A Highly Efficient and Convergent Reaction for the Synthesis of Bridgehead Enone-Containing Polycyclic Ring Systems**

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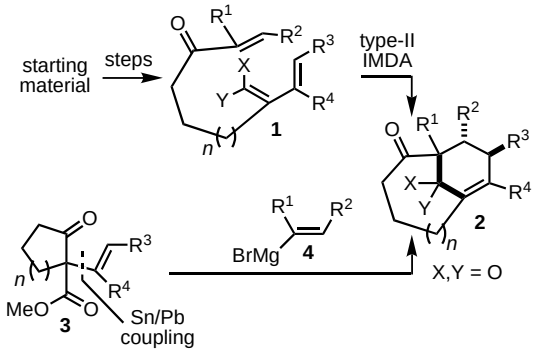
The development of reactions that efficiently generate complex polycyclic molecules from easily accessible starting materials continues to be an important endeavor in organic synthesis. Bridged ring structures represented by **2**[1] (Scheme 1) constitute a particularly challenging system to construct in a short number of steps. One method of assembling ring structures related to **2** is the type-II intramolecular Diels–Alder (IMDA) reaction[2] (**1** →**2**, Scheme 1), a [4+2] cycloaddition that involves tethering the dienophile to an internal position on the diene.[3]



Scheme 1. A comparison of the type-II IMDA and the tandem fragment-coupling/polycyclization approach to olefin-containing bridgehead carbocycles.

Herein multiple examples of a new reaction (**3** + **4** → **2**) that also afforded complex ring systems related to **2** are reported. An attractive feature of this reaction was the ability to combine complex fragments in a stereospecific reaction to give compound **2** directly. Compound **3** was accessed, in most cases, by a convergent Pb^{IV}-promoted coupling reaction between vinylstannanes and cyclic β-ketoesters.[4] The reaction (Scheme 2) that afforded **2** comprised a tandem alkylation, an anion-accelerated oxy-Cope rearrangement,[5] and a transannular Dieckmann-like cyclization. This triple-domino reaction was based upon a transformation we reported earlier that enabled the rapid assembly of the core structure of CP-263,114.[6]

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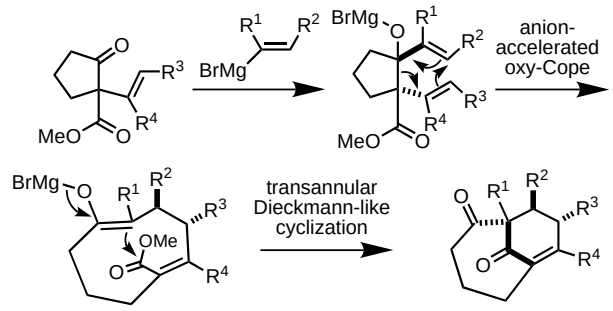
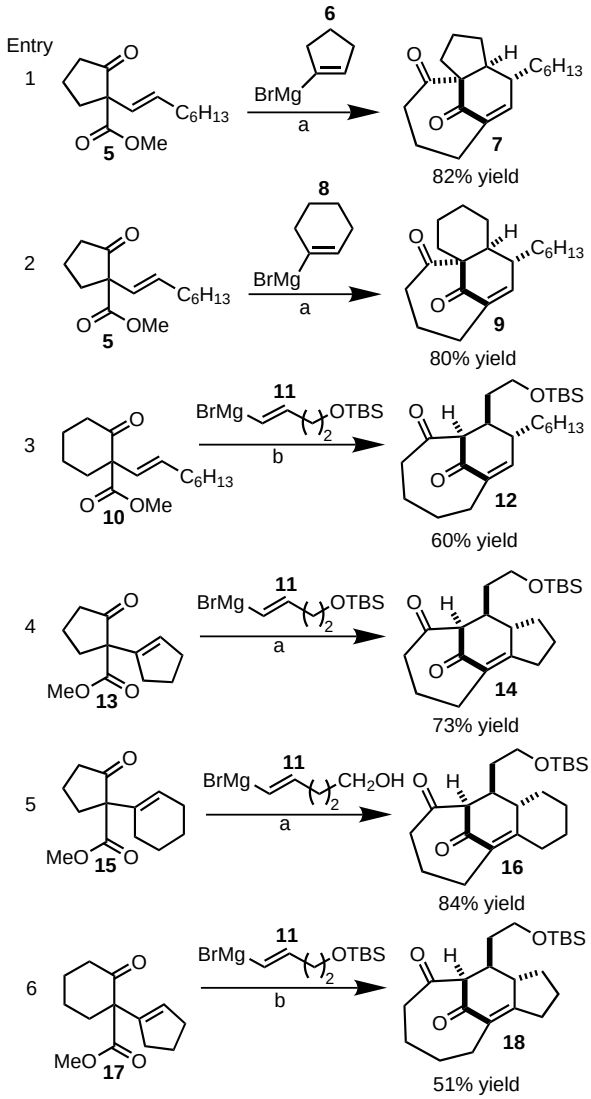


Scheme 2. Mechanism of the tandem reaction.

We began our investigation of the generality of the triple-domino reaction by exploring the synthesis of tricyclic structures using cyclic Grignard reagents (Scheme 3; entries 1 and 2). Exposure of **5** to **6** directly afforded tricycle **7** in 82% yield as a single diastereomer.[7] Treatment of **5** with the



Scheme 3. The tandem fragment-coupling/polycyclization reaction provides a variety of olefin-containing bridgehead polycycles. a) Vinyl Grignard (1.4 equiv), −78 °C, $PhCH_3$/THF (3/1), −78 →25 °C, dilute to 0.01 M, 14 h; b) vinyl Grignard (1.4 equiv), −78 °C, $PhCH_3$/THF (3/1), −78 →60 °C, dilute to 0.01 M, 11 h.

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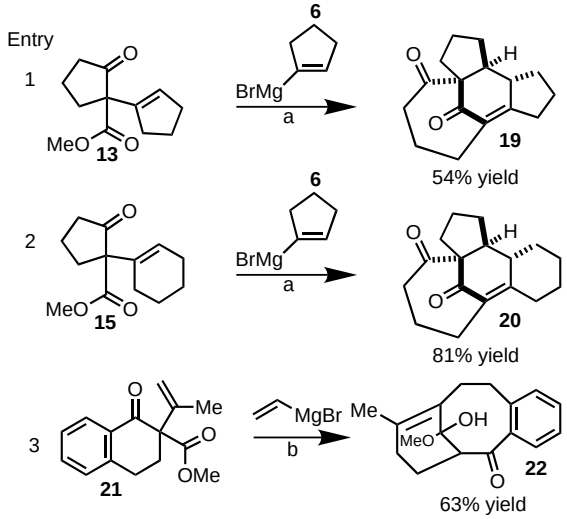
cyclohexene-based nucleophile **8** delivered the 6-6-7 ring system **9** in 80% yield, again as a single diastereomer. To demonstrate that this reaction was not limited to five-membered-ring β-ketoesters, compound **10** (entry 3) was exposed to Grignard reagent **11** and afforded the 8-6 ring system **12** in 60% yield. Compound **12** corresponds to the product of a type-II IMDA reaction which uses a five-atom tether between the diene and dienophile.

The experiments depicted in entries 4–6 of Scheme 3 were performed to explore the result of placing a ring system on the olefin unit of the β-ketoester. The reactions proceeded smoothly in all three cases, to afford tricycles **14** (73% yield), **16** (84% yield), and **18** (51% yield). The 7-6-5 (**14**), 7-6-6 (**16**), and 8-6-5 (**18**) ring systems were produced as single diastereomers in each case.

The successful triple-domino reactions depicted in Scheme 3 that used ring systems on the nucleophile and, in separate experiments, on the electrophile led to the investigation of transformations using ring systems on both reaction partners simultaneously (Scheme 4). Treatment of cyclopentanone **13** with a cyclopentene-based Grignard reagent afforded tetracycle **19**, a 7-6-5-5 ring system, in 54% yield as a single diastereomer. Three contiguous chiral



Scheme 4. Additional complexity is tolerated in the tandem reaction sequence. a) Vinyl Grignard (1.4 equiv), $-78\,^{\circ}C$, $PhCH_3$/THF (3/1), $-78 \rightarrow 25\,^{\circ}C$, dilute to 0.01M, 14 h; b) $MgBr_2$ (1.0 equiv), $-78 \rightarrow -42\,^{\circ}C$, vinylmagnesium bromide (1.4 equiv), $68\,^{\circ}C$, 2 h.

centers, including one quaternary carbon center, were controlled during this transformation. Entry 2 of Table 4 depicts a second example of a tetracycle-forming reaction using a cyclohexyl ring on the electrophile. The 7-6-6-5 tetracycle **20** was formed in 81% yield upon exposure of **15** to a cyclopentene-based Grignard reagent. As a final demonstration of the generality and utility of this reaction, we sought to construct a C-aryl core structure of the taxanes from tetralone-based β-ketoester **21**. Treatment of **21** with vinylmagnesium bromide initiated the triple-domino cyclization, and directly afforded the taxane core structure **22** with an aryl C-ring in 63% yield.[8] Curiously, compound **22** existed as an isolable hemiketal that resisted conversion into the ketone.

In summary, a triple-domino reaction has been developed that affords a wide range of complex polycyclic bridgehead enone-containing molecules. Precursors for the triple-domino reaction were rapidly accessed, with each of the cyclization products provided in at most four steps from commercially available reagents. In essence, the triple-domino reaction is a fragment-coupling reaction combined with a polycyclization reaction. As a result, fragments of comparable complexity can be combined and rearranged, thus offering a highly convergent, flexible, and stereospecific route to diverse polycyclic molecules. This reaction may be useful for rapidly assembling complex naturally occurring structures. In addition, this transformation may be useful in diversity-oriented synthesis where a premium is placed on reactions that greatly increase molecular complexity while simultaneously accessing a diverse set of complex molecules.[9] Our efforts to use this reaction for target-oriented and diversity-oriented synthesis will be reported shortly.

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[1] Naturally occurring molecules that contain this ring system include: a) CP-263,114 and CP-225,917: T. T. Dabrah, H. L. Harwood, L. G. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M. Moshier, T. A. Subashi, M. Therrien, P. C. Watts, *Antibiotics* **1997**, *50*, 1; T. T. Dabrah, T. Kaneko, W. Massefski, Jr., E. B. Whipple, *J. Am. Chem. Soc.* **1997**, *119*, 1594; b) taxol and taxus terpenes: M. C. Wani, M. E. Taylor, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325; c) welwitindolinone: K. Stratmann, D. L. Burgoyne, R. E. Moore, G. M. L. Patterson, *J. Org. Chem.* **1994**, *59*, 7219; K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935.

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[7] Each of the new compounds reported in this article was fully characterized, see the Supporting Information for details.

[8] For the synthesis of taxanes with aryl C-rings, see a) K. C. Nicolaou, W. M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 15; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15, and references therein; b) W. B. Young, J. J. Masters, S. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 5228; c) K. C. Nicolaou, C. G. Claiborne, K. Paulvannan, M. A. D. Postema, R. K. Guy, *Chem. Eur. J.* **1997**, *3*, 399; d) A. G. Fallis, *Acc. Chem Res.* **1999**, *32*, 464; e) see also ref. [3].

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