ORGANIC LETTERS

2013
Vol. 15, No. 3
488–491

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

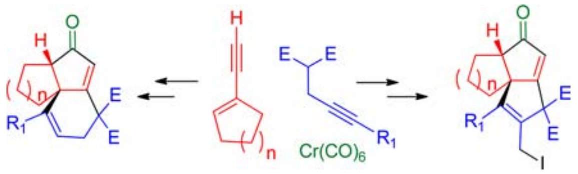
José Barluenga,* Ana Álvarez-Fernández, Tatiana Suárez-Rodríguez, Ángel L. Suárez-Sobrino, and Miguel Tomás

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo,
Julian Clavería 8, 33071 Oviedo, Spain

barluenga@uniovi.es

Received November 30, 2012

ABSTRACT



A simple three-step access to *n*/5/*m* angular tricyclic skeleta from terminal cycloalkenylacetylenes, $Cr(CO)_6$, 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 natural products with important biological properties (Figure 1). Such structures have been of considerable interest to synthetic chemists.[1] In spite of this, the development of efficient synthetic strategies for angular tricyclic systems still represents a challenge.

Traditionally, the most popular direct entries to such structures are based on free-radical cascade processes[2,3] or photoinduced electron transfer methods.[4,5] 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.[6] Although these metal-catalyzed strategies enable the rapid assemblage of the tricyclic core, the synthesis of the structurally complex starting materials can be a major drawback.

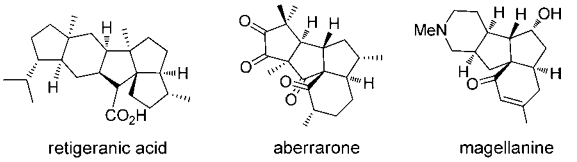


Figure 1. Natural products bearing 5/5/5 and 5/5/6 angular frameworks.

Apart from some approaches based on ring-closing metathesis from appropriately substituted polycycles,[7] the intramolecular Pauson–Khand reaction probably represents the most powerful strategy for building 6/5/6 and

---

(1) Metha, G.; Srikishna, A. *Chem. Rev.* **1997**, *97*, 671–719.

(2) J. McCarroll, A.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224–2248.

(3) Curran, D. P. *Aldrichimica Acta* **2000**, *3*, 104–110.

(4) (a) Rinderhagen, H.; Mattay, J. *Chem.—Eur. J.* **2004**, *10*, 851–874. (b) Tzvetkiov, N. T.; Arndt, T.; Mattay, J. *Tetrahedron* **2007**, *63*, 10497–10510.

(5) Recently, a route to linear and angular triquinanes has been established that involves generation of trimethylenemethane diyls from allenyldiazo compounds followed by intramolecular [3 + 2] cycloaddition: Kang, T.; Kim, W.-Y.; Yoon, Y.; Kim, B. G.; Lee, H.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 18050–18053.

(6) Very recently, a Rh(I)-catalyzed access to angular tricyclic 5/5/6 compounds from 1-yne-vinylcyclopropanes has been described that enables building of the three rings in a single process: Lin, M.; Li, F.; Jiao, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 1690–1693.

(7) (a) Holtsclaw, J.; Koreeda, M. *Org. Lett.* **2004**, *6*, 3719–3722. (b) Gao, F.; Stamp, C. T. M.; Thornton, P. D.; Cameron, T. S.; Doyle, L. E.; Miller, D. O.; Burnell, D. J. *Chem. Commun.* **2012**, *48*, 233–235.

10.1021/ol303269r

5/5/7 tricyclic structures (Figure 2, eq 1).[8] Its major drawback is its reliance on complex substrates. Taking advantage of the reactivity of group 6 enynylcarbene complexes toward enolates,[9,10] we envisioned a novel three-step regioselective strategy for the synthesis of structurally diverse, angularly fused, tricycles from readily accessible materials; it is illustrated in Figure 2, eq 2.

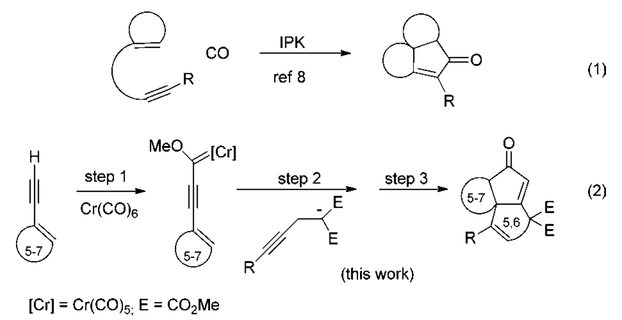
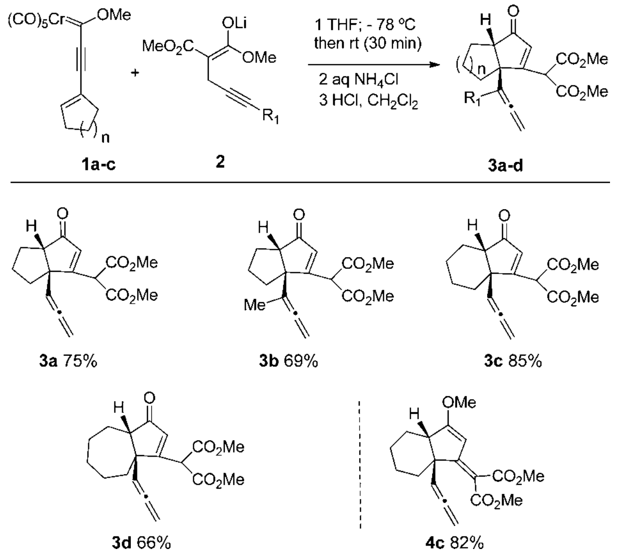


Figure 2. New angular tricycle framework approach.

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 $Cr(CO)_6$ (step 1),[11] is added dropwise at −78 °C to a THF solution of enolates **2**, generated from propargylmalonate esters and LDA, and the reaction was warmed and stirred at room temperature for 30 min (step 2). The mixture is then quenched with ammonium chloride, and the resulting product was 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_2, hexanes/ethyl acetate, 5:1) to obtain the allenylcyclopentenones **3a**−**d** as single isomers in satisfactory yields (66−85%).[12] The enol ether **4c**, a precursor of cyclopentenone **3c**, was isolated in 82% yield after quenching with ammonium chloride and column chromatography purification (SiO_2, 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 ammoniun chloride forming the 1-metallahexatriene species **II**. As expected, the latter readily undergoes cyclopentannulation/$Cr(CO)_5$ elimination to give the propargylcyclopentadiene **III**. The final [3,3] rearrangement to compounds of structure **4** may occur by alkyne-$Cr(CO)_5$ coordination and nucleophilic attack by the methoxydiene function (intermediate **IV**) followed by C−C bond cleavage and metal elimination.[13] 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.

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,

---

(8) (a) Schore, N. E.; Knudsen, M. J. *J. Org. Chem.* **1987**, *52*, 569–580. (b) Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* **2001**, *57*, 2729–2738. (c) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053–4065. (d) Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147–10154.

(9) Barluenga, J.; Álvarez-Fernández, A.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás, M. *Tetrahedron Lett.* **2009**, *50*, 3606–3608.

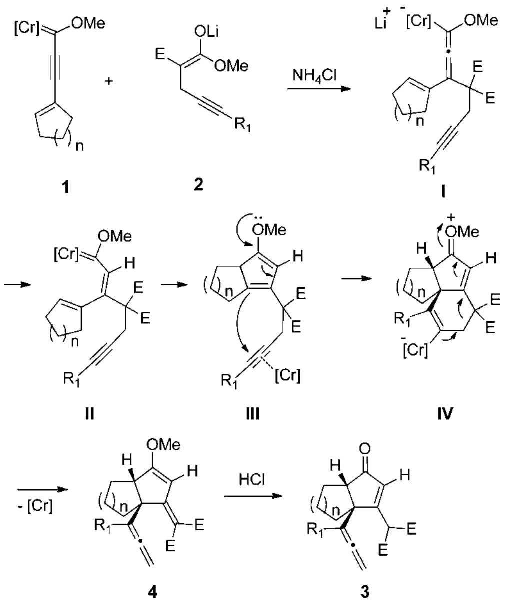
(10) For reviews on Fischer carbene complexes, see: (a) Barluenga, J. *Pure Appl. Chem.* **2002**, *74*, 1317–1325. (b) Barluenga, J.; Rodríguez, F.; Fañanás, F. J.; Flórez, J. *Top. Organomet. Chem.* **2004**, *13*, 59–121. (c) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539–587. (d) Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227–3274.

(11) See ref 9 and Supporting Information.

(12) A single diastereoisomer was detected in crude reaction mixtures.

(13) These processes have precedents. For the cyclopentannulation reaction, see: (a) Barluenga, J.; Aznar, F.; Barluenga, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1973–1974. (b) Barluenga, J.; Aznar, F.; Barluenga, S.; Fernández, M.; Martín, A.; García-Granda, S.; Piñera-Nicolás, A. *Chem.—Eur. J.* **1998**, *4*, 2280–2298. (c) Barluenga, J.; Álvarez-Fernández, A.; Suárez-Sobrino, A. L.; Tomás, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 183–185. For the intramolecular carbometalation, see: (d) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929. (e) Onizawa, Y.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 802–803. For the cyclohexene ring opening, see: (f) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2001**, *4*, 2569–2571. For the Ag(I)-catalyzed [3,3] rearrangement of propargyl carbonates, see: (g) Sugawara, Y.; Yamada, W.; Yoshida, S.; Ikeno, T.; Yamada, T. *J. Am. Chem. Soc.* **2007**, *129*, 12902–12903.

Scheme 2. Proposed Mechanism for the Formation of **3**



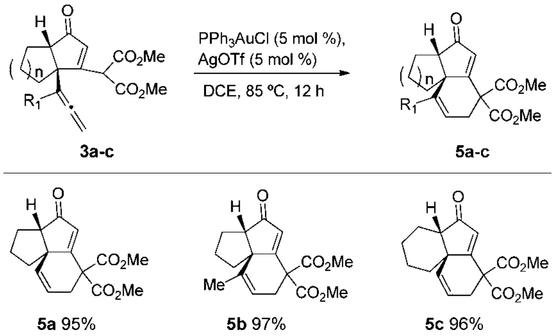
[Cr] = Cr(CO)$_5$ E = CO$_2$Me

while the 5-*exo* cyclization of *ω*-allenyl carbonyl derivatives is a well established process,[14] no examples for the corresponding 6-*endo* cyclizations have been reported.[15,16] To achieve this, we have explored activation of the allenyl unit with a carbophilic transition metal in order to generate a metal-allyl cation[17] that would be amenable to engaging in a cyclization with a terminal allene carbon.[18]

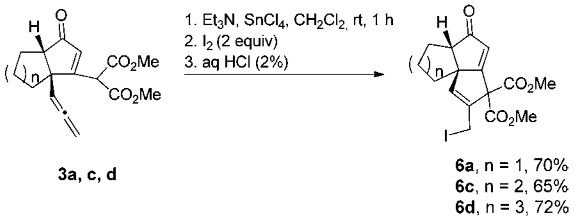
Accordingly, allenyl cyclopentenones **3a**–**c** were heated in DCE at 85 °C for 12 h in the presence of PPh_3AuCl/AgOTf (5 mol %). The resulting reaction mixture was subjected to SiO_2 column chromatography purification (hexanes/ethyl acetate, 5:1) providing exclusively the 6-*endo* cyclization products **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).[19] Thus, allenyl cyclopentenones **3a,c,d** were reacted with triethylamine (1 equiv) and $SnCl_4$ (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_2 chromatographic purification (hexanes/ethyl acetate, 5:1) furnished the functionalized triquinane **6a** (70%) and tricycles **6c** (65%) and **6d** (72%). The structures of **6a,c,d** were 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_3AuNTf_2, 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, $SnCl_4$, dichloromethane, rt and iodine, 2% aqueous HCl) gave the 1,6a-dihydropentalen-2-one **6e** in 76% yield.

In conclusion, a very simple three-step access to functionalized angular tricyclic skeletons from terminal cycloalkenylacetylenes, $Cr(CO)_6$, and propargylmalonate esters has been described.[20] The easy synthesis of

---

[14] Dénès, F.; Pérez-Luna, A.; Chemia, F. *Chem. Rev.* **2010**, *110*, 2366–2447.

[15] Is well established that the analogs 4-butynyl dicarbonyl compounds undergo 5-*exo* cyclization preferably; see for instance the gold(I)-catalyzed Conia-ene of *β*-ketoesters with alkynes: Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527.

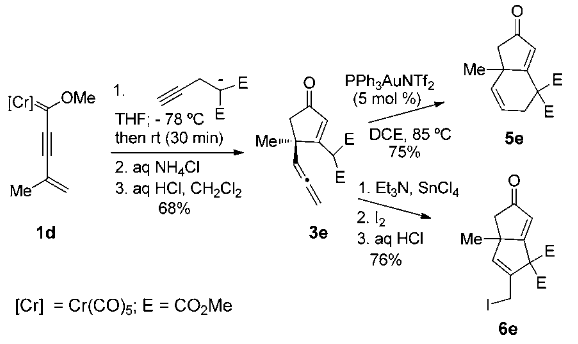
[16] For palladium-catalyzed 6-*endo* arylative cyclizations of allenylmalonates with aryl halides, see: Oh, C. H.; Rhim, C. Y.; Song, C. H.; Ryu, J. H. *Chem. Lett.* **2002**, *31*, 1140–1141.

[17] López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2011**, *17*, 418–428 and references therein.

[18] For a recent gold-catalyzed 5-*endo* cyclization of allenyl acetylacetate, see: (a) Jiang, X.; Ma, X.; Zheng, Z.; Ma, S. *Chem.—Eur. J.* **2008**, *14*, 8572–8578. For a gold(I)-catalyzed 6-*endo* intramolecular hydroarylation of allenes, see: (b) Barluenga, J.; Piedrafita, M.; Ballesteros, A.; Suárez-Sobrino, A. L.; González, J. M. *Chem.—Eur. J.* **2010**, *16*, 11827–1183. (c) Kong, W.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2010**, 6545–6555. For a Pt(II or IV)-catalyzed 6-*endo* intramolecular hydroarylation of allenes, see: (d) Kong, W.; Fu, C.; Ma, S. *Chem. Commun.* **2009**, 4572–4574. (e) Mo, J.; Lee, P. H. *Org. Lett.* **2010**, *12*, 2570–2573.

[19] (a) Kitagawa, O.; Suzuki, T.; Fujiwara, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 2549–2552. (b) Kitagawa, O.; Suzuki, T.; Fujiwara, H.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **2000**, *65*, 6819–6825.

Scheme 5. Construction of Bicycles **5e** and **6e**



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.

Acknowledgment. This research was partially supported by the Goverments of Spain (CTQ2010-20517-C02-01; undergraduate fellowship to T.S.-R.) and Principado de Asturias (IB08-088; Severo Ochoa-PCTI predoctoral fellowship to A.A.-F.).

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.

---

(20) For isolated, limited scope examples of Fischer carbene complexes in the synthesis of tricycles, see: (a) Milic, J.; Schirmer, H.; Flynn, B. L.; Noltemeyer, M.; de Meijere, A. *Synlett* **2002**, 875–878. (b) Wu, H.-P.; Aumann, R.; Frölilich, R.; Wibbeling, B. *Chem.—Eur. J.* **2002**, *8*, 910–916.

The authors declare no competing financial interest.