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# Synthesis of the Tricyclic Core of Colchicine via a Dienyne Tandem Ring-Closing Metathesis Reaction

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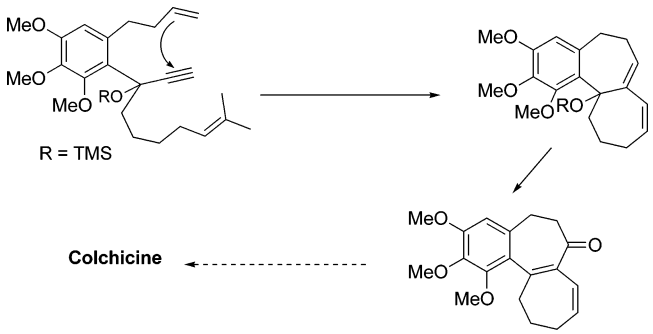
## ABSTRACT




**The synthesis of the tricyclic framework of colchicine has been achieved using a tandem ring-closing metathesis reaction of dienynes as the key step. In this process, both seven-membered rings B and C were formed in one step. Oxidation of tertiary allylic alcohol derived from the tandem metathesis product furnished an intermediate in the total synthesis of colchicine.**

Colchicine (**1**), present as the major alkaloid in *Colchicum autumnale*, is an old drug used in medicine for acute gout attacks and familial Mediterranean fever. It is also effective in treating chronic myelocytic leukemia, but the therapeutic effects are only observed at toxic or nearly toxic doses.[1] Colchicine has also long been known for its remarkable antimitotic activity which results from its specific binding to tubulin preventing microtubule assembly, spindle formation, and consequently cell division.[2] Although its high toxicity has precluded clinical utilization as a potential antitumor agent, it remains an important biochemical probe. Owing to its biological importance and unique structure, colchicine has been the target of a large number of synthetic studies, culminating in several elegant total syntheses.[3] One of the more difficult features of the colchicine synthesis is undoubtedly the construction of the tropolone C-ring, which is condensed to a second seven-membered ring (B). The common feature of early syntheses is that they adopt a stepwise linear approach to the construction of the tricyclic ring system (i.e., A → AB → ABC or A → AC → ABC). Recently, Schmalz and co-workers described a new strategy based on the simultaneous construction of the rings B and C by a Rh-tiggered intramolecular [3 + 2] cycloaddition (A → ABC approach). The resulting oxabicyclic adduct was then converted to the desired tropolone ring system.[4] In a conceptually similar approach, we herein describe a new entry to the colchicine carbon skeleton using a tandem ruthenium-catalyzed dienyne metathesis as a key step.

The tandem ring-closing metathesis (RCM) reaction of dienynes[5] has proved to be a powerful tool for the construc-

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(1) For a summary of the synthesis and biological activity of colchicine and allo congeners see: Brossi, A. *J. Med. Chem.* **1990**, *33*, 2311 and references therein.

(2) For a review on microtubule-targeted drugs see: Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *59*, 163.

(3) For a recent review on the total syntheses of colchicines see: Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230.

(4) Graening, T.; Friedichsen. W.; Lex, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1524. Graening, T.; Bette, V.; Neudörfl, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2005**, *7*, 4317.

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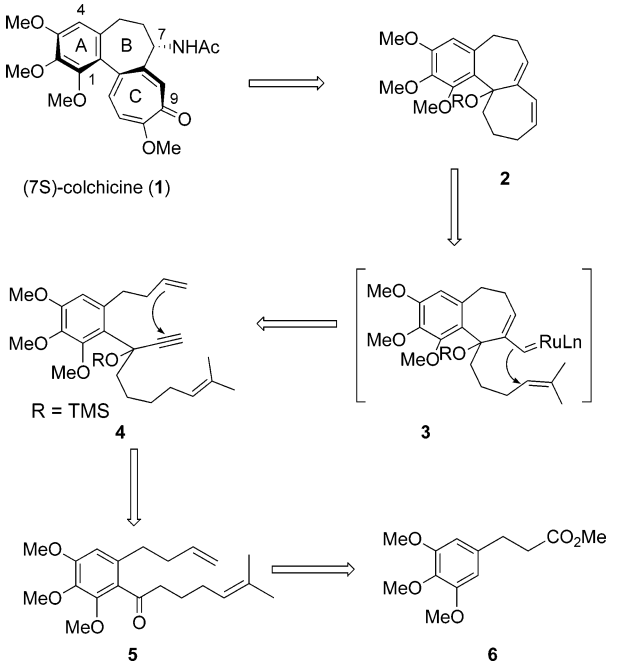
tion of polycyclic ring systems from acyclic starting material. In this highly efficient process, two rings are formed in a single step generally in high yield. Depending on the length of the alkene chains, the newly generated bicyclic systems may contain five, six, seven, or even eight-membered rings.[6] In previous reports, we described the application of this technique for the preparation of various fused bicyclic systems containing medium-sized rings including a concise formal synthesis of guanacastepene A.[7] Our interest in the synthesis of colchicine was therefore stimulated by the possibility that the (6,7,7)-tricyclic framework could be constructed by using a cascade RCM reaction starting from a suitably functionalized dienyne such as **4**.

Our retrosynthetic analysis (Scheme 1) is based on the

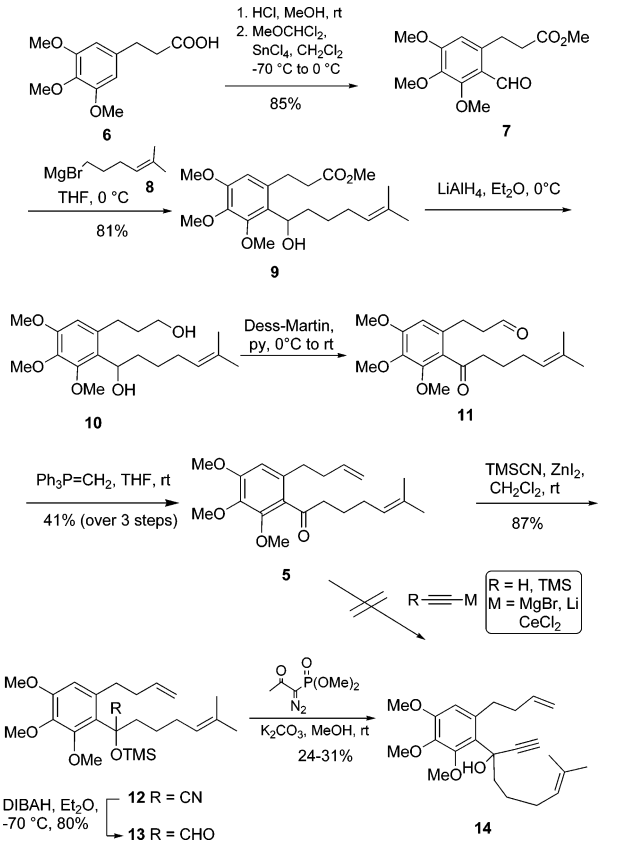
**Scheme 1.** Retrosynthetic Analysis




recognition that the formation of a metal carbene on dienyne **4** should first occur at the least hindered terminal alkene, which can cyclize to give the intermediate **3**. This intermediate could then undergo a second RCM reaction to give the desired tricyclic framework **2**. Although there was no precedent for the construction of a (7,7)-bicyclic ring system by tandem RCM,[8] this process should be facilitated by two favorable factors:[9] first, presence of a pre-existing aromatic ring bearing the alkene and alkyne moieties at adjacent positions makes the enyne RCM easier and, second, the Thorpe−Ingold effect of a quaternary carbon center bearing the trimethylsilyloxy group. The RCM reaction precursor **4** can be traced back to ketone **5** which in turn could be synthesized from the cheap and commercially available acid **6**.

According to this plan, the synthesis commenced with converting the acid functionality in **6** into the methyl ester and subsequent formylation using dichloromethyl methyl ether in the presence of $SnCl_4$ to afford aldehyde **7**[10] (Scheme 2). This aldehyde was treated with the Grignard reagent **8**

**Scheme 2.** Formation of Dienyne **14**




generated from 6-bromo-2-methyl-hex-2-ene[11] to afford alcohol **9**. Reduction of **9** with lithium aluminum hydride ($LiAlH_4$) furnished diol **10** which was oxidized with Dess−Martin's periodinane to furnish ketoaldehyde **11**. Treatment of **11** with methylene triphenylphosphorane resulted in a selective olefination of the aldehyde function affording

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(6) For selected examples of synthesis of polycyclic systems by tandem metathesis of dienynes, see: (a) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291. (b) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073. (c) Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 1483. (d) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323. (e) Garcia-Fandino, R.; Codesido, E. M.; Sobarzo-Sanchez, E.; Castedo, L.; Granja, J. R. *Org. Lett.* **2004**, *6*, 193. (f) Kaliappan, K. P.; Nandurdikar, R. S. *Org. Biomol. Chem.* **2005**, *3*, 3613. (g) Gonzalez, A.; Dominguez, G.; Castells, J. P. *Tetrahedron Lett.* **2005**, *46*, 7267.

(7) (a) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2001**, *3*, 3095. (b) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469. (c) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817. (d) Boyer, F.-D.; Hanna, I. *Eur. J. Org. Chem.* **2006**, 471. (e) Boyer, F.-D.; Hanna, I. *J. Organomet. Chem.* **2006**, *691*, 5181.

(8) Attempts to construct fused 7,7-bicyclic compounds from acyclic dienynes by tandem RCM failed (see ref. 7e).

(9) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

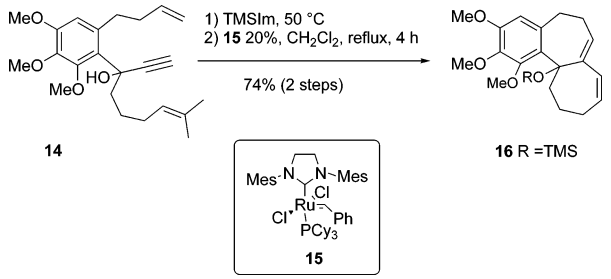
(10) McBride, B. J.; Garst, M. E. *Tetrahedron* **1993**, *49*, 2839.

(11) 6-Bromo-2-methyl-hex-2-ene was prepared in three steps from γ-butyrolactone: reduction with DIBAH followed by Wittig reaction and bromation of the resulting primary alcohol. For details see Supporting Information.

ketone **5** in 41% yield over three steps. At this stage, we planned to prepare propargylic alcohol **14** directly from **5** by addition of a metal acetylide. Unfortunately, all attempts using ethynyl magnesium bromide, lithium acetylide, or other nucleophiles prepared from these reagents and cerium(III) chloride gave only traces of the desired product or left the starting ketone unchanged. It is likely that both steric and electronic factors are responsible for this lack of reactivity. Finally, propargylic alcohol **14** was obtained from **5** using a three-step sequence as indicated in Scheme 2. One-carbon homologation of ketone **5** was achieved by treatment with trimethylsilyl cyanide (TMSCN) in the presence of zinc iodide to afford nitrile **12** (87% yield) which was reduced with diisobutylaluminum hydride (DIBALH) to give aldehyde **13** (80% yield).[12] Treatment of **13** with dimethyl 1-diazo-2-oxopropylphosphonate (the Ohira reagent)[13] in the presence of $K_2CO_3$ in MeOH led to the desired propargylic alcohol **14** albeit in low yield (24−31%). This alcohol was converted into its trimethylsilyl-protected derivative **4** by treatment with 1-(trimethylsilyl)imidazole (TMSIm) at 50 °C and was used without purification in the next step.

When the crude dienyne **4** was treated with 20% of Grubbs' second-generation catalyst **15**[14] in refluxing dichloromethane for 4 h, the tandem RCM reaction took place affording the tricyclic conjugated diene **16** in 74% yield for the two steps (Scheme 3). Unlike its precursor **4**, this

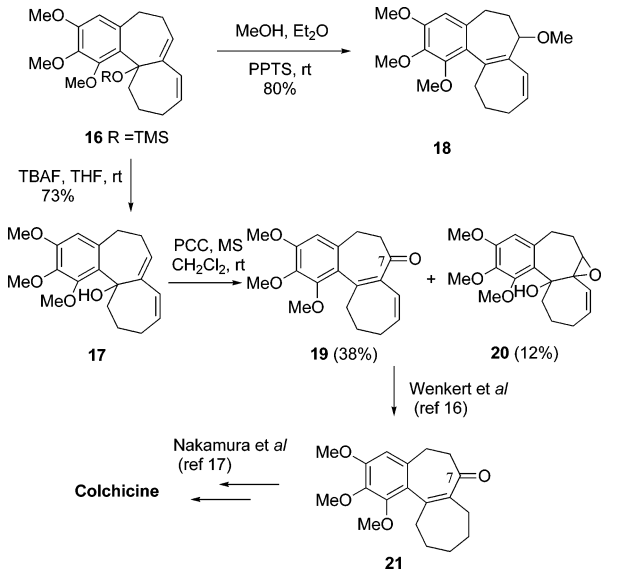
**Scheme 3.** Formation of Tricyclic Compound **16**




compound is stable and was isolated as a pure compound by silica gel column chromatography. It is worth noting that attempts to achieve the ring-closing metathesis reaction on alcohol **14** failed. The starting dienyne was recovered unchanged.

With the tricylic product **16** in hand, we turned next to the construction of a colchicine intermediate bearing an oxygen functionality at C-7. When a solution of trimethylsilyl ether **16** in ether was treated with methanol in the presence of pyridinium *p*-toluenesulfonate (PPTS), allylic rearrangement took place affording methyl ether **18** in high yield (Scheme 4).

**Scheme 4.** Formation of the Wenkert Intermediate **19**




Next, oxidative rearrangement of tertiary alcohol **17**, obtained by desilylation of **16**, was attempted.[15] When a solution of **17** in dichloromethane was stirred with 2 equiv of pyridinium chlorochromate (PCC) in the presence of molecular sieves of 4 A at room temperature for 2 h, dienone **18** was isolated in 38% yield along with epoxide **20** (12%) as a mixture of two isomers. Dienone **19**, described by Wenkert and co-workers[16] in the synthesis of an advanced colchicine intermediate, was transformed by catalytic hydrogenation into enone **21** which is a key intermediate in the Nakamura[17] total synthesis of colchicine.

In conclusion, we have shown for the first time that the tricyclic core of colchicine can be constructed by dienyne ring-closing metathesis. In this process, both seven-memberd rings B and C were formed in one step: formation of the seven-membered ring B by enyne RCM occurred first, followed by closure of the second seven-membered ring by olefin RCM. Our route has the added benefit of installing the desired oxygen functionalities at C-7 position furnishing an advanced colchicine intermediate. Currently, we are focusing on the completion of the synthesis of colchicine.

**Supporting Information Available:** Experimental procedures, characterization data, and $^1H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) To get the indicated yield, it is important to observe the following work up. After the completion of the reaction, silica gel was added at −70 °C, and the reaction mixture was allowed to warm to 0 °C. The crude aldehyde was isolated by filtration and was purified by flash column chromatography. Otherwise, treatment of the reaction mixture with Rochelle's salt (potassium and sodium tartrate solution) resulted in the complete degradation of the product.

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(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(15) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(16) Wenkert, E.; Kim, H.-S. In *Studies in Natural Products Chemistry;* Atta-ur-Rhaman, Ed.; Elsevier: Amsterdam, The Netherlands, 1989; Vol. 3, Part B, p 287.

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