A Tandem Conjugate Addition–Intramolecular Horner–Wadsworth–Emmons Olefination Approach to the Synthesis of Cyclopentene[*c*]chroman-2-ones and Cyclopent-1-enecarboxylates

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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*]tetrahydropyran-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.

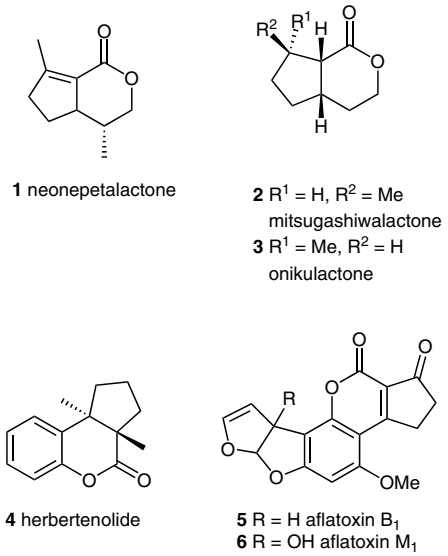

Figure 1 Natural products containing cyclopenta[*c*]tetrahydropyran-2-one and cyclopenta[*c*]chromanone systems

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 allenoates with 3-alkoxycarbonylcoumarin,[3a] intramolecular [3+2] cycloaddition of 2-styrenyl allenoates,[3b] annulation of 3-acetylcoumarin with allenylboronic esters,[3c] and [3+2] cycloaddition of 3-acetylcoumarin with cyclopropenone acetals.[3d] Palladium-catalyzed [3+2] cycloaddition of 2-(trimethylsilylmethyl)-allyl acetates with coumarins has been used to install a cyclopentane ring containing an *exo*-methylene group.[3e]

Despite its potential utility, the approach based on a Michael addition of homoenolate anion equivalents to α-dialkoxyphosphoryl-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.[4a] Bestmann et al. reported that Michael addition of [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide to 3-(diethoxyphosphoryl)coumarin followed by deprotection of the aldehyde group and an intramolecular HWE reaction led to cyclopentene-annulated chromanones.[4b] 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-enoates.[4c]

In spite of these advances, it is evident that methods to access cyclopentannulated 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.[5a] Surprisingly, a strategy for [3+2] cyclopentannulation that utilizes homoenolates generated from 1,4-diketones (γ-oxoketone enolates) as three-carbon fragments has not been exploited.[5]

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 **7**[6] and provides a new and prac-

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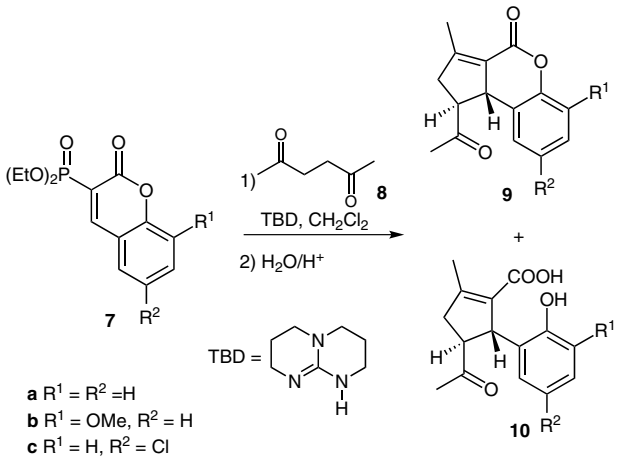
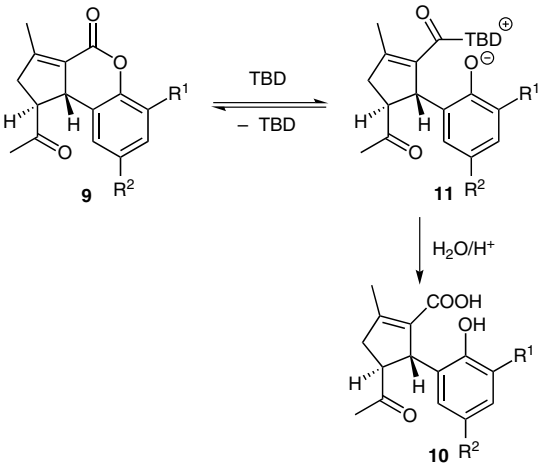
tical entry into cyclopentene-fused chromanones **9a–c** and cyclopentenecarboxylates **10a–c** and **12a–c**.

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-(diethoxyphosphoryl)coumarin **7a** with dione **8** (3 equiv) in the presence of a stoichiometric quantity of TBD proceeded efficiently in CH_2Cl_2 at room temperature and was complete within one day (Scheme 1). ^{31}P 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 CH_2Cl_2 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 CH_2Cl_2 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 dehydratation to yield the *trans*-lactones **9b** and **9c** in 75% and 69% yields, respectively.

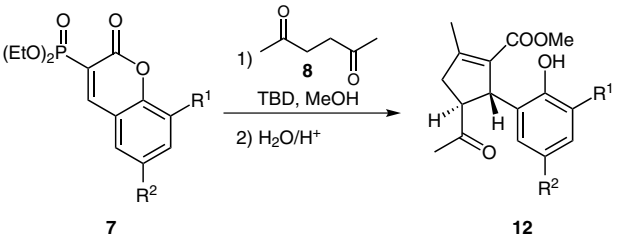


Scheme 1 The reaction pathway in dichloromethane

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[7] (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 dione **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.



Scheme 2 Lactone hydrolysis catalyzed by TBD



Scheme 3 The reaction pathway in methanol

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**[8] (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[6] 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-enecarboxylates which should be widely useful because it is a simple and

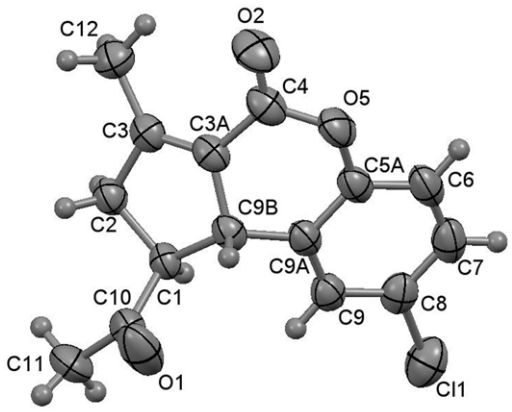
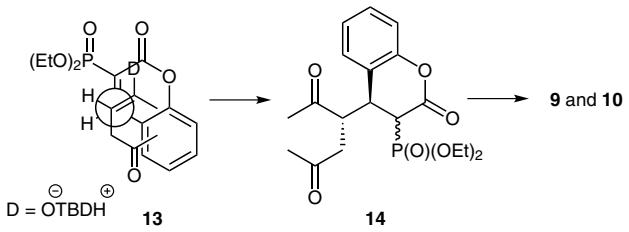


Figure 2 The crystal structure of cyclopentene[*c*]chroman-2-one **9c**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 4 Proposed model for the TBD-promoted Michael reaction between coumarin **7** and 2,5-hexanedione

fully diastereoselective C–C forming process. It demonstrates the previously unrecognized property of 2,5-hexanedione as homoenolate anion equivalent.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: 10.4125/pd0053th.

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(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.

