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Abstract: A strategically new approach to cyclopentene[c]chroman-2-ones and cyclopent-1-enecarboxylates by tandem Michael–Horner–Wadsworth–Emmons reaction of 2,5-hexanedione with 3-(diethoxyphosphoryl)coumarins is described. The products were obtained as single diastereoisomers in high yields.

Key words: Michael addition, Horner–Wadsworth–Emmons olefination, tandem reaction, annulations, 1,5,7-triazabicyclo[4.4.0]dec-5-ene

The cyclopent-1-enecarboxylate moiety is present in many biologically active natural products.1 Within this class of compounds the cyclopenta[c]tetrahydropyrano-2-one ring system is incorporated in the reduced or modified form into natural products such as neonepetalactone (1),2a mitsugashiwalactone (2), onikulactone (3),2b herbertenolide (4),2c aflatoxin B (5), and aflatoxin M (6)2d (Figure 1) which have been shown to possess diverse biological properties.

In recent years considerable research activity has been directed toward the synthesis of cyclopentene-fused chroman-2-ones. The synthetic strategies include [3+2] cycloaddition of allenates with 3-alkoxyacarbonylcoumarin,3a intramolecular [3+2] cycloaddition of 2-styrenyl allenotes,3b annulation of 3-acetyl-coumarin with allenylboronic esters,3c and [3+2] cycloaddition of 3-acetylcoumarin with cyclopropene acetal.3d Palladium-catalyzed [3+2] cycloaddition of 2-(trimethylsilylmethyl)-allyl acetates with coumarins has been used to install a cyclopentane ring containing an exomethylene group.3e

Despite its potential utility, the approach based on a Michael addition of homoenolate anion equivalents to α-dialkoxycarbonyl-α,β-unsaturated lactones followed by an intramolecular Horner–Wadsworth–Emmons (HWE) reaction of the resulting 2-phosphono-6-oxoalkanoates has been exploited only rarely for the preparation of cyclopentene annulated γ- and δ-lactones. Minami et al. reported that the tandem Michael–intramolecular HWE reaction of diethyl 2-oxoalkylmalonates with α-phosphoryl-α,β-unsaturated-γ-lactones provided cyclopentene-fused-γ-lactones.3f Bestmann et al. reported that Michael addition of [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide to 3-(diethoxyphosphoryl)cumarin followed by deprotection of the aldehyde group and an intramolecular HWE reaction led to cyclopentene-annulated chromanones.3b In the course of our earlier studies we have reported that the above [3+2] annulation strategy could be extended for the preparation cyclopent-1-enecarboxylates from the corresponding tert-butyl (E)-2-(diethoxyphosphoryl)alk-2-enoylates.3c

In spite of these advances, it is evident that methods that access cyclopentanannulated lactones, particularly via conceptually different approaches are still of significant interest. It is worthy of note that 1,4-diketones are known to be potent homoenolate equivalents.3a Surprisingly, a strategy for [3+2] cycloannulation that utilizes homoenolates generated from 1,4-diketones (γ-oxoketone enolates) as three-carbon fragments has not been exploited.3f

In this letter we report the first examples of a tandem Michael–intramolecular HWE reaction of 2,5-hexanedione (8) with 3-(diethoxyphosphoryl)coumarins 7a–c in which the dione serves as a γ-oxoketone enolate equivalent. This approach expands greatly the scope of the conjugate addition involving coumarins 7b and provides a new and prac-

Figure 1 Natural products containing cyclopenta[c]tetrahydropyran-2-one and cyclopenta[c]chromanone systems
tical entry into cyclopentene-fused chromanones 9a–c and cyclopentenecarboxylates 10a–c and 12a–c.

Successful development of the reaction sequence required identification of bases that could be used for the enolate generation. After screening of a range of organic and inorganic bases, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was found to be the optimal choice. The reaction of 3-(di-ethoxyphosphoryl)coumarin 7a with diene 8 (3 equiv) in the presence of a stoichiometric quantity of TBD proceeded efficiently in CH₂Cl₂ at room temperature and was complete within one day (Scheme 1). ³¹P NMR spectroscopic analysis of the crude reaction mixture indicated complete consumption of the coumarin 7a and revealed the presence of one signal in the phosphate region (δ = 1.4 ppm). After acidic quench the product was isolated as a mixture of trans-lactone 9a accompanied by the corresponding hydroxyacid trans-10a in a ca. 1:1 ratio. Both compounds could be efficiently separated by column chromatography in 36% and 37% yield, respectively. Dehydration of the hydroxyacid 10a using TFAA (1 equiv) in CH₂Cl₂ at room temperature provided the lactone 9a in an excellent yield of 97%. Notably, treatment of the crude mixture of 9a and 10a obtained with TFAA (1 equiv) in CH₂Cl₂ at room temperature for three hours resulted in complete lactonization of 10a to 9a, which was isolated by chromatography as the sole product in 73% yield. The coumarins 7b and 7c, regardless of the presence of electron-withdrawing or electron-donating substituents on the aromatic ring, participated in this process with high efficiency. The crude products were formed as the mixtures of the trans-lactones 9b,c and the corresponding trans-hydroxyacids 10b,c in a 1:1 ratio. Without purification these mixtures were subjected to dehydration to yield the trans-lactones 9b and 9c in 75% and 69% yields, respectively.

From a mechanistic point of view it is reasonable to assume that the formation of hydroxy acids 10a–c occurs in a stepwise fashion by initial formation of the lactones 9a–c followed by their hydrolysis catalyzed by TBD (Scheme 2). Addition of TBD to the carbonyl group of the lactones 9a–c results in the formation of acylammonium salts 11a–c, which in the presence of water are easily converted into the corresponding carboxylic acids 10a–c. Consequently, it was reasoned that, in the presence of a protic solvent used as both reagent and solvent, the reaction would be driven toward the formation of cyclopentenecarboxylates. Indeed, reaction of coumarins 7a–c with diene 8 and TBD in methanol (Scheme 3) resulted in the efficient formation of methyl trans-cyclopentenecarboxylates 12a–c in 80%, 81% and 77% yield, respectively, as the sole products.

The trans relative configuration of the products 9, 10, and 12 was established by single-crystal X-ray analysis conducted on cyclopentene[c]chroman-2-one 9c (Figure 2). The anti diastereoselectivity in the Michael addition step leading to the formation of the dihydrocoumarins 14 is in accord with the results of our previous studies concerning the conjugate addition of secondary enamines, derived from cycloalkanones and benzylamine, to coumarin 7a. The reaction is proposed to occur via a synclinal acyclic transition state 13 in which the Si⁺ face of the enolate approaches the Re⁺ face of the coumarin (Scheme 4). In conclusion, we have developed the first tandem Michael–intramolecular HWE reaction of 2,5-hexanedione with 3-(diethoxyphosphoryl)coumarins. The method represents a new approach to functionalized cyclopentene[c]chromanones and cyclopent-1-ene-carboxylates which should be widely useful because it is a simple and
fully diastereoselective C–C forming process. It demonstrates the previously unrecognized property of 2,5-hexanedione as homoenolate anion equivalent.

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References and Notes


(8) Crystallographic data (excluding structure factors) for the structure reported herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 966779. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Any request should be accompanied by a full literature citation.