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A MECHANISTIC STUDY OF THE FK-506 TRICARBONYL SYSTEM REARRANGEMENT: SYNTHESIS OF C.9 LABELED FK-506

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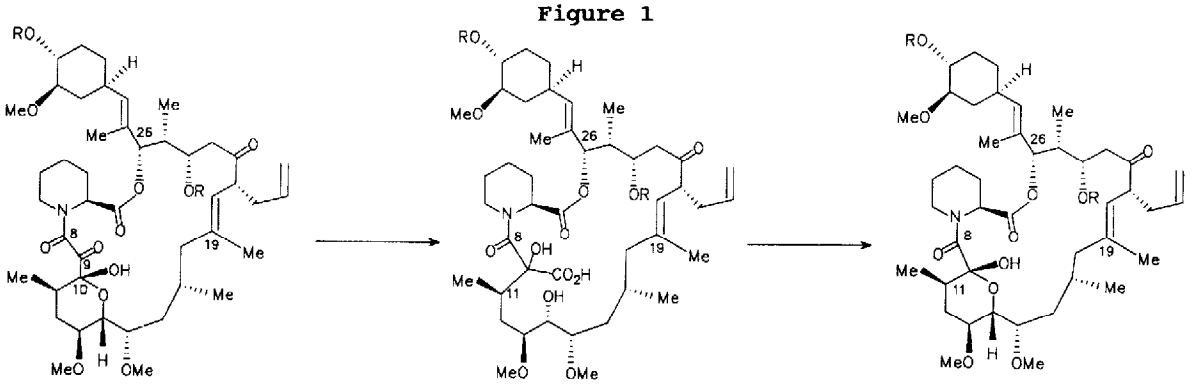
Abstract: Hydroxide mediated benzilic acid rearrangement of a C.9-^{13}C labeled FK-506 derivative gave 97% rearrangement thru a C.8→C.10 acyl shift mechanism.

Recently, we reported a facile hydroxide mediated benzilic acid rearrangement of the FK-506 tricarbonyl system[1]. Treatment of the bis-triisopropylsilyl (TIPS) ether derivative of FK-506 (1) with 1 equivalent of lithium hydroxide at 0°C afforded the rearranged hydroxy-acid 2 (**Figure 1**). Lead tetraacetate mediated decarboxylation then gave the nor-C.9-FK-506 derivative 3 in high overall yield. Due to the extremely facile nature of the rearrangement, coupled with the intriguing possibility that the reactive tricarbonyl system may be responsible for the remarkable biological activity of FK-506[2], we set out to investigate the nature of the bond reorganization.

Our original speculation concerning the rearrangement mechanism was in accord with similar bond reorganizations in naked, non-hemiketalized 1,2,3-tricarbonyl arrays[3]. Thus, initial addition of LiOH to the highly electrophilic C.9 ketone was thought to allow ring-chain tautomerization of the hemiketal linkage, exposing the ketone at C.10 to produce **A** (**Scheme 1**). A 1,2-acyl shift of C.8 to C.10 would then afford the hydroxy-acid **B**.

Figure 1



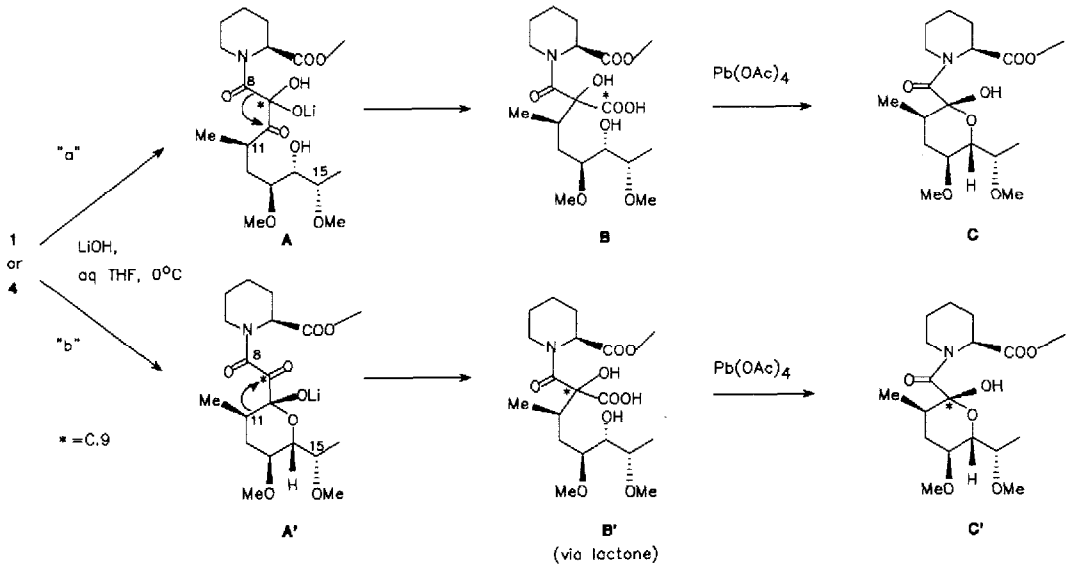
1 R=TIPS
4 R=TES
4* R=TES, C.9=^{13}C

2 R=TIPS
8* R=TES, C.9=^{13}C

3 R=TIPS
9 R=TES
10 R=H

Alternatively, a sequence could be envisaged whereby the alkoxide **A'** generated at C.10 by LiOH would suffer a 1,2-ketol shift[4] of C.11 to C.9, thereby affording an intermediate 7-membered lactone, which would presumably be saponified under the reaction conditions to **B'**. If the rearrangement proceeds thru the acyl shift mechanism "a", then decarboxylation of the intermediate hydroxy-acid **B** would result in the loss of the original C.9 carbonyl group as CO_2 to afford **C**. However, if the rearrangement proceeds thru the ketol shift mechanism "b", then decarboxylation would result in the net loss of the original C.10 hemiketal carbon as CO_2 to afford **C'**. Thus, a ^{13}C labeling experiment of either C.9 or C.10 would distinguish between these two possibilities.

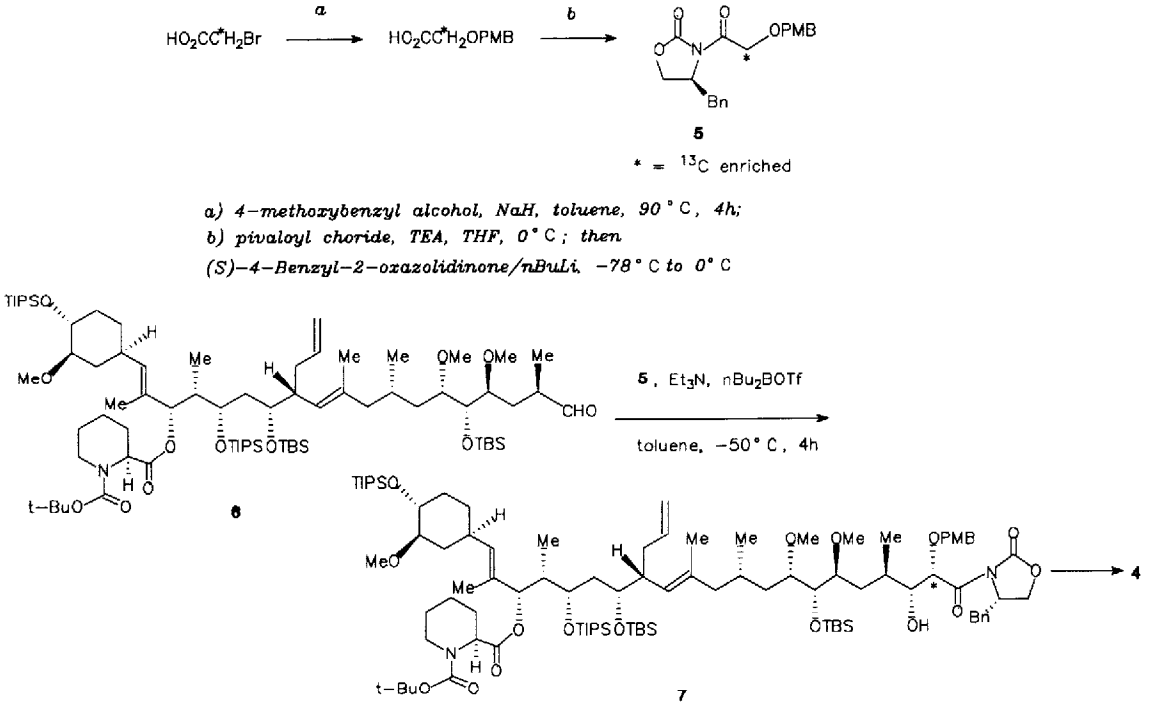
Scheme 1



Toward this end, the FK-506 derivative **4*** ^{13}C-labeled at C.9 was prepared. The bis-triethylsilyl (TES) synthetic intermediate was used for this work, since retroaldol decomposition of FK-506 under basic conditions[5] is effectively prohibited by a C.24 silyl ether protecting group[6]. The 99 atom % ^{13}C enriched imide **5** was synthesized as shown in **Figure 2**. Treatment of the labeled imide **5** with triethylamine and di-n-butylboron triflate followed by aldehyde **6**[7] gave the labeled aldol product **7** (90%). This compound was converted to the C.9-labeled FK-506 derivative **4*** as previously described[7].

Treatment of an admixture of 99 atom % **4*** (11.3 mg) and unlabeled **4**[8] (37.5 mg) with aqueous LiOH (1.08 equiv, THF, 0°C, overnight) followed by acidification with 0.1N citric acid and extractive workup gave the crude rearranged hydroxy acid **8*** (51.7 mg) labeled at the carboxylic acid group (δ_C 174, 171; minor, major rotamers respectively). The isomer of **8*** bearing the label at the quaternary carbon could not be observed at this point. Decarboxylation of the crude hydroxy acid **8*** with $Pb(OAc)_4$ then gave the nor-C.9 derivative **9** (39.6 mg, 83% from **4**) bearing a small amount of the original label at the hemiketal carbon. Integration of the hemiketal resonance (97 ppm) of **10** (obtained by desilylation of labeled **9**) vs. that of unlabeled **10** showed an approximately 60% enhancement of the hemiketal carbon integral from the labeled experiment.[9] This indicates that approximately 3% of the original label is present at the hemiketal carbon[10], implying 3% of rearrangement by the unexpected ketol shift mechanism "b". Thus the major pathway of the rearrangement appears to be thru the acyl shift mechanism "a", verifying our expectation.

Figure 2



References and Notes

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2) (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. **J. Antibiot. 1987**, 1249. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. **J. Antibot. 1987**, 1256.

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4) See, for example: Danheiser, R.L. in "Strategies and Tactics in Organic Synthesis", Thomas Lindberg, ed., Academic Press, Inc. **1984**, p. 54.

5) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. **J. Am. Chem. Soc., 1987**, 109, 5031.

6) Attempts to carry out the rearrangement on FK-506 directly (1 equiv. LiOH, THF, 0°C) did not give clean benzilic acid rearrangement.

7) Jones, T.K.; Mills, S.; Reamer, R.A.; Askin, D.; Desmond, R.; Volante, R.P.; Shinkai, I. **J. Am. Chem. Soc. 1989**, 111, 1157.

8) Prepared by triethylsilylation (TESOTf, 2,6-lutidine, CH_2Cl_2, 25°C) of natural FK-506.

9) To eliminate relaxation effects from nearby protons, a quantitative ^{13}C spectrum was obtained using the inverse gated technique, with a recycle delay of 60 seconds.

10) The enriched starting admixture is 23 atom % ^{13}C at C.9, a 21 fold (2100%) enrichment of the natural abundance (1.1%). Since the observed enhancement of the hemiketal carbon is 60%, this means that about 3% of original label remains.

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