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Facile Synthesis of the "Tricarbonyl" Subunit in the Immunosuppressant Rapamycin

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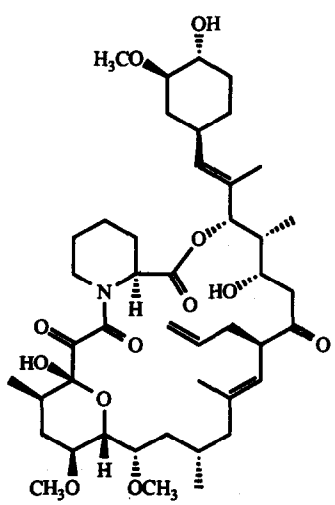
Abstract: *A concise synthetic route to the tricarbonyl subunit (3a) in the immunosuppressant rapamycin (2), based on ruthenium-catalysed oxidation of an acetylenic amide precursor (17) is described, viz (17) → (18) → (20).*

The exciting and potent immunosuppressant activities of the macrocyclic lactones FK 506 (**1**) and rapamycin (**2**), isolated from *Streptomyces sp*,[1] have provided the impetus for extensive researches towards the synthesis of these substances, their hybrids, and several analogous systems. At this time however, only two total syntheses of FK 506 (**1**) have been disclosed,[2] and comparatively little synthetic work on rapamycin (**2**) has been reported.[3] A structural feature that FK 506 and rapamycin have in common is the unusual amide-dione ("tricarbonyl") subunit (**3**). This subunit has at various times featured prominently as one of ***the*** key structural units in FK 506 and rapamycin responsible for their profound biological activities.[4]



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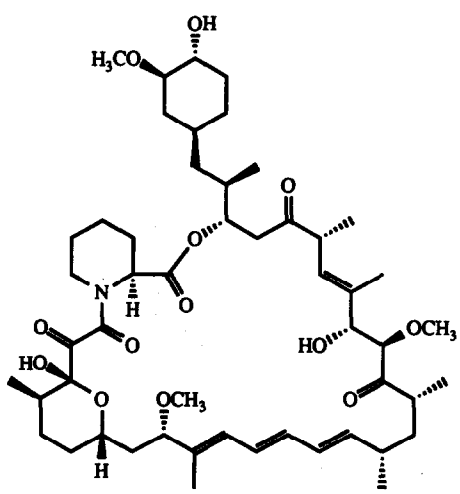
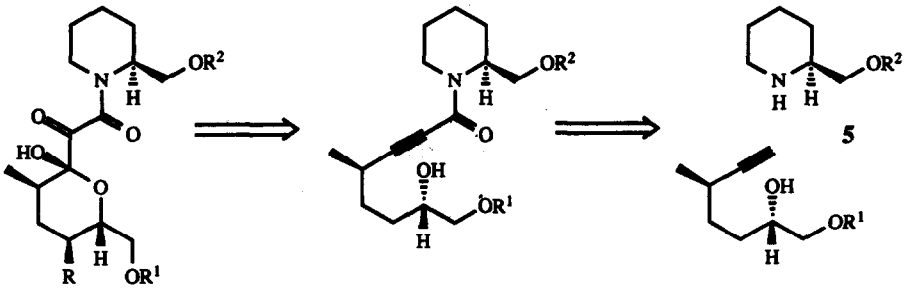


2

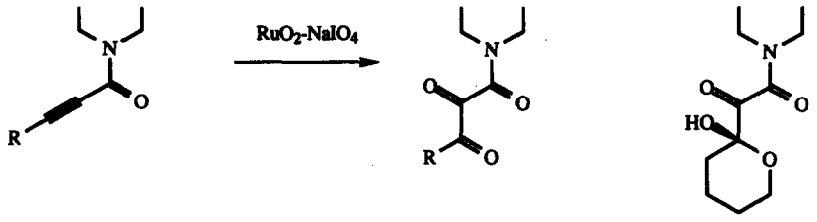
A substantial body of research has been published describing some ingenious synthetic approaches towards the tricarbonyl subunits (**3**) in FK 506 and rapamycin.[5] In this *Letter* we outline a new and concise route to the fully functionalised tricarbonyl subunit (**3a**) in rapamycin (**2**) which has as its focus, the straightforward oxidation of an acetylenic amide (**4**) produced from the piperidine (**5**) and the substituted acetylene (**6**).



3 4 6

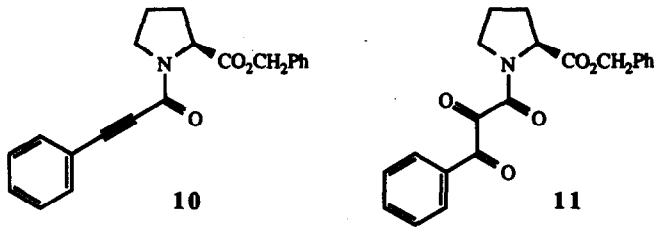
a, R=H; *b*, R=OMe

Although the oxidation of disubstituted acetylenes to α-diketones, using a range of reagents, is precedented,[6] no studies of the corresponding oxidations of deactivated acetylenic derivatives, *e.g.* (**4**), have hitherto been described. We therefore began our investigations by first examining the oxidations of a series of simple acetylenic amides *viz* (**7**) and (**10**) derived from diethylamine and proline.[7,8] A wide range of oxidants including osmium tetroxide and peroxyacids was studied.[6] Eventually we settled on the use of ruthenium tetroxide, which was generated *in situ* from a catalytic quantity of RuO_2 and $NaIO_4$,[9] as the most effective reagent. This method led to the corresponding amide-diones (**8**) and (**11**), as bright yellow-orange oils, in yields of 25-35%.[10] In the case of (**8***c*), deprotection by hydrogenolysis [$Pd(OH)_2$-C, H_2] led to the cyclic hemiacetal (**9**) [*cf.* structure (**3**)].



7 8 9

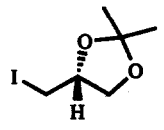
a, R=Ph; *b*, R=C_4H_9; *c*, R=$BnOC_4H_8$



10 11

We next examined a synthesis of the protected acetylenic diol (**16**) for coupling to the piperidine (**5**), on route to the tricarbonyl unit (**3**) in rapamycin (**2**). Thus, radical-initiated addition of the iodide (**12**) derived from the corresponding commercially available carbinol, to methyl methacrylate (Bu_3SnCl-$NaBH_4$, hν, 20°C)[11] first produced a 1:1 mixture of diastereoisomers of the adduct (**13***a*, 55%). After conversion of (**13***a*) into the corresponding aldehyde (**13***b*) (DIBAL-THF, then PCC-NaOAc) a Wittig reaction with dibromomethylene-triphenylphosphoranylide[12] then produced the dibromide (**14**, 76%), precursor to the terminal acetylene (**15**, 95%) (BuLi-THF, -70°C). Exchange of the ketal protective groups in (**15**) for TBS (HCl-MeOH, then TBSCl,

Im, DMF) followed by metallation and carboxylation (BuLi-HMPA, CO_2, -50°C) of the resulting acetylene (**16***a*) next led to the substituted acetylenic acid (**16***b*, 86%). A coupling reaction between the acid (**16***b*) and the piperidine (**5**, R^2=Me) in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, then produced the corresponding acetylenic amide (**17**, 86%). Exposure of (**17**) to catalytic RuO_4 finally led to the amide dione ("tricarbonyl") (**18**, 35%) which was obtained as a mixture of diastereoisomers and rotamers in the form of a bright yellow oil. When the amide dione (**18**) was treated with HF in acetonitrile, work up produced the cyclic hemi-acetal (**3***a*, R^1=H) as a 1:1 mixture of diastereoisomers (**19**) and (**20**) which could be separated cleanly by chromatography. The constitutions of the diastereoisomers (**19**) and (**20**) were established from n.m.r. data and comparison with corresponding data reported for rapamycin[13] and related subunits synthesised in approaches towards FK 506.[14,15]



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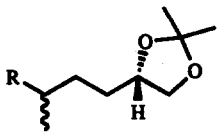
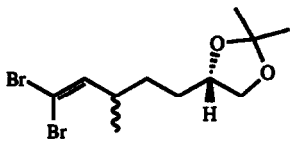


13

a, R=CO_2Me; *b*, R=CHO



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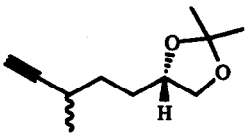

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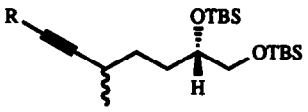
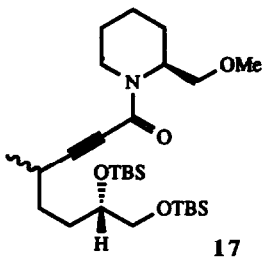
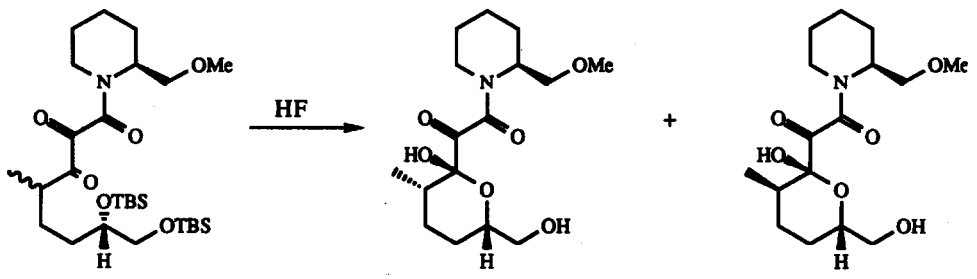


16

a, R=H; *b* R=CO_2H



17



18 **19** **20**

Acknowledgements

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