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CHEMISTRY OF FK-506: BENZILIC ACID REARRANGEMENT OF THE TRICARBONYL SYSTEM

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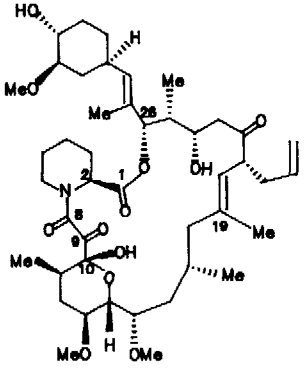
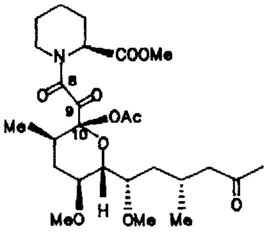
Abstract: Treatment of FK-506 with aqueous hydroxide results in a benzilic acid rearrangement of the C.8-C.10 tricarbonyl portion of the molecule. A corrected structure for a previously reported degradation product as well as oxidative decarboxylation of rearranged FK-506 is presented.

During the course of our ongoing synthetic studies[1] on FK-506[2] (1), we had occasion to investigate the feasibility of macrolactone hydrolysis via cleavage of the pipecolinic ester bond of the natural material. The availability of the resulting hydroxy-acid would have facilitated a study of macrolactonization for our synthetic efforts. The stability of the unusual tricarbonyl array of FK-506 (C.8-C.10) during hydroxide hydrolysis was suggested by Tanaka and co-workers in their original structural work,[2] wherein a fragment with the structure 2 was reported to have been isolated after successive treatment of FK-506 with: 1N NaOH in dioxane; CH_2N_2; acetic anhydride/pyridine; and ozone.

Herein, we wish to disclose the following: 1) a facile hydroxide-promoted benzilic acid rearrangement of the FK-506 tricarbonyl system; 2) a revised structural assignment, 3, for the above mentioned fragment based on ^1H, ^{13}C and 2-D NMR experiments, and 3) the synthesis of a novel decarbonylated 22-membered macrocyclic FK-506 derivative.



1



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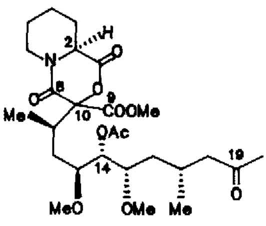
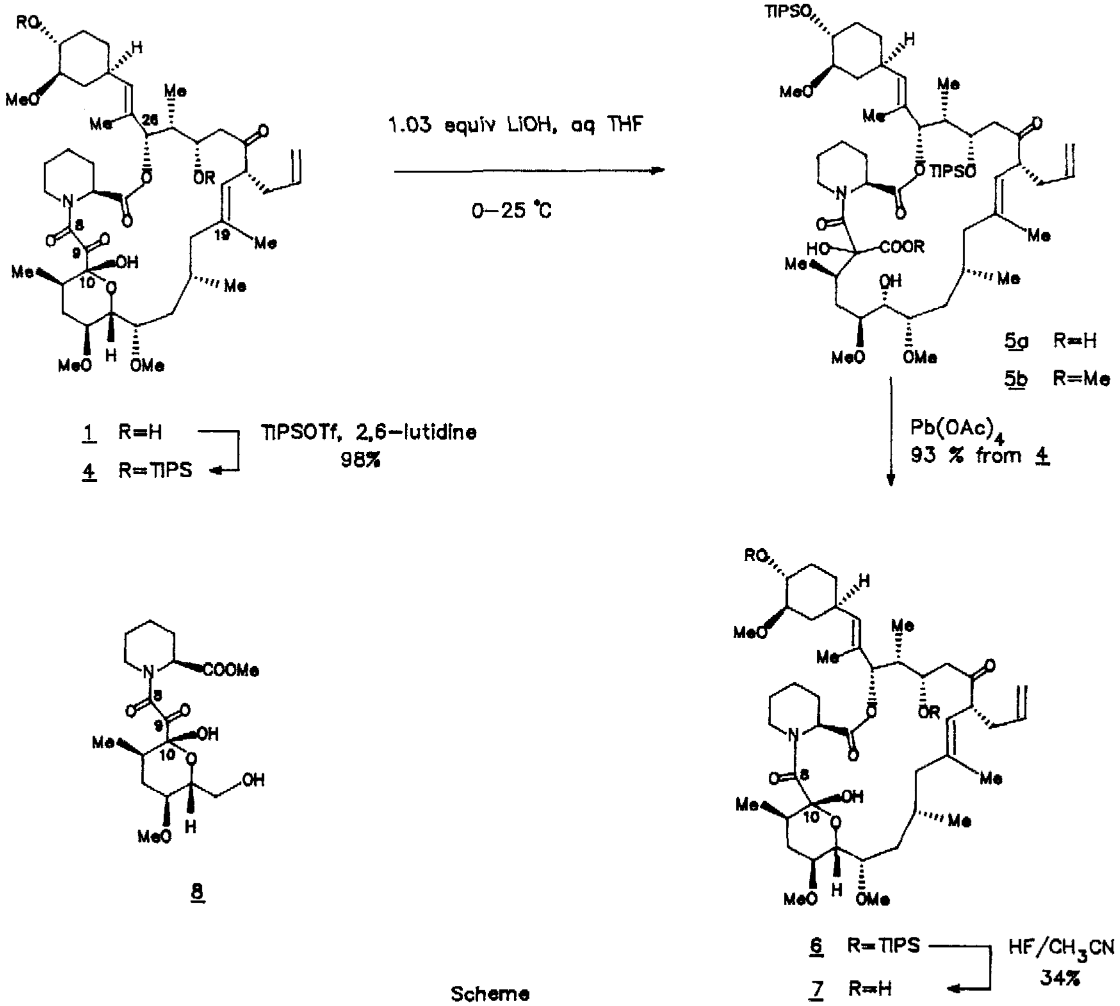


3

Treatment of 1 with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf, 4 equiv, excess 2,6-lutidine, CH_2Cl_2, 25°C) afforded bis-TIPS ether 4 in 98% yield[3] (see Scheme). Exposure of 4 to lithium hydroxide (1.03 equiv, aq. THF, 0-25°C, 5 h) followed by acidification and extractive isolation resulted in complete consumption of starting material and formation of a hydroxy-acid.[4] The presence of a carboxylic acid was indicated by isolation of ester 5b[5] upon treatment with diazomethane. Comparison of the ^{13}C NMR spectrum of the acid with FK-506 and related compounds (vide infra) revealed that a rearrangement of the tricarbonyl linkage had occurred. The characteristic resonance of C.9 (see Table) at 196 ppm (major rotamer of 1 and 4) was absent and a new carbonyl resonance appeared at 173.1 ppm (only observed signal assignable to C.9). Additionally, the C.10 resonance at 97 ppm (major rotamer of 1 and 4)



Scheme

was shifted upfield to 82.4 ppm. The reported tendency of vicinal polyketones to undergo a facile hydroxide induced 1,2-acyl migration,[6] led us to interpret these new signals as arising from nucleophilic addition by LiOH to the C.9 ketone, C.10 hemiketal opening and migration of C.8 to C.10 to give 5a, rather than the desired open-chain hydroxy-acid. Furthermore, oxidation of 5a with lead tetraacetate[7] (1.0 equiv, benzene, 25°C) resulted in clean decarboxylation to produce bis-TIPS ether 6 (93% overall yield from 4). Desilylation (95:5(v/v) CH_3CN:48% aq HF, 25°C) then afforded des-C.9-FK-506 (7), which appeared to exist as a single entity by ^1H and ^{13}C NMR analysis[8].

Table. Selected ^{13}C NMR Chemical Shift Data for FK-506 and Related Compounds.

^{13}C Chemical Shifts for the C.8-C.10 Portion of FK-506 and Related Compounds (Major, Minor Rotamer Values in ppm in $CDCl_3$)

	1	3	4	5a	7	8[13a]
C.8	164.6, 165.8	161.3	164.5, 166.1	170.8	169.7	166.5
C.9	196.1, 192.5	167.4	196.5, 192.0	173.1	--	197.4
C.10	97.0, 98.6	89.3	97.7, 98.8	82.4	97.7	98.9

Repetition of the reported degradation protocol[2] of FK-506 gave a methyl ester monoacetate species that was spectroscopically identical to that described by Tanaka and co-workers. However, extensive ^1H and ^{13}C NMR investigations support the structure of the degradation product to be the rearranged pyridooxazinedione 3,[9] and not the originally proposed tricarbonyl fragment 2. In addition to the ^{13}C NMR data shown in the Table, indicating the loss of the C.9 ketone with formation of an ester carbonyl, the ^1H NMR spectrum showed a doublet of doublets at 5.00 ppm (J = 6.4, 3.9 Hz) that was unequivocally assigned to 14-H (COSY-45 experiment[10]) implying acylation of C.14 oxygen, not at C.10 oxygen. Two different ^{13}C 2-D NMR experiments were also performed to verify the positions of the acetoxy moiety at C.14. A COLOC experiment[11] (COrrelation of LOng range coupling Constants) was performed to assign the acetate carbonyl (170.4 ppm), the C.19 ketone (208.1 ppm), and the methyl ester carbonyl (167.4 ppm). A SELJRES[12] (heteronuclear SELective-J-RESolved) experiment was then used to establish spin-spin coupling between the C.14 methine proton and the acetate carbonyl (^3J = 5.0 Hz), confirming the C.14 acetoxy group. Evidence for formation of the pyridooxazinedione ring in 3 comes from comparison of ^1H NMR data for the pipecolinic acid ring protons, particularly 2-H. In 1, 2-H appears as a broad doublet, the only resolved splitting a 4.5 Hz spin-spin coupling to 3-H_{ax}, thus defining 2-H as equatorial with C.1 axial. In 3, C.1 is constrained to an equatorial orientation and 2-H is now axial as evidenced by spin-spin coupling to both

C.3 methylene protons [$^3J_{2,3}$ = 11.9 Hz (axial, axial), 3.4 Hz (axial, equatorial)]. Further support comes from NOE difference experiments on **3** where a 4% NOE is observed from 6-H_{ax} to 2-H (1,3 diaxial orientation). Compound **3** appears to be >85% isomerically pure; however, the stereochemistry at C.10 is currently unknown.

Further confirmation of the inconsistency of structure **2** with spectral data was gained from synthetic fragment **8**.[13] Comparison of the ^{13}C chemical shifts (see Table) of **8**[13a] with **1** and **4** revealed similar chemical shifts for C.8, C.9 and C.10. The degradation product **3** however, exhibits radically different resonances for C.9 and C.10. Further degradative studies on FK-506 are in progress and will be reported in due course.

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3. All new compounds gave satisfactory ^1H and ^{13}C NMR, mass spectral and IR data.
4. Selected IR data for **5a** ($CHCl_3$): 3600s, 3500-3000b, 1770, 1735, 1710, 1630 cm^{-1}.
5. Selected IR data for **5b** ($CHCl_3$): 1735, 1705, 1640 cm^{-1}.
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8. (a) NMR assignments for **7**, ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_c 9.8(C.25a), 13.7(C.27a), 14.8(C.19a), 15.8(C.11a), 20.1(C.17a), 21.1(C.4), 25.6(C.17,C.5), 28.5(C.3), 30.6(C.34), 31.3(C.33), 32.3(C.12), 33.0(C.16), 34.8(C.30), 35.0(C.29), 35.7(C.21a), 37.2(C.11), 42.0(C.6), 42.2(C.25), 47.6(C.23), 49.3(C.18), 52.0(C.21), 56.9(C.2), 55.9, 56.5, 57.9, (3 x OCH_3), 69.9 (C.24), 73.1(C.14), 73.5(C.13), 73.6(C.32), 76.0(C.15), 78.1(C.26), 84.2(C.31), 97.7(C.10), 116.3(C.21c), 123.3(C.20), 130.5(C.28), 132.5(C.27), 135.8(C.21b), 139.3(C.19), 169.7(C.8), 169.8(C.1), 213.0(C.22). (b) Exact mass calcd for $C_{43}H_{69}NO_{11}$ 775.4871, found 775.4868
9. NMR assignments for **3**, ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_c 14.9 (C.11a), 20.3 (C.17a), 21.0 ($OC(=O)CH_3$), 23.2 (C.4), 23.9 (C.5), 25.7 (C.17) 30.1 ($O-CCH_3$), 30.9 (C.3), 31.9 (C.12), 35.5 (C.11), 36.9 (C.16), 42.8 (C.6) 50.8 (C.18), 53.7 (ester-OCH_3), 56.1 (C.2), 56.9, 58.0 (2 x OCH_3), 74.8 (C.14), 77.4 (C.15), 78.2 (C.13), 89.3 (C.10), 161.3 (C.8), 166.6 (C.1), 167.4 (C.9), 170.4 (acetate C=O), 208.1 (C.19).
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