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Total Synthesis of (+)-Cyperolone

Philipp Klahn,[†,‡] Alexander Duschek,[‡] Clémence Liébert,[‡] and Stefan F. Kirsch*[,†,‡]

Organic Chemistry, Bergische Universität Wuppertal, Gaussstr. 20, 42119 Wuppertal, Germany, and Department Chemie, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany

sfkirsch@uni-wuppertal.de

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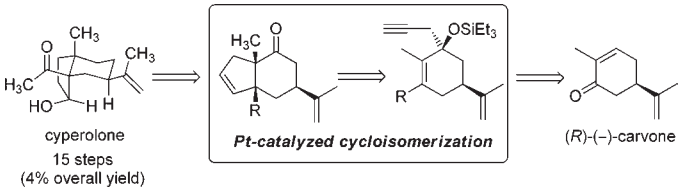
ABSTRACT



The total synthesis of (+)-cyperolone, an eudesmane-derived sesquiterpenoid from *Cyperus rotundus*, is described. The de novo synthesis was accomplished via a 15 step sequence starting from (*R*)-(−)-carvone. The synthetic route features a platinum-catalyzed cycloisomerization to rapidly construct the bicyclic core from a 3-silyloxy-1,5-enyne intermediate.

Cyperolone (**1**) was isolated first in 1966 by Hikino et al. from *Cyperus rotundus* LINNE (Japanese nutgrass).[1] The eudesmane-derived natural product belongs to the rather small class of cyperane-type sesquiterpenoids, all members of which were isolated from cognate plants.[2] Although the rhizomes of Japanese nutgrass have found widespread use in traditional oriental medicine to treat, for example, menstrual disorders and gynecological diseases,[3] the biological activity of cyperolone has not been fully evaluated.[4] We planned to synthesize cyperolone, not only because a chemical synthesis entry would allow the further exploration of the pharmacology but also because a flexible de novo approach would provide a general entry into the entire class of cyperane-type natural products.[5] The structure of cyperolone (**1**) is characterized by a sterically congested bicyclic system where all substituents are directed to the same face and two quaternary all-carbon stereogenic centers are adjacent to each other (Figure 1). The total synthesis of cyperolone was successfully achieved in 1966 by Hikino et al. in a semisynthetic approach starting from α-cyperone, thus, supporting the early structural assignments.[6] Further synthetic entries into cyperane-class natural products are scarce.[7,8] In this letter, we describe the total synthesis of (+)-cyperolone starting from (*R*)-(−)-carvone.

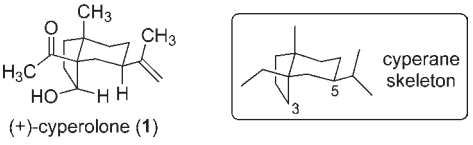


Figure 1. Structures of cyperolone (**1**).

[†] Bergische Universität Wuppertal.
[‡] Technische Universität München.

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(4) Plant growth inhibition was reported: Komai, K.; Seto, N.; Matsubayashi, K.; Hamada, M. *Zasso Kenkyu (Weed Res. Jp.)* **1990**, *35*, 164–168.

(5) Based on ^{1}H NMR data, structural assignments of several cyperanes appear to be inconsistent, e.g.: ref 2a vs ref 2e. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1989**, *45*, 3809–3818.

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Cyperolone (**1**) is a cis-fused bicyclo[4.3]nonane. As outlined in Figure 2, we planned to construct this bicyclic core by use of a domino reaction[9] previously developed in our group: In the presence of noble-metal catalysts, 3-silyloxy-1,5-enynes undergo a 6-endo cyclization followed by a pinacol shift to give five-membered carbocycles.[10,11] According to this strategy, we considered bicycle **2** as a key intermediate that contains the two quaternary stereogenic centers and that can be easily accessed from **3**. Further elaboration to the target compound **1** would involve the removal of the carbonyl group. Additionally, the endocyclic alkene moiety would have to be converted into its epoxide. Powerful hydride nucleophiles are then required to create the hydroxy group at C3 through epoxide opening. To avoid the risk of competing attack at the acetyl moiety, we decided to postpone the installation of this functionality to a late stage of the synthesis. To this end, bicycle **2** (and its direct precursor **3**) were equipped with a stable silyloxy methylene group (R = CH_2OSi*i*-Pr_3) rather than with an acetyl group.[12] We further envisioned that 3-silyloxy-1,5-enyne **3** can be prepared from (*R*)-(−)-carvone incorporating the isopropenyl-bearing stereogenic center at C5.

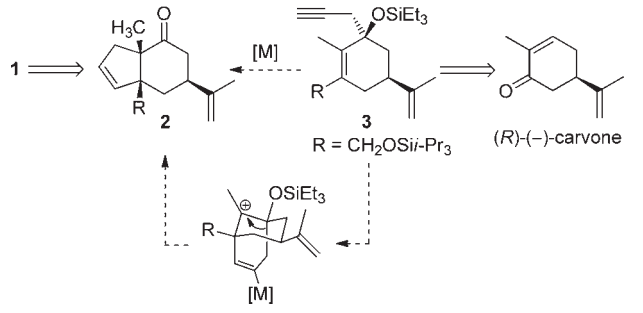
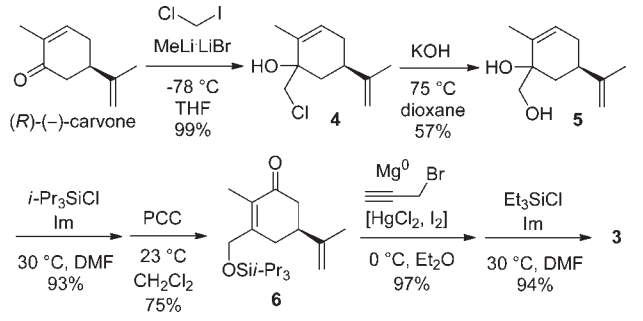


Figure 2. Synthetic plan.

Scheme 1. Synthesis of 3-Silyloxy-1,5-enyne **3**



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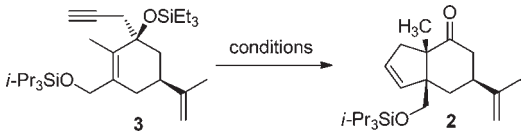
Our synthesis began with the conversion of (*R*)-(−)-carvone into chlorohydrine **4** followed by hydrolysis under basic conditions (Scheme 1). Even though only moderate yields were obtained for the hydrolysis step, we found this two-step sequence to diol **5** advantageous over alternative sequences[13] since it proved scalable and highly reliable in terms of yield. Upon selective protection of the primary hydroxy as triisopropylsilyl ether, oxidative rearrangement[14] to the cyclic enone **6** was achieved by use of pyridinium chlorochromate (PCC). Addition of the Grignard reagent derived from propargyl bromide[15] and subsequent silylation of the tertiary hydroxy smoothly resulted in the formation of key 3-siloxy-1,5-enyne **3**.

Table 1. Optimization of the Conversion **2**→**3**[a]



entry	catalyst (mol %)	additive (mol %)	solvent	temp (°C)	yield (%)[b]
1	$ClAuPPh_3$ (5)	$AgSbF_6$ (5)	CH_2Cl_2	23	–[c]
2	$PtCl_2$ (10)		Ph-Me	100	44
3	$PtCl_2$ (20)	cod (80)	Ph-Me	35	76
4	$PtCl_4$ (10)		Ph-F	50	51
5	$PtCl_4$ (10)	cod (40)	Ph-Me	35	69
6	**$PtCl_4$ (20)**	**cod (80)**	**Ph-Me**	**23**	**80**

[a] Conditions: **3**, catalyst, *i*-PrOH, temperature, solvent. [b] Isolated yield after column chromatography. [c] No conversion.

(8) For an approach to the cyperane framework, see: Srikrishna, A.; Dinesh, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2203–2207.

(9) For leading reviews on domino reactions, see: (a) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514–3522. (b) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (e) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157. (f) Pellisier, H. *Tetrahedron* **2006**, *62*, 2143–2173.

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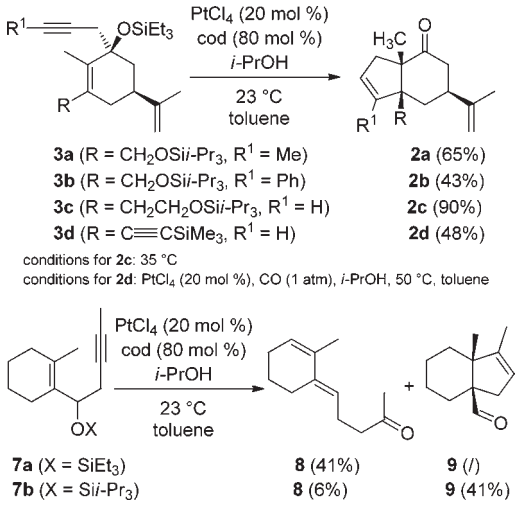
(11) For related strategies, see inter alia: (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (b) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (c) Korotchenko, V. N.; Gagné, M. R. *J. Org. Chem.* **2007**, *72*, 4877. (d) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315. (e) Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178. (f) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2542. For an application in total synthesis, see: (g) Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 7876.

(12) As an alternative approach, we also investigated substrates **3** with R = —CH=CH_2 and R = —C≡CH. However, these substrates failed to undergo noble-metal-catalyzed cycloisomerization to **3** as will be detailed elsewhere.

(13) An established protocol that makes use of methylthiomethyl lithium addition onto carvone did not provide reproducible yields in our hands: Tanis, S. P.; McMills, M. C.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 5887–5889.

We next investigated the key conversion of enyne **3** into bicycle **2**. Unfortunately, when the conditions developed in our 2007 study were employed (10 mol % $ClAuPPh_3$ activated by 5 mol % $AgSbF_6$, stoichiometric amounts of *i*-PrOH, 23 °C, CH_2Cl_2),[10a] not even traces of the desired compound **2** were detected (Table 1, entry 1). We attributed this lack of reactivity to the reduced nucleophilicity of the tetrasubstituted olefin moiety; all the previously reacted 3-silyloxy-1,5-enynes contained internal olefin nucleophiles that were either di- or trisubstituted. Consequently, we started to reexamine the potential of various transition metal catalysts including gold, palladium, and copper complexes to make the conversion **3**→**2** possible.[16] It was finally found that, only in the presence of platinum catalysts, formation of the anticipated product **2** was indeed possible.[17] As shown in Table 1, both $PtCl_2$ and $PtCl_4$ were active precatalysts in the presence of substoichiometric amounts of cyclooctadiene (cod). The best yields were obtained when employing 20 mol % of $PtCl_4$ and 80 mol % of cod in toluene at 23 °C (entry 6). Since in all cases lower catalyst loadings resulted in significantly reduced yields, the conditions shown in entry 6 were also utilized for gram-scale reactions to continue our approach to cyperolone.

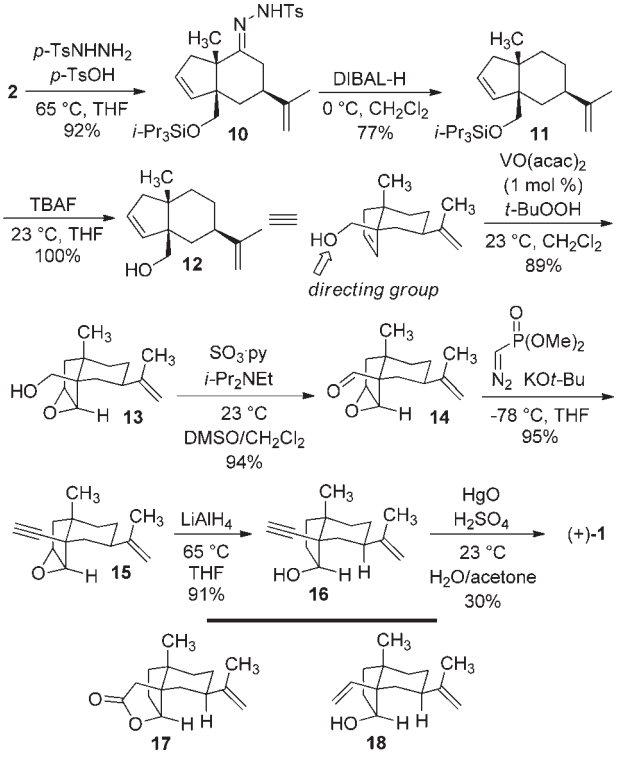
Scheme 2. Cycloisomerization of 3-Silyloxy-1,5-enynes



As summarized in Scheme 2, reaction conditions that utilize $PtCl_4$ as a precatalyst are also successful in the cycloisomerization of other 3-silyloxy-1,5-enynes having tetrasubstituted olefins. It should be pointed out that substituents at the alkyne terminus lead to a marked decrease in yield, presumably due to the increased steric hindrance in the C−C bond-forming event. Notably, enyne **7a** having a triethylsilyloxy group provided diene **8** rather than aldehyde **9**. When switching from triethylsilyloxy to triisopropylsilyloxy, cycloisomerization took place to achieve the formation of **9** in 41% yield.

With conditions for the formation of key intermediate **2** in hand, we finished the total synthesis of (+)-cyperolone as shown in Scheme 3. Removal of the carbonyl group was achieved by forming the tosylhydrazone **10** followed by treatment with DIBAL-H.[18] Deprotection of the primary triisopropylsilyl ether yielded alcohol **12**. Vanadium-catalyzed epoxidation was directed through the homoallylic

Scheme 3. Total Synthesis of (+)-Cyperolone



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(17) For the use of platinum catalysts in π-activation cascades, see inter alia: (a) Umland, K.-D.; Palisse, A.; Haug, T. T.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 9965–9968. (b) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878–5880. (c) Binder, J. T.; Crone, B.; Kirsch, S. F.; Liébert, C.; Menz, H. *Eur. J. Org. Chem.* **2007**, 1636–1647. (d) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547–4550. (e) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469. (f) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245. (g) Nakamura, I.; Sato, Y.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 4198–4199.

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alcohol moiety in **12** and, thus, proceeded with complete diastereocontrol;[19] the isopropenyl group remained unreacted under these conditions.[20] Subsequent oxidation[21] of the hydroxy group followed by homologation with the Seyferth–Gilbert reagent[22] furnished alkyne **15**. Nucleophilic epoxide opening with $LiAlH_4$ gave the secondary alcohol **16** in 91% yield. As expected the hydride reagent opened the epoxide regioselectively from the sterically less hindered side. Finally, terminal alkyne **15** was successfully converted into (+)-cyperolone (**1**) in 30% yield using HgO in aqueous H_2SO_4 and acetone.[23] The spectroscopic data of the synthetic samples were in excellent agreement with those reported in the literature for the natural product.[1] Despite the poor ending step (**16**→**1**), the overall end game strategy (**12**→**1**) proved highly useful due to the fact that (i) it is reasonably short regarding the number of steps and (ii) it does not require additional protecting group operations.[24] It should be mentioned that the major product of the Hg-mediated hydration was the tricyclic lactone **17** resulting in 44% yield from a ready 5-endo cyclization and subsequent oxidation. This result demonstrated how steric crowding hampers the straightforward installation of the acetyl group. A multitude of hydration conditions led to decomposition, no reaction, or predominant five-membered ring formation; in no case, a better yield for the desired cyperolone target was accomplished.[25] Our attempts to react olefin **18** under Wacker conditions[26] most likely failed for the same reasons.

In summary, we have described an expedient, stereocontrolled synthesis of (+)-cyperolone (15 steps, 4.3% overall yield from carvone). The two quaternary stereogenic centers were formed in a novel platinum-catalyzed cycloisomerization step that combines an enyne cyclization with a pinacol-type shift. Furthermore, our approach to cyperolone should provide a general entry into the whole class of cyperane-type natural products by further elaboration of the isopropenyl group. Applications of this synthetic strategy to the synthesis of other cyperanes and studies of the biological activity of cyperolone are currently underway.

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

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(25) When reacting the trimethylsilyl ether derived from **16** under several hydration conditions, the starting material remained unchanged in all cases.

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The authors declare no competing financial interest.