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Synthesis of 6-vinyl and 5-vinylproline analogues of ascomycin

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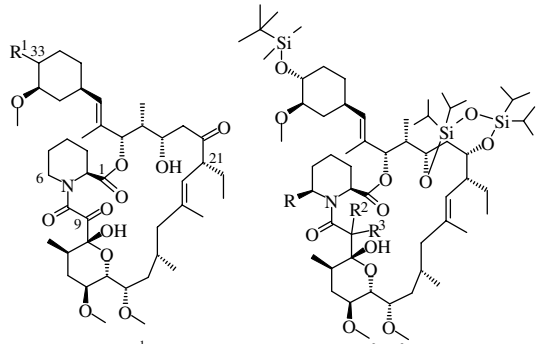
Abstract—6-Vinyl (**12**) and (5*R*)- and (5*S*)-vinylproline (**18**, **19**) analogues of ascomycin are synthesised starting from the known suitably protected (6*S*)-methoxy-9-hydroxy derivative (**4**) of ascomycin. The strategy involves hydrolytic cleavage of the C_ε–N bond of the pipecolic acid moiety, extension of the amino acid side chain by two or one carbon units, functional group manipulations, Pd-catalysed reinstallation of the C_ε–N or C_δ–N bonds, followed by deprotection and oxidation.

The immunomodulatory macrolactam ascomycin (**1**, Fig. 1) is a fermentation product from *Streptomyces hygroscopicus* var. *ascomyceticus*, originally isolated due to its antifungal activities.[1] Pimecrolimus **2** (33-epi-chloroascomycin, Elidel®, SDZ ASM 981) has proven high therapeutic efficacy in patients with inflammatory skin diseases and pimecrolimus cream 1% is on the market for the topical treatment of atopic dermatitis.[2] Ascomycin is a highly functionalised molecule containing several free hydroxy groups, an aldol functionality, and a reactive tricarbonyl attached to pipecolic acid. As demonstrated by studies with the structurally closely related fermentation product FK506 (tacrolimus), the pipecolic acid unit of the macrolactam is involved in the binding to its receptor macrophilin.[3] The amino acid unit adopts a $^2C_5$-conformation both in solution and in the macrophilin binding complex. Hence, derivatives featuring modifications in the amino acid unit are useful probes for elucidating the effect of the new modifications on the conformation of the molecule and, hence, on the biological activity. However, because of the lack of functionalities in this part of the molecule, selective modifications, in particular on the amino acid unit, require complex synthetic strategies.[4] In this context, we have earlier described the photochemistry of unprotected ascomycin and its application for synthesising several derivatives and the phototransformation of the protected ascomycin derivative **3** into the (6*S*)-methoxy-9-hydroxy derivative **4** (MeOH, $\lambda \geqslant 366$ nm, 0–5 °C, 8 h, 69%) featuring a versatile modification in the amino acid unit, in a high yield even on a multigram scale.[5] We report here the transformation of **4** into the 6-vinyl analogue **12** (Scheme 1) and the 5-vinylproline analogues **18** and **19** (Scheme 2) of ascomycin. Synthesis of derivatives of this type using the reported methodologies would require many number of steps. Our strategy is short and has potential for synthesis of several such new analogues.



1: Ascomycin: $R^1 = (R)$-OH
2: Pimecrolimus: $R^1 = (S)$-Cl
3: R = H, (R^2, R^3) = = O
4: R = OMe, R^2 = H, R^3 = OH

Figure 1.

The strategy for conversion of **4** to **12** involves cleavage of the C_ε–N bond in the amino acid moiety, extension of the amino acid side chain by a two carbon unit, functional group manipulations, reinstallation of the C_ε–N

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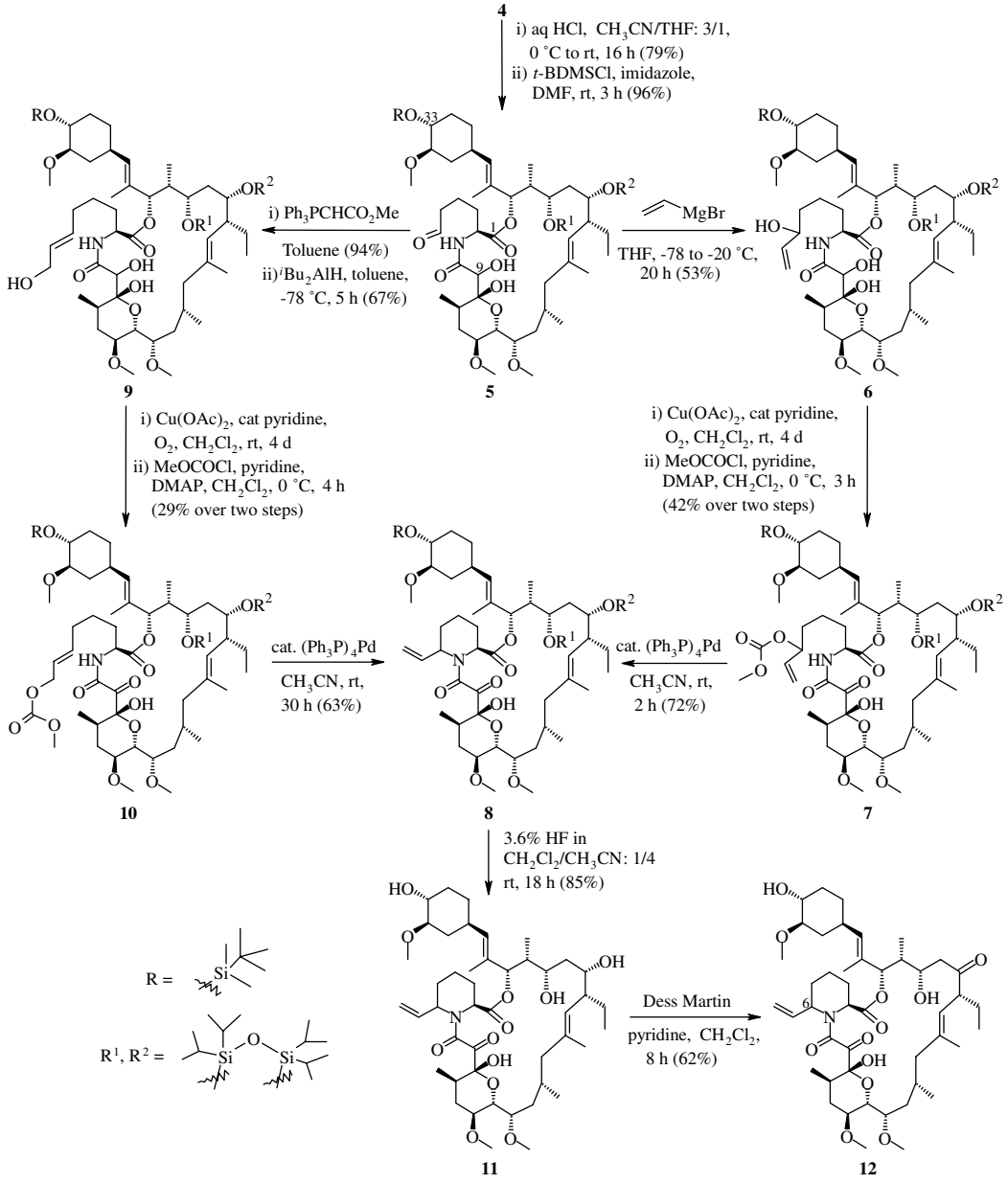
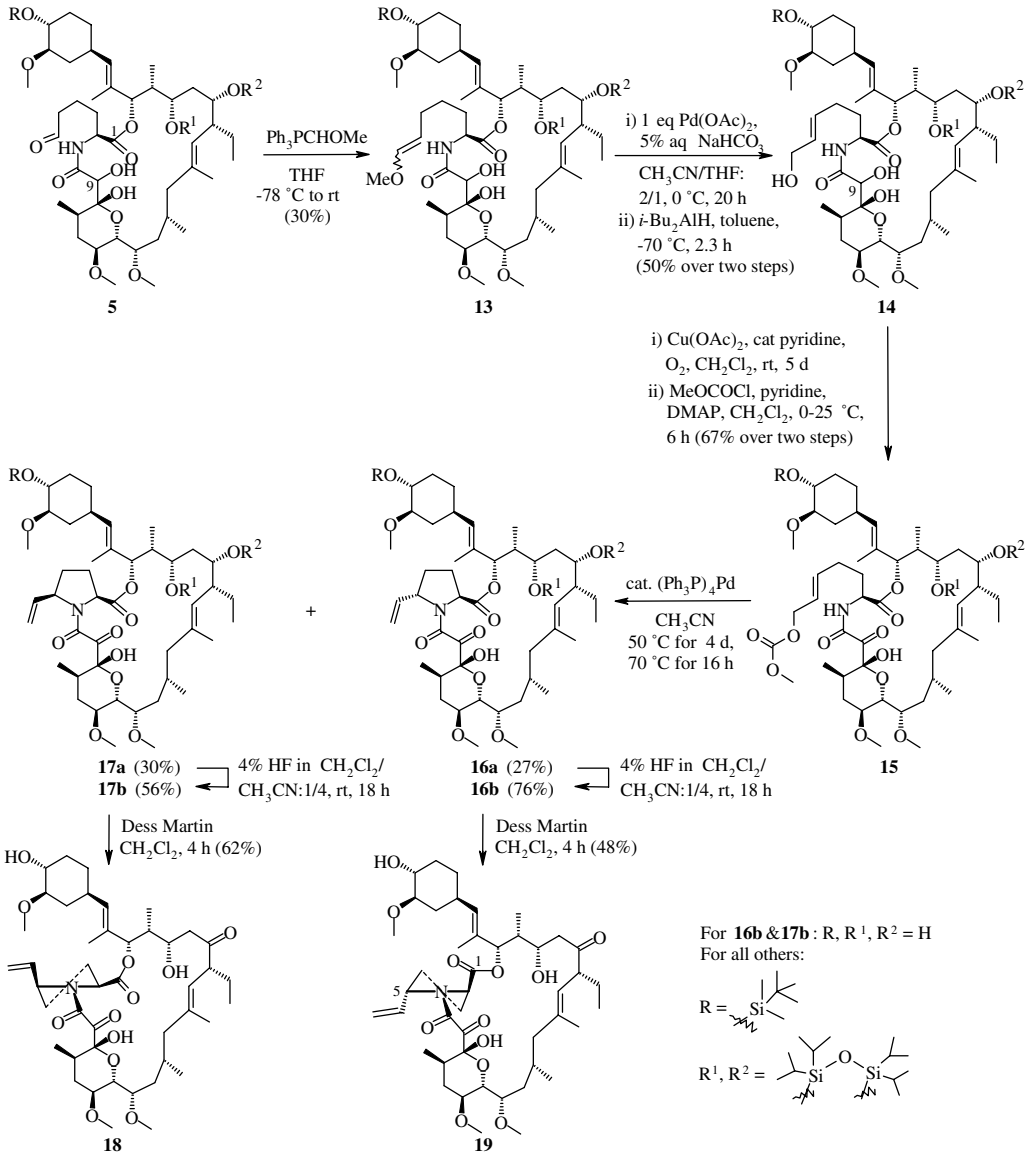


Scheme 1. Synthesis of (6)-vinyl ascomycin **12**.

bond, deprotection and selective oxidation. Thus, the hetero acetal functionality of the photoproduct **4** was hydrolysed to the corresponding aldehyde under mild acidic conditions in a 79% yield (aq 0.1 N HCl, CH_3CN/THF: 3/1, 0 °C to rt, 16 h) with concomitant loss of the *t*-BDMS group on the C(33)–OH (Scheme 1). The *t*-BDMS group could be easily reintroduced using conventional method in a 96% yield (1.9 equiv *t*-BDMSCl, 3 equiv imidazole, DMF, rt, 3 h) affording the protected aldehyde **5**.[6] Addition of vinyl magnesium bromide to the aldehyde **5** gave the allyl alcohol **6** in a 53% yield (4 equiv $CH_2{=}CHMgBr$, THF, −78 to −20 °C, 20 h). Selective oxidation of the C(9)–OH of **6** with Cu(II) acetate (1 equiv $Cu(OAc)_2$, cat. pyridine, O_2, CH_2Cl_2, 4 d, rt),[5] followed by selective activation of the secondary allylic alcohol as methyl carbonate derivative (2.5 equiv CH_3OCOCl, 10 equiv pyridine, cat. DMAP, CH_2Cl_2, 0 °C, 3 h) afforded **7** in a 42% yield over two steps. The key step, namely the reinstallation of the C_ε–N bond, was achieved through Pd-catalysed cyclisation of **7** leading to the protected vinyl analogue **8** in a 72% yield (5 mol% $(PPh_3)_4Pd$, CH_3CN, rt, 2 h).[7]

An alternative route was also explored for the transformation of **5** to **8**. Thus, Wittig olefination of the aldehyde **5** with 1.2 equiv Ph_3PCHCO_2Me in toluene at rt for 1 day afforded the corresponding unsaturated ester in a 94% yield, which upon reduction with diisobutylaluminium hydride led to the primary allylic alcohol **9** in a 67% yield (4 equiv DIBAlH, toluene, −78 °C, 5 h). Transformation of **9** to **10** was effected as described above through Cu(II)-catalysed selective oxidation of the C(9)–OH, followed by selective activation of the primary allylic alcohol as methyl carbonate derivative



Scheme 2. Synthesis of (5*R*)- and (5*S*)-vinylproline analogues **18** and **19** of ascomycin (**1**).

((i) 1 equiv $Cu(OAc)_2$, cat. pyridine, O_2, CH_2Cl_2, rt, 4 d; (ii) 2 equiv CH_3OCOCl, 10 equiv pyr, cat. DMAP, CH_2Cl_2, 0 °C, 4 h; 29% over two steps). Again, similar to the transformation of **7** to **8**, Pd-catalysed cyclisation of **10** afforded the protected vinyl analogue **8** in a 63% yield (5 mol% $(PPh_3)_4Pd$, CH_3CN, rt, 30 h).

The ^1H NMR spectra of the samples of **8** obtained either way, starting from **7** or **10**, are identical to each other, and indicated the presence of three components (in 0.7:1:1.9 ratio; C(6)-epimers/conformers) not separable by chromatography. Desilylation of **8** with HF at rt resulted in **11** in a 85% yield(3.6% HF in CH_2Cl_2/CH_3CN: 1/4, 18 h). Selective oxidation of the C(22)–OH of **11** using Dess Martin's reagent at rt afforded 6-vinyl ascomycin **12** in a 62% yield (3 equiv periodinane, 10 equiv pyridine, CH_2Cl_2, 8 h).[8] The ^1H and ^{13}C NMR spectra of **12** showed it to consist of two major (ca. 1:1 ratio) and two minor components. No coalescence of the signals was observed in the ^1H NMR in d_6-DMSO at 80 °C. Because of overlapping of the signals, no information could be obtained on C(6)-configuration or conformation of the epimers. The basic structure, however, was established using C–H correlation spectra.

Encouraged by the above successful transformation of ascomycin to (6)-vinyl ascomycin through the intermediate **5**, we undertook transformation of **5** to the 5-vinylproline analogues **18** and **19** of ascomycin (Scheme 2). To this end, a strategy, analogous to the one used above, would require one carbon extension of the aldehyde **5** and further functional group manipulations to an allylic alcohol. This was achieved through Wittig reaction of **5** with methoxymethylenetriphenylphosphorane leading to the enol ether **13** as a 2:1 mixture of *E*/*Z* isomers (4 equiv $MeOCHPPh_3Cl$, 3.5 equiv of LiHMDS, THF, 0 °C, 30 min; then **5**, −78 °C for 2 h, 0–25 °C for 1 h, 30%).[9] Reaction of the enol ether **13** with $Pd(OAc)_2$ afforded the corresponding (*E*)-α,β-unsaturated aldehyde,[9] which was reduced with diisobutylaluminium

hydride affording the required allyl alcohol **14** in a 50% yield over two steps ((i) 1.06 equiv $Pd(OAc)_2$, 5% aq $NaHCO_3$, CH_3CN/THF: 2/1, 0 °C, 20 h, workup; (ii) 2.8 equiv $^iBu_2AlH$, toluene, −70 °C, 2.3 h). Oxidation of the C(9)–OH of **14** with Cu(II) acetate, followed by selective activation of the allylic alcohol as methyl carbonate derivative afforded **15** in a 67% overall yield ((i) 4 equiv $Cu(OAc)_2$, 0.3 equiv pyridine, 4 Å MS, O_2, CH_2Cl_2, rt, 5 d; workup; (ii) 4 equiv MeOCOCl in portions, 10 equiv pyridine, cat. DMAP, 0–25 °C, 6 h). Pd-catalysed cyclisation of the allyl carbonate **15**, followed by chromatographic separation of the epimers, led to the protected (5*S*)-vinylproline analogue **16a** (27%) and the (5*R*)-proline analogue **17a** (30%) (10 mol% $(PPh_3)_4Pd$, CH_3CN, 4 d at 50 °C and 16 h at 70 °C). Noteworthy here are the longer reaction time and the higher temperature required for the cyclisation of **15**, compared to those for **7** and **10**. Desilylation of **16a** gave **16b** (4% HF, CH_2Cl_2/CH_3CN, 25 °C, 18 h) in a 76% yield, which after Dess Martin's oxidation afforded **19** in a 48% yield (1.3 equiv periodinane, CH_2Cl_2, rt, 4 h,). Similarly **17a** after desilylation gave **17b** (56%), which after oxidation as above afforded **18** in a 62% yield.

The ^{1}H NMR spectra of the proline derivatives **16a**, **16b** and **19** showed signals at δ 4.51 (dd, $J = 8.5$, 2.1 Hz), 4.70 (dd, $J = 8.5$, 2.3 Hz) and 4.46 (dd, $J = 8.6$, 2.1 Hz), respectively, which are assigned to H–C(2) based on C–H correlation spectra. These splittings are similar to those in (5*R*)-methoxy proline analogue of ascomycin reported earlier,[5] and indicate (5*S*)-configuration for **16a**, **16b** and **19**, with the C(1) placed pseudoaxially as drawn for **19** in Scheme 2. On the other hand, the ^{1}H NMR spectra of **17a**, **17b** and **18** showed signals at δ 4.49 (t, $J = 8.6$ Hz), 4.55 (t, $J = 8.3$ Hz) and 4.41 (t, $J = 8.4$ Hz), respectively, which are assigned to H–C(2). Again, these splittings are analogous to those in (5*S*)-methoxyproline analogue of ascomycin,[5] indicating (5*R*)-configuration for **17a**, **17b** and **18**, with C(1) placed pseudoequatorially as drawn in Scheme 2 for **18**.

In summary, we could synthesise the 6-vinyl analogue **12** and the 5-vinylproline analogues **18** and **19** of ascomycin starting from the aldehyde **5** in fewer steps than would have required using reported strategies. The conformational differences in the amino acid moiety arising from the substitution are interesting. The presence of new reactive terminal double bonds in these vinyl analogues opens scope for further modifications. The easy availability of **5** in multigram quantities from ascomycin via the photo product **4**, and the exemplary syntheses described above, indicate the viability of **5** as a useful intermediate for synthesis of other novel analogues.

Acknowledgements

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