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Synthesis of new echinocandin derivatives via a diol-keto transposition

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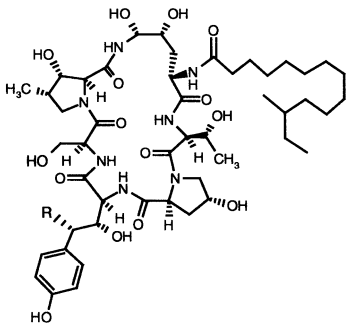
Abstract—A new diol-carbonyl transposition reaction has been discovered in echinocandin type structures. An α-hydroxy hemiaminal moiety has been shown to undergo a pinacol-type rearrangement in the presence of trimethylsilyl iodide to afford ketone derivatives. Applied to deoxymulundocandin, this transposition led to a useful intermediate for further chemical modification.

Fungal infections have been reported to increase over the last decades due mainly to an enlarging population at risk (immuno-compromised patients, invasive surgery, parenteral nutrition…).[1] The armamentarium available in hospitals is limited to amphotericin B and few azoles (fluconazole, itraconazole).[2] While the use of amphotericin B requires the management of severe adverse effects,[3] treatment with azoles fails frequently because of increasing pathogen resistance.[4]

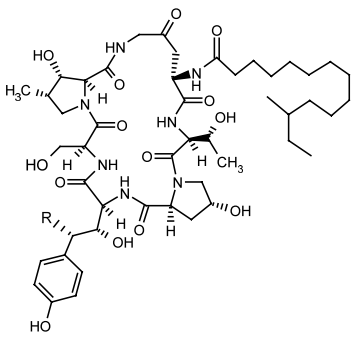
The echinocandins would appear to be promising new anti-fungal agents with respect to their fungicidal activity and efficacy in treating severe fungal infections as observed in clinical trials.[5] Moreover, the pneumocandin derived Cancidas (MK-0991) has been recently approved by the FDA for the treatment of invasive aspergillosis in refractory patients.[6]

We embarked on a chemical programme aiming at discovering new echinocandin derivatives with an improved pharmacological profile over those tested in clinical trials.[5] Our strategy relied on the chemical modification of mulundocandin **1** and deoxymulundocandin **2**, two naturally occurring anti-fungal agents isolated from *Aspergillus sydowii*.[7]

We report here the discovery of a new chemical derivatisation of the echinocandin scaffold, a transposition reaction giving rise to the keto products **3** and **4**. Ketone **4** turned out to be a useful intermediate for the preparation of mulundocandin analogues endowed with original properties.



1: R =OH ; **2** : R=H



3: R=OH ; **4**: R=H

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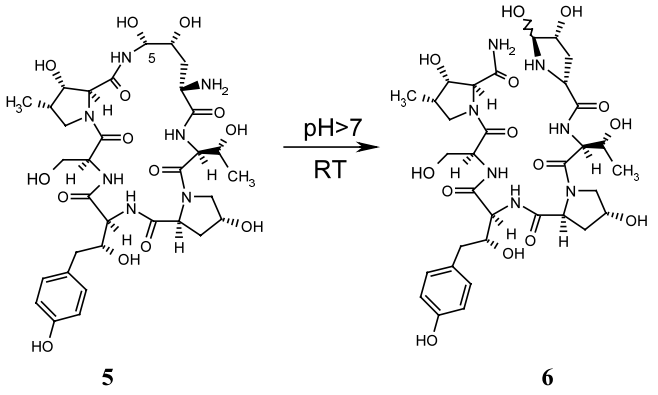
The reactive hemiaminal position at C5 in the echinocandins undergoes readily intramolecular substitution reaction in weakly basic conditions to afford a ring opened product.[8] For example, the cyclopeptide moiety of deoxymulundocandin **5** transforms almost totally into **6** in 24 h at pH 9 (Scheme 1).

In order to increase the stability of our series, we sought to chemically remove the hydroxyl group at the hemiaminal position and to further modify this ornithine residue for activity improvement purposes.

In preliminary dehydration experiments, mulundocandin was submitted to Me_3SiCl/NaI in acetonitrile[9] and a multitude of products were formed (see Scheme 2). Very interestingly, several ketone derivatives were isolated and characterised. Diol-keto rearrangements occurred along with other reactions (dehydration, cyclisation, epimerisation…) leading to ketones **3a** and **3b** in low yields (9% as a non separated mixture). Surprisingly, to the best of our knowledge, the formation of ketones from diol systems in such conditions has never been reported.[10] Furthermore, this carbonyl transposition opens up new opportunities for chemical derivatisation of echinocandin type scaffolds.[11]

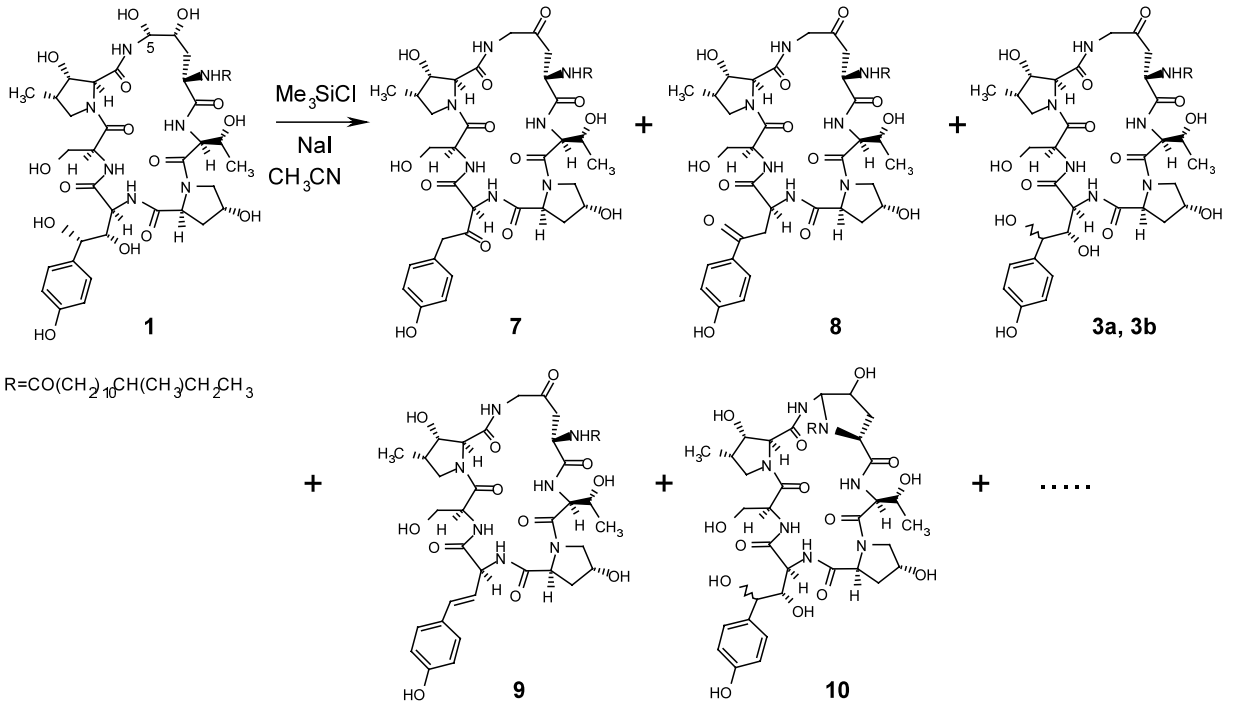


Scheme 1.

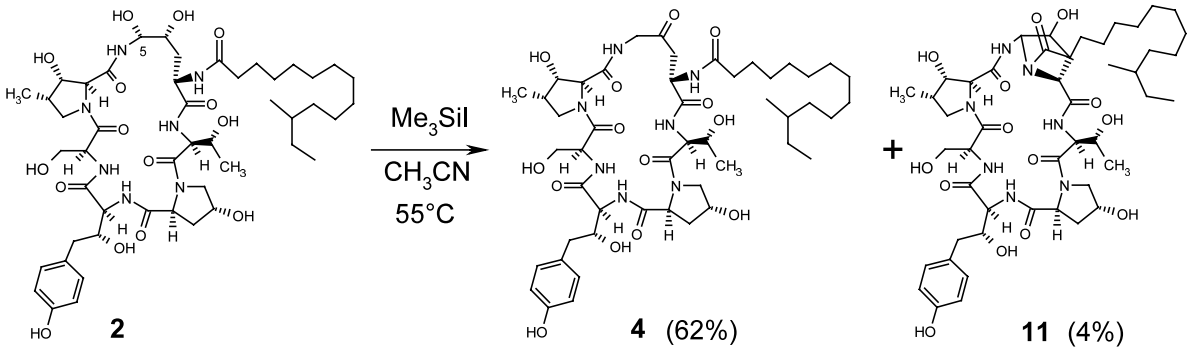
Part of the complexity of the reaction depicted in Scheme 2 relies on the presence of a second reactive *vic*-diol group in the mulundocandin structure (β-hydroxyhomotyrosine moiety). Consequently, the scope of this new transposition reaction was assessed using deoxymulundocandin **2** as starting material and Me_3SiI as reagent. As expected, the rearrangement occurred with a significant yield improvement (62%). Only the formation of the cyclised by-product **11** (see Scheme 3) was deplored albeit to a limited extent (4%).[12]

From a mechanistic standpoint, the carbonyl formation is considered to proceed via a transient carbocation at C5, according to a pinacol type rearrangement. Accordingly, our investigation pointed out that the formation in good yields of ketone **4** was strongly related to the control of the cation generation kinetics in acidic conditions. In more drastic conditions when compared with Me_3SiI (for example *p*-TsOH), degradation products were mainly formed.[13]

Ketone **4** was submitted to chemical derivatisations to obtain mulundocandin analogues with improved chemical stability and increased inhibition of the ß-(1,3)-glucan synthase complex, the biological target of the echinocandins.[14] A series of various oximes, hydrazones and amines were prepared in standard conditions of condensation and reductive amination reactions, respectively.[15] In all series, we observed sub-micromolar



Scheme 2.



Scheme 3.

inhibition of *C. albicans* glucan synthase with up to 30-fold improvement of activity when compared to that of deoxymulundocandin **2**. Further optimisation of these series was successfully conducted and candidates for pre-clinical trials were identified.[16]

Acknowledgements

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12. Preparation of **4**: to a suspension of deoxymulundocandin **2** (4.24 g, 3.94 mmol) in acetonitrile (110 ml) was added under inert atmosphere trimethylsilyl iodide (1.61 ml, 11.82 mmol). The resulting mixture was stirred at 55°C for 15 mn then hydrolysed with an aqueous solution of $Na_2S_2O_3$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/H_2O: 86/13/1 v/v/v) to afford ketone **4** (2.6 g, 62% yield) and derivative **11** (162 mg, 4% yield). Main spectroscopic data of ketone **4**: ^{1}H NMR (500 MHz, d_6-DMSO, ppm), 7.94, 4.50, 4.25 and 1.1 (threonine residue); 4.40, 4.37, 3.84–3.70 and 2.20–1.92 (γ-hydroxy proline residue); 9.08, 7.48 (d), 6.95, 6.65, 4.20, 4.09 and 2.50–2.42 (β-hydroxyhomotyrosine residue); 7.61, 4.92 and 3.67 (serine residue); 4.27, 3.98–3.24, 3.96, 4.27, 2.29 and 0.97 (β-hydroxy-γ-methyl proline residue); 8.36 (t), 7.58, 4.56, 3.69, 2.77–2.67 (ornithine residue); 2.04, 1.44, 1.31–1.11, 1.29, 1.25–1.06, 1.24, 1.21, 0.83, 0.82 (aliphatic chain). ^{13}C NMR (125 MHz, d_6-DMSO, ppm), 66.3, 56.7 and 19.5 (threonine residue); 69.0, 60.9, 55.7 and 37.5 (γ-hydroxy proline residue); 130.1, 114.9, 71.9, 55.8 and 39.4 (β-hydroxyhomotyrosine residue); 62.6 and 51.6 (serine residue); 74.1, 69.7, 50.9, 37.0 and 10.7 (β-hydroxy-γ-methyl proline residue); 49.6, 49.5 and 40.0 (ornithine residue); 36.0, 35.1, 33.7, 28.8, 26.4, 24.9, 19.0 and 11.1 (aliphatic chain). MS *m*/*e*: 974 (MH^+), 956, 865, 836, 667, 580, 566 and 479.
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