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A Synthesis of C1-C22 Fragment of the Immunosuppressant FK 506. Stereoselective Construction of (*E*)-Trisubstituted Double Bond (C19-C20) via Ester-enolate Claisen Rearrangement

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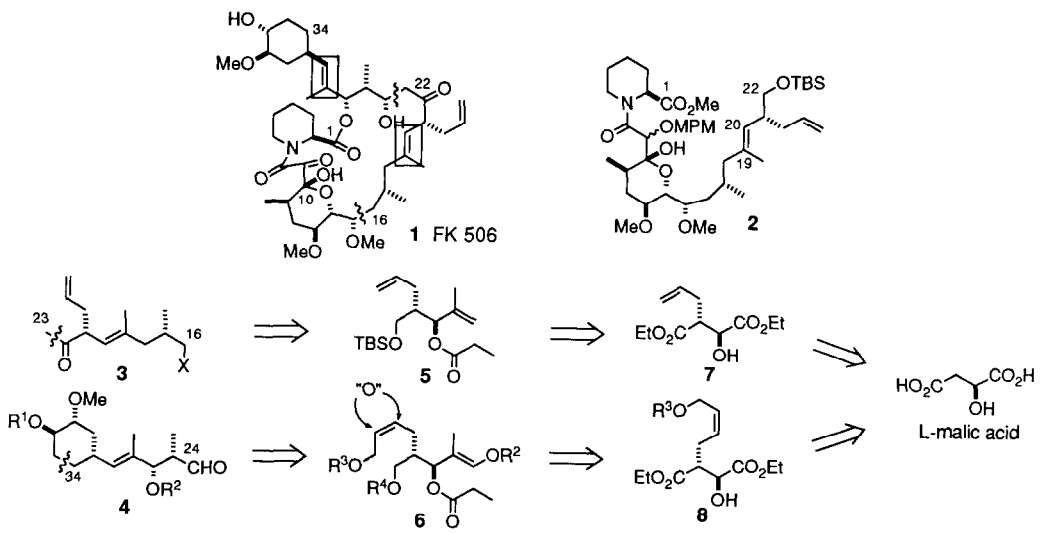
Key Words: FK 506; immunosuppressive agent; (*E*)-trisubstituted double bond; ester-enolate Claisen rearrangement; *anti*-selective.

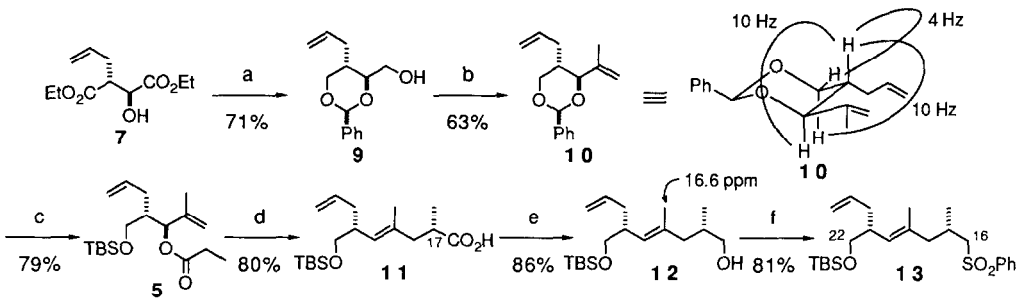
Abstract: An ene-ester **5** prepared from L-malic acid was subjected to the ester-enolate Claisen rearrangement under Ireland's condition to give stereoselectively C16-C22 fragment **11** containing (*E*)-trisubstituted double bond which was further advanced to C1-C22 fragment **2** by sequential coupling with C10-C15 and C1-C9 fragments.

Current interest in the novel macrocyclic lactone FK 506 (**1**), the potent immunosuppressive agent isolated from *Streptomyces tsukubaensis*,[1] has prompted extensive work[2] directed toward the synthesis of this substance. Although four total syntheses[3] of **1** including two formal ones have been reported at present, it seems that it is still necessary to accomplish an efficient synthesis and higher stereoselectivity of C19-C20 (*E*)-trisubstituted double bond in every cases.

In such context we focused on two (*E*)-trisubstituted olefin in the molecule and planned the strategy based on the ester-enolate Claisen rearrangement[4] starting from common chiral source to construct stereoselectively the olefin (Scheme 1). That is, the (*E*)-trisubstituted olefin in the two fragments **3** and **4** divided at the aldol region in a C16-C34 chain of **1** will be synthesized by Claisen rearrangement with ene-esters **5** and **6**, respectively, in which the *anti*-relationship can be easily obtained by *anti*-selective Seebach's alkylation[5] of L-diethyl malate. In this communication we would like to report a highly stereocontrolled synthesis of the C16-C22 fragment **13**



Scheme 1.



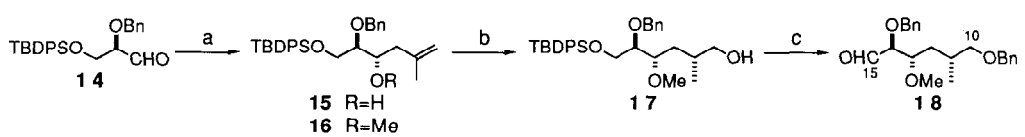
(a) 1) $LiAlH_4$ / THF, rt, 2 h; 2) $PhCH(OMe)_2$, CSA / CH_2Cl_2, rt, 4 h. (b) 1) $(COCl)_2$, DMSO / CH_2Cl_2, then Et_3N; 2) MeLi / Et_2O, rt, 2 h; 3) $(COCl)_2$, DMSO / CH_2Cl_2, then Et_3N; 4) $Ph_3P{=}CH_2$ / THF, rt, 6 h. (c) 1) AcOH-THF-H_2O, 60 °C, 3 h; 2) TBSCl, Et_3N, DMAP / CH_2Cl_2, rt, 3 h; 3) $CH_3CH_2CO_2H$, DCC, DMAP / CH_2Cl_2, rt. (d) LDA, TBSCl / 23% HMPA-THF, -78 °C to reflux, 2.5 h, then NaOH, rt, 30 min. (e) $LiAlH_4$ / THF, rt, 30 min. (f) 1) MsCl, Et_3N / CH_2Cl_2, 0 °C, 30 min; 2) NaI / acetone, reflux; 3) $PhSO_2Na$ / DMF, 80 °C, 15 h.

Scheme 2.

revealing the potentiality for this strategy, [3,3]-sigmatropic rearrangement,[6] and the extension of **13** to C1-C22 fragment **2** by a convergent assembly.

A six-membered benzylidene acetal **9** was provided by reduction of the diester **7**[5] which could be diastereoselectively prepared by *anti*-selective allylation of L-diethyl malate and subsequent regioselective acetalization of the resulting triol (Scheme 2). The acetal **9** was subjected to usual procedures to give diene **10** whose *anti*-stereochemistry was secured from coupling constants in its ^1H NMR spectrum as shown in **10**. The ene-ester **5**, substrate for the ester-enolate Claisen rearrangement, was synthesized by an acidic hydrolysis of **10**, protection of the primary alcohol as a *tert*-butyldimethylsilyl ether,[7] and esterfication of the secondary alcohol.[8] Treatment of **5** with lithium diisopropylamide and *tert*-butylchlorodimethylsilane in 23% HMPA-THF at -78 °C, generating (*Z*)-silyl ketene acetal,[4] followed by heating to reflux for 2.5 h afforded stereoselectively carboxylic acid **11** after alkaline work-up with complete control[9] of the (*E*)-olefin and high chirality transfer to C17 (α:β=20:1, ratio by 400 MHz ^1H NMR). Finally, manipulation of the functionality led **11** to a highly stereocontrolled (*E*)-trisubstituted olefin **13**, C16-C22 fragment of **1**.

Non-chelation-controlled addition of methallylsilane to 2-*O*-benzyl-3-*O*-(*tert*-butyldiphenylsilyl)-glyceraldehyde (**14**) prepared from D-mannitol according to the Reetz's method[11] in the presence of boron trifluoride etherate gave *anti*-adduct **15** (*anti*:*syn*=88:12, 89% total yield) which was separated by column chromatography after methylation of the mixture (Scheme 3). 1,3-Asymmetric induction[12] by hydroboration of **16** with thexylborane proceeded with slight predominance of the desired α-methyl isomer **17** (α:β=3:2, 98% total yield) and the β-methyl isomer was recycled to the olefin **16** by the Grieco-Nishizawa's method.[13] An alcohol **17** was converted to the aldehyde **18**, C10-C15 fragment required for coupling with sulfone **13**, in high overall yield by benzylation, desilylation, and Swern oxidation.

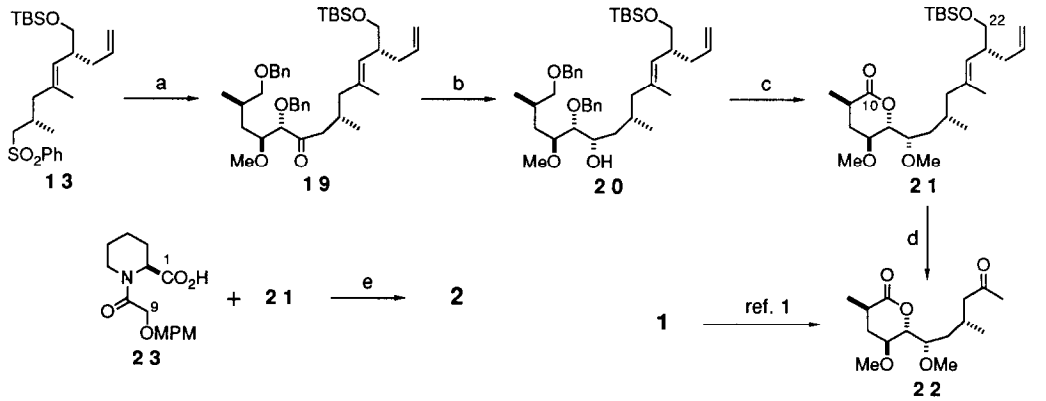


(a) 1) $CH_2{=}C(CH_3)CH_2SiMe_3$, $BF_3{\cdot}OEt_2$ / CH_2Cl_2, -78 °C, 30 min, 89%; 2) KH, MeI / THF, 90%. (b) Thexyl-BH_2 / THF, -78 °C to -15 °C, then H_2O_2, NaOH, 59%. (c) 1) KH, BnBr / THF, rt, 2 h, 94%; 2) TBAF / THF, rt, 1 h, 92%; 3) $(COCl)_2$, DMSO / CH_2Cl_2, then Et_3N, 95%.

Scheme 3.

Addition of an anion of the sulfone **13** to the aldehyde **18** in tetrahydrofuran at -78 °C provided four possible stereoisomeric adducts which were oxidized to α-sulfonylketone followed by reductive removal of the sulfonyl group with tri-*n*-butyltin hydride[2d] to give diastereomerically homogeneous ketone **19**, $[\alpha]_D^{20}$ -26.9° (*c* 1.00, $CHCl_3$) (Scheme 4). A reduction of α-benzyloxyketone **19** with diisobutylaluminum hydride in toluene at -78 °C afforded a desired *syn*-alcohol **20** in 86% isolated yield with high diastereoselectivity (*syn*:*anti*=11:1) which could be explained by Felkin's open-chain model[14] or Cram's dipolar model.[15] Methylation of the alcohol in **20**, debenzylation, and lactonization with pyridinium chlorochromate gave lactone **21**,[16] C10-C22 fragment, whose structure including stereochemistry was proven by the fact that a product **22** obtained by ozonolysis of **21** was identical with the known degradation product[1] of FK 506 in spectroscopic properties (^1H NMR, IR) including optical rotation, $[\alpha]_D^{21}$ +78.9° (*c* 0.13, $CHCl_3$) (lit.[2g] $[\alpha]_D^{23}$ +82.0°, *c* 0.3, $CHCl_3$). Finally, attachment of a pipecolinic acid moiety **23**,[17] C1-C9 fragment, to **21** was achieved by addition[19] of the amide-enolate formed by treatment of **23** with two equivalent of lithium diisopropylamide to the lactone **21** and subsequent work-up with diazomethane to give hemi-ketal **2**,[20] C1-C22 backbone of FK 506 (**1**), as a mixture (ca. 1:1) at the *p*-methoxybenzyloxy substituent.

In conclusion we showed the effectiveness of the ester-enolate Claisen rearrangement starting from L-malic acid by synthesizing highly stereocontrolled C16-C22 fragment **13** possessing (*E*)-trisubstituted double bond and extended **13** to C1-C22 fragment **2** by convergent coupling through a diastereoselective reduction of the ketone **19**. Application of this strategy to the C24-C34 fragment **4** and an effort directed toward the total synthesis of FK 506 (**1**) will be reported in due course.



(a) 1) *n*-BuLi / THF, -78 °C, 10 min, then **18**, -78 °C, 2.5 h, 83%; 2) $(COCl)_2$, DMSO / CH_2Cl_2, then Et_3N, 74%; 3) *n*-Bu_3SnH, AIBN / toluene, reflux, 77%. (b) DIBAL / toluene, -78 °C, 20 min, 86%. (c) 1) KH, MeI / THF, rt, 94%; 2) Li, NH_3 / THF, -78 °C, 95%; 3) PCC, MS4A / CH_2Cl_2, rt, 2 h, 85%. (d) O_3 / MeOH, -78 °C, then Me_2S, rt, 51%. (e) 1) LDA (2 equiv) / THF, -78 °C, then **21**, -78 °C to -10 °C; 2) CH_2N_2 / MeOH, 50%, 2 steps.

Scheme 4.

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17. Pipecolinic acid derivative **23**, $[\alpha]_D^{23}$ -28.6° (*c* 0.90, $CHCl_3$), was prepared from *N-tert*-butoxycarbonyl-pipecolinic acid[18] in 78% overall yield according to the following reaction sequences: 1) BnBr, $NaHCO_3$ / DMF; 2) TFA / CH_2Cl_2; 3) $MPMOCH_2CO_2H$, DCC / CH_2Cl_2; 4) KOH / MeOH.
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19. For relevant addition of the enolate derived from tetrahydropyranyl ethyl glycolate to the C10-C15 lactone, see reference 2 (c).
20. The structure of the hemi-ketal **2** was supported from MS and IR spectra (FAB-MS *m/z* 804 (M^++H); FAB-HRMS calcd for $C_{44}H_{72}O_9NSi$ (M^++H-H_2O) 786.4976, found 786.4954; IR (neat) 3450 (OH), 1744 (ester), 1623 (amide) cm^{-1}, no absorption for ketone) and the stereochemistry of hydroxyl group has been assumed to be β-configuration due to anomeric effect.

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