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Studies on the Chemistry of Rapamycin: Novel Transformations under Lewis-Acid Catalysis

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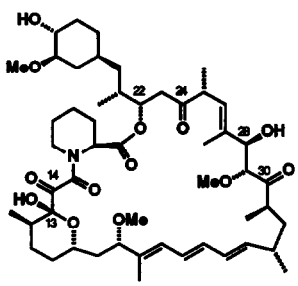
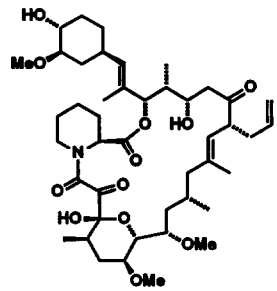
Abstract: The reactivity of rapamycin under mild Lewis-acid catalysis has been investigated. The molecule has been found to be extremely sensitive to basic reagents due to carboxylate elimination β to the C_{24} ketone. However, transformations normally effected under basic conditions, such as C_{13}-C_{14} benzilic acid rearrangement or C_{28}-C_{30} retroaldol, can be achieved on rapamycin itself by catalysis with $ZnCl_2$ in the appropriate solvent. These are novel transformations that circumvent the protection or masking of reactive functional groups and allow efficient degradation of the molecule for synthetic and biological studies.

Rapamycin (**1**) and FK506 (**2**) are potent immunosuppressive antibiotics that have attracted considerable interest due to their potential therapeutic value in organ transplantation. Interestingly, despite their structural similarity and the fact that they interact with the same intracellular receptors, these macrolides have different modes of action, suppressing T-cell activation at different stages.[1] In recent years, a number of reports on the chemistry of FK506 have been published;[2] synthetic derivatives from these studies provide powerful probes to elucidate the interplay between the immunosuppressive and the toxic effects of FK506.[3] The chemistry of rapamycin, by contrast, has remained less widely explored.[4] Herein we report our studies on the reactivity of rapamycin under Lewis-acid catalysis and the application to an efficient degradation of the molecule.

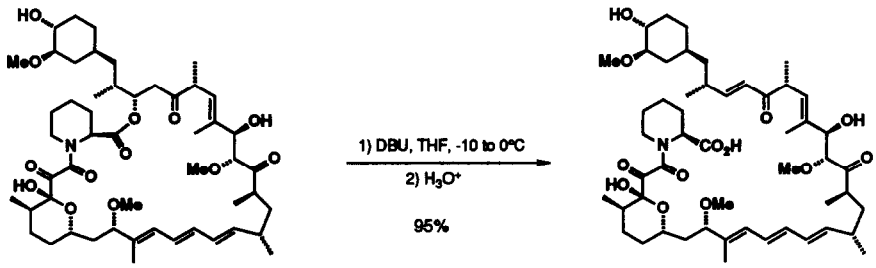


1 Rapamycin



2 FK506

The complex array of functional groups in rapamycin limits considerably the number of transformations that can be carried out on the parent molecule without resorting to protecting/masking protocols. Thus the reaction of rapamycin with base in hydroxylic solvents resulted in a complicated mixture of compounds arising from C_{22} carboxylate elimination, C_{13}-C_{14} benzilic acid rearrangement, C_{28}-C_{29} retroaldol reaction as well as a number of potential epimerizations. The β-acyloxy C_{24} ketone is indeed the most sensitive functionality under basic conditions. C_{21}-C_{22} ring cleavage readily took place with DBU in THF to afford the carboxylic acid **3**, but this reaction could be promoted even by mildly basic reagents (Et_3N or $NaHCO_3$ in MeOH).



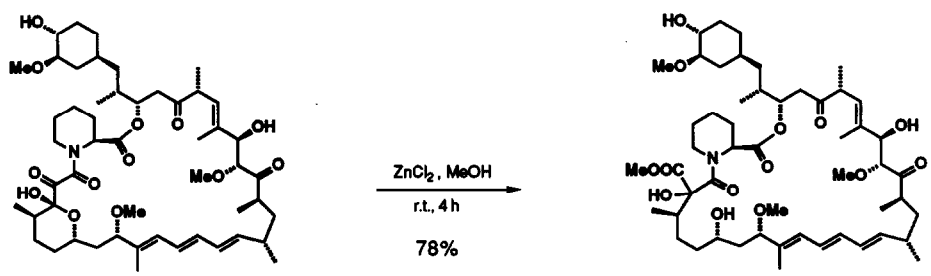
1 3

Because of the incompatibility of bases with the rapamycin molecule, we have explored the use of Lewis-acid catalysis as an alternative for reactions usually carried out under basic conditions, such as benzilic acid rearrangement or retroaldol cleavage. As described below, in the presence of Lewis-acid catalysts, rapamycin has been found to exhibit interesting reactivity that is quite sensitive on the solvent used in the reaction.

Benzilic Acid Rearrangement. Vicinal tricarbonyl compounds undergo facile benzilic acid rearrangement under basic conditions.[5] The rearrangement can also take place with strong acids at higher temperatures.[6] Recently, Danishefsky *et al.*[2h] have reported the rearrangement of FK506 under neutral conditions (methanol at reflux).

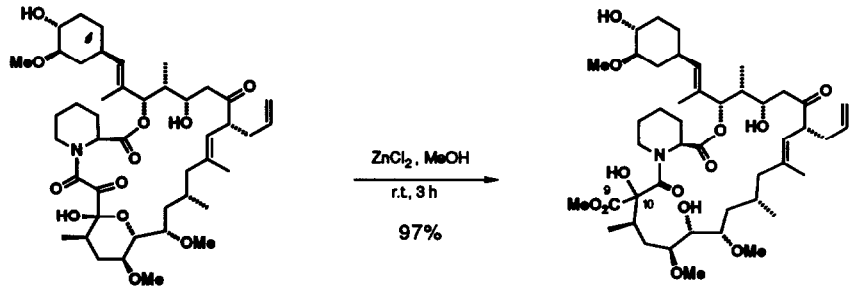
Since rapamycin is not stable in the presence of strong mineral acids,[4a] we tested the possibility of using milder Lewis-acid catalysis. A number of Lewis acids in methanol at room temperature were found to promote the benzilic acid rearrangement; the best result was obtained with $ZnCl_2$ (20 equiv, 4 h, 78% yield); with ZnI_2 or $MgCl_2$ the rearrangement seemed to be faster although not as clean, whereas with $ZnBr_2$, $NiCl_2$ or $Cu(OAc)_2$, it was quite slow. Interestingly, no rearrangement took place in methanol at room temperature in the presence of protic acids (HOAc or Dowex/H^+ resin), rapamycin being recovered unchanged.[7]

With all the Lewis acids examined, a separable mixture of methyl esters **4**, epimeric at C_{13}, was obtained in approximately a 1.3:1 ratio. Assignment of the structures of **4** was based on the ^{13}C-NMR upfield shifts of the C_{13} hemiketal (98.5 in **1** to 82.3 and 81.3 ppm for major and minor **4**) and the C_{14} carbonyl (192.5 in **1** to 172.9 and 171.9 for major and minor **4**, respectively).



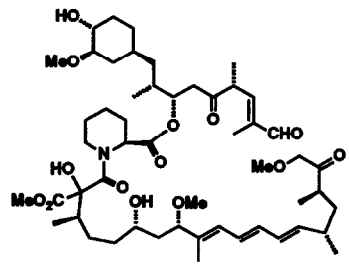
1 4

FK506 exhibited the same behavior as rapamycin. Thus the benzilic acid rearrangement took place readily at room temperature in the presence of $ZnCl_2$ (3 h, 97%); in this case, a single diastereomeric hydroxy ester **5** was obtained (^{13}C-NMR at 171.9 and 81.8 ppm for the rearranged C_9 and C_{10} in **5**). The same transformation in the absence of a Lewis-acid catalyst has been reported to require higher temperatures (3 h in methanol at reflux) and provides the same diastereomer **5**.[2h]



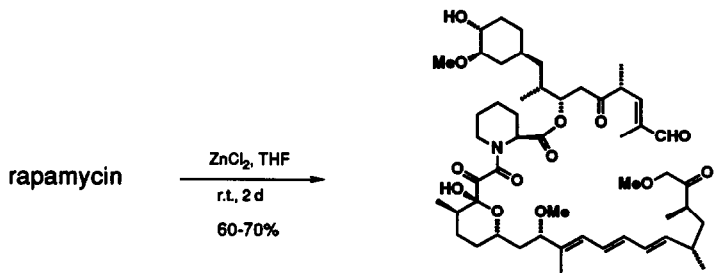
2 **5**

Retroaldol Fragmentation. Treatment of rapamycin with $ZnCl_2$/MeOH for extended periods resulted in formation of aldehydes **6**. These compounds arise from C_{28}-C_{29} retroaldol cleavage and were cleanly obtained when either of the two C_{13} epimeric benzilic-acid rearrangement products, **4**, was resubjected to the reaction conditions.



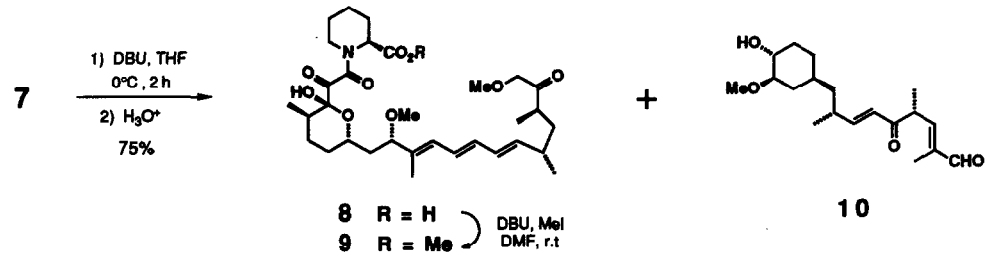
6

Exclusive C_{28}-C_{29} retroaldol fragmentation could be promoted with the same Lewis acid, $ZnCl_2$, by simply switching to THF as solvent (excess $ZnCl_2$, THF, r.t., 2 days) to afford the labile α,β-unsaturated aldehyde **7** in 60-70% isolated yield, without a trace of C_{13}-C_{14} rearrangement; $ZnCl_2$ and ZnI_2 proved to be equally effective in this case. Unlike rapamycin, FK-506 did not undergo retroaldol reaction and was recovered unchanged after treatment under these conditions.



7

Subsequent reaction of **7** with DBU leads to C_{21}-C_{22} fragmentation of rapamycin into compounds **8** and **10**, each containing suitable functionality for additional synthetic manipulations.



In summary, the unusual reactivity of rapamycin under mild Lewis-acid catalysis has been investigated. The chemistry allows efficient manipulation of the molecule without recourse to functional group protection-deprotection schemes. The rapamycin derivatives thus obtained should serve as valuable tools for synthetic and biological studies.

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7. Refluxing rapamycin in methanol gave irreproducible results. Although most times rapamycin was recovered unchanged, in a few cases some benzilic rearrangement, which could not be driven to completion, took place.

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