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A Novel Application of the Dess-Martin Reagent to the Synthesis of an FK506 Analogue and other Tricarbonyl Compounds

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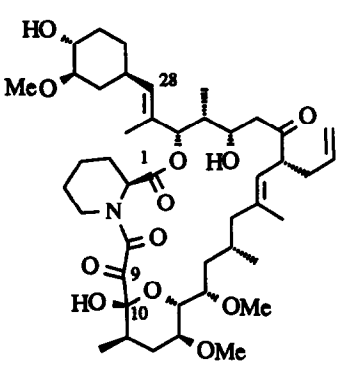
Abstract: The use of the Dess-Martin reagent for the oxidation of β-hydroxy and β-ketoamides, esters and ketones to the corresponding tricarbonyl compounds is reported. The method is shown to be applicable to the synthesis of analogues of the immunosuppressant FK506.

Exciting developments[1] concerning the immunosuppressant activities of FK506[2] **1** and rapamycin[3] **2** have promoted the recognition of striking similarities in the structures of these two mould metabolites. We now wish to report upon the discovery of a new synthetic methodology which we have used to make a structural analogue of FK506. It may also be applicable to the synthesis of rapamycin.



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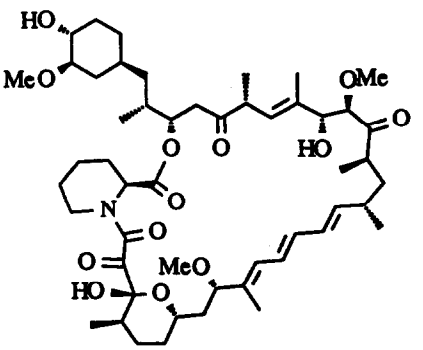

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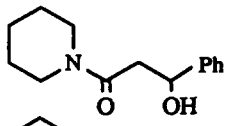
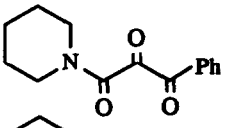
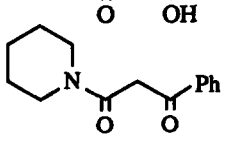
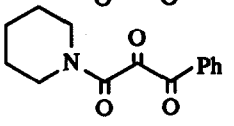
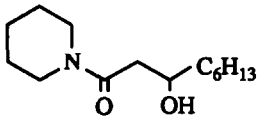
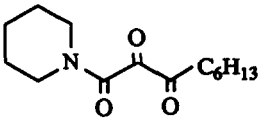
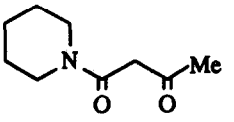
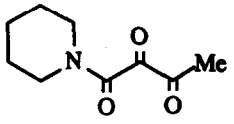
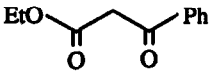
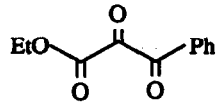
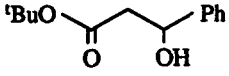
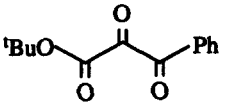
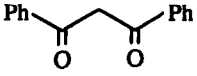
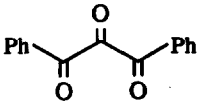
A common feature of both FK506 **1** and rapamycin **2** is the unusual masked α,β-diketoamide system (C_8-C_{10}). The total synthesis of FK506 has been described by two groups[4]. In both syntheses the tricarbonyl group was generated by an aldol addition of a protected α-hydroxyamide or ester to an aldehyde which constituted C_{10}. This protocol resulted in the need for selective deprotection of C_9-OH and stepwise

oxidation of the resulting hydroxyl groups. Much work has also been published describing simpler alternative methods for the synthesis of the tricarbonyl segment[5], but so far none of them have been utilised in the total synthesis of FK506 or structural analogues.

Table 1 Oxidation of β-Hydroxycarbonyl and β- Dicarbonyl compounds

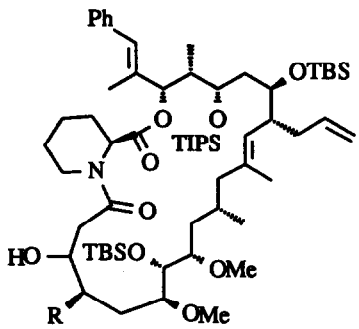
Entry	Substrate	Equiv. DMP[g] (Time)	Product[a,c]	Yield[b] (%)	Note
1		4 (2.5h)		74	
2		2 (1h)		75	
3		3 (2h)		52	
4		2 (1.25h)		56	
5		2 (0.75h)		80	d
6		4 (2h)		73	e
7		1.5 (1h)		57	f

(a) All products gave satisfactory ^{1}H and ^{13}C NMR, IR, and MS data; (b) yields were calculated based on the tricarbonyl form of the product and not optimised; (c) products were isolated as mixtures with their hydrates; (d) Ref. 8; (e) Ref. 6; (f) Benzil (18%) also isolated-Ref. 9; (g) 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(*1H*)-one.

Schank[6] reported that ozonolysis of the ylide formed by the reaction of iodosobenzene diacetate {I(III)-reagent} with β-diketones, β-ketoesters, and β-ketoamides gave the corresponding tricarbonyl

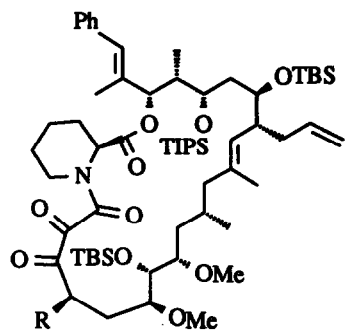
compounds. It occurred to us that the Dess-Martin periodinane reagent (DMP)[7] {I(V)-reagent} might convert β-dicarbonyl and β-hydroxycarbonyl compounds to tricarbonyl compounds in one step. Similar direct transformations can be effected by selenium dioxide, but its lack of selectivity means that it is unlikely to be a useful reagent in FK506 synthetic studies.

β-Diketones, β-ketoamides, and β-ketoesters were treated (Table 1) with 1.5-2.0 equivalents of the Dess-Martin reagent in a methylene chloride solution containing 3-4 equivalents of pyridine. For the oxidation of the β-hydroxy compounds we used 3-4 equivalents of the Dess-Martin reagent and 6-8 equivalents of pyridine. Reactions were complete in 0.75-2.5h. at room temperature. Workup involved the addition of a mixture of aqueous sodium thiosulphate and sodium bicarbonate, followed by solvent extraction, removal of pyridine from the extract with aqueous copper sulphate, and purification (flash chromatography) to give the products as mixtures with their hydrates.



3a R=H

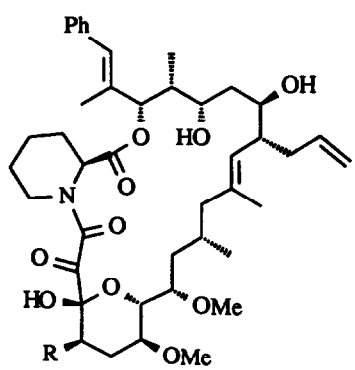
3b R=Me



4a R=H

4b R=Me

TBS= t-butyldimethylsilyl
TIPS= triisopropylsilyl



5a R=H

5b R=Me

Having shown that β-hydroxyamides (Table 1 entries 1 and 3) are converted in good yield into their corresponding tricarbonyl derivatives in one step, we were ready to apply the methodology to the total synthesis of FK506 analogues. To this end we prepared the macrocyclic β-hydroxyamides **3a** and **3b**[10]. These compounds differed from substrates for a total synthesis of FK506 only in that the C_{28}-cyclohexyl substituent had been replaced by a phenyl group in compound **3b**, and in addition, in compound **3a** the C_{11}

methyl substituent had been replaced by hydrogen.

The compounds **3a** and **3b** were treated with 5 equivalents of the Dess-Martin reagent and 10 equivalents of pyridine during 2h yielding the tricarbonyl compounds **4a** (59%) and **4b** (78%). Compounds **4a** and **4b** were treated with hydrofluoric acid in acetonitrile at room temperature for 17h to give compounds **5a** and **5b**[11]. All four tricarbonyl compounds **4a**, **4b**, **5a**, and **5b** showed appropriate carbonyl derived signals[12] in the ^{13}C NMR spectra comparable to those reported for analogous compounds[4].

Notes and References

1. For a recent review see Schreiber, S. L.; Liu, J.; Albers, M. W.; Rosen, M. K.; Standaert, R. F.; Wandless, T. J.; Somers, P. K. *Tetrahedron* **1992**, *48*, 2545.
2. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031.
3. Sehgal, S. N.; Baker, H.; Vézina, C. *J. Antibiot.* **1975**, *28*, 727. Vézina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721.
4. Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157. Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.
5. Hoffman, R. V.; Huizenga, D. J. *J. Org. Chem.* **1991**, *56*, 6435. Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785. Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 11. Linde II, R. G.; Jeroncic, L. O.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 2534. Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Manners, A. *Tetrahedron Lett.* **1988**, *29*, 4481. Rao, A. V. R.; Chakraborty, T. K.; Reddy, K. L. *Tetrahedron Lett.* **1990**, *31*, 1439. Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4644. See these papers for general references to tricarbonyl systems.
6. Schank, K.; Lick, C. *Synthesis* **1983**, 382.
7. For leading references and notes on safety see Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
8. Dayer, F.; Lê Dao, H.; Gold, H.; Rodé-Gowal, H.; Dahn, H. *Helv. Chim. Acta.* **1974**, *57*, 2201. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Marini, F. *J. Org. Chem.* **1991**, *56*, 5207.
9. Rubin, M. B. *Chem. Rev.* **1975**, *75*, 177.
10. The synthesis of compounds **3a** and **3b** will be reported in full elsewhere.
11. Compounds **5a** and **5b** showed ^{1}H NMR, ^{13}C NMR, and mass spectra in accordance with the reported structures.
12. Compound **4a** ^{13}C NMR ($CDCl_3$) 165.0 (C_8), 186.0 (C_9), 197.7 (C_{10}), 168.9 (C_1); compound **4b** ^{13}C NMR ($CDCl_3$) 165.6 (C_8), 185.8 (C_9), 199.2 (C_{10}), 168.9 (C_1); compound **5a** ^{13}C NMR ($CDCl_3$) 165.0 (C_8), 197.3 (C_9), 95.7 (C_{10}), 169.1 (C_1); compound **5b** ^{13}C NMR ($CDCl_3$) 165.9 (C_8), 199.6 (C_9), 98.8 (C_{10}), 169.3 (C_1). Where rotamers and hydrates are present the major signals are given. Assignments refer to FK506 **1** numbering.

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