Interrupted Polymerization of Acrylates: Sequential Michael-Michael-Dieckmann Cyclizations for Easy, One-Pot, 2 + 2 + 2 Construction of Polyfunctionalized Cyclohexanones

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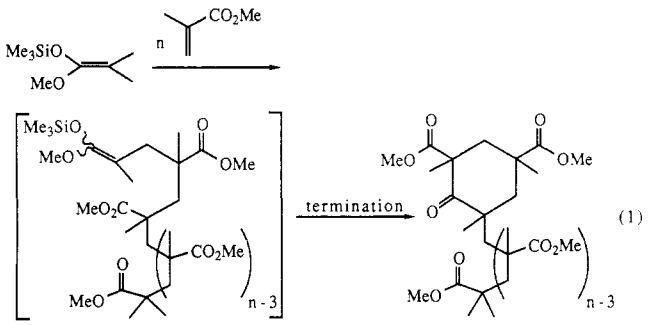
Summary: In THF at −78 °C, lithio enolates of several different acyclic and cyclic carboxylate esters react cleanly with 2 equiv of an acrylate ester via a Michael–Michael–Dieckmann cyclization sequence to form polyfunctionalized cyclohexanones in 45–72% overall yields; this process represents useful, controlled interruptions of polymerization reactions.

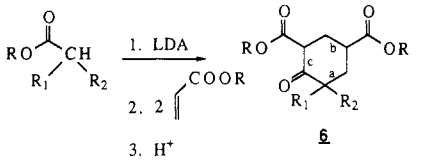
Sir: Anionic polymerization of acrylic and methacrylic acid esters is a well-known industrial process of worldwide chemical interest.[1] Development of group-transfer polymerization (GTP) at Du Pont using silyl ketene acetals as initiators has led recently to considerable understanding of the mechanistic details of this commercially important, controlled, living polymerization.[1a,2] Even more recently, metal-free (e.g. tetraalkyl ammonium) anionic polymerization of α-activated olefins has been reported, like GTP, to form valuable macromolecules of defined molecular weight and of narrow molecular weight distribution.[1g] Like the back-biting step which terminates anionic polymerization of methacrylates,[1e,3] termination of the GTP process also involves a final cyclization step (eq 1).[2] Much effort



(1)

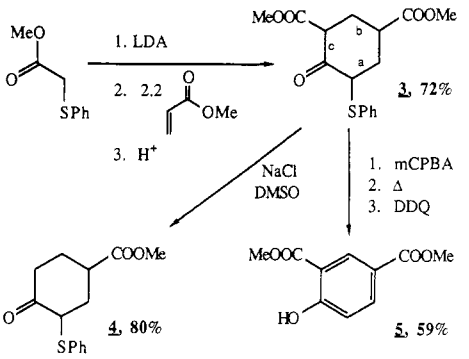
now is being devoted internationally to understanding those factors that influence the balance between anionic chain propagation (i.e. polymerization) vs termination (i.e. cyclization).[1e] From our interest in developing synthetic methods based on multicomponent annulations,[4] we have found that polymerization of acrylates using lithium enolates of acetate esters as initiators is effectively interrupted after only 2 equiv of acrylate have reacted forming ultimately diverse cyclohexanone products **2** in good yields (eq 2). It seems likely that an oxophilic lithium cation, as illustrated by proposed structure **1** for the intermediate in this process, is crucial for promoting intramolecular Claisen ester condensation and therefore for stopping polymerization.[1e,5] That the three-component ring-forming reaction shown in eq 2 proceeded smoothly is especially

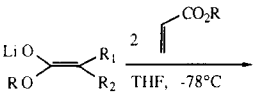
Scheme I

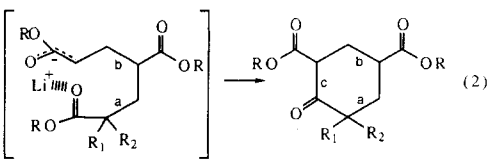


R	R_1	R_2	% Yield
Et	H	H	49
Et	H	CH_3	70
Et	H	Ph	66
Me	H	SPh	72
Et			58
Me			64
Et			45

Scheme II







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noteworthy because of the considerable potential for proton transfer from one ester α-CH unit to the various ester enolate intermediates in this process. This easy, one-pot, 2 + 2 + 2, Michael–Michael–Ring–Closure (MIMIRC) process,[4] involving a terminating Dieckmann cyclization[6] with overall formation of three carbon–carbon bonds (**2a–c**), represents a simple, convenient, and potentially versatile synthetic method for joining three 2-carbon components into 6-membered carbocycles of varied substitution pattern.[4e]

The generality of this synthetic method is illustrated in Scheme I. For example, methyl phenylthioacetate reacted with lithium diisopropylamide (LDA) in THF at −78 °C and then with 2.2 equiv of methyl acrylate to form, after acidic workup, trisubstituted cyclohexanone **3** on a multigram scale as a mixture of stereoisomers in 72% yield (Scheme II). Lower yields of dimethyl ester cycloadduct **3** were obtained when the ester group of the initiator was different from the ester group of the acrylate; lithium alkoxides formed in the terminal Dieckmann cyclization caused transesterifications. Stereoisomeric β-keto esters **3** were decarboxylated (NaCl, DMSO, 150 °C, 4.5 h)[7] to form stereochemically homogeneous, polyfunctional ketone **4** in overall 57% yield based on starting methyl phenylthioacetate. Alternatively, stereoisomeric α-thio ketones **3** were oxidized into the corresponding sulfoxides (MCPBA, 0 → 25 °C, 1 h);[8] pyrolysis (refluxing benzene)[9] produced a conjugated cyclohexenone having substantial dienol character. Dehydrogenation (DDQ, refluxing benzene)[10] formed regiospecifically trisubstituted benzene **5** in overall 42% yield based on starting methyl phenylthioacetate.

Spirobicyclic compounds, often useful synthons[11] and characteristic of different families of biologically active natural products,[12] in general are not easily prepared directly from simple components. As shown in Scheme I, lithium enolates of several carbocyclic and heterocyclic carboxylate esters reacted cleanly with 2 equiv of an acrylate ester to form spirobicyclic adducts **6** in 45–64% yields. This one-pot, three-component coupling process represents interrupted polymerizations leading easily and directly to regiospecifically polyfunctionalized spirobicyclic adducts.

In summary, the results reported here demonstrate (1) that lithio acetates, in which the α-carbon atom is either unsubstituted or mono- or disubstituted, initiate polymerization of acrylate esters; (2) that in THF at −78 °C such polymerization is effectively interrupted by a terminating Dieckmann cyclization; and (3) that this three-component coupling process leads rapidly and conveniently on a multigram scale to regiospecifically tri- and tetrasubstituted 6-membered carbocycles including spirobicyclic adducts. We are continuing to explore the scope and applications of these interrupted polymerizations.

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Supplementary Material Available: A complete experimental section including descriptive procedures and full characterization data (6 pages). Ordering information is given on any current masthead page.

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Efficient Enantiospecific Synthesis of Key A-Ring Synthons for the Preparation of 1α,25-Dihydroxyvitamin D_3 Using a Chromium(II)-Mediated Reaction

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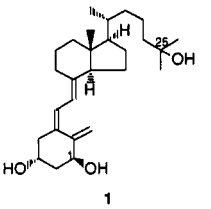
Summary: Key A-ring synthons for the synthesis of 1α,25-dihydroxyvitamin D_3 have been prepared efficiently from (*R*)-(−)-carvone by use of diastereoselective chromium(II)-mediated addition of an allylic halide to an aldehyde as a key step.

Sir: Of the known vitamin D_3 metabolites, 1α,25-dihydroxyvitamin D_3 (**1**), is considered to be the most potent stimulator of calcitropic effects such as intestinal calcium absorption and bone calcium mobilization.[1] Recently, this hormone has also been found to suppress proliferation and induce differentiation in human myeloid leukemia cells.[2] These potent biological activities therefore have stimulated efforts toward the synthesis of 1α,25-dihydroxyvitamin D_3 (**1**).[2-4]



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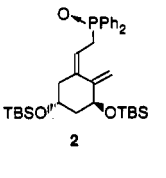

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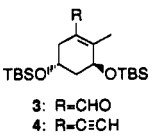

3: R=CHO
4: R=C≡CH

TBS=^{t}BuMe$_2$Si–

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