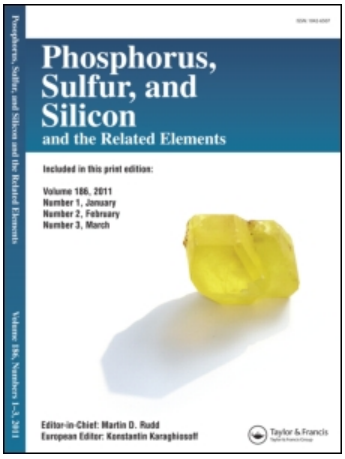

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A New Approach to Cyclopentane Annulated Compounds *via* 1-Cyclopent-1-Enylcarbonyl)Vinylphosphonates, and Synthesis and Synthetic Application of α-Diethoxyphosphoryl-Δαß-Butenolides

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A NEW APPROACH TO CYCLOPENTANE ANNULATED COMPOUNDS *VIA* 1-(CYCLOPENT-1-ENYLCARBONYL)VINYLPHOSPHONATES, AND SYNTHESIS AND SYNTHETIC APPLICATION OF α-DIETHOXYPHOSPHORYL-$\Delta^{\alpha,\beta}$-BUTENOLIDES

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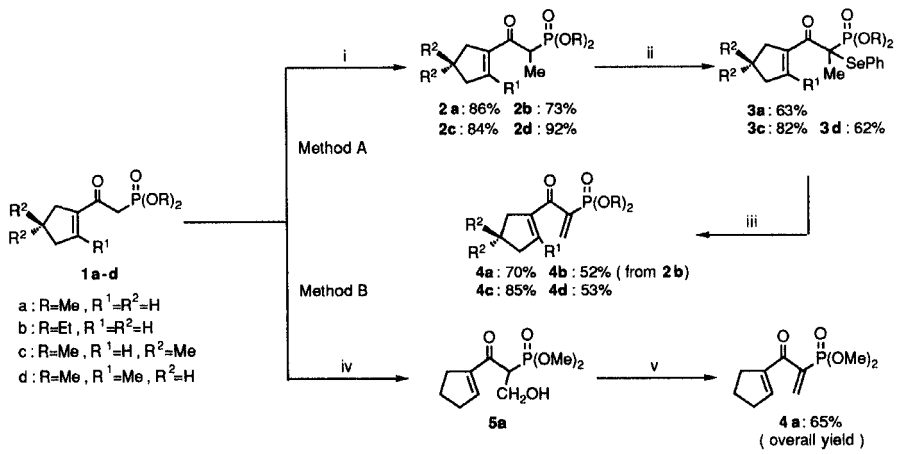
Abstract Fused ring systems, containing two or three five-membered rings, were constructed by utilizing 1-(cyclopent-1-enylcarbonyl)vinylphosphonates which function as versatile annulating agents. Facile synthesis of α,β-carbocyclic fused γ-lactones was provided by the reaction of α-phosphono-$\Delta^{\alpha,\beta}$-butenolide with carbon nucleophiles containing the carbonyl or the masked carbonyl group at a γ or δ-position.

Development of convenient synthetic routes to cyclopentanoid frameworks has been one of challenging themes to synthetic chemists, since many naturally occurring diquinane and triquinane terpenoids have been shown to have useful antibiotic or antitumor properties.

Reported herein is the synthesis of versatile cyclopentane annulating reagents, 1-(cyclopent-1-enylcarbonyl)vinylphosphonates **4** and their synthetic applications to the preparation of functionalized cyclopentanoids.

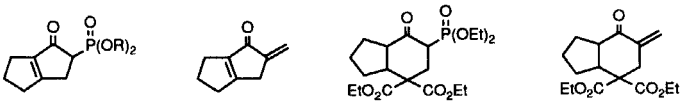
As shown in Scheme 1, methylation of 1-(cyclopent-1-enylcarbonyl)-methylphosphonates **1** and phenylselenenylation of the resulting 1-(cyclopent-1-enylcarbonyl)ethylphosphonates **2** into the selenides **3** followed by oxidation led to the corresponding 1-(cyclopent-1-enylcarbonyl)vinylphosphonates **4** (Method A). The vinylphosphonate **4a** was alternatively synthesized by the condensation of **1a** with paraformaldehyde (Method B).

The Nazarov cyclization of the 1-(cyclopent-1-enylcarbonyl)vinylphosphonates **4a** or **4b** was carried out in the presence of 1.1-3.0 equiv of $SnCl_4$ or $FeCl_3$ at room temperature for 12-30 h in CH_2Cl_2, which produced 2-(dialkoxyphosphoryl)-2,3,4,5,6-pentahydropentalen-1-ones **6a**



Scheme 1 *Reagents and conditions*: i, $Bu_4N^+Br^-$, NaOH, CH_3I, CH_2Cl_2-H_2O, room temp., 10h; ii, NaH, PhSeBr, THF, -78°C, 2h iii, H_2O_2, CH_2Cl_2-H_2O, 0°C, 1h; iv, Piperidine, $(HCHO)_n$, EtOH, reflux, 5h; v, p-TosOH, Benzene, 80°C, 3h

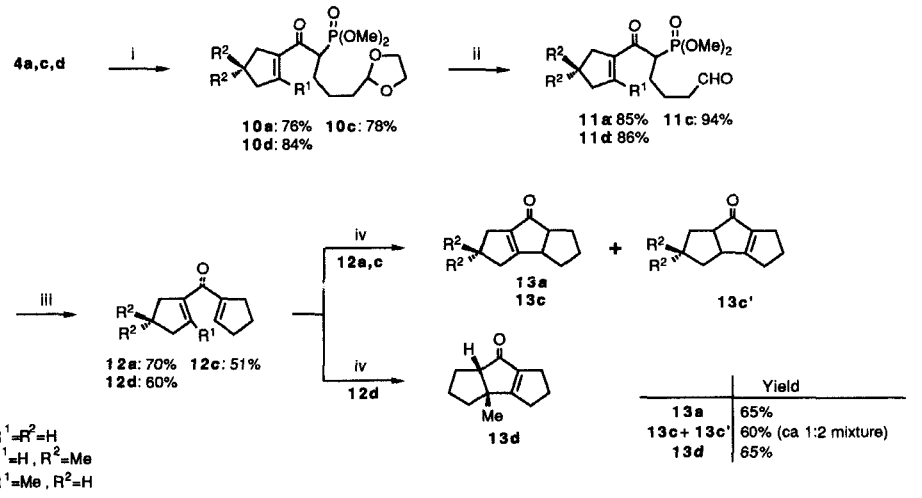
in 25-40% or **6b** in 35-37% yields, respectively. The low yields of the products **6a,b** in these reactions were due to the formation of unidentified polymeric materials. The use of $AlCl_3$, $TiCl_4$ or polyphosphoric acid as a catalyst did not result in the expected Nazarov cyclization products **6**, and only unidentified polymeric products were obtained. In addition, the vinylphosphonate **4b** easily underwent the intramolecular double Michael addition of diethyl sodiomalonate to give the 3-diethoxyphosphorylbicyclo-[4.3.0]nonan-2-one **8** in 83% yield. As one of synthetic applications of the thus synthesized β-ketophosphonates **6** and **8**, the Horner-Wittig reaction with paraformaldehyde was performed to afford the corresponding enones **7** and **9** in 48% and 44% yields, respectively.



Furthermore, by making use of the α-ketovinylphosphonate moiety in **4** as a cyclopentene annulation reagent,[1] we have been able to achieve the synthesis of dicyclopent-1-enyl ketones which when treated with acids lead to Nazarov cyclization products. Thus, the Michael addition of (1,3-dioxolan-2-yl)ethylmagnesium bromide to **4** to provide **10** (76-84%),

followed by acidic hydrolysis to the aldehydes **11** (85-94%) and the intramolecular Horner-Wittig reaction gave the desired dicyclopent-1-enyl ketones **12** (51-70%) (Scheme 2). A polyphosphoric acid-catalyzed cyclization of the resulting divinyl ketones **12** produced the expected tricyclo[6.3.0.$0^{3,7}$]undecenone system **13**.

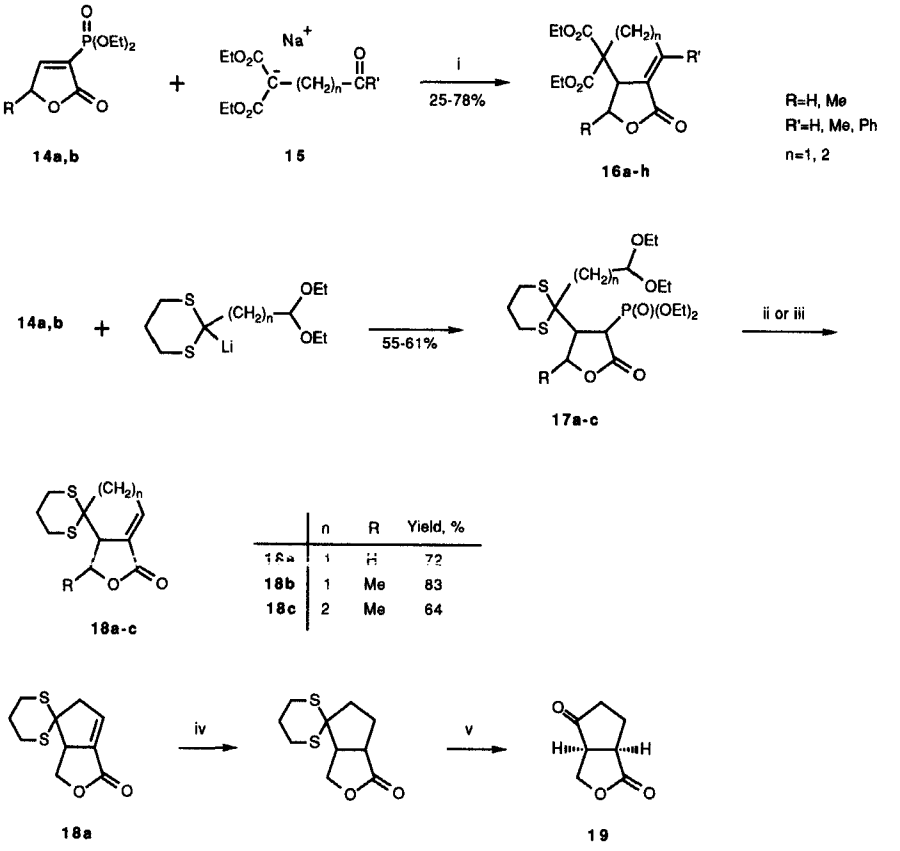
Thus, 1-(cyclopent-1-enylcarbonyl)vinylphosphonates have been proved to be useful for the construction of triquinane ring systems *via* a sequence of the Michael addition, the intramolecular Horner-Wittig reaction, and the Nazarov reaction.



Scheme 2 *Reagents and conditions*: i,  CH_2CH_2MgBr, tetrahydrofuran (THF), -78°C, 2h; ii, 1N-HCl, THF, reflux, 5h; iii, NaH, THF, room temp., 10h; iv, polyphosphoric acid (PPA), 100°C, 0.5h

In addition, we have developed α-diethoxy-$\Delta^{\alpha,\beta}$-butenolides **14** as useful γ-lactone annulation reagents. Thus, the reaction of butenolides **14** with diethyl 2-oxoalkyl- and 3-oxoalkylmalonate carbanions **15** in THF afforded the expected α,,β-carbocyclic fused γ-lactones **16** in 24-78% yields. Similar reaction of **14** with 1,3-dithianes containing the masked carbonyl moiety provided the corresponding Michael adducts **17** in 56-61% yields. Deprotection of the masked carbonyl group in **17** with 1N HCl (or *p*-toluenesulfonic acid), followed by the Wittig-Horner reaction led to bicyclic γ-lactones **18** in good yields (Scheme 3). Hydrogenation of **18a** and subsequent hydrolysis led to cyclosarkomycin

19 in good yield. This methodology using **14** can provide a remarkably simple route to α,β-carbocyclic fused γ-lactones.



	n	R	Yield, %
18a	1	H	72
18b	1	Me	83
18c	2	Me	64

Scheme 3 *Reagents and conditions* : i, THF, -78 °C → room temp., then reflux, 2h; ii, 1 N HCl, THF, reflux, 5h then NaH, THF, room temp., 3h or TLC (SiO_2, hexane/ethyl acetate=2/1); iii, *p*-TsOH (0.1 equiv.)/aq acetone, reflux, 5h then NaH, THF, room temp., 3h; iv, Pd-C, H_2 EtOH; v, $AgNO_3$, NCS, CH_3CN-H_2O

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