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A Concise Total Synthesis of Pyrovellerolactone Using a Rhodium-Catalyzed [(3 + 2) + 2] Carbocyclization Reaction

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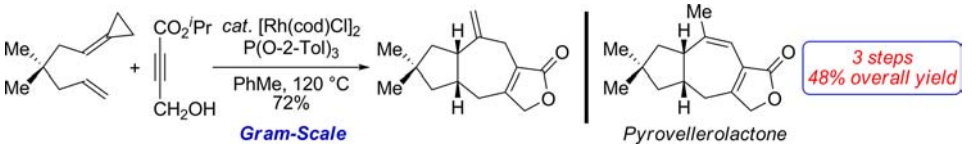
ABSTRACT



A concise and highly convergent three-step total synthesis of the lactarane natural product, pyrovellerolactone, is described. The key step involves a regio- and diastereoselective rhodium-catalyzed [(3 + 2) + 2] carbocyclization of an alkenylidenecyclopropane with a 4-hydroxybut-2-ynoate followed by an *in situ* intramolecular lactonization to generate the tricyclic core in a single operation. This represents the first example of a higher-order [3 + 2 + 2] carbocyclization reaction in total synthesis, which is likely to provide an important strategy for the construction of related targets within this sesquiterpene family.

The total synthesis of complex naturally occurring polycyclic sesquiterpenes remains a challenging endeavor for modern synthetic organic chemistry. Stimulated by their interesting and diverse biological properties, the ability to assemble such motifs in a concise and atom-economical manner has been the focus of significant attention.[1] In this context, transition-metal-catalyzed [$m + n + o$] carbocyclizations represent an important class of reactions, due to their ability to prepare polycyclic scaffolds with a high degree of molecular complexity in an atom-economical manner.[2]

We recently reported a novel regio- and diastereoselective rhodium-catalyzed [(3 + 2) + 2] carbocyclization reaction of alkenylidenecyclopropanes (ACPs) with unsymmetrical alkynes for the synthesis of 5,7-bicyclic scaffolds,[3] which are structural motifs embedded in several families of sesquiterpenes, as illustrated in Figure 1. We envisioned that the [(3 + 2) + 2] carbocyclization reaction would permit the expeditious synthesis of the all carbon core of the lactarane family of natural products, which consist of more than 100 structurally characterized derivatives.

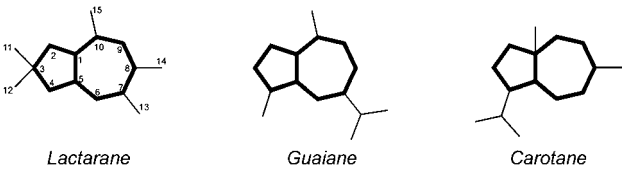


Figure 1. Classification of bicyclo[5.3.0]decane sesquiterpene scaffolds.

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(1) For comprehensive reviews of sesquiterpene total syntheses, see: (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2007; Vol. 5. (b) *Total Synthesis of Natural Products*; Goldsmith, D., Pirrung, M. C., Morehead, A. T., Jr., Young, B. G., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2007, Vol. 11.

(2) For selected reviews on [$m + n + o$] carbocyclization reactions, see: (a) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (b) Aubert, C.; Malacria, M.; Ollivier, C. In *Science of Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2011; Vol. 3, p 145 and pertinent references cited therein.

(3) Evans, P. A; Inglesby, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 12838.

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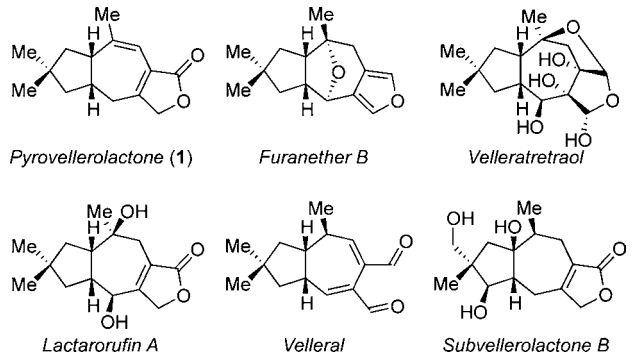
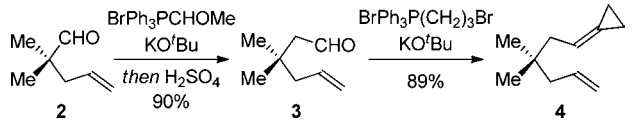


Figure 2. Representative lactarane natural products.

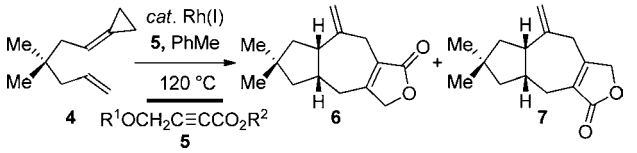
Figure 2 depicts several examples of lactarane natural products, many of which have a tricyclic scaffold.[4] Moreover, the lactarane natural products generally have a *cis*-ring-fusion, which was established by either two-dimensional NMR or X-ray crystallography. Although the biological activity of the majority of this family has not been fully determined, the agents that have been studied have interesting and diverse medicinal properties. For example, lactarorufin A is a potent fish antifeedant, subvellerolactone B is cytotoxic, velleral is active against Gram-positive and -negative bacteria, and velleratretraol is cytotoxic and has anti-HIV activity. Several total syntheses of lactaranes have been reported, including pyrovellerolactone.[5−7] Herein, we now report a three-step total synthesis of pyrovellerolactone (**1**) using a regio- and diastereoselective rhodium-catalyzed [(3 + 2) + 2] carbocyclization as the key step to construct the tricyclic core of this agent.

Scheme 1. Preparation of the ACP **4** from Commercially Available Materials



The ACP **4** was prepared *via* the Wittig olefination reaction of the commercially available, albeit expensive, aldehyde **3** (Scheme 1). Alternatively, the 2,2-dimethyl-4-pentenal **2**, which is relatively inexpensive, was subjected to a one-pot olefination/hydrolysis to provide **3**. This set the stage to examine the key rhodium-catalyzed [(3 + 2) + 2] carbocyclization reaction of **4** with the unsymmetrical alkyne **5a** to afford the tricyclic lactone **6** upon *in situ* deprotection and lactonization of the allylic γ-hydroxy-ester (Table 1). Gratifyingly, treatment of the ACP **4** and alkyne **5a** with the catalyst derived from the modification of $[Rh(cod)Cl]_2$ with $P(O\text{-}2\text{-}Tol)_3$ afforded the tricyclic lactones **6**/**7** in 75% yield after the removal of the *tert*-butyldimethylsilyl ether (entry 1).[3,8] Although the reaction proceeds with excellent diastereocontrol (*ds* ≥19:1), it favors the formation of the undesired lactone **7**, albeit readily separable from **6** *via* flash chromatography.

Table 1. Optimization of the Sequential Rhodium-Catalyzed [(3 + 2) + 2] Carbocyclization/Lactonization Reaction[a]



	alkyne **5**				
entry	R^1	R^2		ratio of **6**/**7**[b]	yield of **6**/**7** (%)[c]
1	TBS	Me	**a**	1:3	75
2	Bn	"	**b**	1:1	72
3	Ac	"	**c**	4:1	63
4	H	"	**d**	4:1	78
5	"	^{i}Pr	**e**	6:1	85[d]
6	"	^{t}Bu	**f**	6:1	76

[a] All reactions were carried out on a 0.25 mmol scale using $[Rh(cod)Cl]_2$ (4 mol %) and $P(O\text{-}2\text{-}Tol)_3$ (24 mol %) with 1.2 equiv of the alkyne **5** in a sealed tube at 120 °C in toluene (0.1 M). For cases where $R^1 \neq H$, the crude reaction mixtures were deprotected to afford the corresponding lactones **6**/**7** for analysis. [b] Determined by 500 MHz ^1H NMR analysis of the crude reaction mixture. The diastereoselectivities (≥19:1) were also determined on the crude reaction mixture. [c] Isolated yield of **6**/**7**. [d] The reaction could also be conducted on gram scale (1.053 g, 7.0 mmol) with an improved 92% overall yield, albeit with lower selectivity (*rs* = 3.5:1), which afforded **6** in an analogous 72% yield (1.176 g).

In our preliminary report, we demonstrated that varying the steric and electronic parameters of the alkyne dramatically impacts regioselectivity, whereas altering the ancillary ligands is ineffectual on selectivity.[9] In light of this observation, we sought to examine the effect of the hydroxy methyl protecting group and the carboxylic ester on the alkyne insertion. In this context, changing the *tert*-butyldimethylsilyl ether **5a** to the benzyl ether **5b** provides modest improvement in selectivity (entry 1 *vs* 2), whereas the acetate **5c** is significantly more selective for the desired

(4) Vidari, G.; Vita-Finzi, P. In *Studies in Natural Products Chemistry, Structure and Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1995; Vol 17, pp 153−206.

(5) For the isolation and initial assignment of pyrovellerolactone, see: Magnusson, G.; Thorén, S. *Acta Chem. Scand.* **1973**, *27*, 1573.

(6) For the total synthesis of pyrovellerolactone and the structural reassignment, see: (a) Froborg, J.; Magnusson, G.; Thorén, S. *J. Org. Chem.* **1975**, *40*, 1595. (b) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.

(7) For selected total syntheses of lactarane natural products, see: (a) Price, M. E.; Schore, N. E. *J. Org. Chem.* **1989**, *54*, 5662. (b) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5979. (c) Molander, G. A.; Carey, J. S. *J. Org. Chem.* **1995**, *60*, 4845. (d) Seki, M.; Sakamoto, T.; Suemune, H.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1707. (e) Wockenfuss, B.; Wolff, C.; Tochtermann, W. *Tetrahedron* **1997**, *53*, 13703. (f) Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1998**, *63*, 122.

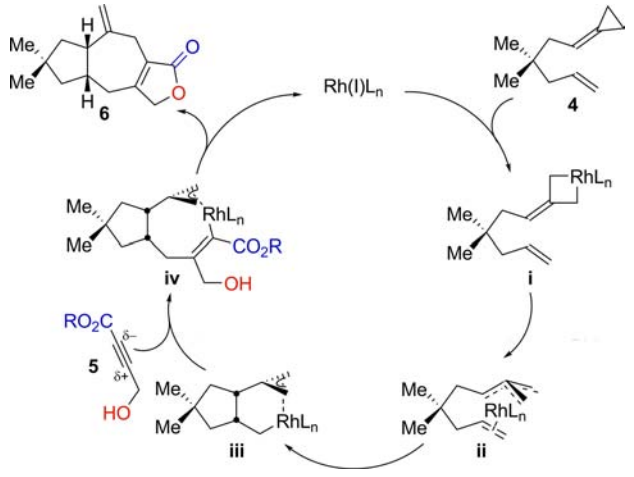
(8) Mazumder, S.; Shang, D.; Negru, D. E.; Baik, M.-H.; Evans, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 20569.

(9) In the present case, the use of phosphine ligands and/or cationic rhodium complexes result in poor regioselectivity (*rs* = 1:1) and poor yield (~20%).

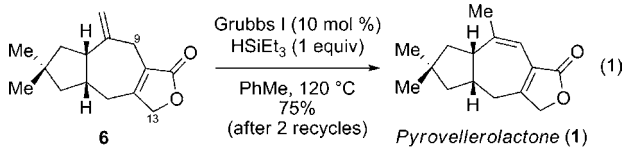
cycloadduct **6** (entry 3). Gratifyingly, the reaction with the unprotected hydroxyl group **5d** provided the tricyclic lactone **6** without the necessity to unmask the propargylic alcohol and with similar selectivity (entry 4).[10] Additional studies probed the effect of changing the ester group in an attempt to further enhance the selectivity for the desired cycloadduct. Interestingly, the isopropyl ester **5e** afforded optimal yield and selectivity for **6** (entry 5), whereas the *tert*-butyl ester **5f** provided similar selectivity but with diminished efficiency (entry 6). *Overall, this transformation provides all 15 carbons of the lactarane, including three rings and two stereocenters in a single operation with excellent efficiency and selectivity*.

Based on our recent theoretical and mechanistic investigations,[8,11] we envisage the reaction proceeds as outlined in Scheme 2. Oxidative addition of the rhodium(I) complex into the distal bond of the cyclopropane **4** affords metallacyclobutane **i**, which upon rearrangement generates the rhodium(III) trimethylenemethane species **ii** *en route* to metallacycle **iii**. Insertion of the alkyne **5** presumably occurs with the more nucleophilic Rh−C bond (*vs* Rh-allyl) adding to the LUMO of the alkyne to afford **iv**,[12] which places the electron-withdrawing group adjacent to the metal center.[13,14] Finally, facile C(sp^2)-Rh-allyl reductive elimination and lactonization affords the desired cycloadduct **6**.

Scheme 2. Proposed Mechanism of the Rhodium-Catalyzed [(3 + 2) + 2] Carbocyclization of ACPs with Alkynes



The final objective with respect to the total synthesis of pyrovellerolactone was the selective isomerization of the *exo*cyclic olefin. Interestingly, the attempted olefin migration with strong acids and bases led to recovered starting material **6**. In order to garner additional insight into this process, treatment of the tricyclic lactone **6** with potassium *tert*-butoxide followed by quenching with CD_3OD demonstrated the selective incorporation of deuterium at C13 (Figure 1). Additionally, the conversion of the lactone in **6** to the *tert*-butyldimethylsilyloxyfuran and attempted isomerization of the *exo*cyclic olefin also failed to provide **1**. Hence, given these problems we decided to examine the feasibility of metal hydride olefin isomerization reactions. Gratifyingly, the isomerization of **6** with the triethylsilane modified Grubbs first generation catalyst[15] provided pyrovellerolactone (**1**) in 52% yield in addition to the unreacted *exo*-isomer **6** (34%). Separation of the two adducts and resubjection of **6** to the reaction conditions afforded, after two cycles, (±)-pyrovellerolactone (**1**) in 75% overall yield (eq 1). Although this recycling protocol is somewhat tedious, prolonged reaction times result in a complex mixture of isomers.



A comparison of the spectroscopic data for the synthetic and natural material revealed a few anomolies, which prompted further studies. For instance, although the proton NMR is in good agreement with the reported data, the omission of several resonances from the original assignment prevent a direct and comprehensive comparison.[16] Furthermore, there is an anomalous peak in the ^{13}C NMR, which we attribute to an error in the original assignment since the other carbon resonances all correlate with the reported data.

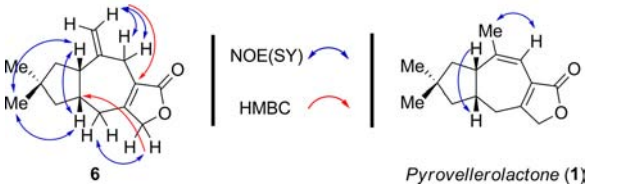


Figure 3. Key NOE(SY) and HMBC correlations for stereochemical confirmation.

Figure 3 provides additional spectroscopic support for cycloadduct **6** and pyrovellerolactone (**1**), which unambiguously confirm both the regio- and diastereocontrol in

(10) For an example of a sequential rhodium-catalyzed conjugate addition/lactonization reaction, see: Alfonsi, M.; Arcadi, A.; Chiarini, M.; Marinelli, F. *J. Org. Chem.* **2007**, *72*, 9510.

(11) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 3635.

(12) Pitcock, W. H., Jr.; Lord, R. L.; Baik, M.-H. *J. Am. Chem. Soc.* **2008**, *130*, 5821.

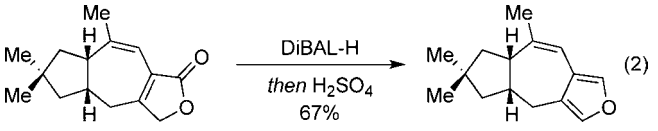
(13) For an example of this type of insertion, see: Evans, P. A.; Sawyer, J. R.; Inglesby, P. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 5746 and pertinent references cited therein.

(14) For a review on steric and electronic effects during alkyne insertion into rhodacycles, see: Liu, P.; Houk, K. N. *Inorg. Chim. Acta* **2011**, *369*, 2.

(15) For examples of ruthenium-catalyzed olefin isomerizations, see: (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732. (b) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. (c) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672. (d) Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014.

(16) Although the total synthesis of the natural product has been previously reported, the data for this agent was only reported in the original isolation paper.[5]

the [(3 + 2) + 2] carbocyclization reaction leading to the natural product. Nevertheless, the problems associated with the original structural assignment[5] coupled with the fact that both synthetic routes[6] were centered around a 1,5-hydride shift of vellerolactone present the possibility that the ring junction may have epimerized to provide the *trans*-configuration. In order to address this concern, we provide additional evidence for the relative configuration of pyrovellerolactone (**1**) by reducing the γ-lactone to the corresponding tricyclic furan **8**, which was a key intermediate in an alternative route that does not involve a 1,5-hydride shift (eq 2). For example, the relative configuration of the ring junction in **8** was originally established by analogy, using X-ray crystallography (see Supporting Information for details). Gratifyingly, the proton NMR data for the tricyclic furan **8** is in good agreement with the reported material, albeit several proton resonances are again absent.



Pyrovellerolactone (**1**) **8** (2)

In conclusion, we have developed a highly regio- and diastereoselective rhodium-catalyzed [(3 + 2) + 2] carbocyclization of the ACP **4** with the 4-hydroxybut-2-ynoates **5**. This work demonstrates that both steric and electronic parameters impact the alkyne insertion. Additionally, 4-hydroxybut-2-ynoates provide butyrolactone surrogates, which afford tricyclic scaffolds in a single operation, thereby making this a highly expeditious process in the context of a complexity building transformation. This is exemplified in the concise three-step total synthesis of pyrovellerolactone (**1**) in 48% overall yield from the commercially available aldehyde **3**. Finally, this strategy should facilitate the total synthesis of related lactarane natural products using biosynthetically inspired oxidation and reduction reactions to decorate the carbon skeleton.

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Supporting Information Available. Experimental procedures, characterization data, and spectra are included. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.