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Synthesis of the northern sector (C8-C19) of rapamycin via Chan rearrangement and oxidation of an α -acyloxyacetate

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Abstract

Two routes to the masked tricarbonyl segment of the immunosuppressant rapamycin comprising C8-C19 were explored beginning from D-xylose. The first approach employed a protected form of 2,4,5-trihydroxypentanol to obtain dithiane **43**, which failed to react with dimethyl oxalate to give a 1,2,3-tricarbonyl unit corresponding to the northern sector of rapamycin. A second approach employing carboxylic acid **61** derived from **43** utilized base-mediated (Chan) rearrangement of α -acyloxyacetate **62** with trapping of the resultant enediolate as bis silyl ether **63**. Epoxidation of this diene afforded masked tri-keto ester **65** which underwent acid-catalyzed methanolysis to produce cyclic ketal **67**.

1. Introduction

In 1975, a substance named rapamycin (**1**) was isolated from the soil fungus *Streptomyces hygroscopicus* during a search for naturally occurring antifungal agents¹. Although the antifungal properties of **1** were not particularly impressive, it later became apparent that rapamycin was a potent immunosuppressant² with a mode of action similar to a related *Streptomyces* metabolite FK-506 (**2**).³ Both **1** and **2** were studied as prospective therapeutic agents for treatment of graft rejection that accompanies organ and tissue transplantation, and rapamycin is known to be particularly effective in suppressing the immune response with relatively few side effects. The ability of **1** to prevent the formation of antibodies against cell surface antigens of transplanted tissue has placed it at the forefront of medical practice in the area of organ transplantation and rapamycin is now a recognized drug in combination with cyclosporine A for treatment of host vs. graft disease.⁴

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Supplementary data

Experimental procedures and characterization data for new compounds. These data can be found in the online version at

Rapamycin (1) **FK-506 (2)**

The piperolic keto amide sector of the rapamycin and FK-506 structures plays an important role as a peptidomimetic when these immunosuppressants are bound to certain cytosolic enzymes (immunophilins). Specifically, the rapamycin-immunophilin complex acts as a prolyl cis-trans isomerase⁵ in which the C1-C10 segment of **1** mimics the transition state of a bound proline-containing peptide.⁶ This results in inhibition of at least three protein kinases and interferes with a signaling pathway that originates in the interleukin-2 receptor.⁷ Thus, the functionality present in the terminal portion of this “northern” domain of **1** is a pivotal component of the architecture of this macrolide.

In addition to efforts directed toward clarifying the mode of action of rapamycin and FK-506,⁸ a large number of synthetic studies on these immunosuppressive agents has been carried out. These investigations have resulted in five total syntheses of rapamycin⁹ and three of FK-506,¹⁰ as well as numerous publications reporting approaches to the tricarbonyl subunits of **1** and **2**.¹¹

Integral to any strategy for assembling the “northern” (C8-C19) subunit of **1** is the correct installation of stereocenters at C11, 14 and 16. Additionally, connection of this sector to a second major subunit at C19-C20 requires placement of a functionalized trisubstituted (*E*) alkene at C17-C18. With these prerequisites in mind, a plan was conceived for synthesis of the C8-C19 portion **3** of rapamycin that envisioned this segment of the molecule as the acylation-hydrolysis product from dithiane **4** and dimethyl oxalate (Scheme 1). Precedent for this strategy

existed in Corey's synthesis of aplasmomycin,¹² a macrolide that contains a borate-complexed 2,7-dihydroxy-3-ketolactone masked as a cyclic hemiketal. Dithiane **4** was foreseen as emanating from a 2,4,5-trihydroxypentanal **5** whose (2*R*,4*S*) configuration would originate in D-xylose (**6**). As it happened, this approach to **3** failed and a second generation plan was devised that employed **4** in a manner different from the approach projected in Scheme 1. Specifically, dithiane **4** was advanced to an α -acyloxy acetate designed to undergo base-mediated (Chan) rearrangement to a conjugated enediolate which, upon subsequent epoxidation, would yield an α,β -diketo ester.

2. Results and discussion

2.1 First generation approach via acylation of a dithiane

The known diol **7**, prepared in two steps from D-xylose (**6**),¹³ was selectively esterified at the primary alcohol with pivaloyl chloride¹⁴ to give **8** from which the residual secondary hydroxyl group was excised by reduction of xanthate **9** with tri-*n*-butylstannane (Scheme 2).¹⁵ Although hydrolysis of acetone **10** proceeded cleanly to diol **11**, attempts to homologate the open form of this cyclic hemiacetal by means of Wittig olefination were unsuccessful. The apparent sensitivity of **11** towards basic conditions caused us to redirect our planned route towards dithioacetal **12**, which was conveniently obtained by exposure of **10** to ethanethiol in hydrochloric acid. For reasons that became evident subsequently, it was necessary to protect diol **12** as a relatively robust ketal for which 1,1-dimethoxycyclohexane proved to be the reagent of choice. Dithioacetal **13** was then carefully hydrolyzed to aldehyde **14**, a sensitive substance that was transformed irreversibly into its isomer **15** in the presence of acid.

Continuation towards dithiane **4** was initially pursued via coupling of aldehyde **14** with sulfone **16** (Scheme 3). The latter had been used successfully in a previous Julia olefination in these laboratories,¹⁶ and the expected hydroxysulfone **17** (as a mixture of stereoisomers) was obtained in good yield. Unfortunately, reductive elimination of **17** proceeded with only modest efficiency to give trans alkene **18** which was contaminated with a significant quantity of alcohol **19**. Consequently, we turned towards Wittig olefination as an alternative tactic for advancing aldehyde **14** towards **4**.

An initial attempt along this line was disappointing since the ylide from phosphonium iodide **20** produced cis alkene **21** in only fair yield (Scheme 4). A more effective option proved to be use of the ylide from phosphonium salt **22** in the presence of trimethylsilyl chloride,¹⁷ a process that afforded silyl ether **23** and then alcohol **24** without the potentially troublesome deprotection of *p*-methoxybenzyl ether **21**.

Although hydrogenation of alkene **24** could be accomplished over a platinum catalyst (palladium catalysts led to hydrogenolysis of the allylic C-O bond), the most effective reagent for saturating the double bond of **24** was diimide prepared in a pyridine-acetic acid mixture (Scheme 5).¹⁸ Oxidation of the resultant alcohol **25** furnished aldehyde **26** which upon exposure to methanol in the presence of acid yielded α and β acetals **27** and **28**. The acetals, in which axial anomer **28** predominated, were readily identified by their proton-proton coupling constants at C1 and C2 (8.3 Hz for **27** and 3.2 Hz for **28**) and were separated by radial chromatography; each was carried forward separately. First, the alcohols were converted to their methyl ethers **29** and **30**. Reduction of the pivalate ester then gave alcohols **31** and **32** which were oxidized to the corresponding aldehydes **33** and **34**. Conversion of **33** to ketone **35** was carried out in a two-step process that involved Grignard addition of methylmagnesium bromide followed by oxidation. However, significant erosion of configuration at the methoxy-bearing carbon of **35** occurred during this sequence which, it was discovered, could be avoided by replacing the Grignard reagent with a less basic methylating agent prepared from methyllithium and cerium(III) chloride.¹⁹

At this juncture, it became possible to correlate **36** with a known compound, lactone **37**, which had been synthesized by Ley and also isolated from degradation of rapamycin (Scheme 6).²⁰ Acidic hydrolysis of methyl glycoside **36** followed by oxidation of the resultant hemiacetal yielded **37** with ¹H and ¹³C NMR spectra identical to those of the same lactone provided by Professor Ley.

With the structures of **35** and **36** secure, our next task was extension of these methyl ketones towards subunit **4** by attaching an (*E*) trisubstituted alkene needed for C17-C18 of rapamycin. In planning this construction, it was crucial to leave a functional group at C19 that would permit linkage with the “southern” segment of the macrolide, and to this end **35** and **36** were each subjected to a Horner-Wadsworth-Emmons reaction with the anion of ethyl diethylphosphonoacetate (Scheme 7). The resulting α,β -unsaturated esters **38** and **39** were both obtained with an *E*:*Z* ratio of approximately 14:1. The *E*/*Z* mixture of esters was reduced to the corresponding allylic alcohols **40** and **41**, each of which was treated with 1,3-propanedithiol in the presence of boron trifluoride etherate to yield a single dithiane **42**. This diol was then exhaustively silylated to give bis-silyl ether **43**.

With dithiane **43** in hand, we were ready to test our plan for constructing the 1,2,3-tricarbonyl substructure of **1** by acylating the dithiane anion from **43** with dimethyl oxalate. To our surprise, the outcome from this reaction after workup was not the expected β -dithianyl α -keto ester but instead was α,β -unsaturated aldehyde **50** (Scheme 8). The latter presumably arises from hydrolysis of silyloxy diene **51**, a result which informs us that lithiation of **43** has occurred, not at the dithiane carbon, but at the allylic carbon (C10). Subsequent 1,4-elimination of methoxide leads transiently to pre-hydrolysis intermediate **51**, which in the course of its conversion to **50** undergoes isomerization of the trisubstituted alkene into conjugation.

2.2 Second generation approach via Chan rearrangement-oxidation

Our failure to acylate **43** with dimethyl oxalate caused us to revise our plan outlined in Scheme 1 for acquiring **3** and prompted us to consider a strategy used previously in our laboratory for assembling a similar structural motif to **3** present in the macrolides aplasmomycin²¹ and boromycin.²² Our new approach was based upon reorganization of an α -acyloxyacetate **52** to an α -hydroxy β -keto ester **53** (Scheme 9).²³ This rearrangement, initially discovered by Chan,²⁴ is nominally an O $\rightarrow$ C acyl migration which takes place by internal attack of enolate **54** to give transient epoxide **55**. The latter then collapses to **56**. Standard work up from **56** produces **53**, but **56** can react with a second equivalent of base to form enediolate **57** which, as bis silyl ether **58**, serves as a masked version of **56**. For the purpose of reaching **3**, oxidation of the Chan rearrangement product would be needed and this could be programmed from either **53** or **58**.

Synthesis of the precursor for this new approach to **3** began by conventional transformation of dithiane **43** to aldehyde **60**²⁵ and then oxidation to carboxylic acid **61**²⁶ (Scheme 10). Treatment of the potassium carboxylate from **61** with methyl bromoacetate afforded α -acyloxy acetate **62** which was reacted with excess LDA in the presence of trimethylsilyl chloride. An initial UV-active product shown to be α,β -unsaturated ester **63** was formed but this compound was unstable and was therefore treated promptly with *m*-chloroperoxybenzoic acid in order to elevate the protected enediol to the tricarbonyl oxidation level. Epoxide **64** was not seen in this Rubottom²⁷ oxidation since it rearranged spontaneously to bis-silyl ketal **65** which was purified by chromatography and was fully characterized. Exposure of **65** to acidic ion-exchange resin in the presence of methanol led directly to methyl ketal **67** presumably via the acyclic diketo ester **66**.

3. Conclusion

We have shown that an α -acyloxy ester bearing the three stereocenters corresponding to C11, 14 and 16 of rapamycin undergoes rearrangement and subsequent oxidation to provide the masked tricarbonyl unit embedded in the C8-C19 portion of **1**. The congested functional groupings in this sector of rapamycin limit practical approaches to its synthesis, but internal reorganization of a substrate such as **62** is a viable strategy for gaining access to this important domain of the immunosuppressant. The overall yield for the 25 steps from D-xylose to **67** is approximately 3%.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

- (a) Sehgal SN, Baker G, Vezina C. J. Antibiot 1975;28:727. [PubMed: 1102509] (b) Findlay JA, Radics L. Can. J. Chem 1980;58:579.
- Martel RR, Klicius J, Galet S. Can. J. Physical Pharmacol 1977;55:48.
- (a) Tanaka H, Kuroda A, Marusawa H, Kino T, Buto T, Hashimoto M, Taga T. J. Am Chem. Soc 1987;109:5031. (b) Starzl TE, Todo S, Fung S, Demetris AJ, Jain A. Lancet 1989;11:1000. [PubMed: 2478846]
- Morris, EE. In New Immunosuppressive Modalities and Anti-Rejection Approaches in Organ Transplantation. Kupiec-Weglinski, JW., editor. Austin, TX: R.G. Landes Co; 1994.
- Hardschumacher RE, Harding MW, Rice J, Durge RJ. Science 1994;226:544.
- Rosen MK, Standoert RF, Galat A, Natatsuka M, Schreiber SL. Science 1990;248:863. [PubMed: 1693013]
- Schreiber SL, Albers MW, Brown EJ. Acc. Chem. Res 1993;26:412.
- (a) Harding MW, Galat A, Uehling DE, Schreiber SL. Nature 1989;341:758. [PubMed: 2477715] (b) Seikierka JH, Hung SHY, Poe M, Lin CS, Sigal NH. Nature 1989;341:755. [PubMed: 2477714]
- (a) Nicolaou KC, Chakraborty TK, Piscopio AD, Minowa N, Bertinato P. J. Am. Chem. Soc 1993;115:4419. (b) Romo D, Meyer SD, Johnson DD, Schreiber SL. J. Am. Chem. Soc 1993;115:7906. (c) Hayward CM, Yohannes D, Danishefsky SJ. J. Am. Chem. Soc 1993;115:9345. (d) Smith AB III, Condon SM, McCauley JA, Leazer JL Jr, Leahy JW, Maleczka RE Jr. J. Am. Chem. Soc 1995;117:5407. (e) Ball M, Gaunt MJ, Hook DF, Jessiman AS, Kawahara S, Orsini P, Sclaro A, Talbot AC, Tanner HR, Yamanoi S, Ley SV. Angew. Chem. Int. Ed 2005;44:5433. (f) Maddess ML, Tackett MN, Watanabe H, Brennan PE, Spilling CD, Scott JS, Osborn DP, Ley SV. Angew. Chem. Int. Ed 2007;46:591.
- (a) Jones TK, Mills SG, Reamer RA, Askin D, Desmond R, Volante RP, Shinkai I. J. Am. Chem. Soc 1989;111:1157. (b) Jones TK, Reamer RA, Desmond R, Mills SG. J. Am. Chem. Soc 1990;112:2998. (c) Nakatsuka M, Ragan JA, Sammakia T, Smith DB, Uehling DE, Schreiber SL. J. Am. Chem. Soc 1990;112:5583. (d) Ireland RE, Gleason SL, Gegnas LD, Highsmith TK. J. Org. Chem 1996;61:6856. [PubMed: 11667580] (e) Ireland RE, Liu L, Roper TD. Tetrahedron 1997;53:13221. (f) Ireland RE, Liu L, Roper TD, Gleason JL. Tetrahedron 1997;53:13257.
- (a) Kocienski P, Stocks M, Donald D, Cooper M, Mannes A. Tetrahedron Lett 1988;29:4481. (b) Williams DR, Benbow JW. J. Org. Chem 1988;53:4643. (c) Egbertson M, Danishefsky SJ. J. Org. Chem 1989;54:11. (d) Wasserman HH, Rotello VM, Williams DR, Benbow JW. J. Org. Chem 1989;54:2785. (e) Rama Rao AV, Chakraborty TK, Laxma Reddy K. Tetrahedron Lett 1990;31:1439. (f) Linde RG II, Jeroncic LO, Danishefsky SJ. J. Org. Chem 1991;56:2354. (g) Hoffman RV, Huizenga DJ. J. Org. Chem 1991;56:6435. (h) Batchelor MJ, Gillespie RJ, Golec JMC, Hedgecock

- CJR. *Tetrahedron Lett* 1993;34:167. (i) Pattenden G, Tankard M. *Tetrahedron Lett* 1993;34:2677. (j) Rama Rao AV, Desibhatla V. *Tetrahedron Lett* 1993;34:711.
12. Corey EJ, Hua DH, Pan B-C, Seitz SP. *J. Am Chem. Soc* 1982;104:6818.
 13. Matsuda F, Terashima S. *Tetrahedron* 1988;44:4721.
 14. Schuda PF, Heimann MR. *Tetrahedron* 1983;24:4267.
 15. Nicolaou KC, Daines RA, Uenishi J, Li WS, Papahatjis DP, Chakraborty TK. *J. Am. Chem. Soc* 1988;110:4672.
 16. White JD, Kawasaki M. *J. Am. Chem. Soc* 1990;112:4991.
 17. Kozikowski AP, Chen Y-Y, Wang BC. *Tetrahedron* 1984;40:2345.
 18. Imamoto T, Sugiura Y, Nobuyuki T. *J. Org. Chem* 1965;30:3885.
 19. Rand L, Mohar AF. *Tetrahedron Lett* 1984;25:4233.
 20. Ley SV, Norman J, Pinel C. *Tetrahedron Lett* 1994;35:2095.
 21. White JD, Vedananda TR, Kang M, Choudhry S. *J. Am Chem. Soc* 1986;108:8105.
 22. White JD, Avery MA, Choudhry SC, Dhingra OP, Gray BD, Kang M, Kuo S, Whittle AJ. *J. Am Chem. Soc* 1989;111:790.
 23. White JD, Jeffrey SC. *J. Am Chem. Soc* 1996;61:2600.
 24. Lee SD, Chan TH, Kwon KS. *Tetrahedron Lett* 1984:3399.
 25. Takano S, Hatakeyama S, Ogasawara K. *J. Chem. Soc. Chem. Commun* 1977:68.
 26. Dalcanale E, Montanari F. *J. Org. Chem* 1986;51:567.
 27. Rubottom GM, Vazquez MA, Pelegrina DR. *Tetrahedron Lett* 1974:4319.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.