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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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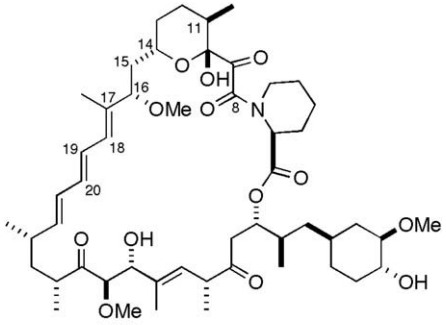
ABSTRACT

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**.

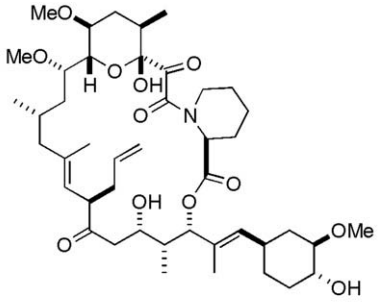
1. Introduction

In 1975, a substance named rapamycin (**1**) was isolated from the soil fungus *Streptomyces hygroscopicus* during a search for naturally occurring antifungal agents.[1] Although the antifungal properties of **1** were not particularly impressive, it later became apparent that rapamycin was a potent immunosuppressant[2] 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 graph 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]

The pipecolic 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 isomerase[5] 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



Rapamycin (1)



FK-506 (2)

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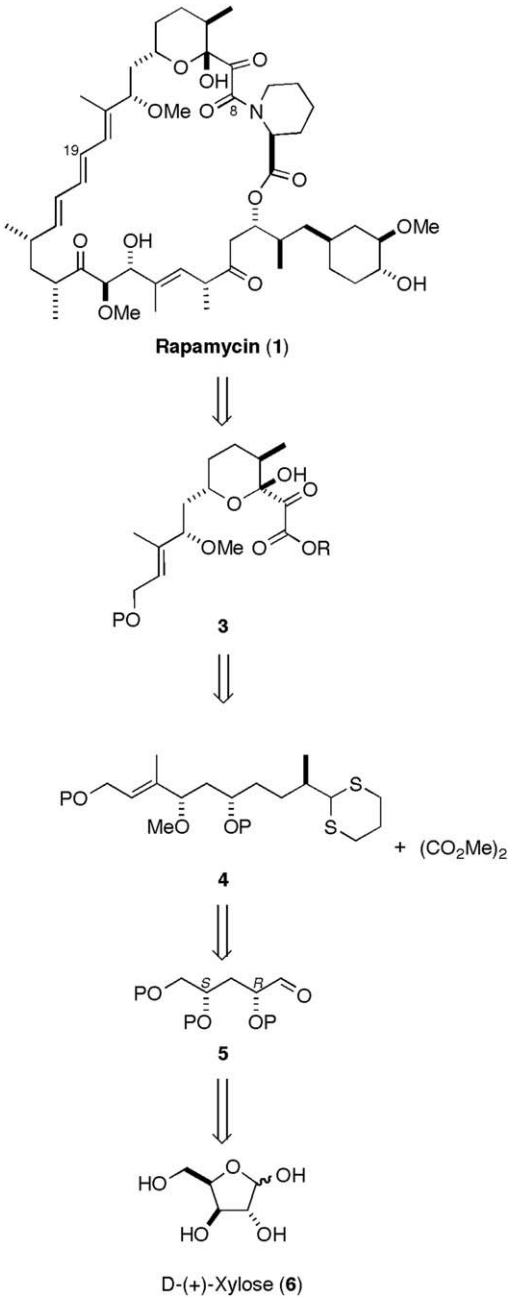
terminal portion of this 'northern' domain of **1** is a pivotal component of the architecture of this macrolide.

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 rapamycin[9] 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.

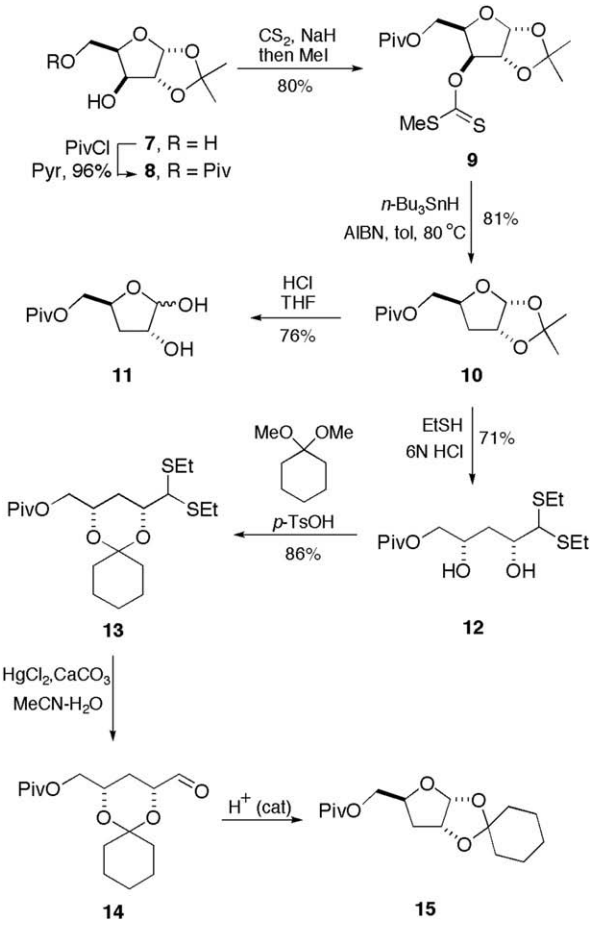


Scheme 1.

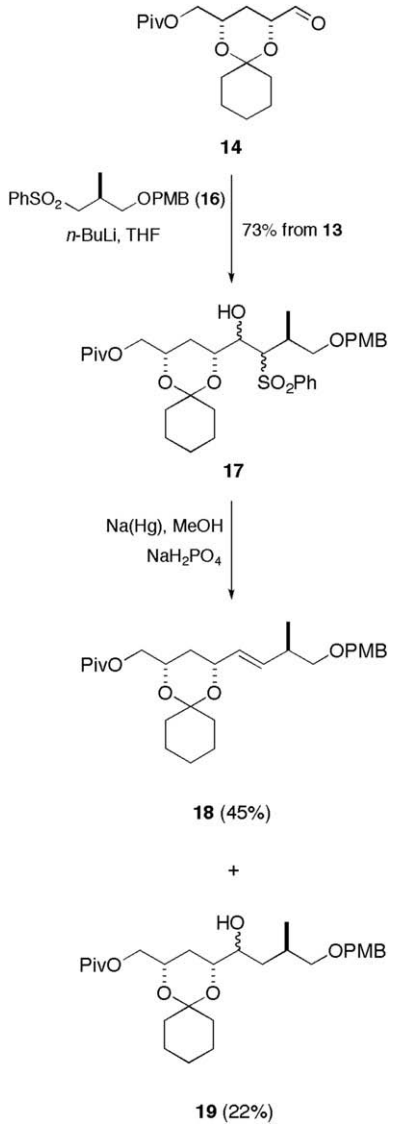
2. Results and discussion

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 chloride[14] 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 acetonide **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



Scheme 2.



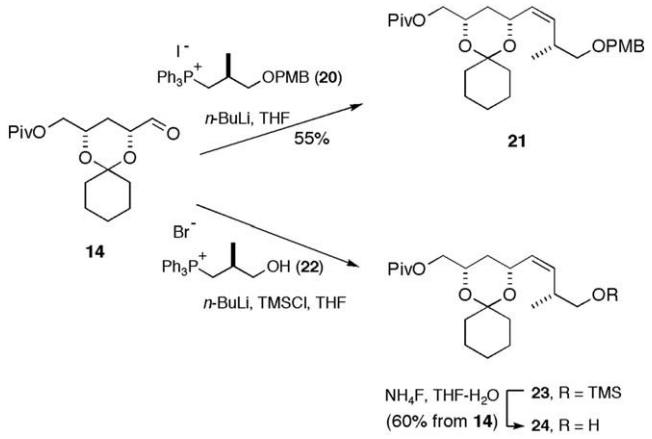
Scheme 3.

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**.

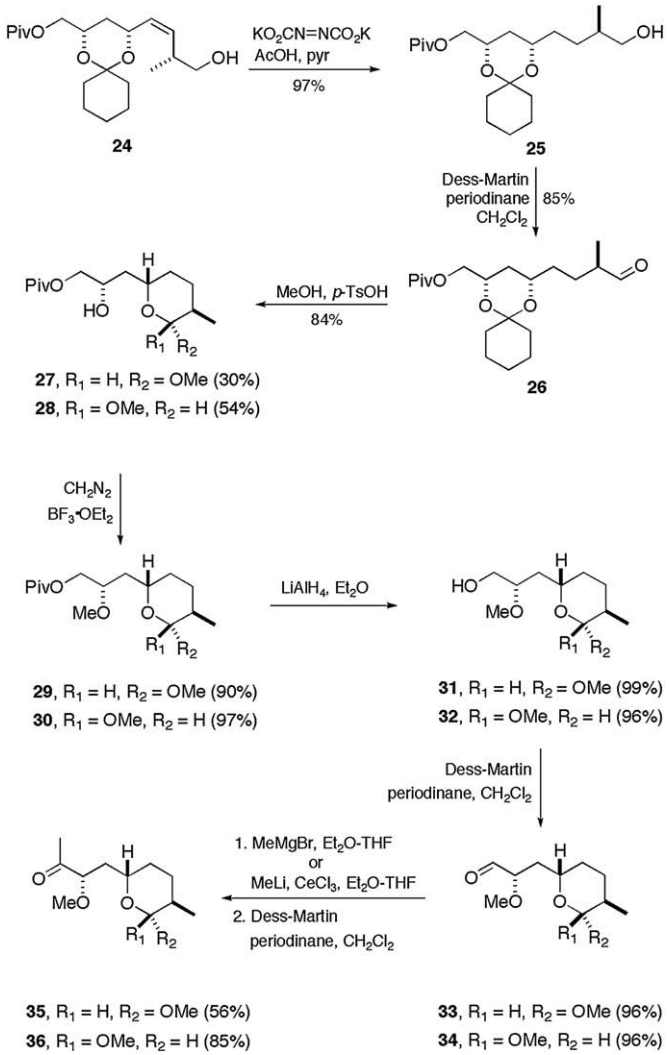
An initial attempt along this line was disappointing since the ylide from phosphonium iodide **20** produced cis alkene **21** in only fair yield (Scheme 4). A more effective option proved to be use of the ylide from phosphonium salt **22** in the presence of trimethylsilyl chloride,[17] a process that 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

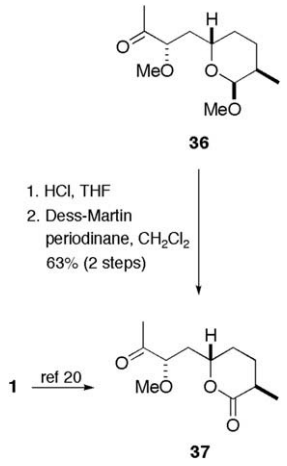


Scheme 4.

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**

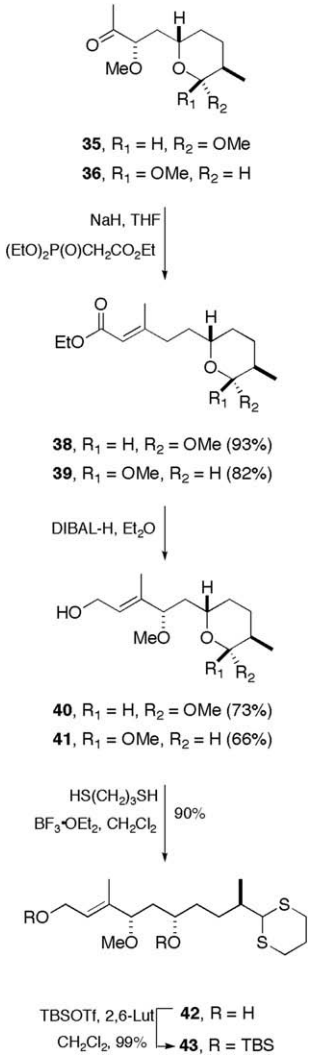


Scheme 5.



Scheme 6.

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.



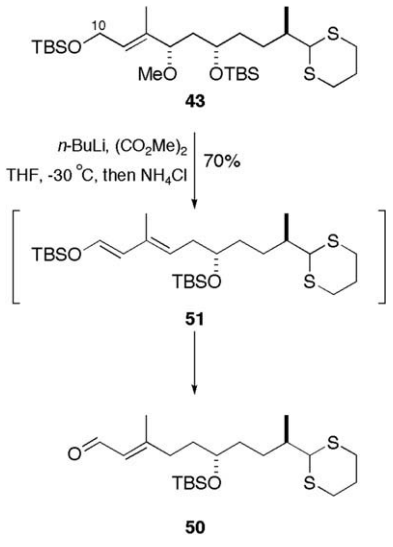
Scheme 7.

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 ^{13}C 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 isomerizaton of the trisubstituted alkene into conjugation.

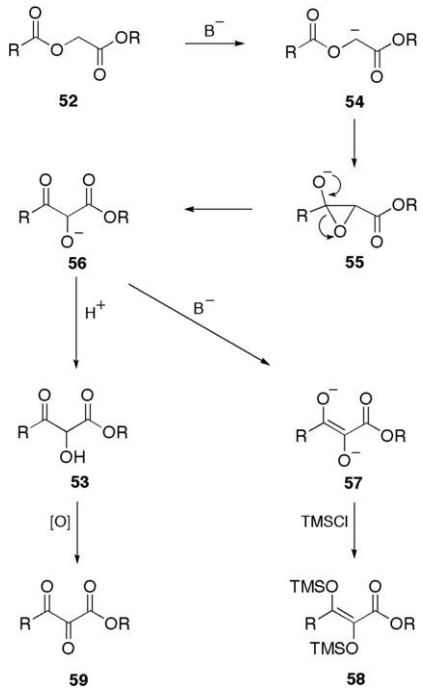


Scheme 8.

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 aplasmomycin[21] 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→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**.

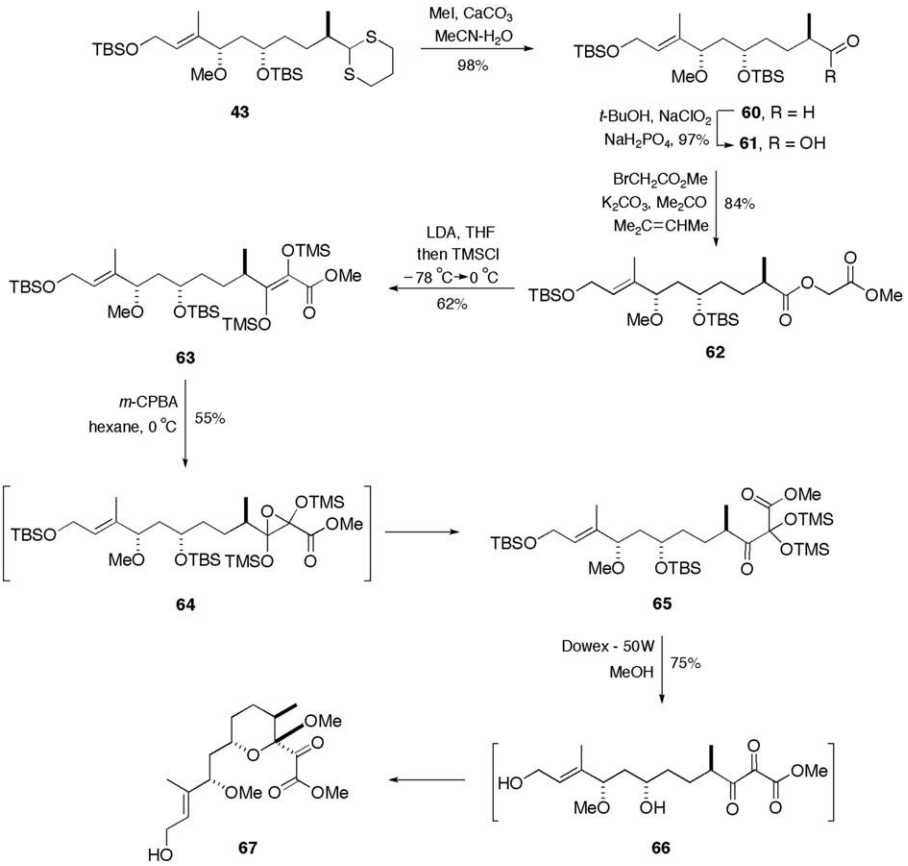


Scheme 9.

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 Rubuttom[27] 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 acylic 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



Scheme 10.

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%.

Acknowledgements

We are indebted to Professor Steven Ley and Michael Willis, Cambridge University, for ^{1}H and ^{13}C NMR spectra of **37**. This research was assisted financially by the National Institutes of Health through Grant No. GM50574.

Supplementary data

Experimental procedures and characterization data for new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.026.

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