL) and HCl (0.5 M aq.; 10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL). Then the aqueous layer was treated with solid $NaHCO_3$ until the pH remained >7. The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, gradient 0–5 % MeOH in acetone) to give ester **12a** (0.061 g, 0.297 mmol, 90 %) as a colourless oil. R_f = 0.35 (100 % acetone) $KMnO_4$. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.54 (dd, J = 15.3, 0.6 Hz, 1 H, 5-H), 7.41 (s, 1 H, 2-H), 6.47 (d, J = 15.3 Hz, 1 H, 6-H), 5.86 (ddt, J = 17.1, 10.1, 5.6 Hz, 1 H, 10-H), 5.13 (dq, J = 10.1, 1.6 Hz, 1 H, 11-H *cis*), 4.95 (ddd, J = 17.1, 3.2, 1.8 Hz, 1 H, 11-H *trans*), 3.72 (s, 3 H, 8-H), 3.52 (s, 3 H, 1-H), 3.48 (dt, J = 5.6, 1.8 Hz, 2 H, 9-H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 168.6 (C-7), 139.4 (C-2), 135.7 (C-5), 135.4 (C-3), 134.3 (C-10), 132.7 (C-4), 117.2 (C-11), 114.6 (C-6), 51.7 (C-8), 32.1 (C-1), 27.6 (C-9) ppm. IR: $\tilde{\nu}$ = 3103 (w), 2950 (w), 2852 (w), 1701 (s), 1634 (s), 1515 (m), 1434 (m), 1302 (m), 1274 (s), 1172 (s), 1037 (w), 976 (m), 912 (w), 809 (w), 743 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}N_2O_2$ $[M + H]^+$ 207.1134; found 207.1140.

For syntheses of 4-bromo-5-(2-hydroxyethyl)-1-methylimidazole (**14**), see the Supporting Information.

1-(*tert*-Butyl)-5-{[2-(1-methyl-4-bromo-1*H*-imidazol-5-yl)ethyl]-thio}-1*H*-tetrazole: 4-(Bromohydroxyethyl)imidazole **14** (5.0 g, 24.38 mmol), triphenyl phosphine (10.23 g, 39.01 mmol) and 1-(*tert*-Butyl)-5-mercapto-1*H*-tetrazole (6.17 g, 39.01 mmol) were dissolved in THF (350 mL), and the solution was cooled to 0 °C. This solution was treated dropwise with diisopropyl azodicarboxylate (DIAD; 95 %; 8.64 mL, 43.88 mmol) at 0 °C over a period of 30 min with stirring. The cooling bath was removed, and the mixture was stirred

at 23 °C for a further 2 h. The mixture was quenched with sat. aq. NH_4Cl (15 mL), and most of the solvents were removed by distillation. The residue was dissolved in HCl (2 M aq.; 40 mL) and EtOAc (300 mL), and the organic layer was extracted with HCl (2 M aq.; 2 × 40 mL) and HCl (1 M aq.; 2 × 25 mL). The combined aqueous phases were treated with NaOH (10 M aq.) until the pH remained >10. The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, EtOAc) to give the bromo thioether (7.74 g, 22.42 mmol, 92 %). For data, see the Supporting Information.

1-(*tert*-Butyl)-5-{[2-(1-methyl-4-bromo-1*H*-imidazol-5-yl)ethyl]-sulfonyl}-1*H*-tetrazole (13): 1-(*tert*-Butyl)-5-{[2-(1-methyl-4-bromo-1*H*-imidazol-5-yl)ethyl]thio}-1*H*-tetrazole (5.58 g, 15.58 mmol) was dissolved in EtOH (100 mL), and the pH of the solution was adjusted to 6 by the addition of HCl (1 M aq.). The mixture was cooled to 0 °C, and a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (3.86 g, 3.12 mmol) in H_2O_2 (35 % aq.; 13.34 mL, 155.82 mmol; stirred for 15 min at 23 °C before addition) was added dropwise with stirring. Then, the cooling bath was removed, and the mixture was stirred at 23 °C overnight. The mixture was then diluted with water (100 mL), and then sat. aq. $NaHCO_3$ was added until a basic pH was achieved. The mixture was extracted with CH_2Cl_2 (1 × 100 mL, 3 × 50 mL), and the combined organic layers were dried (Na_2SO_4). The solvents were removed in vacuo, and the residue was purified by column chromatography (silica gel, gradient 50–100 % EtOAc in petroleum ether) to give bromosulfone **13** (4.18 g, 12.75 mmol, 82 %) as a white solid, m.p. 80–84 °C. R_f = 0.40 (100 % EtOAc) Schlittler stain. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 1 H, 1-H), 3.98–3.91 (m, 2 H, 6-H), 3.72 (s, 3 H, 4-H), 3.31–3.24 (m, 2 H, 5-H), 1.83 (s, 9 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6 (C-7), 137.5 (C-1), 124.2 (C-3), 115. (C-2), 65.7 (C-8), 54.6 (C-6), 32.8 (C-4), 29.7 (C-9), 17.8 (C-5) ppm. IR: $\tilde{\nu}$ = 3109 (w), 2988 (w), 2941 (w), 1498 (m), 1375 (m), 1329 (s), 1245 (s), 1211 (m), 1159 (s), 1123 (m), 939 (w), 808 (w), 734 (w), 693 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}N_6O_2SBr^{23}Na$ $[M + Na]^+$ 399.0215; found 399.0215.

1-Methyl-4-bromo-5-(3-methylbut-2-en-1-yl)-1*H*-imidazole (23a): Sulfonyl imidazole **13** (0.5 g, 1.33 mmol) in dry THF (100 mL) was deprotonated by the dropwise addition of LiHMDS (1 M in THF; 1.46 mL, 1.46 mmol) at –60 °C with stirring. After 1 h at –60 °C, acetone (**22a**; 0.15 mL, 2.0 mmol) was added, and the mixture was stirred for a further 1 h. Then, the cooling bath was removed, and the mixture was stirred at 23 °C overnight. The reaction was quenched with some drops of sat. aq. NH_4Cl, and the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and $NaHCO_3$ (5 % aq.; 10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed in vacuo, and the crude product was purified by column chromatography (silica gel, gradient 50–100 % EtOAc in petroleum ether) and preparative HPLC (Nucleosil 50–5, 40 % *i*PrOH/hexanes, 64 mL/min, 110 bar) to give bromo prenyl imidazole **23a** (0.26 g, 1.14 mmol, 86 %) as a colourless oil. HPLC: k = 0.8; t_R = 4.5 min. R_f = 0.40 (100 % EtOAc) $KMnO_4$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 1 H, 1-H), 5.05–4.99 (m, 1 H, 6-H), 3.50 (s, 3 H, 4-H), 3.25 (d, J = 7.0 Hz, 2 H, 5-H), 1.71 (s, 3 H, 8-H), 1.67 (d, J = 1.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4 (C-1), 134.0 (C-7), 128.7 (C-3), 119.2 (C-6), 113.6 (C-2), 32.5 (C-4), 25.6 (C-8), 22.9 (C-5), 18.0 (C-9) ppm. IR: $\tilde{\nu}$ = 3103 (w), 2971 (w), 2912 (w), 2856 (w), 2727 (w), 1552 (w), 1495 (s), 1446 (m), 1375 (m), 1243 (s), 1169 (m), 982 (m), 906 (w), 847 (w), 801 (w), 666 (w) cm^{-1}. HRMS (ESI): calcd. for $C_9H_{14}N_2Br$ $[M + H]^+$ 229.0340; found 229.0347.

3-[1-Methyl-5-(3-methyl-2-butenyl)-1*H*-imidazol-4-yl]-2*E*-propenoic Acid Methyl Ester (Fungerin; 1a): Bromoimidazole **23a** (50 mg, 0.218 mmol), methyl acrylate (**24a**; 94.0 mg, 1.091 mmol), potassium carbonate (75 mg, 0.545 mmol), $Pd(OAc)_2$ (2.2 mg, 9.8 µmol) and tri-(*p*-tolyl)phosphine [$P(Tol)_3$; 6.0 mg, 19.6 µmol] were suspended in DMF (3 mL) in a carefully sealed pressure tube. The mixture was heated to 120 °C overnight. The mixture was then cooled, and the solvent was removed in vacuo. The residue was dissolved in HCl (1 M aq.; 5 mL) and EtOAc (20 mL), and the organic layer was extracted with HCl (1 M aq.; 2 × 1 mL). Then, the pH of the combined aqueous phases was adjusted to >10 by the dropwise addition of NaOH (10 M aq.). The aqueous phase was extracted with CH_2Cl_2 (5 × 5 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, gradient 10–50 % acetone in EtOAc) to give fungerin (**1a**; 0.013 g 0.059 mmol, 27 %) as a white solid, m.p. 92–94 °C (lit.[8a] 93–95 °C). For further data, see refs.[8a,12] and the Supporting Information.

3-[1-Methyl-5-(3-methyl-2-butenyl)-1*H*-imidazol-4-yl]-2*E*-propenoic Acid *N*,*N*-Dimethylamide (26a): A reaction with bromoimidazole **23a** (0.050 g, 0.218 mmol) acrylic acid *N*,*N*-dimethylamide (**24b**; 0.108 g, 1.091 mmol), potassium carbonate (0.075 g, 0.545 mmol), $Pd(OAc)_2$ (2.5 mg, 10.9 µmol), and $P(Tol)_3$ (6.6 mg, 21.8 µmol) was carried out following the procedure described for fungerin (**1a**). Purification by column chromatography (silica gel, gradient 50–100 % acetone in EtOAc) gave amido fungerin **26a** (0.016 g, 0.063 mmol, 29 %) as a white solid, m.p. 103–106 °C. R_f = 0.24 (100 % acetone) UV/$KMnO_4$. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.52 (d, J = 14.7 Hz, 1 H, 5-H), 7.33 (s, 1 H, 1-H), 7.02 (d, J = 14.7 Hz, 1 H, 6-H), 5.07–5.01 (m, 1 H, 10-H), 3.50 (s, 3 H, 4-H), 3.42 (d, J = 6.8 Hz, 2 H, 9-H), 3.13 (s, 3 H, 8-H), 2.98 (s, 3 H, 8-H), 1.75 (s, 3 H, 12-H), 1.71 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 167.4 (C-7), 138.5 (C-1), 135.1 (C-3), 134.2 (C-11), 133.5 (C-2), 132.9 (C-5), 120.1 (C-6), 114.1 (C-10), 37.5 (C-8), 35.8 (C-8), 31.9 (C-4), 25.6 (C-12), 22.6 (C-9), 18.0 (C-13) ppm. IR: $\tilde{\nu}$ = 3391 (br), 3106 (w), 2921 (m), 2877 (m), 1648 (s), 1596 (s), 1514 (m), 1450 (m), 1385 (s), 1264 (m), 1134 (s), 976 (m), 853 (w), 730 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{22}N_3O$ $[M + H]^+$ 248.1763; found 248.1759.

For further experimental details, data and ^{1}H and ^{13}C NMR spectra, see the Supporting Information.

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[1] For selected examples, see: a) E. Marsault, M. L. Peterson, *J. Med. Chem.* **2011**, *54*, 1961–2004; b) M. Kato, K. Ito, S. Nishino, H. Yamakuni, H. Takasugi, *Chem. Pharm. Bull.* **1994**, *42*, 2546–2555; c) Y. Hu, N. Green, L. K. Gavrin, K. Janz, N. Kaila, H.-Q. Li, J. R. Thomason, J. W. Cuozzo, J. P. Hall, S. Hsu, C. Nickerson-Nutter, J.-B. Telliez, L.-L. Lin, S. Tam, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6067–6072; d) D. B. Hauze, M. V. Chengalvala, J. E. Cottom, I. B. Feingold, L. Garrick, D. M. Green, C. Huselton, W. Kao, K. Kees, J. T. Lundquist IV, C. W. Mann, J. F. Mehlmann, J. F. Rogers, L. Shanno, J. Wrobel, J. C. Pelletier, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1986–1990; e) R. C. A. Isaacs, M. G. Solinsky, K. J. Cutrona, C. L. Newton, A. M. Naylor-Olsen, D. R. McMasters, J. A. Krueger, D. S. Lewis, B. J. Lucas, L. C. Kuo, Y. Yan, L. Lynch, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2062–2066; f) K. Kanoh, S. Kohno, J. Katada, J. Takahashi, I. Uno, Y. Hayashi, *Bioorg. Med.*

Chem. **1999**, *7*, 1451–1457; g) U. Anthoni, K. Bock, L. Chevolot, C. Larsen, P. H. Nielsen, C. Christophersen, *J. Org. Chem.* **1987**, *52*, 5638–5639; h) S. Bernasconi, G. Jommi, R. Pagliarin, P. Tavecchia, *J. Heterocycl. Chem.* **1988**, *25*, 725–729; i) S. Ohno, Y. Adachi, M. Kuomori, K. Mizukochi, M. Nagasaka, K. Ichihara, E. Kato, *Chem. Pharm. Bull.* **1994**, *42*, 1463–1473; j) K. Högenauer, L. Arista, N. Schmiedeberg, G. Werner, H. Jaschke, R. Bouhelal, D. G. Nguyen, B. G. Bhat, L. Raad, C. Rauld, J. M. Carballido, *J. Med. Chem.* **2014**, *57*, 10343–10354.

[2] For selected examples, see: a) N. Shangguan, M. M. Joullié, *Tetrahedron Lett.* **2009**, *50*, 6755–6757; b) H.-W. Cho, C.-H. Oh, J.-S. Lee, J.-Hu. Choi, J.-Hy Choi, *Arch. Pharm.* **2003**, *336*, 495–503; c) M. G. Simpson, M. Pittelkow, S. P. Watson, J. K. M. Sanders, *Org. Biomol. Chem.* **2010**, *8*, 1181–1187; d) M. Sonegawa, M. Yokota, H. Tomiyama, T. Tomiyama, *Chem. Pharm. Bull.* **2006**, *54*, 706–710; e) P. K. Bridson, H. Huang, X. Lin, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2257–2260.

[3] For selected examples, see: a) R. P. Subrayan, E. L. Thurber, P. G. Rasmussen, *Tetrahedron* **1994**, *50*, 2641–2656; b) T. L. Smalley Jr., S. Boggs, J. A. Caravella, L. Chen, K. L. Creech, D. N. Deaton, I. Kaldor, D. J. Parks, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 280–284; c) N. Yasuda, A. Nakamura, M. Tsuboi, *J. Heterocycl. Chem.* **1987**, *24*, 303–307; d) B. L. Lam, G. R. Wellman, C. S. Labaw, *J. Org. Chem.* **1982**, *47*, 144–147.

[4] D. Przybyla, U. Nubbemeyer, *Synthesis*, DOI: 10.1055/s-0036-1588324.

[5] a) H. Bredereck, G. Theilig, *Chem. Ber.* **1953**, *86*, 88–96; b) T. Kimura, N. Watanabe, M. Matsui, K. Hayashi, H. Tanaka, I. Ohtsuka, T. Saeki, M. Kogushi, H. Kabayashi, K. Akasaka, Y. Yamagishi, I. Saitou, I. Yamatsu, *J. Med. Chem.* **1993**, *36*, 1641–1653; for a review, see: c) H. Bredereck, R. Gompper, H. G. V. Schuh, G. Theilig, *Angew. Chem.* **1959**, *71*, 753–774.

[6] a) W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2354–2373; b) R. Gompper, *Chem. Ber.* **1956**, *89*, 1762–1768; c) N. Xi, S. Xu, Y. Cheng, A. S. Tasker, R. W. Hungate, P. J. Reider, *Tetrahedron Lett.* **2005**, *46*, 7315–7319; d) S. A. Laufer, D. R. J. Hauser, A. J. Liedke, *Synthesis* **2008**, 253–256; e) A. K. Dhawas, T. Thakare, *Indian J. Heterocycl. Chem.* **2012**, *21*, 217–220.

[7] a) Z. Su, L. Peng, C. Melander, *Tetrahedron Lett.* **2012**, *53*, 1204–1206; b) N. S. Aberle, G. Lessene, K. G. Watson, *Org. Lett.* **2006**, *8*, 419–421; c) T. Itoh, Y. Matsuya, K. Nagata, A. Ohsawa, *Chem. Pharm. Bull.* **1997**, *45*, 1547–1549; d) J. C. Boehm, J. G. Gleason, I. Pendrak, H. M. Sarau, D. B. Schmidt, J. J. Foley, W. D. Kingsbury, *J. Med. Chem.* **1993**, *36*, 3333–3340.

[8] a) Y. Kato, H. Koshino, J. Uzawa, K. Anzai, *Biosci. Biotechnol. Biochem.* **1996**, *60*, 2081–2083; b) S. P. Putri, K. Ishido, H. Kinoshita, S. Kitani, F. Ihara, Y. Sakihama, Y. Igarashi, T. Nihira, *J. Biosci. Bioeng.* **2014**, *117*, 557–562.

[9] a) A. Visconti, M. Solfrizzo, *J. Agric. Food Chem.* **1994**, *42*, 195–199; b) M. Solfrizzo, A. Visconti, *Toxicol. in Vitro* **1994**, *8*, 461–465; c) A. Visconti, M. Solfrizzo, *Food Addit. Contam.* **1995**, *12*, 515–519.

[10] Y. Koizumi, M. Arai, H. Tomoda, S. Omura, *J. Antibiot.* **2004**, *57*, 415–420.

[11] a) U. Höller, A. D. Wright, G. F. Matthee, G. M. Konig, S. Dreager, H.-J. Aust, B. Schulz, *Mycol. Res.* **2000**, *104*, 1354–1365; b) R. Uchida, R. Imasato, Y. Yamaguchi, R. Masuma, K. Shiomi, H. Tomoda, S. Omura, *J. Antibiot.* **2005**, *58*, 804–809; c) J. M. Rieder, J. Lepschy, *Tetrahedron Lett.* **2002**, *43*, 2375–2376 including revision of the structure of visoltricin (**2a**) to that of fungerin (**1a**).

[12] R. Benhida, R. Lezama, J.-L. Fourrey, *Tetrahedron Lett.* **1998**, *39*, 5963–5964.

[13] Benzyloxyacetyl chloride (**7**), synthesis and data: a) M. J. Kukla, J. M. Fortunato, *J. Org. Chem.* **1984**, *49*, 5003–5006; b) L. F. Tietze, K. M. Gericke, C. Guentner, *Eur. J. Org. Chem.* **2006**, 4910–4915.

[14] Synthesis of glycine methyl ester hydrochloride: a) G. Naturale, M. Lamblin, C. Commandeur, F.-X. Felpin, J. Dessolin, *Eur. J. Org. Chem.* **2012**, 5744–5788 Synthesis of *N*-(diphenylmethylene)glycine methyl ester (**5**): b) Y. Mao, K. M. Mulvihill, J. A. Rechka, P. A. Tavares-Greco, WO 123792, **2010**; c) K. Li, G. Tan, J. Huang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 12942–12945; *Angew. Chem.* **2013**, *125*, 13180–1384.

[15] *N*-Formylglycine methyl ester (**6**), synthesised in analogy to: a) W. K. C. Park, M. Auer, H. Jaschke, C.-H. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 10150–10155. Synthesis and data: b) L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, J. G. de Fries, A. J. Minnaard, *J. Org. Chem.* **2006**, *71*, 2026–2036.

[16] In analogy to: a) Á. Pintér, G. Haberhauer, *Eur. J. Org. Chem.* **2008**, 2375–2387; b) Á. Pintér, G. Haberhauer, *Tetrahedron* **2009**, *65*, 2217–2225; c) J. Ackrell, J. M. Muchowski, E. Galeazzi, A. Guzman, *J. Org. Chem.* **1986**, *51*, 3374–3376.

[17] In analogy to: T. Misaki, R. Nagase, K. Matsumoto, Y. Tanabe, *J. Am. Chem. Soc.* **2005**, *127*, 2854–2855.

[18] E. Winterfeldt, *Synthesis* **1975**, 617–630.

[19] R. Tamura, K. Watabe, N. Ono, Y. Yamamoto, *J. Org. Chem.* **1992**, *57*, 4895–4903.

[20] The use of acetone and ammonium formate in the presence of stoichiometric amounts of palladium gave some alcohol **8**.

[21] A. J. Birch, *J. Chem. Soc.* **1944**, 430–436.

[22] For further information and alternative leaving groups attached to the C-5 hydroxymethyl group, see the Supporting Information.

[23] L. Horner, H. Hoffmann, H. G. Wippel, *Chem. Ber.* **1958**, *91*, 61–63.

[24] J. M. Dener, L.-H. Zhang, H. Rapoport, *J. Org. Chem.* **1993**, *58*, 1159–1166.

[25] A. Shafiee, N. Rastkary, M. Jorjani, B. Shafaghi, *Arch. Pharm.* **2002**, *335*, 69–76.

[26] J. P. Collman, M. Zhong, S. Costanzo, C. Zhang, *J. Org. Chem.* **2001**, *66*, 8252–8256.

[27] J. J. Lee, L.-F. Huang, K. Zaw, L. Bauer, *J. Heterocycl. Chem.* **1998**, *35*, 81–89.

[28] B. D. Palmer, W. A. Denny, *J. Chem. Soc. Perkin Trans. 1* **1989**, 95–99.

[29] Y.-J. Shi, L. F. Frey, D. M. Tschaen, T. R. Verhoeven, *Synth. Commun.* **1993**, *23*, 2623–2630. However, the use of 4-bromo-5-hydroxymethylimidazoles **18** and **19** carrying out oxidation, enol-ether-forming chain elongation and subsequent enol ether cleavage and reduction allowed us to synthesise key compounds **14** and **15**, respectively. For procedures and data, see the Supporting Information.

[30] Alternatively, 4-iodination also succeeded (for procedure and data, see the Supporting Information). Unfortunately, the subsequent sulfur removal was accompanied by a significant amount of deiodination, which forced us to abandon this attempt. Selective C-4 iodination using 1-methyl-5-hydroxyethylimidazole failed.

[31] For data, see the Supporting Information.

[32] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.

[33] Sulfone: P. Furet, V. Guagnano, P. Holzer, J. Kallen, R. Mah, K. Masuya, A. Schlapbach, A. Vaupel, WO 115077 **2014**.

[34] a) P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26–28; b) P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* **2000**, 365–366; c) for tetrazole reagent synthesis, see: R. Wong, S. J. Dolman, *J. Org. Chem.* **2007**, *72*, 3969–3971.

[35] Starting from 1-methyl-5-hydroxyethylimidazole **12**, the analogous sequence of sulfide formation by Mitsunobu reaction and oxidation smoothly delivered the sulfone bearing a small C-4 hydrogen substituent. Julia–Kociensky olefination using such a C-4-H imidazole gave 5-allylimidazoles, which suffered from double bond migration to form 5-vinylimidazoles. For data for the sulfide and sulfone, see the Supporting Information.

[36] R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320–2322. Because of the failure of iodine introduction, the Heck reaction had to be run using the bromides. Stille cross-coupling as a final step was avoided, since residual tin impurities might influence the phytological tests.

[37] a) E. Assen, B. Kantchev, G.-R. Peh, C. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 3949–3952; b) G.-R. Peh, E. Assen, B. Kantchev, C. Zhang, J. Y. Ying, *Org. Biomol. Chem.* **2009**, *7*, 2110–2119; c) C-5 acceptor C=O substituent: A. G. Chittiboyina, C. R. Reddy, E. B. Watkins, M. A. Avery, *Tetrahedron Lett.* **2004**, *45*, 1869–1872.

[38] S.-M. T. Toguem, P. Langer, *Synlett* **2010**, 1779–1782.

[39] For selected examples, see: a) V. Cerezo, A. Alfonso, M. Planas, L. Feliu, *Tetrahedron* **2007**, *63*, 10445–10453; b) G.-L. Shapiro, *J. Org. Chem.* **1994**, *59*, 5524–5526; c) M. L. Meketa, S. M. Weinreb, Y. Nakao, N. Fusetani, *J. Org. Chem.* **2007**, *72*, 4892–4899; d) H. Yashioka, T. Choshi, E. Sugino, S. Hibino, *Heterocycles* **1995**, *41*, 161–174; e) Y. Ishida, E. Iwasa, Y. Matsuoka, H. Miyauchi, K. Saigo, *Chem. Commun.* **2009**, 3401–3403; f) S. Grosse, C. Pillard, F. Himbert, S. Massip, J. M. Leger, C. Jarry, P. Bernard, G. Guillaumet, *Eur. J. Org. Chem.* **2013**, 4146–4155.

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