New asymmetric synthesis of protein farnesyltransferase inhibitors *via* palladium-catalyzed cross-coupling reactions of 2-iodo-imidazoles†

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Palladium catalyzed cross-coupling reactions of 2-iodoimidazole have been studied to synthesize imidazole-containing protein farnesyltransferase inhibitors. The Suzuki coupling reaction proved to be very efficient to introduce functionalized alkyl chains at the 2-position of the imidazole ring and a new synthesis of the required alkenylboronates was realised by a reaction of cross metathesis. Asymmetric synthesis of allyl succinic derivatives allowed us to synthesize chiral protein farnesyltransferase inhibitors through Suzuki coupling and to determine the influence of the stereochemistry of our inhibitors on the enzymatic activity.

Introduction

Protein farnesyltransferase (FTase) is a heterodimeric enzyme which catalyzes the post-translational modification of several cell signaling proteins.[1] It has emerged as a promising target in cancer therapy[2] and more recently in the anti-parasitic field.[3] In the course of our search for new protein farnesyltransferase inhibitors (FTI) we synthesized C-2,C-5 disubstituted imidazole derivatives with encouraging activities (Fig. 1).[4] Our best inhibitor **1** (n = 3) bears a racemic 2-propylsuccinic chain and a tripeptide at the C-5 position. To examine both the influence of the stereochemistry and the peptide functionality of the imidazole ring (4 or 5) on the FTase inhibition we needed to synthesize the (*R*)-**1** and (*S*)-**1** enantiomers and their 4-substituted analogues **2** (Fig. 1).

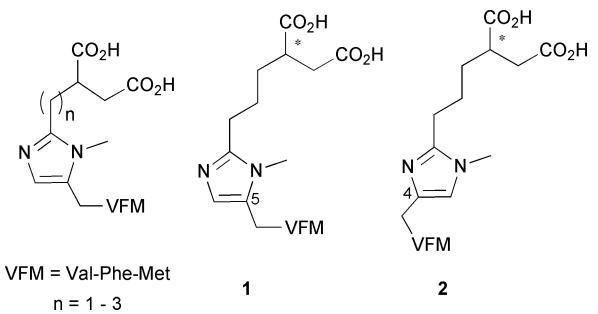
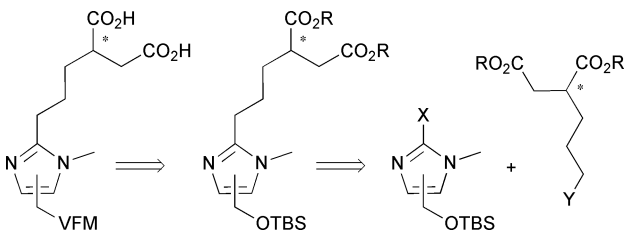


Fig. 1 Structure of imidazole-containing protein farnesyltransferase inhibitors.

To achieve the asymmetric synthesis of the imidazole-containing protein farnesyltransferase inhibitors **1** and **2** in enantiomerically pure form, we needed to find a straightforward synthesis to introduce each enantiomeric pure form of the 2-propylsuccinic chain on both 4-((*tert*-butyldimethylsilyloxy)methyl)-1-methyl-1*H*-imidazole **3** and 5-((*tert*-butyldimethylsilyloxy)methyl)-1-methyl-1*H*-imidazole **4** (Scheme 1) and to develop an efficient preparation of compound **3**.



Scheme 1 Retrosynthetic pathway.

We present here a new palladium-catalyzed cross-coupling reaction of 2-iodoimidazole derivatives as well as the synthesis of the (*R*)- and (*S*)-allylsuccinic derivatives involved in the palladium-catalyzed reaction. This article describes also a new synthesis of 4-((*tert*-butyldimethylsilyloxy)methyl)-1-methyl-1*H*-imidazole **3** and the formation and biological evaluation of compounds **1** and **2**.

Results and discussion

1. Palladium-catalyzed cross-coupling of 2-iodoimidazole derivatives

Few examples of palladium-catalyzed cross-coupling reactions between 2-iodoimidazole and alkene derivatives have been described in the literature.[5] A first example of a palladium-catalyzed coupling at the C-2 position of the imidazole ring under the Heck conditions has been reported with styrene olefins yielding only to homocoupling product **5** (Fig. 2).[6] No Heck coupling has been successfully realized on 2-iodoimidazole derivatives yet. When we tried this reaction on 2-iodo-1-trityl-1*H*-imidazole with methyl acrylate and palladium acetate in the presence of a phosphine,

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† Electronic supplementary information (ESI) available: Experimental data for Heck cross-coupling reaction and for compounds **1a–b**, **2b**, **10a**, **10b**, **12**, **14**, **17a**, **15–17b**, **24b**, **25a–b**, **26b**, **27a–b**, **28b**, **29a–b**, **30b**, **31a–b**, and crystallographic data for compound **19a**. CCDC reference number 719966. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b902601k

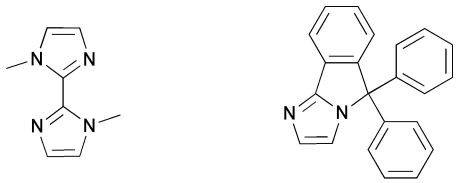
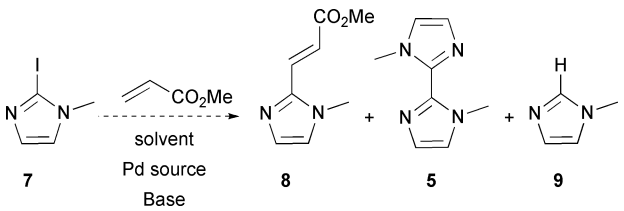


Fig. 2 Products of Heck cross-coupling assays.

5,5-diphenyl-5*H*-imidazo[2,1-*a*]isoindole **6** was surprisingly obtained by an intramolecular arylation, a reaction occurring with many 1-benzylimidazole derivatives (Fig. 2).[7]

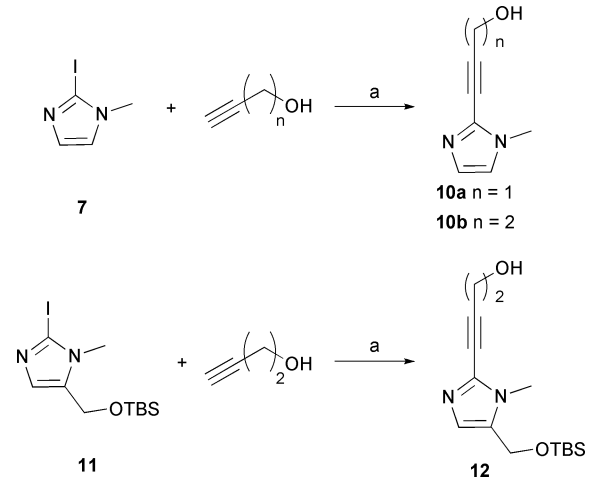
To avoid the possibility of an intramolecular arylation process during our study of the Heck reaction on 2-iodoimidazoles we pursued our efforts on 1-methyl-2-iodoimidazole **7** with methyl acrylate as alkylating agent (Scheme 2).[8]



Scheme 2 Heck cross-coupling reaction.

A range of conditions was examined for the Heck coupling varying the catalyst, base, phosphine, solvent and temperature and, unfortunately, none afforded the expected alkylated compound **8**.[9] In most conditions we tried, the starting compound **7** was recovered. The use of a bulky and a more electron-enriched phosphine (P(*o*-Tol)$_3$), known to produce highly reactive catalysts, did not improve the conversion. Increased temperature, longer reaction time or a higher catalyst load afforded dehalogenated 1-methylimidazole **9** or decomposition. When 5% mol. [Pd(PPh$_3$)$_4$] was used with KOAc as base the homocoupling product **5** was observed in low yield (5–15%). This side product, which can act as a poison for Pd-catalyst, might be the reason for the low reactivity of 2-iodo imidazole in this case. To increase the reactivity of our system, we finally tried a reaction with bis(phosphinito) donor palladium (II) complex as a catalyst which has been reported to be a efficient and highly active catalyst for Heck reaction.[10] Unfortunately, no conversion was observed which indicated a possible degradation of the catalyst during the time of the reaction that often occurs with this type of complex. Substitution of iodide by bromide or of methyl by a Boc group on N-1 did not afford the expected alkylation product under standard Heck conditions.

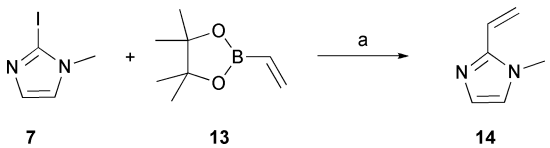
Therefore we next tried to employ the Sonogashira cross-coupling as an alternative C–C bond forming reaction to functionalize the C-2 position of the imidazole ring. This reaction has been realized on several 2-iodoimidazole derivatives in variable yields.[6,11,12] Under the Kerwin conditions,[12] with 5% mol [Pd(PPh$_3$)$_4$], 10% mol. CuI and NEt$_3$ as a base, we successfully alkylated 1-methyl-2-iodoimidazole **7** with propargylic or homopropargylic alcohols with a total conversion albeit moderate yields due to difficulties during the purification step. When the reaction was performed on compound **11** (see below), the product **12** was obtained in 89% yield (Scheme 3).



Scheme 3 *Reagents and conditions:* a) NEt$_3$, Pd(PPh$_3$)$_4$ 5 mol%, CuI 10 mol%, for n = 1: RT, 3d, 44%, for n = 2: 40 °C, 18h, 26%, for **13**: 40 °C, 18 h, 89%.

Negishi cross-coupling between 1-methyl-2-imidazole-zinc iodide and unsaturated iodides has been reported by Knochel in good to excellent yields.[8] However it would be more interesting for the synthesis of our compounds to realize Negishi coupling with an alkylzinc iodide as it has been described on the iodo derivative of Boc-histidine.[11] Unfortunately when we performed this reaction on compound **11** only traces of the expected compound were obtained.

Suzuki cross-coupling between iodoimidazole and a vinylboronate has only been described at the C-4 position of the imidazole ring but in a moderate yield.[13] We explored this reaction between commercially available pinacol vinyl boronate **13** and compound **7**. After optimization, 1-methyl-2-vinylimidazole **14** was obtained in excellent yield (Scheme 4).



Scheme 4 *Reagents and conditions:* a) DMF, Na$_2$CO$_3$, Pd(PPh$_3$)$_4$ 5 mol%, 130 °C, 3 h, 94%.

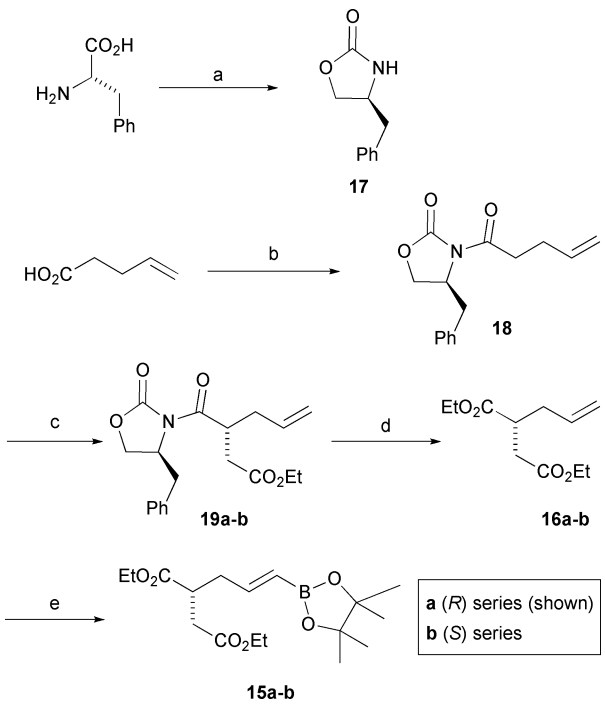
Stille cross-coupling at the C-2 position of the imidazole ring with halo-olefins has only been realized with 2-(tributylstannyl)-1*H*-imidazole.[14] In our hands, cross-coupling of compound **7** with commercially available vinyltributyltin afforded also 1-methyl-2-vinylimidazole **14** in good yield.

Though the Sonogashira cross-coupling reaction was effective with alcohol derivatives we were unable to apply this reaction to ethyl propiolate or homopropiolate. Therefore a synthetic pathway using this reaction would require many subsequent steps to obtained the desired esters **1** and **2**. Stille and Suzuki cross-couplings were both effective to form C–C bond at the C-2 position of the imidazole ring. Because of tin toxicity we turned to the Suzuki cross-coupling to synthesize **1** and **2** from 4(or 5)-((*tert*-butyldimethylsilyloxy)methyl)-1-methyl-1*H*-imidazole **3** (or **4**) and the enantiopure vinyl boronates **15**. An enantioselective

synthesis of **15** has been designed to obtain both (*R*) and (*S*) isomers.

2. Enantioselective synthesis of diethyl 2-allylsuccinate 16

The chiral vinyl boronates **15** have been obtained by cross metathesis between the pinacol vinyl boronate **13** and the chiral diethyl 2-allylsuccinates **16** synthesized by asymmetric alkylation using Evans chiral auxiliary methodology (Scheme 5).[15] Optically pure (*R*)- and (*S*)-4-benzyl-2-oxazolidinone **17** were both obtained in 3 steps from L- or D-phenylalanine respectively in 45% overall yield. Phenylalanine was reduced into the corresponding alcohol by sodium borohydride/iodine[16] then the amine was protected by a Boc group[17] and the oxazolidinone was formed by addition of tBuOK.[18] The 4-benzyl-2-oxazolidinones **17** reacted with pent-4-enoic acid through activation with pivaloyl chloride to yield the desired chiral imides **18**. The alkylation of (*S*)- and (*R*)-imides **18** with ethyl bromoacetate afforded **19a** (74% yield, d.e. (*S*,*R*) > 98%) and **19b** (85% yield, d.e. (*R*,*S*) = 65%) respectively. The **19b** diastereoisomers were easily separated by column chromatography and the absolute configuration was confirmed by X-ray crystallography of compound **19a**. Removal of the chiral auxiliary and esterification of the remaining acid provided (*R*)- and (*S*)-2-allyl diethylsuccinate **16a** and **16b**. The vinyl boronates **15a–b** were easily obtained in excellent yield by a cross metathesis between compounds **16a–b** and pinacol vinyl boronate **13** using 10% mol. of Grubbs I catalyst. The *E*-compound was mainly obtained together with a small amount of the *Z*-isomer in 6:1 and 5:1 ratios for the (*R*) and (*S*) series respectively.[19] Our results are similar to those previously reported for the synthesis of functionalized vinyl boronates by olefin cross-metathesis and thus enlarge the scope of this methodology.[20]

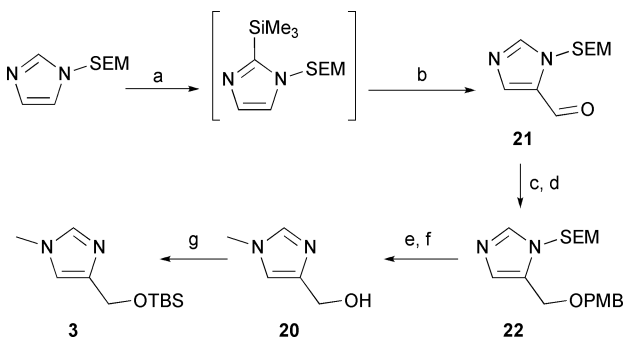


Scheme 5 *Reagents and conditions:* a) *i*- $NaBH_4$, I_2, THF, reflux, overnight, 75%; *ii*- Boc_2O, H_2O, 30–35 °C, 1 h; *iii*- *t*BuOK, THF, 0 °C, 2 h, 60% (2 steps); b) PivCl, Et_3N, Et_2O, 0 °C, 1 h, then −78 °C BuLi, **17**, −78 °C 15 min, 0 °C 1 h, (*R*): 94%, (*S*): 88%; c) NaHMDS, $BrCH_2CO_2Et$, THF, −78 °C to RT, overnight, from **18-*R***: 85% d.e. (*RS*) = 65%, from **18-*S***: 74% d.e. (*SR*) > 98%; d) *i*- LiOH, H_2O_2, THF/H_2O, 0 °C, 1 h; *ii*- EtOH, HCl, reflux, overnight, (*R*)-**16a** 66%, (*S*)-**16b** 64%; e) **13**, Grubbs I catalyst 10 mol%, CH_2Cl_2, reflux, overnight, **15a** 92% (*E*:*Z* = 6:1), **15b** 90% (*E*:*Z* = 5:1).

3. Synthesis of 4-hydroxymethyl-1-methyl-1*H*-imidazole 20

Before applying the Suzuki cross-coupling reaction to get our desired inhibitors **1** and **2**, we needed a straightforward synthesis of 1-methyl-4-hydroxymethyl imidazole **20**. The N-methylation of 4(5)hydroxymethyl-1-methyl-1*H*-imidazole represents the more rapid way to synthesize this compound. However, this method affords a mixture of both N-methylated products and C-4 and C-5 isomers are hardly separable.[21] Compound **20** has also been synthesized from 2-amino-3-(methylamino)propanoic acid through the formation of the imidazoline that was further oxidized into imidazole.[22] However the synthesis of the imidazoline and the oxidation step were not reproducible in large scale and we looked for another way to synthesize **20** in large amounts.

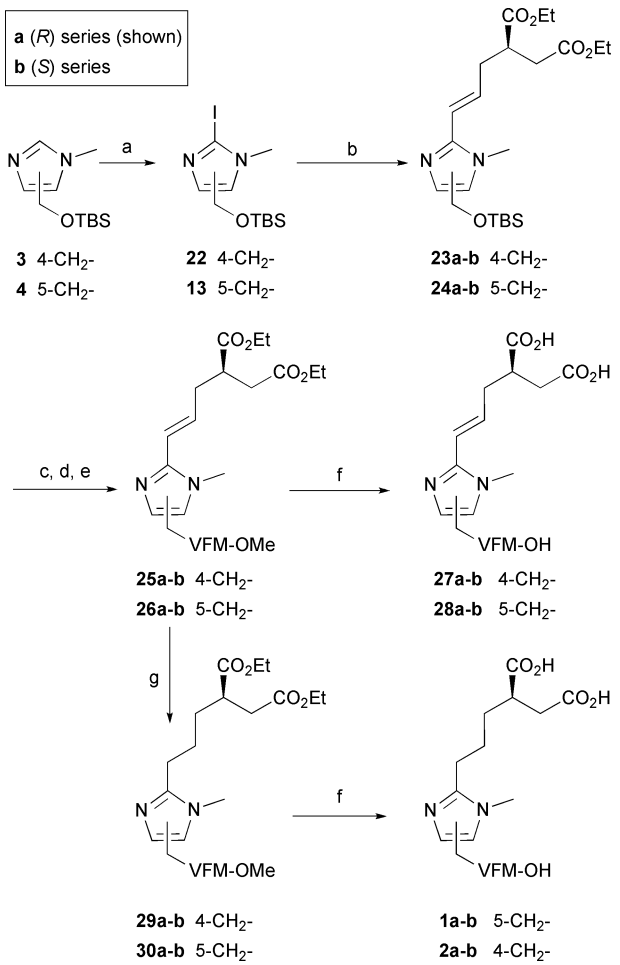
We took advantage of the ability of 1-substituted imidazole to be alkylated at the N-3 position to afford imidazolium and of the selective C-5 formylation according to Lipshutz methodology.[23] The C-2 position of 1-SEM-imidazole[24] was first deprotonated and silylated then, a second deprotonation occurred exclusively at the C-5 position allowing the selective C-5 formylation. Direct methylation on compound **21** did not afford reproducibly the imidazolium derivative. Therefore we reduced the aldehyde by sodium borohydride and protected the resulting alcohol by a p-methoxybenzyl (PMB) group. The PMB-protecting group was chosen by the observation in preliminary experiments that bulky protective group such as *tert*-butyldimethylsilyl (TBS) prevented further alkylation of the imidazole ring and that the benzyl group was difficult to remove after methylation. The PMB group had the additional advantage to be concomitantly removed with the SEM group. Methylation of compound **22** by methyl triflate afforded the imidazolium derivative that was submitted without purification to deprotection with TFA to yield the desired 1-methyl-4-hydroxymethylimidazole **20**. Protection of the alcohol by a TBS group was realized on the crude product to facilitate its purification. Compound **3** was obtained in five steps from imidazole in 38% overall yield (Scheme 6).



Scheme 6 *Reagents and conditions:* a) *n*BuLi THF, −78 °C 45 min then TMSCl, RT, 1 h 30 min; b) *t*BuLi, THF, −78 °C, 45 min then DMF, RT, 2 h, 76% (2 steps); c) $NaBH_4$, MeOH, RT, 2 h, 93%; d) NaH, DMF, RT, 20 min then PMBCl, RT, overnight, 70%; e) TfOMe, toluene, 0 °C, 2 h; f) TFA, 0 °C, 2 h; g) TBSCl, imidazole, DMF, RT, overnight, 82% (3 steps).

4. Synthesis of protein farnesyltransferase inhibitors 1 and 2

As described above, the synthesis of our inhibitors **1** and **2** goes through a Suzuki coupling reaction between boronates **15a–b** and the 2-iodo-4(or 5)-methylimidazole derivatives as a key step. Iodination at the C-2 position of compounds **3** and **4** was carried out according the reported procedure and provided **23** and **11** respectively.[4] Suzuki cross coupling reaction of the *E*-isomer of **15a** and **15b** with respectively **23** and **11** afforded the expected *E*-compounds **24a–b** and **25a–b** in 60% to 92% yield. Attachment of the tripeptide VFM was realized as previously described using a TBS-deprotection-oxidation sequence followed by a reductive amination.[4] A part of compounds **26a–b** and **27a–b** was saponified to determine the influence of a more rigid alkyl chain at the C-2 position of imidazole ring on the interaction with FTase. The other part was hydrogenated to reduce the double bond before saponification to afford compounds **1a–b** and **2a–b** in each enantiomeric pure form (Scheme 7). This synthetic pathway is more rapid and more efficient than our previous method: we have synthesized 8 chiral compounds in 5 or 6 steps from the 1-methyl-4(5)-hydroxymethylimidazole **3** and **4** in 20–28% yield compared to our first synthesis of racemic compound **1** achieved in 10 steps from 1-methyl-5-hydroxymethyl imidazole in 17% overall yield.[4] This method is also more convergent and allows the introduction of a large variety of alkyl chains at the C-2 position of the imidazole ring.



Scheme 7 *Reagents and conditions:* a) *n*BuLi, I_2, THF, −78 °C to RT, 3 h, 83–87%; b) DMF, Na_2CO_3, $Pd(PPh_3)_4$ 10 mol%, **15a–b**, 130 °C, 3 h 30 min, 60–92%; c) TBAF, THF, 0 °C, 2 h, 81–96%; d) MnO_2,CH_2Cl_2, RT, overnight, 70–80%; e) NH_2-VFM-OMe, MS 4Å, CH_2Cl_2/MeOH, RT, 10 min then $NaBH_3CN$ in MeOH-1% AcOH, RT, overnight, 61–80%; f) $LiOH{\cdot}H_2O$, THF/H_2O (1/1), 0 °C→RT, overnight, quant.; g) H_2, Pd/C 10%, EtOAc, 24 h, 57–75%.

Table 1 Activity on yeast and human FTases

Compound	Enantiomer	Double bond	IC_{50} (μM) human FTase	IC_{50} (μM) yeast FTase
1	R,S	no	—	80 ± 5
29a	R	*E*	85 ± 6	170 ± 20
29b	S	*E*	144 ± 8	176 ± 20
1a	R	no	57 ± 4	51 ± 4
1b	S	no	58 ± 4	56 ± 3
28a	R	*E*	146 ± 8	170 ± 13
28b	S	*E*	120 ± 3	220 ± 40
2a	R	no	109 ± 5	370 ± 40
2b	S	no	87 ± 8	151 ± 16

5. Biological evaluation

Compounds **1**, **2**, **28** and **29** in (*R*) or (*S*) configuration were evaluated for their inhibitory activity against recombinant yeast[25] and human[26] FTases using a fluorescent-based assay[27,28] adapted to 96-well plate format. Results are reported in Table 1.

It should be pointed out that the presence of a double bond in the propylsuccinic side chain is detrimental to the activity (**29** *versus* **1** and **28** *versus* **2**). The absolute configuration of this chain seems to have very little influence on the inhibition of protein farnesyltransferase (compounds **a** *versus* compounds **b**). Finally our compounds are generally more active on human FTase and the 5-substituted derivatives are better inhibitors than the 4-substituted compounds.

Conclusions

The aim of this article was to determine whether the position of the peptidic chain and the stereochemistry of the succinyl moiety could have an influence on the inhibitory activity of our imidazole-containing inhibitors **1** and **2**. To address these questions we have developed a more convenient synthesis of 1-methyl-4-hydroxymethylimidazole. We have also explored the palladium-catalyzed cross-coupling reaction at the C-2 position of the imidazole ring. Among the different C–C bond coupling reactions we tried, the Suzuki cross-coupling conditions proved to be the most efficient and represent the first example of Suzuki cross-coupling on the C-2 position of imidazole derivatives with aliphatic vinyl boronates which have been successfully synthesized in enantiomerically pure form from the corresponding allylsuccinates. The scope and limitations of this Suzuki cross-coupling reaction are currently under investigation, especially with other functionalized vinyl boronates or alkyl boranes, as well as the olefin cross-metathesis with shorter acidic chains.

Biological evaluation of our compounds has shown the little influence of the stereochemistry of the succinic moiety on the FTase inhibition. The presence of a more rigid chain at the C-2 position of the imidazole ring is detrimental to the activity and the position of the peptidic chain seems to be important for the inhibition. Therefore, in the course of our search for new protein

farnesyltransferase inhibitors, we are pursuing our investigations into highly substituted imidazoles where the peptidic chain is located at the C-5 position of the imidazole ring and with other acidic chains.

Experimental

General method

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in case of air- or moisture-sensitive compounds reactions were carried out in oven-dried glassware under argon. Syringes were used to transfer the reagents and the solvents were purged with argon prior to use. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine and toluene were distilled over calcium hydride. *N*,*N*′-Dimethylformamide (DMF) was dried over $MgSO_4$ followed by distillation under reduced pressure. Analytical thin-layer chromatography was carried out on precoated silica gel glass plates (Merck TLC plates, silica gel $60F_{254}$). The silica gel (silicagel 60 (35–70 μm)) used for column chromatography was purchased from S.D.S. Company. ^{1}H and ^{13}C NMR spectra were recorded at Bruker Avance 300 MHz. ^{1}H chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for *d*-chloroform (residual $CHCl_3$) and the singlet (0.00 ppm) for TMS. ^{13}C Chemical shifts (δ) are reported in ppm relative to the central line of the triplet at 77.2 ppm for *d*-chloroform. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad and combinations thereof. Coupling constants *J* are reported in hertz (Hz). IR spectra were recorded with an FTIR Perkin-Elmer Spectrum BX spectrometer. Low and high resolution mass spectra were recorded by navigator LC/MS (source AQA) for electron spray ionization (ESI—low resolution) and electron ionization (EI—high resolution). Optical rotations were measured with a JASCO 1010 polarimeter in a 1-dm cell and the sodium D line (589 nm) at the temperature, solvent, and concentration indicated. X-ray structure was realized at the X-Ray Crystallography Laboratory of the ICSN-Gif-sur-Yvette and data were collected by a Enraf-Nonius KappaCCD diffractometer with graphite-monochromated MoKa radiation (λ = 0.71069 Å). Elemental analyses were performed by the Microanalytical Laboratory of the ICSN-Gif-sur-Yvette.

General procedure A. Sonogashira cross-coupling

Under argon atmosphere, 1-methyl-2-iodo-1H-imidazole **7** was added to a solution of $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%) in NEt_3 (2 ml). After addition of the alkyne alcohol, the mixture was degassed and stirred. The reaction was followed by TLC control and the reaction mixture was filtered on a pad of celite and concentrated under vacuum after the time indicated in Scheme 4. The residue was purified by chromatography on silica gel.

General procedure B. Suzuki cross-coupling

To a solution of iodoimidazole derivative **11** or **23** in anhydrous DMF under argon was added the palladium catalyst (10 mol%), the alkenylboronate **15a** or **15b** (1.6 equiv.) as well as powdered Na_2CO_3 (1.1 equiv.). The mixture was heated under an argon atmosphere at 135 °C for 3 h 30 min. After the mixture had been cooled down to room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel.

General procedure C

a—Removal of TBS group. A solution of tetrabutylammonium fluoride (1 M in THF, 2 equiv.) was added to a THF solution of compounds **24** or **25** at 0 °C. After stirring 2 h at 0 °C, the reaction mixture was evaporated. The residue was purified by column chromatography on silica gel to afford the required primary alcohols.

b—Oxidation of the primary alcohol. Manganese dioxide (6.5 equiv.) was added to a CH_2Cl_2 solution of alcohols. The mixture was refluxed overnight. The reaction was filtered through a pad of celite (EtOAc) and concentrated. The residue was purified by column chromatography to afford the required aldehydes.

c—Reductive amination. Tripeptide NH_2-VFM-OMe[4] in $MeOH/CH_2Cl_2$ (3/1) was treated with molecular sieves powder 4 Å and triethylamine (1 equiv.). After stirring for 20 min at room temperature, a solution of the aldehyde in $MeOH/CH_2Cl_2$ (1/1) was added to the mixture. After 4 h, a solution of sodium cyanoborohydride (1.5 equiv.) in MeOH/AcOH (1:0.1) was added and the solution was stirred for 18 h at room temperature. Then, the mixture was filtered through a pad of celite (CH_2Cl_2) and concentrated. The mixture was taken into H_2O and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford compound **26** or **27**.

General procedure D. Saponification

To a solution of **26**, **27**, **30** or **31** in $THF/MeOH/H_2O$ 1:1:1 was added lithium hydroxide monohydrate (3–6 equiv.) at 0 °C. After 1–2 h at this temperature and 1–16 h at room temperature, Amberlite IRC 50 resin (H^+) was added and the mixture was stirred until pH = 7.0. Then, the reaction was filtered and the resin was washed with MeOH (3×). Evaporation of the solvents afforded the target compounds **28**, **29**, **2** or **1**.

4-(*S*)-Benzyl-3-pent-4-enoyloxazolidin-2-one (18a). To a cooled solution (−78 °C) of 4-pentenoic acid (1.09 ml, 10.7 mmol, 1 equiv.) and Et_3N (1.7 ml, 11.9 mmol, 1.1 equiv.) in diethyl ether (45 ml) was added pivaloyl chloride (1.32 ml, 10.7 mmol, 1 equiv.). After 5 min, the reaction mixture was warmed to 0 °C and stirred for 1 h. In a separate flask, a solution of **17a** (1.9 g, 10.7 mmol) in THF (13 ml) was cooled to −78 °C whereupon *n*BuLi (1.6 M in hexane, 6.7 ml, 10.7 mmol, 1 equiv.) was added slowly. The solution was stirred for 10 min at −78 °C. The flask containing the mixed anhydride was cooled to −78 °C, and the lithiated oxazolidinone transferred *via* cannula into the mixed anhydride. After being stirred for 15 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched with water, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 25 ml). Combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by flash chromatography

(heptane/EtOAc : 75/25) afforded pure **18a** (2.5 g, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43–2.51 (m, 2H), 2.77 (dd, J = 9.5, 13.0 Hz, 1H), 2.96–3.17 (m, 2H,), 3.39 (dd, J = 3.5, 13.0 Hz, 1H), 4.14–4.23 (m, 2H), 4.64–4.72 (m, 1H), 5.04 (dd, J = 1.5, 10.0 Hz, 1H), 5.12 (dd, J = 1.5, 17.0 Hz, 1H), 5.89 (m, 1H), 7.20–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 34.8, 37.9, 55.2, 66.2, 127.3, 128.9, 129.4, 135.3, 136.7, 153.5, 172.5. MS (ESI+) m/z 282 [M + Na]$^+$. $[\alpha]_D^{23}$ = +60 (c 1.9 in $CHCl_3$).

Ethyl 3-(*R*)-(4-(*S*)-benzyl-2-oxazolidine-3-carbonyl) hex-5-enoate (19a). To a solution of compound **18a** (2.35 g, 9.1 mmol) in THF (90 ml) cooled to −78 °C was added 2M NaHMDS in THF (5 ml, 10 mmol, 1.1 equiv.) over 10 min. The reaction mixture was allowed to stir for an additional 20 min. at −78 °C and ethyl bromoacetate (1.5 ml, 13.6 mmol, 1.5 equiv.) in THF (9 ml) was added. The solution was stirred for 1 h at −78 °C and then stirred for 4 h at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the reaction mixture was concentrated. The residue was extracted with dichloromethane (3 × 50 ml) and organic layers were washed with water and brine then dried over sodium sulfate. Purification by flash chromatography on silica gel (heptane/EtOAc : 9/1 to 8/2) afforded pure (3*R*,4*S*)-**19a** (2.34 g, 74%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 2.19–2.29 (m, 1H), 2.40–2.50 (m, 1H), 2.55 (dd, J = 4.0, 17.0 Hz, 1H), 2.76 (dd, J = 10.0, 13.0 Hz, 1H), 2.91 (dd, J = 11.0, 17.0 Hz, 1H), 3.36 (dd, J = 3.0, 13.0 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 4.16–4.21 (m, 2H), 4.26–4.35 (m, 1H), 4.63–4.71 (m, 1H), 5.07–5.15 (m, 2H), 5.72–5.87 (m, 1H), 7.25–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 35.5, 36.3, 37.6, 38.9, 55.5, 60.7, 66.0, 118.0, 127.2, 128.9, 129.5, 134.3, 135.6, 136.7, 153.1, 171.9, 174.9. MS (ESI+) m/z 368 [M + Na]$^+$. $[\alpha]_D^{23}$ = +51 (c 1.5 in $CHCl_3$).

Diethyl 2-(*R*)-allylsuccinate (16a). To a solution of compound **19a** (1.5 g, 4.35 mmol) in THF/H_2O (4:1, 40 ml) at 0 °C was added H_2O_2 (30% aqueous, 2.5 ml, 22 mmol, 5 equiv.) followed by aqueous LiOH solution (274 mg in 3 ml, 6.5 mmol, 1.5 equiv.). The reaction mixture was stirred at 0 °C for 1 h and then an aqueous solution of Na_2SO_3 (2.4 g in 17 ml, 19 mmol, 4.4 equiv.) was added. After stirring for an additional 20 min, THF was evaporated under reduced pressure and the residue was diluted with CH_2Cl_2 and water. The organic layer that contained the chiral auxiliary was separated. The aqueous layer was acidified with 5 N aqueous HCl solution and was extracted with CH_2Cl_2. The combined organic extracts were washed with water, brine and dried over Na_2SO_4. After concentration in vacuum the product was dissolved in ethanol (10 ml) and concentrated HCl (0.3 ml) was added. After stirring for 20 h at reflux, the reaction was concentrated and purified by flash chromatography on silica gel (heptane/EtOAc: 75/25 to 50/50) to afford pure **16a** (617 mg, 66%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (m, 6H), 2.25 (m, 1H), 2.39 (m, 2H), 2.64 (m, 1H), 2.87 (m, 1H), 4.10 (m, 4H), 5.03 (m, 2H), 5.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.3, 35.3, 36.0, 40.9, 60.6, 60.7, 117.8, 134.6, 171.9, 174.2. MS (ESI+) m/z 237 [M + Na]$^+$. $[\alpha]_D^{23}$ = +5.2 (c 2.2 in $CHCl_3$).

Diethyl 2-(*R*)-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-allyl)succinate (15a). To a solution of compound **16a** (500 mg, 2.34 mmol) in dichloromethane (23 ml) under argon atmosphere was added pinacol vinylboronate **13** (1.17 ml, 6.9 mmol, 3 equiv.) and Grubbs I catalyst (287 mg, 0.35 mmol, 0.15 equiv.). The mixture was stirred at reflux for a night. The solution was cooled to ambient temperature, diluted with dichloromethane and filtrated over celite. After concentration and purification by flash chromatography on silica gel (heptane/EtOAc: 9/1 to 8/2) pure (*E*)-**15a** (633 mg, 79%) and (*Z*)-**15a** (111 mg, 14%) were obtained as white amorphous solids. (***E*)-15a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 18H), 2.38 (m, 1H), 2.47 (dd, J = 6.0, 16.0 Hz, 1H), 2.51 (m, 1H), 2.69 (dd, J = 9.5, 16.0 Hz, 1H), 2.97 (m, 1H), 4.15 (m, 4H), 5.50 (d, J = 18.0 Hz, 1H), 6.51 (dt, J = 13.0, 18.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.2, 24.7, 24.8, 24.9, 34.1, 35.1, 41.0, 60.5, 60.6, 83.1, 83.4, 149.9, 172.1, 174.3. MS (ESI+) m/z 363 [M + Na]$^+$.

(*Z*)-15a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (m, 18H), 2.45 (dd, J = 4.0, 16.0 Hz, 1H), 2.73 (m, 3H), 2.94 (m, 1H), 4.15 (m, 4H), 5.48 (d, J = 13.5 Hz, 1H), 6.36 (dt, J = 13.5, 14.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.4, 24.8, 24.9, 25.0, 34.3, 35.3, 41.2, 60.7, 60.8, 83.3, 83.6, 150.1, 172.3, 174.5. MS (ESI+) m/z 363 [M + Na]$^+$.

1-((2-(Trimethylsilyl)ethoxy)methyl)-5-formyl-1*H*-imidazole (21). To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (1 g, 5 mmol)[24] in THF (22 ml) at −78 °C, *n*-butyllithium (3.7 ml, 1.6 M in hexane, 5.9 mmol, 1.2 equiv.) was added slowly. After stirring for 45 min at the same temperature, trimethylsilyl chloride (0.77 ml, 6.02 mmol, 1.2 eq.) was added and the mixture was stirred for 1 h 30 min at room temperature. The solution was cooled to −78 °C and *t*-butyllithium (4.7 ml, 1.4 M in hexane, 6.6 mmol, 1.3 equiv.) was added slowly. After stirring for 45 min at −78 °C, dimethylformamide (2.8 ml, 36 mmol, 7.2 equiv.) was added and the mixture was stirred for 2 h at room temperature. Water was added and the product was extracted with ethyl acetate (3 × 50 ml). Combined organic layers were washed with water (3 × 100 ml), brine (100 ml), dried over sodium sulfate and concentrated. After flash chromatography on silica gel (CH_2Cl_2/MeOH : 100/0 to 95/5) pure **21** (869 mg, 76%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.94 (t, J = 8.0 Hz, 1H), 3.61 (t, J = 8.0 Hz, 1H), 5.72 (s, 1H), 7.85 (s, 1H), 7.89 (s, 1H), 9.81 (s, 1H).

5-((4-Methoxybenzyloxy)methyl)-1-((2-(trimethylsilyl) ethoxy)-methyl)-1*H*-imidazole (22). To a solution of compound **21** (1,28 g, 5.66 mmol) in methanol (15 ml) was added sodium borohydride (310 mg, 9.2 mmol, 1.5 equiv.) and the solution was stirred at room temperature for 2 h. When the reaction was completed, saturated aqueous solution of ammonium chloride was added. The product was extracted with ethyl acetate and combined organic layers were washed with brine, dried over sodium sulfate, filtrated and concentrated. To the crude product in DMF (15 ml) was added sodium hydride (60% in oil, 280 mg, 7 mmol, 1.2 equiv.) and the solution was stirred at room temperature for 20 min then 4-methoxybenzyl chloride (0.925 ml, 6.8 mmol, 1.2 equiv.) was added. After stirring for 12 h at room temperature, the reaction was quenched with water and the mixture was concentrated. Water was added to the mixture and product was extracted with ethyl acetate. The organic layers were washed with water, brine, dried over sodium sulfate, filtrated and concentrated. Pure product **22** (1.29 g, 65%) was obtained after flash chromatography on silica gel

(CH_2Cl_2/MeOH : 100/0 to 98/2) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9H), 0.98 (t, 2H, J = 5.0 Hz), 3.56 (t, J = 5.0 Hz, 2H), 3.91 (s, 3H), 4.53 (s, 2H), 4.64 (s, 2H), 6.98 (d, J = 6.0 Hz, 2H), 7.13 (s, 1H), 7.33–7.36 (m, 2H), 7.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.3, 19.2, 56.7, 62.1, 67.6, 72.7, 75.9, 115.3, 129.1, 131.0, 131.2, 132.0, 140.5, 160.6. MS (ESI+) m/z 349 $[M + H]^+$, 371 $[M + Na]^+$.

4-Hydroxymethyl-1-methyl-1*H*-imidazole (20). Compound **22** (1.29 g, 3.7 mmol) was dissolved in toluene (18 ml) at 0 °C and methyl trifluoromethanesulfonate (0.49 ml, 4.5 mmol, 1.2 equiv.) was added. After stirring for 2 h, the solution was concentrated. The mixture was then dissolved in trifluoroacetic acid (9.8 ml) at 0 °C and a catalytic amount of water was added. The solution was stirred for 2 h at 0 °C and concentrated. Diethyl ether was added to help the evaporation of the trifluoroacetic acid. The residue was dissolved in CH_2Cl_2/MeOH (2/1, 9 ml) and solid $NaHCO_3$ was added until pH of the solution was basic. The solution was filtered and concentrated to afford crude **20**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 4.44 (bs, 1H), 4.62 (s, 2H), 6.88 (s, 1H), 7.55 (s, 1H).

4-((*tert*-Butyldimethylsilyloxy)methyl)-1-methyl-1*H*-imidazole (3). To a solution of crude compound **20** in dimethylformamide (41 ml) was added imidazole (620 mg, 9.1 mmol, 2.5 equiv.) and *tert*-butyldimethylsilylchloride (760 mg, 5 mmol, 1.4 equiv.). After stirring for 12 h at room temperature, the solution was quenched with water and concentrated. Water was added to the mixture and the product was extracted with ethyl acetate. Organic layers were washed with water and brine, dried over sodium sulfate, filtered and concentrated. Pure **3** (688 mg, 82%) was obtained after flash chromatography on silica gel (EtOAc/MeOH : 99/1 to 90/10) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 3.62 (s, 3H), 4.65 (s, 2H), 6.77 (s, 1H), 7.33 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) −5.4, 18.4, 25.7, 33.2, 60.2, 117.1, 137.2, 143.1. MS (ESI+) m/z 227 $[M + H]^+$. HRMS (ESI^+) calcd for $C_{11}H_{23}N_2OSi$ $[M + H]^+$ 227.1561 found: 227.1580.

4-((*tert*-Butyldimethylsilyloxy)methyl)-2-iodo-1-methyl-1*H*-imidazole (23). To a solution of compound **3** (1.04 g, 4.6 mmol) in THF (11 ml) under argon atmosphere at −78 °C was added a 1.6 M solution of *n*-butyllithium in THF (3.45 ml, 5.5 mmol, 1.2 equiv.). The solution was stirred for 45 min at the same temperature and a solution of iodine (3.5 g, 13.8 mmol, 3 equiv.) in THF (11 ml) was added dropwise at −78 °C. The solution was warmed to ambient temperature and stirred for 3 h. The reaction was quenched with ethanol and then concentrated. An aqueous saturated solution of sodium thiosulfate (50 ml) was added and the product was extracted with ethyl acetate (3 × 50 ml), dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel (heptane/Et_2O: 7/3) afforded pure 4-((*tert*-butyldimethylsilyloxy)methyl)-2-iodo-1-methyl-1*H*-imidazole **22** (1.41 g, 4.0 mmol, 87%) as an amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 0.89 (s, 3H), 3.56 (s, 3H), 4.63 (s, 2H), 6.92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 18.6, 31.3, 36.9, 60.4, 90.1, 121.3, 146.5. HRMS (ESI^+) calcd for $C_{11}H_{22}IN_2ONaSi$ $[M + Na]^+$: 375.0366 found: 375.0363.

5-((*tert*-bButyldimethylsilyloxy)methyl)-2-iodo-1-methyl-1*H*-imidazole (11). This compound was obtained under the same conditions from compound **4**.[4] Further crystallization in heptane afforded pure **11** (1.35 g, 83%) as pale yellow crystals. Mp 96.2–97.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 0.89 (s, 3H), 3.61 (s, 3H), 4.65 (s, 2H), 6.95 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 18.3, 25.9, 34.5, 55.7, 92.6, 130.9, 135.0. MS (ESI+, MeOH) m/z 353 $[M + H]^+$. Elemental analysis calcd (%) for $C_{11}H_{21}IN_2OSi$: C 37.50, H 6.01, N 7.95; found C 37.41, H 5.87, N 7.85.

(*E*)-Diethyl 2-(*R*)-(3-(4-((*tert*-butyldimethylsilyloxy) methyl)-1-methyl-1*H*-imidazol-2-yl)allyl)succinate 24a. Prepared according to general procedure B with **23** (528 mg, 1.5 mmol) in DMF (6 ml) with (***E*)-15a** (795 mg), Na_2CO_3 (172 mg) and $Pd(PPh_3)_4$ (172 mg). After a classical work-up, purification by flash chromatography on silicagel (heptane/EtOAc : 1/1) afforded pure **24a** (566 mg, 86%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0,84 (s, 9H), 1.15–1.21 (m, 6H), 2.37–2.45 (m, 1H), 2.48 (dd, J = 3.0, 18.0 Hz, 1H), 2.56–2.65 (m, 1H), 2.68 (dd, J = 9.0, 18.0 Hz, 1H), 2.92–3.01 (m, 1H), 3.55 (s, 3H), 4.10 (q, J = 6 Hz, 2H), 4.12 (q, J = 6 Hz, 2H,), 4.51 (s, 2H), 6.25 (d, J = 15 Hz, 1H), 6.47–6.60 (m, 1H), 6.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 25.1, 26.0, 32.9, 35.2, 35.5, 41.1, 58.7, 60.8, 61.0, 118.6, 131.4, 141,4, 142.2, 171.9, 174.1. HRMS (ESI^+) calcd for $C_{22}H_{39}N_2O_5Si$ $[M + H]^+$: 439.2628 found: 439.2643. IR 1463, 1730 cm^{-1}. $[\alpha]_D^{23}$ = +4.0 (c 1.0 in $CHCl_3$).

Compound 26a. Prepared according to general procedure C. **a-** From **24a** (566 mg, 1.3 mmol) in THF (5 ml) with TBAF (1M in THF, 2.5 ml). Purification by flash chromatography on silicagel (CH_2Cl_2/MeOH: 95/5) afforded the expected alcohol (418 mg, quant.) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15–1.21 (m, 6H), 2.37–2.45 (m, 1H), 2.48 (dd, J = 3.0, 18.0 Hz, 1H), 2.56–2.65 (m, 1H), 2.68 (dd, J = 9.0, 18.0 Hz, 1H), 2.92–3.01 (m, 1H), 3.55 (s, 3H), 4.10 (q, J = 6.0 Hz, 2H), 4.12 (q, J = 6.0 Hz, 2H,), 4.51 (s, 2H), 6.25 (d, J = 15.0 Hz, 1H), 6.47–6.60 (m, 1H), 6.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.0, 32.9, 35.2, 35.5, 41.1, 58.7, 60.8, 61.0, 118.6, 131.4, 141,4, 142.2, 171.9, 174.1. HRMS (ESI^+) calcd for $C_{16}H_{25}N_2O_5$ $[M + H]^+$: 325.1763 found: 325.1769. IR 1464, 1729, 2978, 3409 cm^{-1}. $[\alpha]_D^{23}$ = +4.5 (c 1.0 in $CHCl_3$).

b- From the alcohol (418 mg) in CH_2Cl_2 (13 ml) with MnO_2 (730 mg). Purification by flash chromatography on silicagel (CH_2Cl_2/MeOH: 98/2) afforded the expected aldehyde (285 mg, 69%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 6.0 Hz, 3H), 1.20 (t, J = 6.0 Hz, 3H), 2.41–2.51 (m, 2H), 2.58–2.73 (m, 2H), 2.93–3.01 (m, 1H), 3.65 (s, 3H), 4.10 (q, J = 6.0 Hz, 2H), 4.12 (q, J = 6.0 Hz, 2H), 6.27 (d, J = 15.0 Hz, 1H), 6.68–6.78 (m, 1H), 7.48 (s, 1H), 9.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.1, 33.7, 35.1, 35.6, 41.0, 60.9, 61.1, 117.7, 127.1, 134.9, 141.1, 147.0, 171.7, 173.9, 185.9. HRMS (ESI^+) calcd for $C_{16}H_{23}N_2O_5$ $[M + H]^+$: 323.1607 found: 323.1601. IR 1447, 1537, 1679, 1725, 2978 cm^{-1}. $[\alpha]_D^{23}$ = +7.0 (c 1.0 in $CHCl_3$).

c- From NH_2-VFM-OMe (360 mg, 0.88 mmol) in MeOH/CH_2Cl_2 (3/1, 13.2 ml), and the aldehyde (285 mg, 0.88 mmol) in MeOH/CH_2Cl_2 (1/1, 2 ml) then sodium cyanoborohydride (114 mg) in MeOH/AcOH (1/0.1, 2 ml). Purification by flash chromatography on silicagel (CH_2Cl_2/MeOH: 98/2 to 95/5) afforded the compound **26a** (490 mg, 78%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (d, J = 6.0 Hz, 3H), 0.75 (d, J = 6.0 Hz, 3H), 1.24 (t, J = 6.0 Hz, 3H), 1.25 (t, J = 6.0 Hz, 3H), 1.84–1.99 (m, 2H), 2.05 (s, 3H), 2.06–2.14 (m, 1H), 2.41 (t, J = 9.0 Hz, 1H), 2.43–2.56 (m, 2H), 2.56–2.70 (m, 1H), 2.73 (dd, J = 9.0, 15.0 Hz, 1H), 2.94 (d, J = 3.0 Hz, 1H), 2.97–3.14

(m, 2H), 3.19 (dd, J = 6.0, 15.0 Hz, 1H), 3.47 (d, J = 12.0 Hz, 1H), 3.58 (d, J = 12.0 Hz, 1H), 3.59 (s, 3H), 3.72 (s, 3H), 4.13 (q, J = 6.0 Hz, 2H), 4.16 (q, J = 6.0 Hz, 2H), 4.59–4.72 (m, 2H), 6.29 (d, J = 18.0 Hz, 1H), 6.48–6.58 (m, 1H), 6.68 (s, 1H), 7.05 (d, J = 9.0 Hz, 1H), 7.18–7.30 (m, 5H), 8.01 (d, J = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.2, 14.2, 15.6, 19.3, 29.8, 31.2, 31.5, 32.7, 35.1, 35.4, 37.3, 41.0, 45.9, 51.5, 52.4, 54.4, 60.6, 60.8, 67.5, 118.6, 118.9, 126.8, 128.6, 129.2, 131.3, 136.9, 139.2, 144.9, 171.2, 171.7, 171.8, 173.9, 174.5. HRMS (ESI$^+$) calcd for $C_{36}H_{54}N_5O_8S$ [M + H]$^+$: 716.3693 found: 716.3683. IR 1439, 1513, 1643, 1730, 2956, 3295 cm^{-1}. $[\alpha]_D^{23} = -41$ (c 0.81 in $CHCl_3$).

Compound 30a. To a solution of compound **26a** (120 mg, 0.17 mmol) in ethyl acetate (3 ml) was added palladium on activated carbon 10% Pd (50% w/w), the mixture was purged with hydrogen and stirred for 24 hours under hydrogen (1 atm.). The mixture was filtered over celite, washed with ethyl acetate and the filtrate was concentrated. Purification on by preparative TLC silica gel (CH_2Cl_2/MeOH: 95/5, v/v) afforded pure **30a** (75 mg, 62%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (d, J = 6.0 Hz, 3H), 0.66 (d, J = 6.0 Hz, 3H), 1.16 (t, J = 6.0 Hz, 3H), 1.17 (t, J = 6.0 Hz, 3H), 1.48–1.57 (m, 1H), 1.59–1.72 (m, 3H), 1.78–1.94 (m, 2H), 1.97 (s, 3H), 2.00–2.05 (m, 1H), 2.32–2.40 (m, 3H), 2.56–2.67 (m, 3H), 2.73–2.81 (m, 1H), 2.84 (d, J = 3.0 Hz, 1H), 3.00 (dd, J = 6.0, 15.0 Hz, 1H), 3.12 (dd, J = 6.0, 15.0 Hz, 1H), 3.33 (d, J = 12.0 Hz, 1H), 3.45 (s, 3H), 3.49 (d, J = 12.0 Hz, 1H), 3.64 (s, 3H), 4.03 (q, J = 6.0 Hz, 2H), 4.07 (q, J = 6.0 Hz, 2H), 4.52–4.63 (m, 2H), 6.56 (s, 1H), 6.99 (d, J = 9.0 Hz, 1H), 7.01–7.25 (m, 5H), 7.97 (d, J = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.4, 15.6, 17.8,19.5, 25.7, 26.7, 30.0, 31.3, 31.7, 31.8, 32.7, 36.4, 37.4, 41.2, 45.9, 51.7, 52.6, 54.6, 60.8, 60.9, 67.4, 118.5, 127.0, 128.8, 129.4, 137.1, 148.1, 171.4, 172.0, 174.7. HRMS (ESI$^+$) calcd for $C_{36}H_{55}N_5O_8NaS$ [M + Na]$^+$: 740.3669 found: 740.3636. IR 1439, 1454, 1504, 1537, 1644, 1650, 1730, 2954, 3294 cm^{-1}. $[\alpha]_D^{23} = -39$ (c 0.88 in $CHCl_3$).

Compound 28a. Prepared according to general procedure D on **26a** (54 mg, 0.075 mmol) in 1.5 ml solvent with LiOH·1H_2O (11 mg, 3.5 equiv.). Compound **28a** (49 mg, quant.) was obtained as a white amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.64 (d, J = 6.0 Hz, 3H), 0.67 (d, J = 6.0 Hz, 3H), 1.66–1.77 (m, 1H), 1.78–1.93 (m, 1H), 1.95 (s, 3H), 1.96–2.10 (m, 1H), 2.32–2.40 (m, 4H), 2.41–2.57 (m, 2H), 2.69–2.76 (m, 1H), 2.80 (d, J = 6.0 Hz, 1H), 2.84 (dd, J = 6.0, 15.0 Hz, 1H), 3.13 (dd, J = 6.0, 15.0 Hz, 1H), 3.23 (d, J = 12.0 Hz, 1H), 3.36 (d, J = 12.0 Hz, 1H), 3.53 (s, 3H), 4.20 (dd, J = 3.0, 6.0 Hz, 1H), 4.67 (dd, J = 3.0, 9.0 Hz, 1H), 6.33 (d, J = 15.0 Hz, 1H), 6.44–6.54 (m, 1H), 6.69 (s, 1H), 7.01–7.19 (m, 5H). ^{13}C NMR (75 MHz, CD_3OD) δ 15.4, 18.8, 19.7, 31.3, 32.5, 33.6, 34.1, 36.8, 38.7, 39.3, 44.7, 45.4, 55.7, 55.8, 68.4, 118.1, 121.5, 127.9, 129.7, 130.5, 136.7, 137.4, 138.7, 146.5, 172.7, 175.3, 177.7, 178.9, 181.0. HRMS (ESI$^+$) calcd for $C_{31}H_{43}N_5O_8NaS$ [M + Na]$^+$: 668.2730 found: 668.2736. $[\alpha]_D^{23} = -19$ (c 0.32 in $CHCl_3$).

Compound 2a. Prepared according to general procedure D on **30a** (60 mg, 0.0584 mmol) in 1.4 ml solvent with LiOH (13 mg, 6.4 equiv.). Compound **2a** (48 mg, 88%) was obtained as a white amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.75 (d, J = 6.0 Hz, 6H), 0.67 (d, J = 6.0 Hz, 1H), 1.54–1.82 (m, 5H), 2.05 (s, 3H), 1.92–2.18 (m, 2H), 2.34–2.56 (m, 4H), 2.64–2.82 (m, 3H), 2.86 (d, J = 5.5 Hz, 1H), 2.97 (dd, J = 10.0, 14.0 Hz, 1H), 3.24 (dd, J = 5.0, 14.0 Hz, 1H), 3.33 (d, J = 14.0 Hz, 1H), 3.48 (d, J = 14.0 Hz, 1H), 4.31 (dd, J = 4.5, 7.0 Hz, 1H), 4.78 (dd, J = 4.5, 10.0 Hz, 1H), 6.79 (s, 1H), 7.12–7.33 (m, 5H). ^{13}C NMR (75 MHz, CD_3OD) δ 15.4, 18.9, 19.8, 26.6, 26.7 31.2, 32.5, 32.6, 33.6, 34.1, 36.8, 38.7, 40.4, 44.8, 45.0, 55.7, 55.8, 68.3, 121.0, 127.9, 129.7, 130.5, 135.6, 138.7, 149.7, 172.7, 175.5, 177.7, 179.5, 182.3. HRMS (ESI$^-$) calcd for $C_{31}H_{45}N_5O_8NaS$ [M-H]$^-$: 646.2911 found: 646.2897. $[\alpha]_D^{23} = -14$ (c 0.37 in MeOH).

FTase assays

Assays were realized on 96-well plates, prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read on Wallac Victor fluorimeter from Perkin-Elmer. Per well 20 µL of farnesyl pyrophosphate (10 µM) was added to 180 µL of a solution containing 2 µL of varied concentrations of **1a–b**, **2a–b**, **27a–b** and **28a–b** (dissolved in DMSO) and 178 µL of a solution composed by 0.1 ml of partially purified recombinant yeast or human FTase (2.2 mg/mL and 1.5mg/ml respectively) and 7.0 ml of Dansyl-GCVLS peptide (in the following buffer: 5.8 mM DTT, 6 mM $MgCl_2$, 12 µM $ZnCl_2$, 0.09% (w/v) CHAPS for yeast FTase or 0.18% (w/v) Octyl-D-glucopyranoside for human FTase, 53 mM Tris/HCl, pH 7.5). Then the fluorescence development was recorded for 15 min (0.7 seconds per well, 20 repeats) at 30 °C with an excitation filter at 340 nm and an emission filter at 486 nm. Each measurement was realized twice as duplicate or triplicate.

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