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STUDIES DIRECTED TOWARDS THE SYNTHESIS OF IMMUNOSUPPRESSIVE AGENT FK-506 : CONSTRUCTION OF THE TRICARBONYL MOIETY

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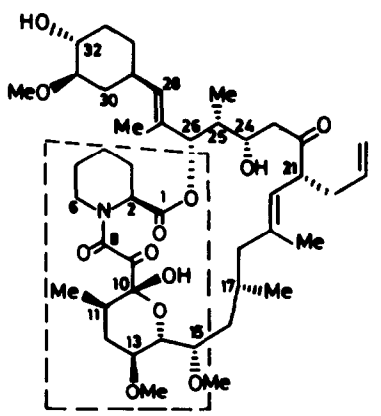
Abstract: Alkylation of a suitably functionalised dithiane precursor with L-N-(α-haloacetyl)-pipecolic acid methyl ester, followed by oxidation of the active methylene group provided an easy route to 1,2,3-tricarbonyl functionality of FK-506.

In the continuing search for new immunosuppressive agents no other compound has evoked so much interest as it has been done by FK-506[1] (1) in the recent years. FK-506 inhibited production and expression of IL-2 at concentration 100 times lower than that of cyclosporin[2]. The presence of tricarbonyl moiety is one of the most characteristic structural features associated with this novel 23-membered macrolide lactone isolated from Streptomyces tsukubaensis and related compounds like Rapamycin[3](2). This unique structural backbone coupled with vast array of stereogenic centers has drawn considerable attention recently[4].



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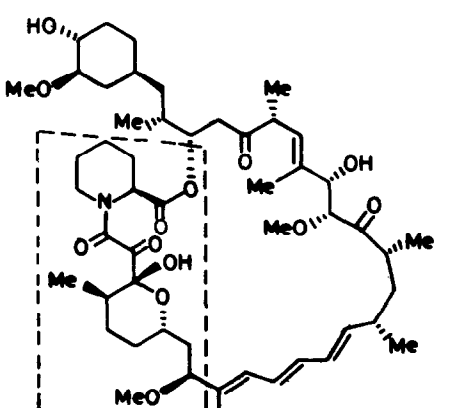

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Focussing our attention on the tricarbonyl region of the molecule we envisaged that the best way to achieve its construction is to have first a suitably functionalized 1,3-dicarbonyl precursor whose active methylene group can then be utilized to incorporate the third carbonyl function via "enamine or enone followed by ozonolysis" sequence. There are several ways to synthesize 1,3-dicarbonyl functionality. Our choice fell on the alkylation of 1,3-dithiane with α-halocarbonyl compound with subsequent demasking of the dithiane moiety leading to the requisite 1,3-dicarbonyl compound. A closer look at FK-506 prompted us to decide in favour of having dithiane function at C-10 instead of its being the other way, i.e. at C-8, obviously because of

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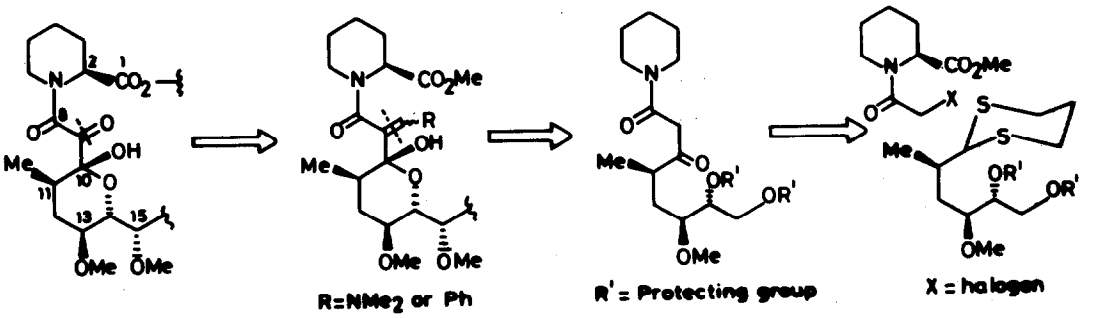
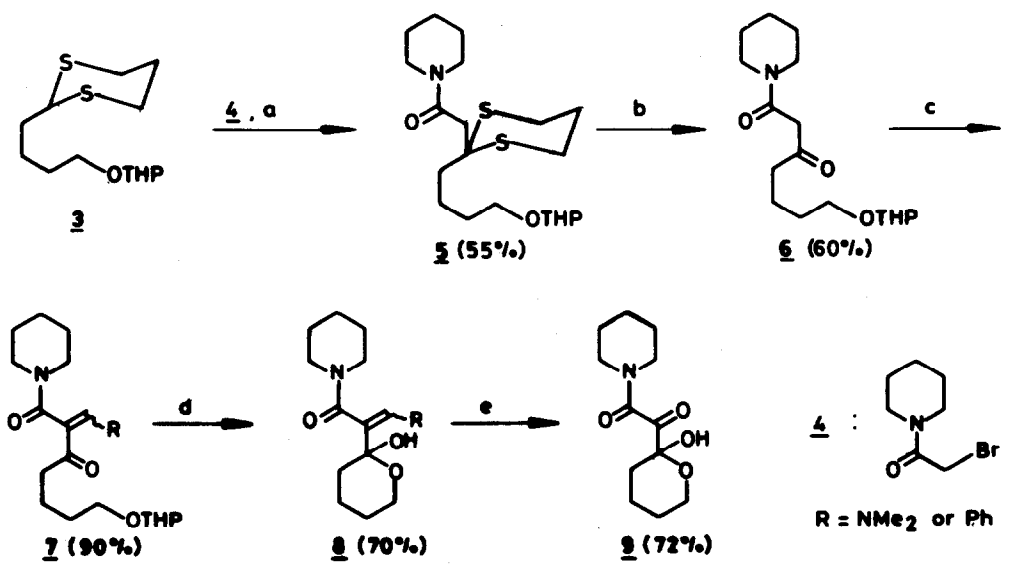
the presence of an adjacent nitrogen. An easy conversion of L-pipecolic acid into N-(α-bromoacetyl)pipecolic acid methyl ester provided the α-halocarbonyl component.



In order to test the viability of our strategy first a model study was carried out using 2-(5-tetrahydropyranyloxy)-1,3-dithiane **3** and N-(α-bromoacetyl)piperidine **4** (scheme I) as principal fragments. Lithiation of **3** with n-BuLi followed by the addition of **4** gave the alkylated product **5** which on deprotection with $HgCl_2$-HgO gave the 1,3-dicarbonyl precursor **6**[5]. A two-step protocol was followed to introduce the third carbonyl group. Treatment of **6** with benzal-

Scheme I

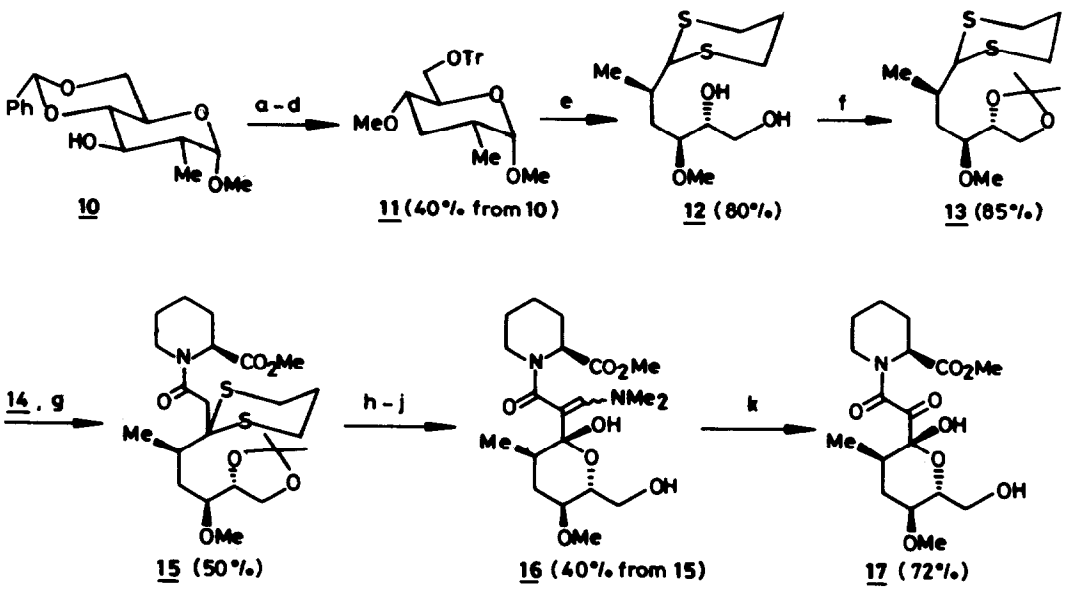


a) n-BuLi, THF, -15°C, 4 h; then **4** (1.1 eq) -78°C, 4-5 h; b) HgO(1.1 eq), $HgCl_2$(2.2 eq), 20% aq CH_3CN, r.t., 1 h; c) NaOMe(1.3 eq), PhCHO(1.2 eq), MeOH or $(MeO)_2CHNMe_2$(2 eq), neat, 80°C, 2 h; d) 10-Camphorsulfonic acid (0.2 eq), MeOH, 55°C, 10 h; e) O_3, CH_2Cl_2, -78°C, 5-10 min.

dehyde (or N,N-dimethylformamide dimethylacetal)[6] gave the enone (or enamine) **7**. Mild acid treatment freed the primary hydroxyl group which immediately cyclized to the lactol **8**. Ozonization of **8** provided the target triketo compound **9**[5,7]. Having successfully completed our

model study we then embarked upon the real system with appropriate functionalities. For dithiane component the starting material was methyl-4,6-O-benzylidine-2-deoxy-2-methyl-α-D-glucopyranoside **10** prepared conveniently from methyl-α-D-glucopyranoside[8]. Standard functional group manipulations, namely, (i) deoxygenation at 3-position, (ii) removal of 4,6-O-benzylidene protection, (iii) protection of primary hydroxyl as trityl ether and finally (iv) methylation of 4-hydroxy group provided the necessary intermediate **11**[5] (scheme II). Treatmet of **11** with 1,3-propane dithiol in presence of acid opened the pyranoside ring to provide the dithioketal as well as removed the trityl group. Lithiation of **13** with n-BuLi followed by treatment with **14** gave the alkylated product **15**[5]. From hereon following the same sequence of steps as established in our model study the final triketo compound **17** was obtained[8].

Scheme II



14 : L-N-(α-Bromoacetyl) pipecolic acid methyl ester

a) NaH(1.3 eq), CS_2(1.2 eq), Et_2O, reflux, 3 h, followed by addition of MeI(1.2 eq); b) n-Bu_3SnH (1.5 eq), AIBN(Cat), toluene, reflux, 12 h; c) p-Toluenesulfonic acid (0.4 eq), MeOH, r.t., 6-7h; d) (i) TrCl(1.2 eq), pyridine, 60-55°C, 4 h; (ii) NaH(1.5 eq), MeI(1.5 eq), DMF:THF(3:7), 0°C, 2 h; e) 1,3-propanedithiol (1.1 eq), $BF_3.Et_2O$(1 eq), CH_2Cl_2, 0°C, 2 h; f) $Me_2C(OMe)_2$, p-toluenesulfonic acid (0.2 eq), 12 h; g) n-BuLi, THF, -15°C, 4 h, followed by addition of **4** at -78°C, 6-7 h; h) $BF_3.Et_2O$ (2 eq), HgO (2 eq), 15% aq THF, followed by addition of **15**, 0°C, 4 h; i) $(MeO)_2$-$CHNMe_2$(2 eq), 80°C, 2 h; j) p-Toluenesulfonic acid (0.2 eq), 10% aq. MeOH 55°C, 12 h; k) O_3, CH_2Cl_2, -78°C, 5-10 min.

Thus in conclusion, simple alkylation of a dithiane moiety with α-halocarbonyl compound, followed by oxidation of the active methylene group provided an easy access to the characteristic 1,2,3-tricarbonyl functionality in FK-506.

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9. Compound **17** showed identical spectroscopic properties as reported earlier, see ref. 4b.

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