Tetrahedron Letters Vol.30,No.39 pp 5235-5238 1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

ENANTIOSELECTIVE SYNTHESIS OF THE C(18) - C(35) SEGMENT OF IMMUNOSUPPRESSANT FK-506 USING EFFICIENT NEW METHODOLOGY

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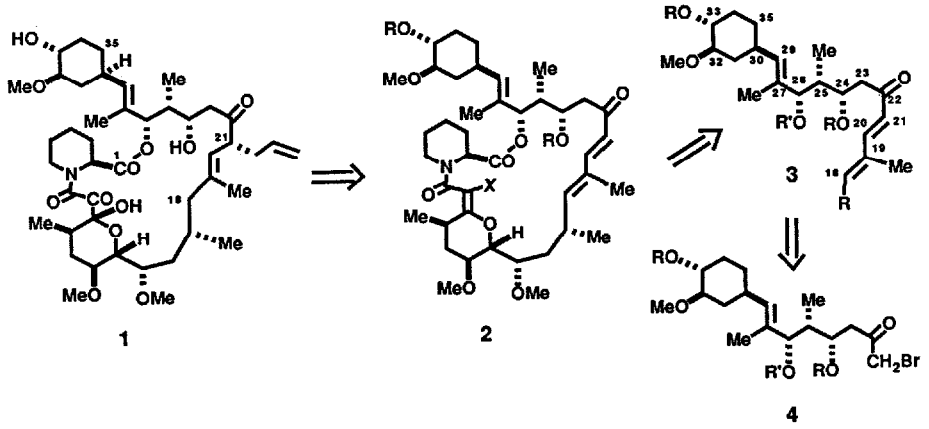
Summary: A simple, enantiocontrolled and efficient route to an intermediate containing carbons 18 to 35 of the macrocyclic immunosuppressant FK-506 (**1**) is described which depends on a sequence of three enantioselective C-C bond forming reactions.

Research in our group has recently led to the development of new and highly effective enantioselective versions of such major synthetic processes as the Diels-Alder, aldol and carbonyl allylation reactions.[1,2] In this paper we demonstrate the power of this methodology as applied to the construction of a key intermediate for the synthesis of the novel immunosuppressant FK-506 (**1**). The structural novelty and biological potency of FK-506 have made this substance a popular target for synthesis despite a level of toxicity which discourages clinical use.[3] One line of retrosynthetic analysis which leads to effective structural simplification of FK-506[4] is shown below. Clearance of the allyl appendage and stereocenter from C(21) (triethylsilane reduction, α-allylation transform) leads to **2**, with reliance on macroring geometry[4] to ensure stereoselectivity at C(21) and C(19) - C(20). Macroring disconnection to **3** and Wittig disconnection to **4** are among several possible further retrosynthetic disconnections. Described herein is a simple synthesis of **4** and its elaboration to **3**, *R*=i-Pr, to validate the Wittig step (which might also be used for macroring closure). Dienone **3** corresponds to the C(18) - C(35) segment of FK-506.

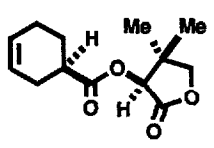


The cyclohexane unit and the C(30) stereocenter were established by $TiCl_4$-catalyzed Diels-Alder reaction[5] of butadiene (30 equiv) with the acrylate ester of *(S)*-(+)-pantolactone[6] in CH_2Cl_2 at -32°C for 120 h to form **5** (91% de as determined by 500 MHz ^1H NMR analysis) which was carried through the next two steps without purification: (1) saponification with 3.9 equiv of 3.5*M* LiOH-H_2O and THF at 23°C for 1.5 h, removal of THF and acidification to give by extraction with 4% CH_2Cl_2 in hexane *(R)*-cyclohex-3-en-1-carboxylic acid and, by heating of the aqueous layer (60°C, 2 h) and further extraction with EtOAc, recovered *(S)*-(+)-pantolactone (91%); and (2) reaction of the unsaturated acid with 1.1 equiv of *m*-chloroperoxybenzoic acid in CCl_4 at 0° for 4 h, addition of triethylamine and heating (55°C, 3 h) to afford after silica gel (sg) chromatography and recrystallization pure hydroxy lactone **6**, mp 163.5 - 165°, $[\alpha]_D^{23}$ -21.5° (c=2),[7] in 61% overall yield from starting acrylate ester. Silylation of **6** with 1.3 equiv of *t*-butyldimethylsilyl chloride (TBSCl) and 1.5 equiv of 4-dimethylaminopyridine in CH_2Cl_2 at reflux for 21 h produced the TBS derivative **7** which crystallized after passage through a sg column and removal of solvent (100%, mp 79-81.5°) and which was converted by reaction in methanol containing 0.5 equiv of sodium bicarbonate at 23°C for 3 h into the oily hydroxy ester **8** (98%), $[\alpha]_D^{23}$ -33.2° (c=4). Methylation of **8** using 3.3 equiv of methyl triflate and 3.3 equiv of 2,6-di-*t*-butyl-4-methylpyridine in CH_2Cl_2 at 23°C for 64 h gave the oily methyl ether **9** (94%), $[\alpha]_D^{23}$ -44.6° (c=5), which was reduced by 1.2 equiv of diisobutylaluminum hydride in hexane at -78°C for 0.5 h to aldehyde **10**, used directly in the next step without purification.

Chain extension of aldehyde **10** was accomplished using the lithio derivative of the *N*-cyclohexylimine of 2-triethylsilylpropionaldehyde[8] in THF at -20°C for 1.5 h followed by reaction with trifluoracetic acid in THF at 0°C for 1 h and addition of water and stirring at 0°C for a further 15 h to afford the *E*-aldehyde **11** (87%), $[\alpha]_D^{23}$ -23.3° (c=4), as a colorless oil after sg chromatography. Further chain extension was effected by the recently described enantioselective aldol reaction of **11** using reagent **12**. The reagent **12** was generated from the corresponding cyclic bromoborane (derived from *R,R*-1,2-diphenyl-1,2-diaminoethane bis *p*-nitrobenzenesulfonamide and boron tribromide[1]), *S*-phenyl thiopropionate and diisopropylethylamine in CH_2Cl_2 at -45° for 2.5 h. Reaction of **12** in situ in CH_2Cl_2 with aldehyde **11** at -78°C for 2 h gave the syn aldol product **13** (92% de) which was readily freed from the contaminant of less polar diastereomer by flash sg chromatography (hexane-EtOAc, 10 : 1); yield of **13**, 85%, $[\alpha]_D^{23}$ -0.9° (c=2). The bissulfonamide from which **12** was derived was recovered in high yield. Protection of the hydroxyl group in **13** (6.2 equiv of bromomethyl methyl ether, 7 equiv of diisopropylethylamine in CH_2Cl_2 at 0°C initially, and then 23°C for 24 h) provided the corresponding methoxymethyl (MOM) ether (94%, $[\alpha]_D^{23}$ -48.2°) which after reduction with diisobutylaluminum hydride in hexane at -78°C for 30 min afforded aldehyde **14** (95%), $[\alpha]_D^{23}$ -89.1° (c=1).

Further elaboration of **14** was carried out using a new method for 2-acetoxyallylation which is equivalent to enantioselective carbonyl addition of a functionalized acetone unit and which is also based on the 1,2-diphenyl-1,2-diaminoethane controller group.[2] The specific allylation reagent employed was the cyclic borane **15** which was prepared by reaction of the corresponding *S,S*-bromoborane[2] with 2-acetoxyallyltri-n-butylstannane[9] (in CH_2Cl_2 for 5 min at -78°C, then at 23°C for 1.5 h). Reaction of the CH_2Cl_2 solution of **15** in situ with aldehyde **14** at -78°C for 1 h produced homoallylic alcohol **16** as major product with 17 : 1 diastereoselectivity as determined by 500 MHz ^1H NMR analysis; pure **16** was isolated in 92% yield after stirring of the crude product with sat. aq KF solution (to remove tin co-products) and sg

flash chromatography. The bistosylamide from which reagent **15** was derived was efficiently recovered for reuse. Silylation of **16** using 4.2 equiv of *t*-butyldimethylsilyl triflate and 6.7 equiv of 2,6-lutidine in CH_2Cl_2 at 0°C for 1 h provided the corresponding silyl ether **17** (88%), $[\alpha]_D^{23}$ -61° (c=2). Reaction of **17** with 1.3 equiv of *N*-bromosuccinimide in acetonitrile at 0°C for 1.5 h produced bromo ketone **4** (95%), $[\alpha]_D^{23}$ -61.3° (c=2), after isolation by sg chromatography.



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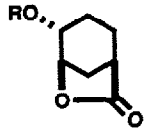
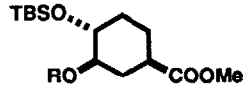
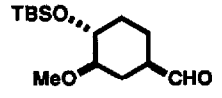


6 R = H
7 R = TBS



8 R = H
9 R = Me



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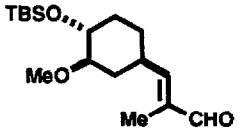

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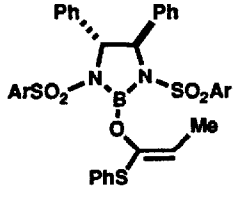
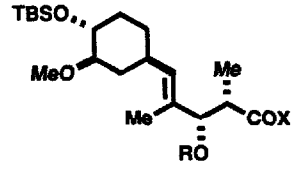
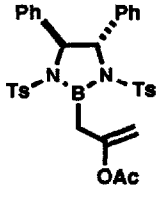


12 Ar = *p*-$NO_2C_6H_4$



13 R = H, X = SPh
14 R = MOM, X = H



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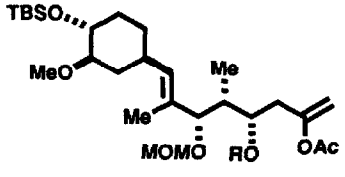
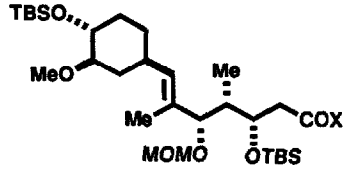
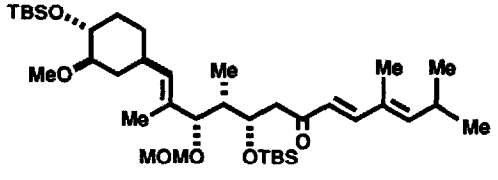


16 R = H
17 R = TBS



4 X = CH_2Br
18 X = $CH{=}PMe_2Ph$



19

Further elaboration of bromo ketone **4** to dienone **19**, a model for key intermediate **3**, was carried out efficiently and with stereocontrol using Wittig methodology. The bromo ketone **4** was stirred with 1 equiv of dimethylphenylphosphine in acetonitrile for 10 min at 0°C and then treated with 1,4-diazabicyclo[2.2.2]octane at 22°C for 1 h to generate ylide **18** which was obtained by removal of solvent, addition of ether-hexane, filtration, and concentration of the filtrate, and used directly. Reaction of ylide **18** in ether solution with *E*-2,4-dimethyl-2-pentenal at 23°C for 5 h provided, after purification by sg chromatography, dienone **19** (85%), $[\alpha]_D^{23}$ -78.1° (c=2).

The synthesis of **19** as described above is expeditious, efficient and novel and represents an excellent route to a key intermediate (**3**) for the synthesis not only of FK-506 but of structural analogs which may be of more therapeutic value. It also provides a clear demonstration of the merit of newly introduced[1,2] enantioselective and diastereoselective methodology.[10]

References and Notes

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2. E. J. Corey, C.-M. Yu and S. S. Kim, *J. Am. Chem. Soc.*, **111**, 5495 (1989).
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4. Structure of FK-506: H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, and M. Hashimoto, *J. Am. Chem. Soc.*, **109**, 5031 (1987).
5. T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Letters*, **38**, 2189 (1985).
6. *(S)*-(+)-Pantolactone was synthesized from *(R)*-(-)-pantolactone (Aldrich Co.) by the sequence: (1) conversion to the triflate ester using 1.2 equiv of triflic anhydride and 1.5 equiv of 2,6-lutidine in CH_2Cl_2 at -20°C for 1.5 h; (2) reaction with potassium acetate in acetone at 60°C for 2 h; and (3) deacetylation with 3.5 equiv of 1.7 M LiOH-H_2O and THF at 23°C for 2 h followed by acidification and extractive isolation with EtOAc (90% overall yield, 97% ee).
7. All rotations determined using $CHCl_3$ solutions. Satisfactory spectroscopic data were obtained for each reaction product. All reactions involving air-sensitive reactants or products were carried out under Ar or N_2 using flame-dried glassware and dry solvents.
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9. Prepared as described by Y. Uena, M. Ohta and M. Okawara, *J. Organomet. Chem.*, **197**, C1, (1980).

10. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

(Received in USA 21 July 1989)