

# A Simple Metal-Promoted Three-Step Access to $n/5/m$ Angular Carbocyclic Systems

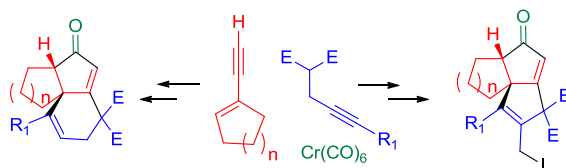
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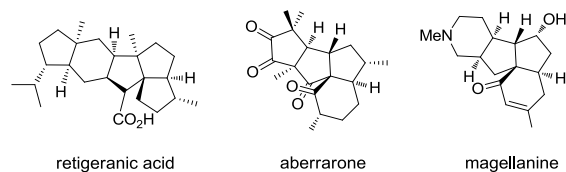
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## ABSTRACT



A simple three-step access to  $n/5/m$  angular tricyclic skeleta from terminal cycloalkenylacetylenes,  $\text{Cr}(\text{CO})_6$ , and propargylmalonate esters is described. The process involves a cyclopentannulation of propargylmalonates and enynyl Fischer carbenes, followed by a metal-promoted Cope-type fragmentation of the propargyl unit. The resulting 4-allenyl-carbonyl derivatives can undergo either a 5-exo annulation via a tin enolate or an unprecedented gold catalyzed 6-endo cyclization.

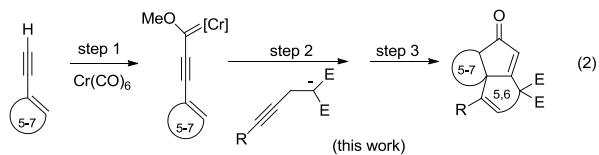
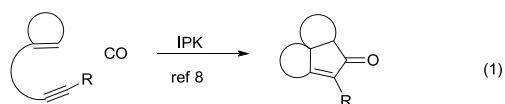
Angularly fused carbocyclic frameworks, such as the 5/5/5 system of angular triquinanes and the 5/5/6 system of the lycopodiaceae family, are present in many occurring natural products with important biological properties (Figure 1). Such structures have been of considerable interest to synthetic chemists.<sup>1</sup> In spite of this, the development of efficient synthetic strategies to angular tricyclic systems still represents a challenge.



**Figure 1.** Natural products bearing 5/5/5 and 5/5/6 angular frameworks

Traditionally, the most popular direct entries to such structures are based on free-radical cascade processes<sup>2,3</sup> or photoinduced electron transfer methods.<sup>4,5</sup> However, the assistance of transition metals for the construction of such angular ring systems is limited, and most of the existing methods involve the annulation of two ring systems onto a monocyclic substrate.<sup>6</sup> Although these metal-catalyzed strategies enable a rapid assemblage of the tricyclic core, the synthesis of the structurally-complex starting materials can be a major drawback.

Apart from some approaches based on ring-closing metathesis from appropriately substituted polycycles,<sup>7</sup> the intramolecular Pauson-Khand reaction probably represents the most powerful strategy for building 6/5/6 and 5/5/7 tricyclic structures (Figure 2, eq 1).<sup>8</sup> Its major drawback is its reliance on complex substrates. Taking advantage of the reactivity of group 6 enynylcarbene complexes toward enolates<sup>9, 10</sup> we envisioned a novel three-step regioselective strategy for synthesis of structurally-diverse, angularly-fused, tricycles from readily accessible materials; it is illustrated in Figure 2 eq 2.



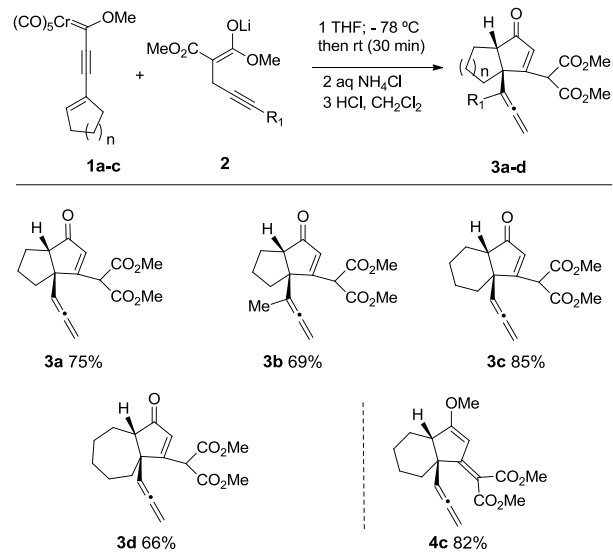
[Cr] = Cr(CO)<sub>5</sub>, E = CO<sub>2</sub>Me

**Figure 2.** New angular tricycle framework approach

Some examples of the execution of steps 1,2 are displayed in Scheme 1. Thus, a THF solution of chromium enynylcarbenes **1**, readily made from the corresponding acetylide and Cr(CO)<sub>6</sub> (step 1),<sup>11</sup> is added dropwise at  $-78\text{ }^{\circ}\text{C}$  to a THF solution of enolates **2**, generated from propargylmalonate esters and LDA, and the reaction warmed and stirred at room temperature for 30 minutes (step 2). The mixture is then quenched with ammonium chloride and the resulting product isolated (extraction with diethyl ether and removal of solvents). The resulting crude material is treated with concentrated HCl in methylene chloride, isolated (extraction with methylene chloride and removal of solvents) and purified by column chromatography (SiO<sub>2</sub>, hexanes/ethyl acetate, 5:1) to obtain the allenylcyclopentenones **3a-d** as single isomers in satisfactory yields (66–85%).<sup>12</sup> The enol ether **4c**, precursor of cyclopentenone **3c**, was isolated in 82% yield after quenching with ammonium chloride and column chromatography purification (SiO<sub>2</sub>, hexanes/ethyl acetate, 5:1).

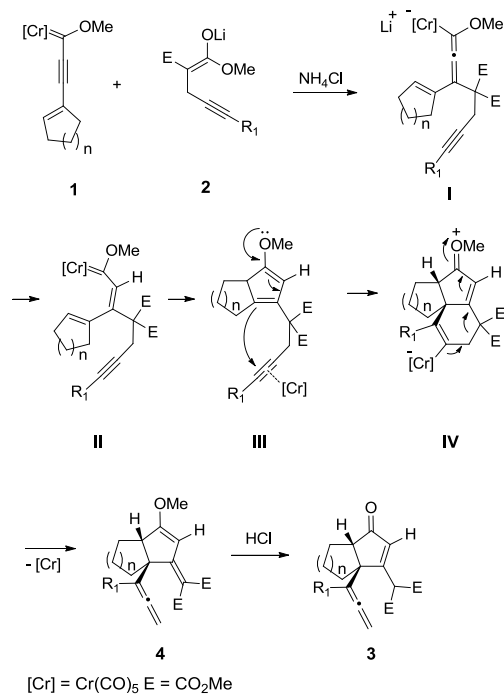
As shown in Scheme 1 the reaction provides access to 5/5, 5/6, and 5/7 bicyclic structures. Moreover, the reaction works well for malonates having unsubstituted and Me-substituted alkynyl appendages. The structure of compound **3c** was confirmed by X-ray analysis.

**Scheme 1.** Reaction of enynylcarbene complexes **1a-c** and propargylmalonates **2**



The structure of the allenyl cyclopentenones obtained suggests that a cyclopentannulation and a Cope-type fragmentation of the propargyl unit are involved. On this basis a possible route for the formation of **3** is depicted in Scheme 2. The initial Michael-type addition of enolate **2** to carbene **1** would provide intermediate **I**, which protonates on treatment with aqueous ammonium chloride forming the 1-metallahexatriene species **II**. As expected, the latter readily undergoes cyclopentannulation/Cr(CO)<sub>5</sub> elimination to give the propargylcyclopentadiene **III**. The final [3,3] rearrangement to compounds of structure **4** may occur by alkyne-Cr(CO)<sub>5</sub> coordination and nucleophilic attack by the methoxydiene function (intermediate **IV**) followed by C-C bond cleavage and metal elimination.<sup>13</sup> It should be noted that chromium(0), as its carbene substrate, is responsible for the cyclopentannulation reaction and, subsequently, it is assumed to catalyze both steps (ring-closing and ring-opening) of the [3,3] rearrangement.

**Scheme 2.** Proposed mechanism for the formation of **3**



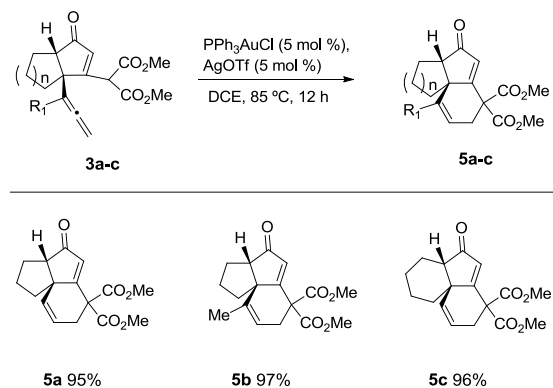
Compounds **3a-d** are intrinsically attractive since they feature a structurally novel and highly functionalized 2-cyclopentenone core. In particular they appear as potential precursors of diverse angular-fused polycycles via controlled construction of a five- and six-membered carbocycle (*endo*- and *exo*-cyclization, respectively) from the malonate and allenyl functionalities (step 3). Interestingly, while the 5-*exo* cyclization of  $\omega$ -allenyl carbonyl derivatives is a well established process,<sup>14</sup> no examples for the corresponding 6-*endo* cyclizations have been reported.<sup>15,16</sup> To achieve this, we have explored activation of the allenyl unit with a carbophilic transition metal in order to generate a metal-allyl cation<sup>17</sup> that would be amenable to engaging in a cyclization with a terminal allene carbon.<sup>18</sup>

Accordingly, allenyl cyclopentenones **3a-c** were heated in DCE at 85 °C for 12 h in the presence of PPh<sub>3</sub>AuCl/AgOTf (5 mol %). The resulting reaction mixture was subjected to SiO<sub>2</sub> column chromatography purification (hexanes/ethyl acetate, 5:1) providing exclusively the 6-*endo* cyclization products **5a-c** in yields as high as 95-97% (Scheme 3). The structure of compound **5c** was confirmed by X-ray analysis.

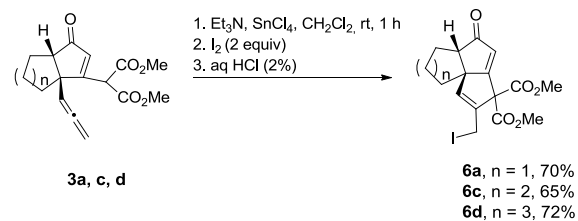
The 5-*exo*-cyclization was accomplished via tin enolates and iodine treatment following the protocol described by Taguchi et al (Scheme 4).<sup>19</sup> Thus, allenyl cyclopentenones **3a,c,d** were reacted with triethylamine (1 equiv) and SnCl<sub>4</sub> (1 equiv) in methylene chloride at room temperature for 1 h. The reaction mixture was then quenched with iodine (1 equiv), and 2% aqueous HCl.

Extraction (methylene chloride and solvents removal) and SiO<sub>2</sub> chromatographic purification (hexanes/ethyl acetate, 5:1) furnished the functionalized triquinane **6a** (70%) and tricycles **6c** (65%) and **6d** (72%). The structure of **6a,c,d** was confirmed by 1D NMR experiments.

**Scheme 3.** 6-*Endo* cyclization of **3a-c** to tricycles **5a-c**

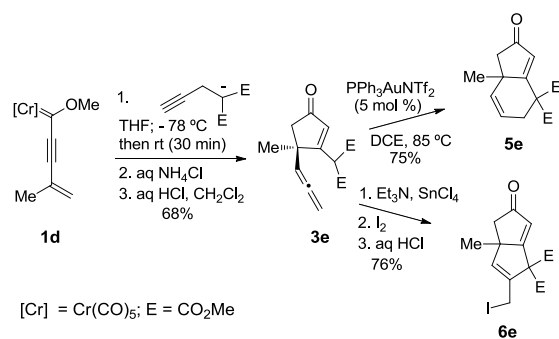


**Scheme 4.** 5-*Exo* cyclization of **3** to tricycles **6**



Finally, the flexibility of this protocol enables the preparation of simpler bicyclic structures by starting from an acyclic enyne (Scheme 5). Thus, the carbene complex **1**, derived from 2-methylbut-1-en-3-yne, affords allenyl-substituted cyclopentenone **3e** (68% yield) when reacted with the corresponding propargylmalonate enolate via the standard procedure given in Scheme 1. Subsequently, gold-catalyzed *endo*-cyclization of **3e** (PPh<sub>3</sub>AuNTf<sub>2</sub>, 5 mol %; DCE, 85 °C, 12 h) provided the 4,5-dihydro-2-indenone **5e** in 75% yield. On the other hand, *exo*-cyclization (triethylamine, SnCl<sub>4</sub>, dichloromethane, rt and iodine, 2% aqueous HCl) gave the 1,6a-dihydropentalen-2-one **6e** in 76% yield.

### Scheme 5. Construction of bicycles 5e and 6e



In conclusion, a very simple three-step access to functionalized angular tricyclic skeletons from terminal cycloalkenylacetylenes, Cr(CO)<sub>6</sub>, and propargylmalonate esters has been described.<sup>20</sup> The easy synthesis of 4-allenyl-2-cyclopentenones **3** enabled us to design synthetically useful protocols to access five structurally different angular fused tricycles: i) 5/5/6 and 6/5/6 polycycles via 6-*endo* cyclization, and ii) 5/5/5, 6/5/5 and 7/5/5 polycycles via 5-*endo* cyclization. In addition, the first 6-*endo* cyclization involving allene and carbonyl partners has been described. Since some of the basic structures constructed are present in natural products, the methodology described herein might be useful for discovering new biologically-active compounds.

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**Supporting Information Available** Experimental procedures, compound characterization data, and X-ray crystallographic information files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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