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Application of stereocontrolled aldol coupling to synthesis of segments of immunosuppressants FK-506 and rapamycin

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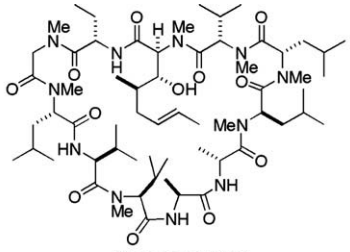
ABSTRACT

The sector comprising C24–C34 of FK-506 containing five of the stereogenic centers in this macrolide was synthesized from (−)-quinic acid. Aldol coupling of the C24–C34 unit with a methyl ketone representing C20–C23 of FK-506 proceeded with complete Felkin stereoselectivity to afford the C20–C34 portion of the immunosuppressant. A chelate transition state invoking coordination of a lithium enolate with a trityl ether is proposed to explain this stereoselectivity. The strategy adopted for construction of the C26–C34 moiety of FK-506 was extended to the C34–C42 subunit of rapamycin. A Mukaiyama asymmetric *anti*-aldol coupling was used to set in place the vicinal diol functionality at C27,28 in the C26–C33 segment of this macrolide.

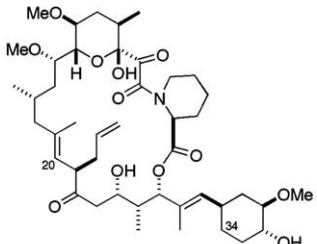
1. Introduction

Suppression of the immune response is an important and generally necessary adjuvant of surgical procedures involving organ or tissue transplantation.[1] The search for immunosuppressive agents effective in treating host versus graft disease, i.e., tissue rejection, has centered principally on substances that interfere with the production of lymphokines by T lymphocytes.[2] This technique suppresses the formation of antibodies against cell surface antigens of transplanted tissue. The cyclic peptide cyclosporine A (**1**) has long been considered the gold standard in clinical medicine for treatment of host versus graft disease but its prolonged use carries risks of side effects.[3] The nephrotoxicity of cyclosporine A is a particular concern in this regard.

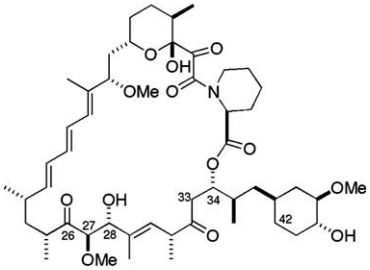
In 1987, an antibiotic FK-506 (**2**) was isolated from the soil fungus *Streptomyces tsukubaensis* and was found to possess immunosuppressive properties similar to cyclosporine A.[4] In contrast to cyclosporine A, FK-506 displays no serious side effects. Discovery of the immunosuppressive action of FK-506 rekindled interest in a structurally similar natural product rapamycin (**3**) that had been isolated in 1975 from *Streptomyces hygroscopicus* before cyclosporine A and FK-506 were known.[5] Originally investigated for its antifungal properties, rapamycin was subsequently found to suppress the immune response in rats and is now recognized as a clinically useful immunosuppressive drug.[6]



Cyclosporin A (1)



FK-506 (2)



Rapamycin (3)

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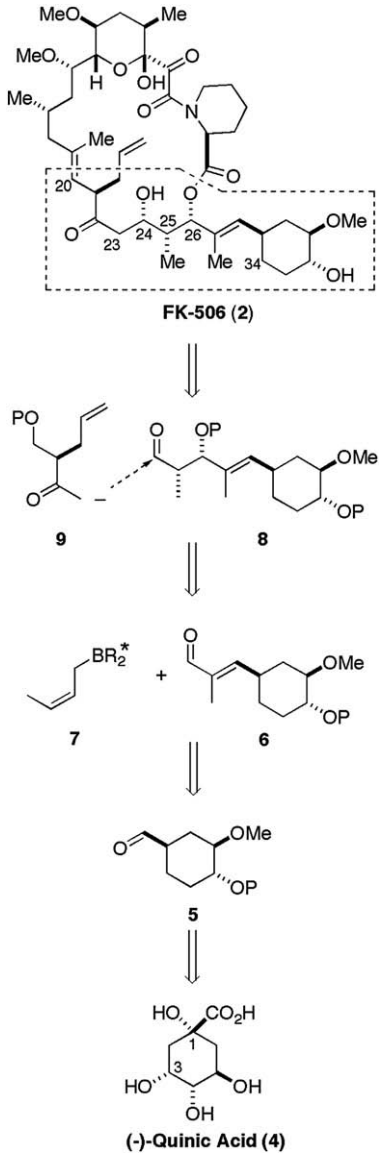
The complex architecture of **2** and **3** has inspired a variety of approaches to their synthesis, resulting in five completed syntheses of rapamycin[7] and three of FK-506.[8] The presence of structural motifs common to **2** and **3**, particularly a 1,2,4-trisubstituted cyclohexane bearing a polyketide derived side chain,[9] led us to propose a synthetic pathway to this segment which could provide access to the corresponding subunits of FK-506 and rapamycin. In this report, we describe a route to the C20–C34 portion of FK-506[10] and its extension to a subunit of rapamycin. A key feature of our synthesis of the C26–C33 portion of **3** is an asymmetric *anti*-aldol reaction that correctly installs vicinal oxygen substituents at C27 and C28.[11]

Our strategy for constructing the trisubstituted cyclohexane portion of FK-506 and rapamycin envisioned (−)-quinic acid (**4**) as the point of departure (Scheme 1). Although this required stripping away superfluous hydroxyl groups at C1 and C3 of **4**, procedures already developed in our laboratory[12] together with the ready availability of enantiomerically pure quinic acid made this approach not only economically attractive but eminently feasible. The first objective in this scenario was synthesis of cyclohexanecarboxaldehyde **5** which would be advanced to α,β-unsaturated aldehyde **6**. Asymmetric crotylation of **6** with chiral boronate **7**[13] would set in place *syn* substituents corresponding to the C25 methyl group and C26 oxygen function of FK-506. Stereocontrolled aldol coupling of aldehyde **8** with methyl ketone **9** would then afford the complete C20–C34 sector of FK-506 containing all seven of its stereocenters in the correct orientation.

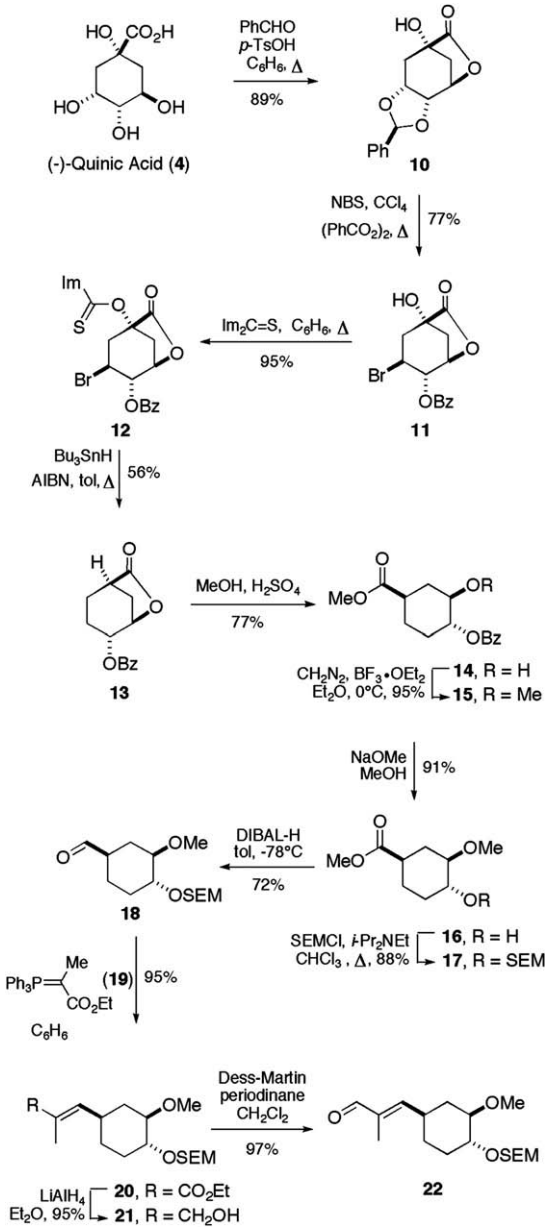


Scheme 1.

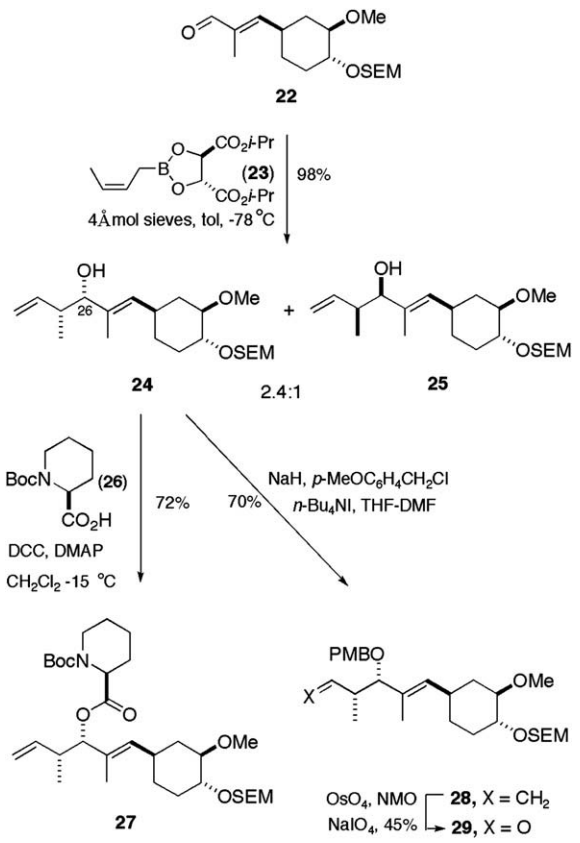
2. Results and discussion

2.1. FK-506 (2): C20–C34 subunit

As previously described, exposure of (−)-quinic acid (**4**) to benzaldehyde in the presence of an acidic catalyst afforded lactone **10**[14] (Scheme 2) which was oxidized with *N*-bromosuccinimide and benzoyl peroxide to bromo benzoate **11**.[15] The tertiary hydroxyl of **11** was removed by reduction of the derived imidazoyl thioate **12**[16] with tri-*n*-butylstannane to give **13**. Acidic methanolysis of this lactone produced hydroxy ester **14** which was reacted with diazomethane in the presence of boron trifluoride etherate to yield methyl ether **15**. Basic methanolysis of **15** cleaved the benzoate and furnished alcohol **16** which was protected as its SEM ether **17**. Reduction of ester **17** to aldehyde **18** followed by Wittig olefination with phosphorane **19** furnished (*Z*) unsaturated ester **20** as a single



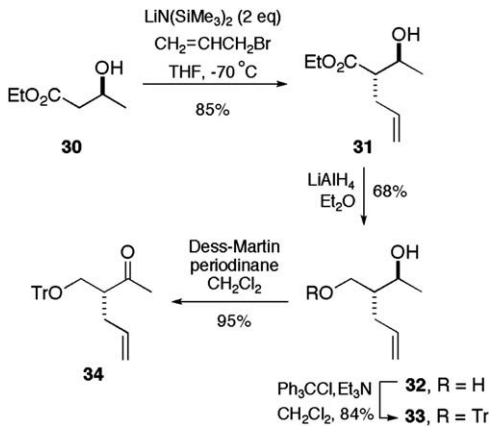
Scheme 2.



Scheme 3.

isomer. Subsequent reduction of **20** to alcohol **21** followed by oxidation of the latter with Dess–Martin periodinane gave α,β-unsaturated aldehyde **22**. This improved ten-step sequence from (−)-quinic acid to the C26–C34 portion of **2** proceeds in an overall 15% yield from a readily available, enantiomerically pure starting material and is easily scalable.

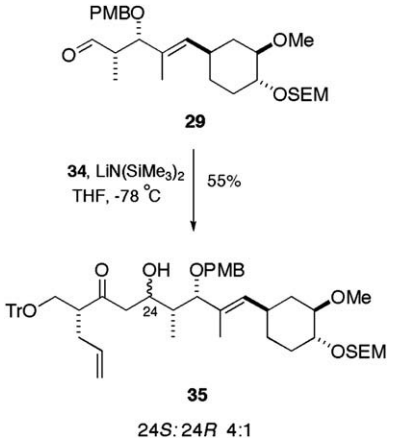
Treatment of aldehyde **22** with (*Z*)-crotylboronate **23**, prepared from the corresponding diethanolamine complex and (*R*,*R*)-diisopropyl tartrate,[13] at low temperature resulted in an excellent yield of *syn* homoallylic alcohols **24** and **25** (Scheme 3). Although the ratio of desired alcohol **24** to its diastereomer **25** was only 2.4:1, **24** was readily separable from the mixture. It had been our initial intention to attach the pipecolate residue of FK-506 at C26 of **24** by esterification with *N*-Boc pipecolic acid (**26**)[17] and then cleave the terminal alkene to an aldehyde. However, although esterification of **24** with **26** proceeded efficiently, oxidative cleavage of **27** produced an intractable mixture in which none of the desired aldehyde was present. In light of this result, a different route from alcohol **24** was investigated in which **24** was converted to its *p*-methoxybenzyl (PMB) ether **28**. This diene upon Lemieux–Johnson oxidation underwent clean scission of the vinyl group to afford aldehyde **29** in acceptable yield.



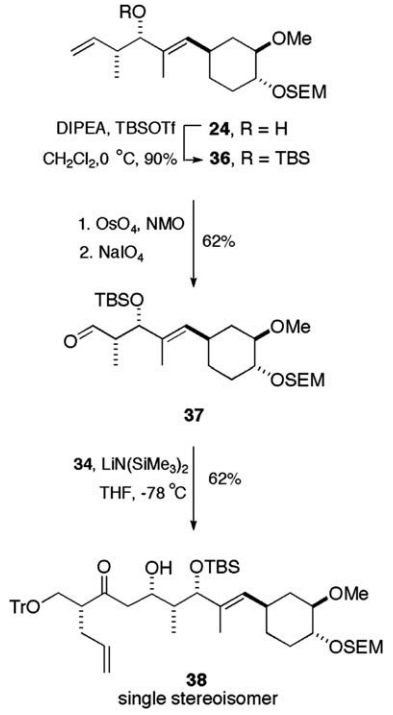
Scheme 4.

The plan outlined in Scheme 1 for appending a C20–C23 subunit **9** to aldehyde **8** called for aldol coupling of the latter with a protected (*R*)-2-allyl-3-oxobutanol. Synthesis of this ketone began with allylation of the dianion of (*S*)-ethyl 3-hydroxybutyrate (**30**) to give **31**,[18] reduction of which yielded diol **32** (Scheme 4). The primary alcohol **32** was protected as its trityl ether **33** and the secondary alcohol was oxidized to ketone **34**.

Aldol coupling of the lithium enolate of **34** with aldehyde **29** at low temperature produced β-hydroxy ketone **35** as a 4:1 mixture of C24 epimers (Scheme 5).[19] Modification of the reaction conditions did not appreciably change this ratio. Assignment of configuration at C24 of **35** was made by converting the mixture to a cyclic *p*-methoxyphenyl acetal by treatment with DDQ and using NOE experiments to establish the *syn* relationship of C24 and C26 hydrogens. This analysis proved that the major alcohol from **29** and **34** possessed (24*S*) configuration and was therefore the result of Felkin addition.



Scheme 5.



Scheme 6.

The mixture of epimers produced in the aldol coupling of **29** with **34** led us to suspect that the *p*-methoxybenzyl ether of **29** had played a spoiler role in this reaction through its complexation with the lithium enolate of **34**, thus leading to diminished stereoselectivity. In order to test this postulate, alcohol **24** was silylated and the resulting alkene **36** was cleaved oxidatively to aldehyde **37** (Scheme 6). In this case, coupling of the lithium enolate of **34** with **37** produced a *single aldol product* **38** with (24*S*) configuration corresponding to the major diastereomer of **35** from **29**. A proposed transition state for coupling of **37** with **34** is shown in Figure 1, where Felkin approach of reactants is reinforced by complexation of the lithium enolate of **34** with the trityl ether oxygen. It is likely that this complexation is disrupted by the *p*-methoxybenzyl ether of **29** resulting in an 'intrinsic' Felkin distribution of ca. 4:1.

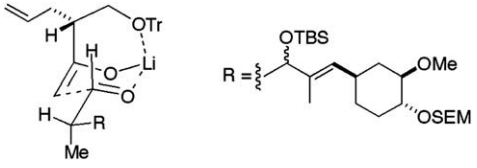


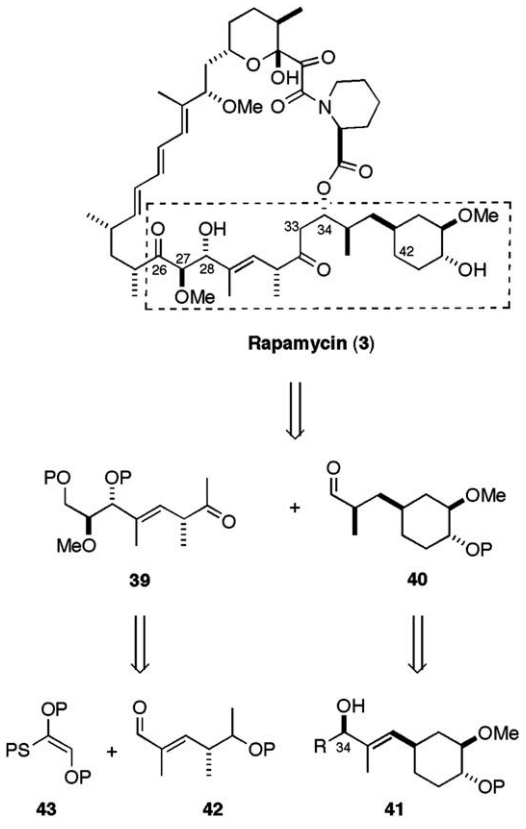
Figure 1. Chelate transition state for coupling of **34** with **37** to yield **38**.

The route to the C20–C34 subunit of FK-506 described above completes a portion of the structure that houses seven of the fourteen stereogenic centers. Further elaboration from **38** requires its connection to the tricarbonyl segment embedded in the C1–C19 section of the macrolide. Efforts along this line will be described in a future publication.

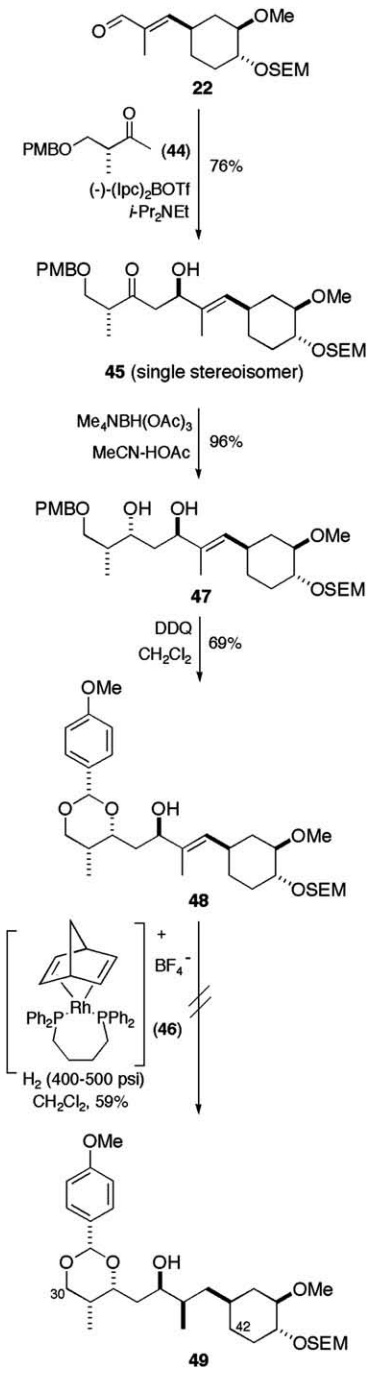
2.2. Rapamycin (3): C34–C42 subunit

Our strategy for assembling the C26–C42 segment of rapamycin (**3**) envisioned an aldol connection at C33–C34 between ketone **39** and aldehyde **40** (Scheme 7). The latter is the saturated version of **22** used in our approach to FK-506 and it was assumed that the distinguishing feature of **40**, its (35*R*) methyl substituent, could be installed via directed hydrogenation of (*E*)-alkene **41**. If this hydrogenation was to be guided by a suitably positioned allylic alcohol at C34, as in Brown's model which posits *anti*-selective delivery of hydrogen in the homogeneous hydrogenation of acyclic allylic alcohols by a coordinated rhodium species,[20] we presumed that a (34*R*) hydroxyl substituent was needed for our purpose. The assumption underlying this plan was that a relatively hindered trisubstituted alkene would respond selectively to our hydrogenation conditions.

Asymmetric aldol coupling of the (−)-isopinylcampheylboron enolate of ketone **44**[21] with aldehyde **22** gave allylic alcohol **45** as a single stereoisomer (Scheme 8). However, attempts to



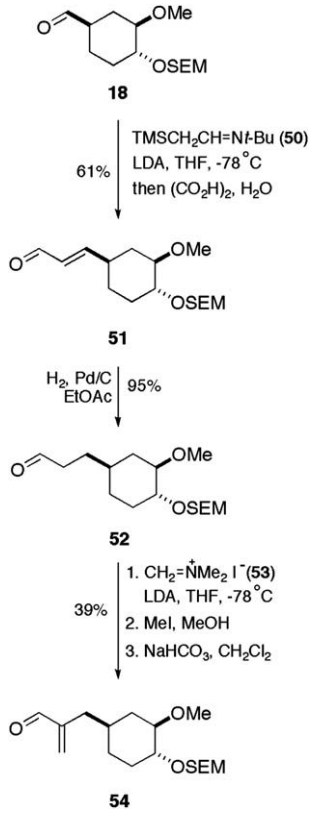
Scheme 7.



Scheme 8.

hydrogenate alkene **45** in the presence of rhodium catalyst **46**[22] produced a mixture in which both the ketone and olefin had been saturated. Therefore, ketone **45** was reduced with tetramethylammonium acetoxyborohydride to *anti* diol **47**,[23] which upon dehydrogenation with DDQ furnished acetal **48**. Unfortunately, exposure of alkene **48** to hydrogen under pressure in the presence of **46** failed to give more than a trace of **49**.

The disappointing outcome from hydrogenation of **48** and a subsequent examination of hydrogenation studies carried out by Kinoshita[24] suggested that an *exo* methylene function would be a better substrate for alcohol-directed hydrogenation. Implementation of this plan required a return to aldehyde **18**, and addition of the lithio anion of imine **50**[25] to **18** followed by acid-catalyzed Peterson elimination cleanly furnished (*E*)-enal **51** (Scheme 9). Catalytic hydrogenation of **51** produced saturated aldehyde **52** which was subjected to a Mannich reaction with Eschenmoser's salt **53**[26] to give the unstable acrolein derivative **54**. Unfortunately, rapid polymerization of **54** made this substance unusable as a progenitor of the C34–C42 segment of rapamycin and it is now clear that an alternative to **22** or **54** will be needed to install the (35*R*) methyl substituent of rapamycin.

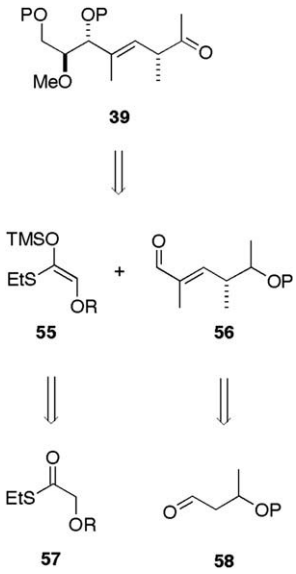


Scheme 9.

2.3. Rapamycin (3): C26–C33 segment

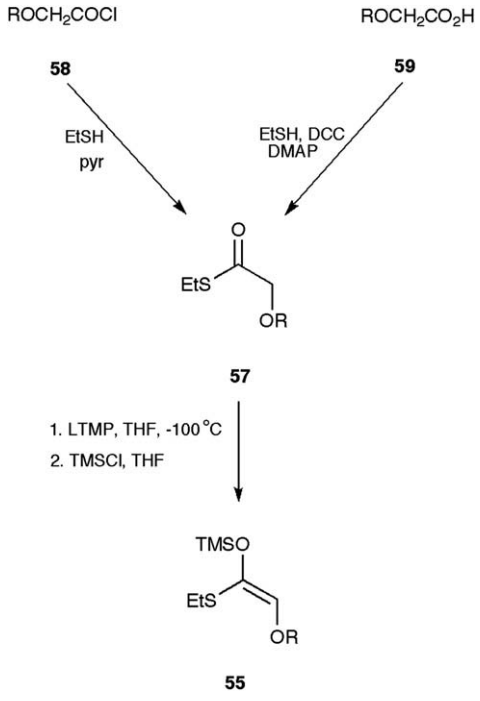
Ketone **39** envisioned as the aldol partner for **40** in Scheme 7 presents the challenge of establishing an *anti* diol moiety at C27,28. For this construction, we planned to draw upon a reaction devised by Mukaiyama and Kobayashi[27] and exemplified in Fukuyama's synthesis of leinomycin[28] which employs asymmetric coupling of an α-alkoxythioketene acetal **55** with an enal **56** (Scheme 10). These components are derived from thioglycolate **57** and aldehyde **58**, respectively.

Uncertainty regarding the feasibility of asymmetric addition of **55** to an α,β-unsaturated aldehyde such as **56** caused us to first examine the reaction in the context of the simple enal tiglaldehyde.



Scheme 10.

Alkoxythioketene acetals (**55**) were prepared by silylation at low temperature of the corresponding α-alkoxythioacetate ester (**57**) in the presence of lithium tetramethylpiperidide and were obtained predominately as (*Z*) isomers (Scheme 11). Esters **57** were obtained from either α-alkoxyacetyl chlorides **58** or from the corresponding α-alkoxycarboxylic acids **59** (Table 1).[27b]



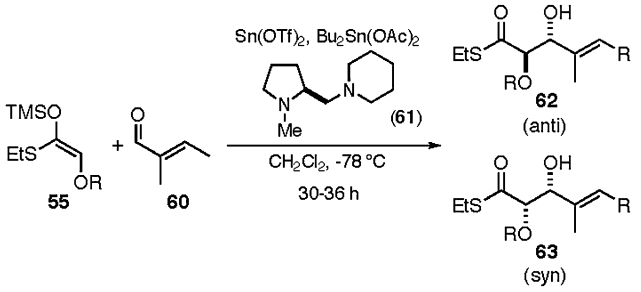
Scheme 11.

Table 1
Synthesis of α-alkoxythiol esters **57** and α-alkoxythioketene acetals **55**

Entry	Starting materials	**57**		**55**	
		R	Yield (%)	Yield (%)	*Z*:*E*
1	**58**	Me	88	36	4:1
2	**58**	Bn	88	92	12:1
3	**59**	PMB	72	76	10:1
4	**59**	3,4-DMB	67	58	6:1

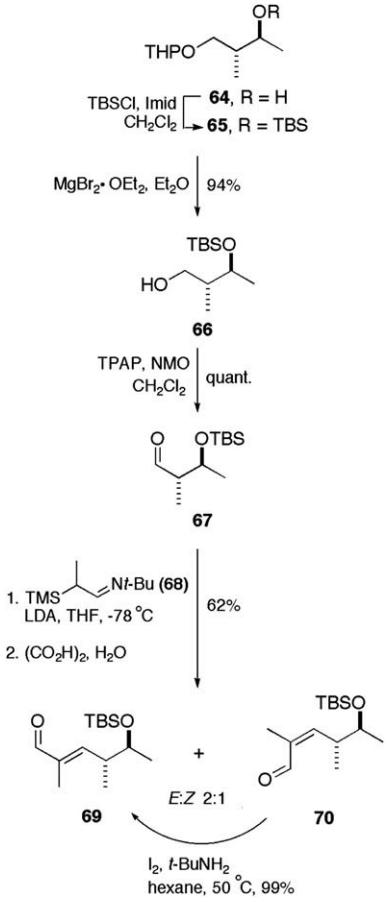
Exposure of tiglaldehyde (**60**) to ketene thioacetals **55**, tin(II) triflate, di-*n*-butyltin diacetate and (*S*)-1-methyl-2-[(1-piperidyl)methyl]pyrrolidine (**61**)[29] gave *anti* and *syn* aldol products **62** and **63**, respectively, in good yield for R=Bn, PMB, and 3,4-DMB and with good relative and absolute stereoselectivity for *anti* diol **63** (Table 2). In practical terms, the optimal thioketene acetal for this asymmetric *anti* aldol coupling was that prepared from 3,4-dimethoxybenzyloxyacetic acid (entry 4).

Table 2
Reaction of α-alkoxythioketene acetals (**55**) with tiglaldehyde (**60**)

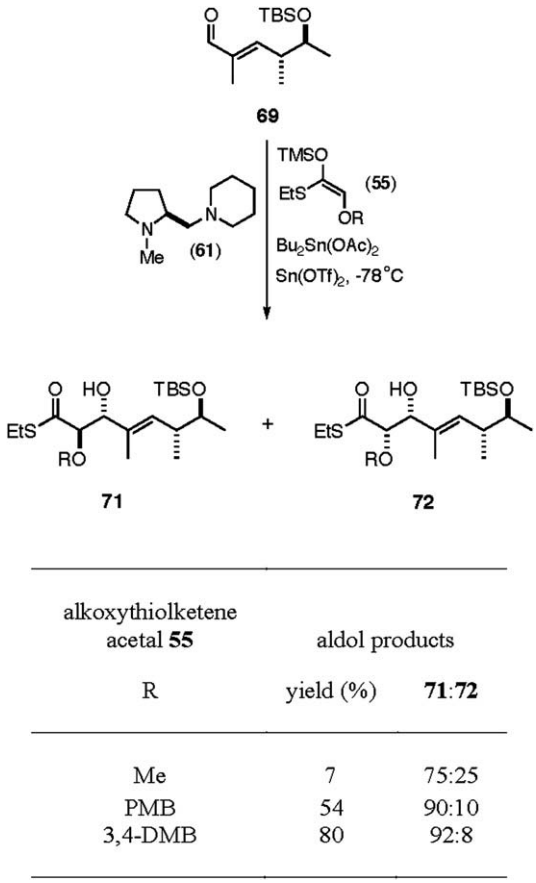


Entry	Ketene acetal (**55**) R	Aldol products		
		Yield (%)	**62**:**63**	ee of **62** (%)
1	Me	32	70:30	87
2	Bn	82	85:15	93
3	PMB	74	90:10	96
4	3,4-DMB	80	95:5	92

The projected enol partner for **55** was prepared from alcohol **64** (Scheme 12), the enantiomer of a substance previously obtained by Baker from methyl (*S*)-3-hydroxy-2-methylpropionate.[30] After protection of **64** as silyl ether **65**, the primary alcohol was unmasked and **66** was oxidized to aldehyde **67** with catalytic perruthenate.[31] Condensation of **67** with the lithio anion of imine **68**,[32] followed by acid-catalyzed Peterson elimination and hydrolysis of the imine,[27] produced a mixture of α,β-unsaturated aldehydes **69** and **70** in the ratio 2:1, respectively. The (*Z*)-enal **70** underwent clean isomerization to (*E*)-aldehyde **69** in the presence of catalytic quantities of iodine and *tert*-butylamine in warm hexane.[33]



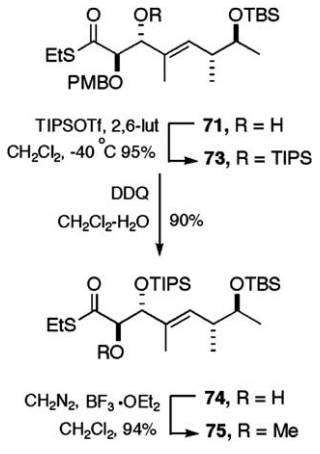
Scheme 12.



alkoxythiolketene acetal **55**	aldol products	
R	yield (%)	**71**:**72**
Me	7	75:25
PMB	54	90:10
3,4-DMB	80	92:8

Scheme 13.

Asymmetric coupling of **69** with alkoxythioketene acetals **55** (R=Me, PMB, and 3,4-DMB) under conditions used with tiglaldehyde (**60**) afforded *anti*-aldol product **71** along with *syn* product **72** in yields and ratios that were dependent on the substituent R (Scheme 13). As with **60**, the optimal reaction favoring *anti* product **71** was observed with the ketene acetal prepared from ethyl 3,4-



Scheme 14.

dimethoxybenzyloxythiolate (**55**, R=3,4-DMB). *Thus, increased electron donation into the ketene enhances both yield and stereoselectivity in this asymmetric aldol reaction*.

Hydroxythiol ester **71** obtained above was advanced via silylation of the free alcohol to its TIPS ether **73**; subsequent cleavage of the *p*-methoxybenzyl ether then furnished **74** (Scheme 14). This alcohol was reacted with diazomethane to yield methyl ether **75** representing C26–C33 of rapamycin. This fragment will be linked to C34–C42 subunit **43** for eventual assembly of the framed segment of **3** shown in Scheme 7.

3. Conclusion

Enantiopure quinic acid provides a useful starting material for acquiring the 1,3,4-trisubstituted cyclohexane unit of FK-506 and rapamycin. The key C23–C24 connection for FK-506 can be forged with complete stereospecificity by means of an aldol coupling, leading to a fragment in which all seven of the stereogenic centers as well as the (*E*)-trisubstituted alkene in the C20–C42 segment of the macrolide are installed correctly. Unfortunately, the 35(*R*) methyl configuration of rapamycin is not solved by this approach. Nevertheless, an asymmetric aldol protocol does permit access to the *anti* diol unit present in the C26–C33 sector of this immunosuppressant.

Acknowledgements

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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.2009.06.030.

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