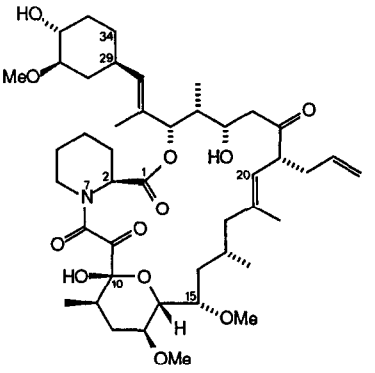
Tetrahedron Letters,Vol.29,No.35,pp 4481-4484,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A SYNTHESIS OF THE C(1)-C(15) SEGMENT OF TSUKUBAENOLIDE (FK 506).

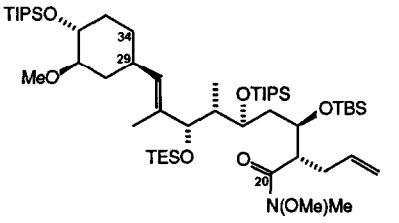
Philip Kocienski* and Michael Stocks
Chemistry Department, The University, Southampton, SO9 5NH, U. K.
and
David Donald*, Martin Cooper, and Anthony Manners
Fisons Pharmaceuticals PLC, Bakewell Road, Loughborough, Leicestershire, LE11 0RH, U.K.

Abstract: A synthesis of the C(1)-C(15) segment (**4**) of Tsukubaenolide (**1**) from Tri-O-acetyl-D-glucal and (S)-Pipecolinic acid methyl ester is described.

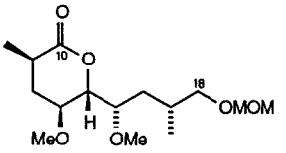
Tsukubaenolide (**1**)[1] is a powerful immunosuppressant isolated from *Streptomyces tsukubaensis* with potential for use in bone marrow and organ transplants. Extensive chemical and spectroscopic studies in conjunction with a single crystal x-ray analysis[2] revealed that (**1**) is a novel 23-membered macrolide ring adorned with 14 chiral centres. Recently a Merck group reported the synthesis of the C(10)-C(18) and C(20)-C (34) segments (Tsukubaenolide numbering) (**2**) and (**3**)[3]. We now report a synthesis of the C(1)-C(15) segment (**4**) which harbours the unusual 1,2,3-tricarbonyl moiety masked as a hemiacetal which is a notable feature of Tsukubaenolide.



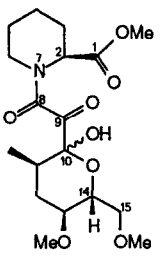
(1)



(2)



(3)



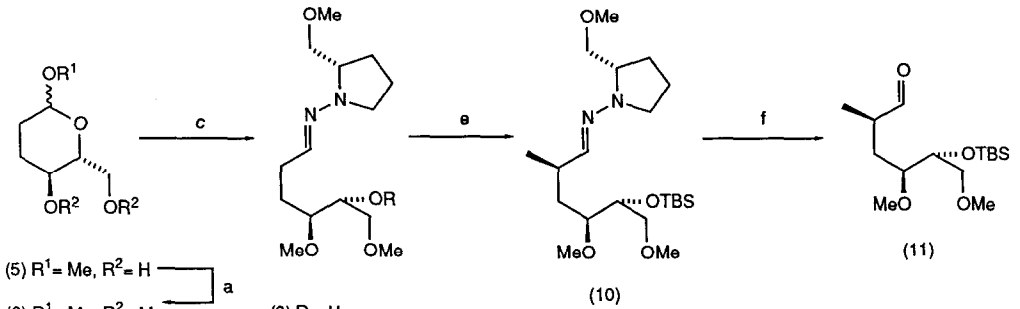
(4)

Two principal fragments were used to construct the target: the aldehyde (**11**) and the lithiated N-diazoacetyl pipecolinic acid methyl ester (**12**). The aldehyde (**11**) was synthesised (Scheme 1) in six steps (27% overall yield) from the diol (**5**) which itself was prepared in 3 steps (81% overall yield) from commercial tri-*O*-acetyl-D-glucal as described by Sinaÿ and co-workers[4]. A key step in the fabrication of aldehyde (**11**) was the highly diastereoselective alkylation of the SAMP-hydrazone[5] (**9**) which gave an inseparable 97 : 3 mixture of diastereoisomers (64% yield) in which the desired product (**10**) was the major component. The diastereoselectivity of the alkylation was easily assayed by nmr spectroscopy at 270 MHz ($CDCl_3$) since the hydrazone protons at C(10) were clearly differentiated. In the case of (**10**) the hydrazone proton appeared as a doublet (J = 6.5 Hz) at δ6.43 whereas the minor diastereoisomer revealed a doublet (J = 6.0 Hz) at δ6.53. Subsequent ozonolytic cleavage of the hydrazone was achieved without epimerisation of the C(11) chiral centre to give an inseparable 97 : 3 mixture of diastereoisomeric aldehydes.

The fulcrum of our synthetic plan was the ß-keto amide (**14**) (Scheme 2) which we prepared from aldehyde (**11**) by a 3-step sequence beginning with an aldol condensation using the unstable lithiated N-diazoacetyl (S)-pipecolinate ester (**12**). Successful union of (**11**) and (**12**) was best achieved by adding a solution of lithium di-isopropylamide to a mixture of (**11**) and N-diazoacetyl (S)-Pipecolinic acid methyl ester[6] in THF at -70°C in which case the anion (**12**) reacted rapidly *in situ* with the aldehyde. Under these conditions a 57% yield of the diastereomeric α-diazo-β-hydroxy amides (**13**) was obtained after chromatography on silica gel (1 :1 Et_2O-hexanes). When (**13**) was treated with a catalytic amount of Rh (II) in dimethoxyethane[7] at room temperature, smooth nitrogen evolution occurred in a remarkably clean reaction to give the desired ß-keto amide (**14**) in quantitative yield.

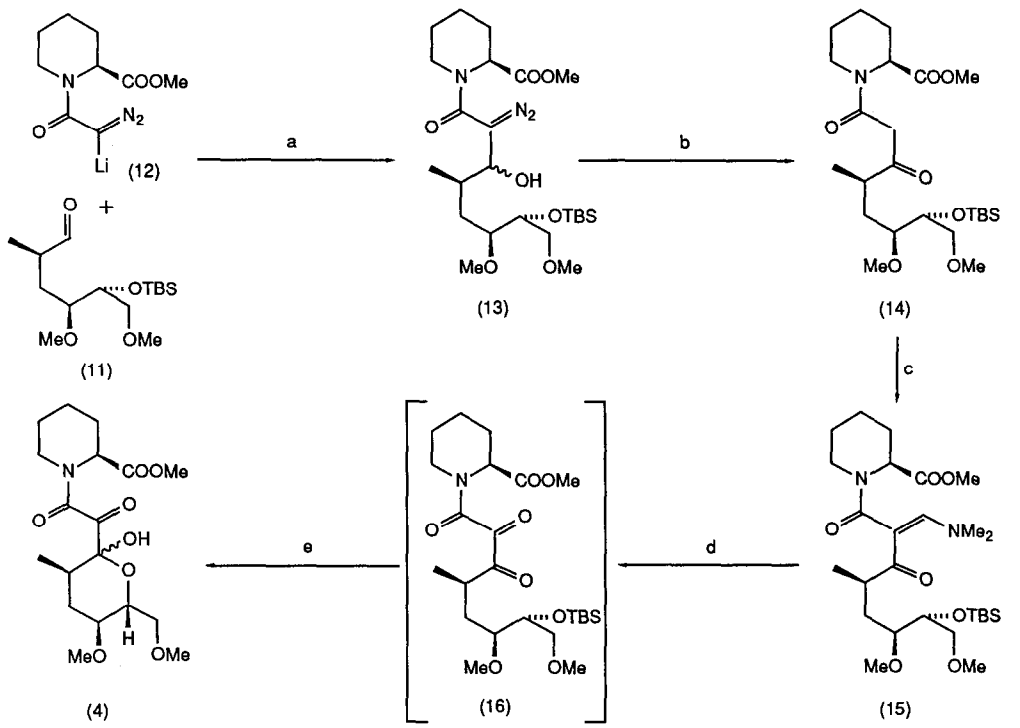
The final stage of the synthesis involved the oxidation of (**14**) to the 1,2,3-tricarbonyl intermediate (**16**) by the 2-step procedure of Wasserman and Han[8]. Thus (**14**) reacted with 2 eq. of dimethylformamide dimethylacetal (neat) at 80°C to give a 93% yield of the enamine (**15**). Subsequent ozonolysis of (**15**) at -30°C gave the 1,2,3-tricarbonyl intermediate (**16**) in 70% yield after chromatography on silica gel (1 : 2 Et_2O-hexanes)[IR (film) 1750 (s), 1720 (m), 1660 (s), and 1650 (s) cm^{-1}] which was immediately treated with HF in MeCN[9] to give the Tsukubaenolide segment (**4**) (95%): IR (film) 3400 (br), 2960 (s), 2900 (m), 1750 (s), 1670 (sh), 1660 (s), 1655 (sh), 1460 (s), 1110 (s), and 740 (s) cm^{-1}; MS (Discharge Assisted Thermospray): found (M^++1), 388.1990; $C_{18}H_{30}NO_8$ requires M, 388.19714; base peak (M-H_2O) found 370.1909; $C_{18}H_{28}NO_7$ requires M, 370.18658.

The ^1H and ^{13}C nmr spectra of (**4**) (360 MHz, $CDCl_3$) revealed that (**4**), like Tsukubaenolide and the closely related Rapamycin[10], exists as an equilibrium mixture of two isomers in solution. This behaviour has been attributed[2] to restricted rotation about the amide bond. Thus all the signals in the ^{13}C spectrum were doubled with the exception of a methylene carbon at δ21.1. Further evidence that restricted rotation was responsible for the observed spectroscopic complexity was gleaned from the large chemical shift difference between the signals due to the C-2 and C-6 carbons flanking the nitrogen as observed in Tsukubaenolide and Rapamycin: ^{13}C NMR ($CDCl_3$, 90.56 MHz)[197.5, 195.4] (s)(C-9), [171.0, 170.4] (s) (C-1), [166.6, 165.6] (s) (C-8), [98.4, 98.0] (s) (C-10), [74.8, 74.5] (d) (C-13 or C-14), [72.9, 72.8] (d) (C-13 or C-14), [72.6, 72.2] (t) (C-15), [59.0, 58.4] (q) (MeO), [56.7, 51.5] (d) (C-2), [56.34, 56.30] (q) (MeO), [52.6, 52.4] (q) (COOMe), [44.6, 39.1] (t) (C-6), [34.8, 34.2] (d) (C-11), [31.90, 31.75] (t) (C-5), [26.9, 26.5] (t), [24.9, 24.4] (t) , 21.1 (t), [15.7, 15.5] (q) (C-11 Me).



REAGENTS			
(a) MeI, NaH/THF	92%	(d) TBSCL, imidazole/DMF	75%
(b) HOAc-H_2O, reflux	97%	(e) LDA, MeI/THF	64%
(c) SAMP/CH_2Cl_2	86%	(f) O_3/CH_2Cl_2, -78°C	73%

Scheme 1*



REAGENTS	
(a) THF, -78°C	57%
(b) $Rh_2(OAc)_4$/DME, 20°C	100%
(c) $(MeO)_2CHNMe_2$ (1 eq., neat), 80°C, 2h	93%
(d) O_3/CH_2Cl_2, -30°C, 10 min.	70%
(f) HF/MeCN	95%

Scheme 2*

*All compounds except (16) were characterised by IR, ^1H and ^{13}C NMR, and high resolution MS including accurate mass

Acknowledgements. This is a contribution from the Southampton University Institute of Biomolecular Science.

References

1. FK 506 is too bland a name for such a fascinating structure. We suggest the trivial name Tsukubaenolide as a more euphonious alternative.

2. H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, and T. Taga, *J. Am. Chem. Soc.*, 1987, **109**, 5031.

3. D. Askin, R. P. Volante, R. A. Reamer, K. M. Ryan, and I. Shinkai, *Tetrahedron Lett.*, 1988, **29**, 277; S. Mills, R. Desmond, R. A. Reamer, R. P. Volante, and I. Shinkai, *ibid.*, 1988, **29**, 281.

4. L. Stamatos, P. Sinaÿ, and J. Pougny, *Tetrahedron*, 1984, **40**, 1713.

5. D. Enders, H. Eichenauer, U. Baus, H. Schubert, and K. Kremer, *Tetrahedron*, 1984, **40**, 1345; D. Enders and H. Baus, *Liebigs Ann. Chem.*, 1983, 1439; D. Enders and H. Eichenauer, *Chem. Ber.*, 1979, **112**, 2933.

6. Prepared in 75% yield by the reaction of (S)-Pipecolinic acid methyl ester hydrochloride with diazoacetyl chloride [H. Bestmann and F. Saliman, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 947] in Et_2O-triethylamine.

7. R. Pelliciari, R. Fringuelli, P. Ceccherelli, and E. Sisani, *J. Chem. Soc., Chem. Commun.*, 1979, 959,

8. H. Wasserman and W. Han, *Tetrahedron Lett.*, 1984, **25**, 3743.

9. E. Collington, H. Finch, and I. Smith, *Tetrahedron Lett.*, 1985, **26**, 681.

10. J. A. Findlay and L. Radics, *Can. J. Chem.*, 1980, **58**, 579.6

(Received in UK 14 July 1988)