The Orthoester Claisen Rearrangement in the Synthesis of Mycophenolic Acid†

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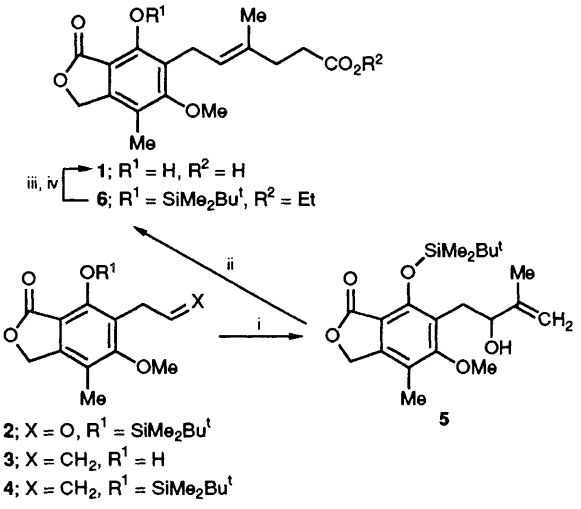
The orthoester Claisen rearrangement is used as a key reaction in the facile conversion of an acetaldehyde moiety stereospecifically into the (*E*)-4-methylhex-4-enoic acid side-chain of mycophenolic acid.

There has been a resurgence of interest in mycophenolic acid **1** in recent years and particularly in its use as an immunosupressant[1] with possible utility in the treatment of organ transplant rejection and rheumatoid arthritis. Analogue studies,[2] showing many variants of the hex-4-enoic acid side-chain to have low biological activity, have focused our attention on methods of introducing the naturally occurring side-chain into readily available intermediates. In the various literature syntheses of mycophenolic acid[3–6] introduction of the hexenoic acid side-chain has been accomplished in several ways. However, each of these methods suffers from too many steps, poor overall yield or were inappropriate for a wide variety of substrates. A new approach to the synthesis of the hex-4-enoic acid side-chain, namely the orthoester Claisen rearrangement,[7] is described here.

The requisite intermediate for the synthesis of mycophenolic acid *via* the orthoester Claisen rearrangement is the phenyl acetaldehyde **2** which is available by ozonolysis of the allyl substituted phthalide **3** as demonstrated in the Birch synthesis.[6] Reaction of aldehyde **2** with prop-2-enylmagnesium bromide gave the allylic alcohol **5**,‡ m.p. 133–134 °C, in 79% yield, indicating a high degree of selectivity for Grignard addition to the aldehyde carbonyl group. Claisen rearrangement of **5** with excess triethyl orthoacetate in the presence of propionic acid gave the ethyl hex-4-enoate **6** (55%). The ^{13}C



Scheme 1 *Reagents and conditions*: i, prop-2-enylmagnesium bromide (1.0 equiv.), tetrahydrofuran (THF), −70 to −30 °C, 30 min; ii, $MeC(OEt)_3$ (solvent), propionic acid (0.4 equiv.), 70 to 110 °C, 3 h; iii, Bu^n_4NF (1.2 equiv.), THF, 25 °C, 15 min; iv, LiOH (2.2 equiv.), aq. MeOH, 25 °C, 1 h

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‡ Satisfactory analytical and spectral data were obtained for all new compounds.

and ^{1}H NMR spectra of this material contained no duplicate signals indicating the orthoester Claisen rearrangement proceeded with a high degree of stereospecificity. Removal of the silyl ether group (83%) and hydrolysis of the ethyl ester moiety gave mycophenolic acid **1** (71%), identical to the natural product obtained by fermentation, confirming the expectation that the orthoester Claisen rearrangement did produce the desired *E* double bond geometry. This orthoester Claisen sequence transforms the phenylacetaldehyde **2** into mycophenolic acid **1** in four steps in 26% overall yield. This method has distinct advantages over existing procedures. The method[5] of introducing the side-chain by C-alkylation with methyl 6-bromo-4-methylhex-4-enoate, followed by methylation of the 5-hydroxy group and ester hydrolysis proceeds in only 13% overall yield. Furthermore, the preparation of methyl 6-bromo-4-methylhex-4-enoate requries nine steps from geraniol. Although the acetylene–cyclobutenone annulation method of Danheiser[3] is short and high yielding, the nature of the starting materials limits the type of substituents which can be incorporated into mycophenolic acid analogues. We have used the orthoester Claisen method to synthesize a variety of mycophenolic acid analogues. This work will be the subject of a future communication.

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