Synthesis of the "Tricarbonyl" Region of FK-506 through an Amidophosphorane

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Summary: A protected C_1–C_{15} segment of FK-506 has been prepared by coupling of the acid chloride **4** with the ylide amide **3** derived from (–)-pipecolinic acid. A method for the conversion of this unit to the vicinal diketo amide **6** and to the corresponding hemiketals **7** and **8** is outlined.

Sir: Current interest in the macrocyclic lactone FK-506, the potent immunosuppressant isolated from *Streptomyces tsukubaensis*,[1] has prompted extensive work directed toward the synthesis of this substance and analogous systems.[2,3] Particular attention[4,5] has been directed toward the formation of the unusual 1,2,3-tricarbonyl fragment incorporated in FK-506 and the related antifungal antibiotics rapamycin[6] and 29-demethoxyrapamycin.[7]

In the course of recent studies on the chemistry of vicinal tricarbonyl systems, we have explored methods for the formation of these highly electrophilic structural units.[8] Of the methods available, we have found one sequence to be of special interest because of its general applicability. As shown in Scheme I, this procedure involves the coupling of an activated acid with an acylphosphoranylidene in the presence of bis(trimethylsilyl)acetamide (BSA) to form a keto ylide carboxylate.[9] Keto ylide carboxylates are stable entities in a variety of synthetic operations and may then be oxidized with ozone or singlet oxygen to generate the tricarbonyl system. We have now applied this procedure to the formation of the C_1–C_{15} α,β-diketo amide subunit of FK-506 (outlined in Figure 1) recently synthesized in the Indiana laboratories.[4] Our method, notable for its simplicity, leads to vicinal tricarbonyl units in excellent yields, thus providing a useful route to the α,β-diketo amide system present in FK-506 and related compounds of biological interest.[10]

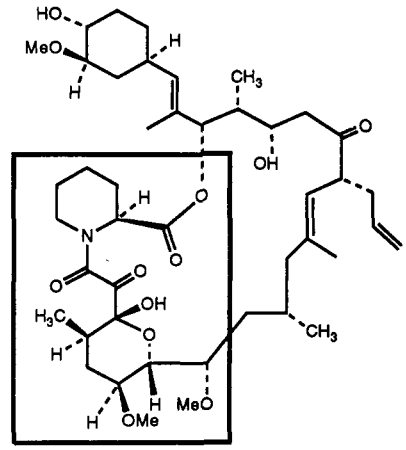
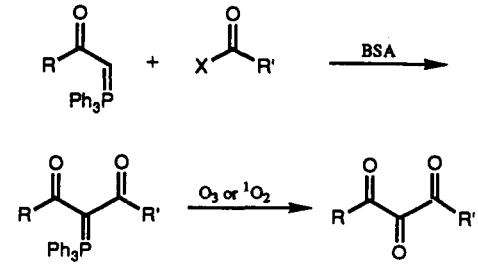
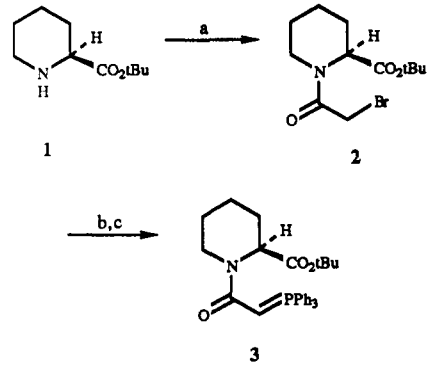


Figure 1.

Scheme I



Scheme II[a]



[a] (a) $BrCH_2CO_2H$, DCC (99%); (b) Ph_3P (97%); (c) NaOH(aq) (99%).

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(10) In model studies we have found that trisubstituted olefins undergo reaction with singlet oxygen at rates competitive with the oxidation of keto ylide carboxylates, providing a possible limitation of this method in FK-506 synthesis.

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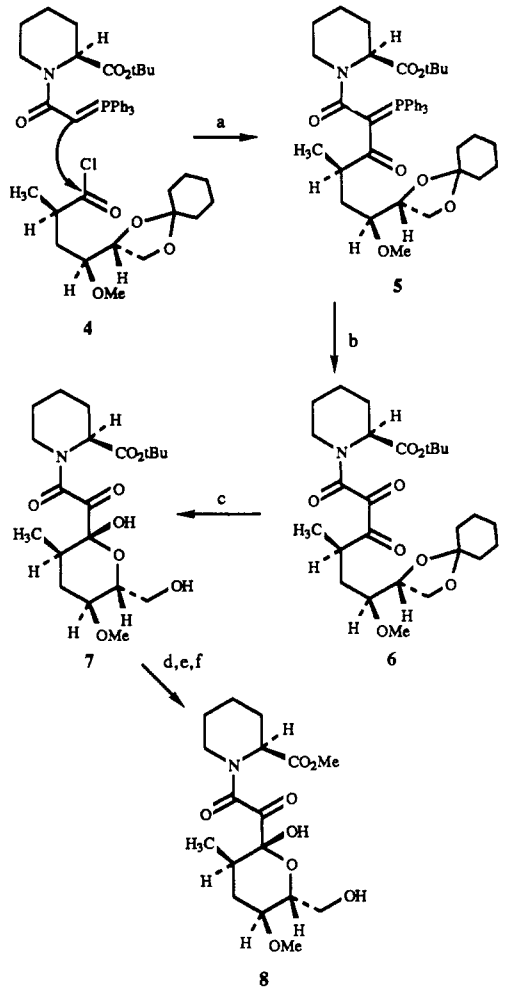
Scheme III[a]



[a] (a) BSA (91%); (b) $^1O_2$ (69%) or O_3 (88%); (c) MeOH/HCl(dil) (100%); (d) HCOOH; (e) CH_2N_2; (f) MeOH/HCl(dil) (83% from 7).

Our synthesis began (Scheme II) with the *tert*-butyl ester of (−)-pipecolinic acid **1**,[5b] which was coupled with α-bromoacetic acid (DCC) to give the bromoacetyl derivative **2**. Treatment of **2** in benzene with triphenylphosphine gave the phosphonium salt, which was then deprotonated with dilute NaOH to give the ylide **3**. Compound **3** was reacted directly with the Williams' acid chloride **4**[4] in the presence of BSA to yield the keto ylide intermediate **5** (Scheme III).[9] Oxidative cleavage of **5** using either ozone or singlet oxygen yielded the α,β-diketo amide **6**[11] after removal of triphenylphosphine oxide by chromatography. The tricarbonyl **6** was then readily converted in dilute acidic methanol to the hemiketal **7**.

Compound **7** shows spectroscopic properties[12] that are in full accord with the assigned structure. For comparison with the Williams end product **8**, the *tert*-butyl ester **7** was converted to the methyl ester. This was accomplished by cleavage of the *tert*-butyl group in formic acid, followed by methylation of the free carboxyl with diazomethane.[13,14] The methyl ester **8** prepared in this way is completely identical (NMR, IR) to the keto amide ester synthesized by an independent route and fully characterized in an earlier communication.[4]

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Supplementary Material Available: Experimental data for **2**, **5**, **6**, and **7** (2 pages). Ordering information is given on any current masthead page.

(11) Tricarbonyl **6** was determined to be in the unhydrated form by NMR and IR spectroscopy.

(12) ^1H NMR (FK-506 numbering) (500MHz, $CDCl_3$) δ 5.09 (br d, 1 H, J = 5 Hz, C_2H), 3.84 (t of d, 1 H, J = 11 Hz, 2.5 Hz, $C_{15}H$), 3.77 (m, 1 H, $C_{15}H$), 3.75 (br s, 1 H, $C_{10}OH$), 3.65 (m, 1 H, $C_{14}H$), 3.53 (m, 1 H, $C_{13}H$), 3.38 (s, 3 H, $C_{13}OCH_3$), 3.35 (m, 1 H, C_6H), 3.27 (t of d, 1 H, J = 13 Hz, 3 Hz, C_6H), 3.10 (d of d, 1 H, J = 11 Hz, 2 Hz, $C_{15}OH$), 2.36 (m, 1 H, $C_{11}H$), 2.24 (br d, 1 H, J = 13 Hz, C_3H), 2.02 (m, 1 H, $C_{12}H$), 1.79–1.30 (m, 6 H, C_3H, C_4H_2, C_5H_2, $C_{12}H$), 1.47 (s, 9 H, $C_{10}OtBu$), 0.88 (d, 3 H, J = 6 Hz, $C_{11}CH_3$).

(13) Egbertson, M. Ph.D. Dissertation, Yale University, 1989.

(14) Any formate generated at the site of the primary hydroxyl was hydrolyzed with dilute methanolic HCl.