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Sequential Cycloaddition Approach to the Tricyclic Core of Vibsanin E. Total Synthesis of (±)-5-*epi*-10-*epi*-Vibsanin E

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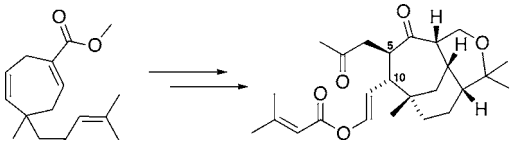
ABSTRACT



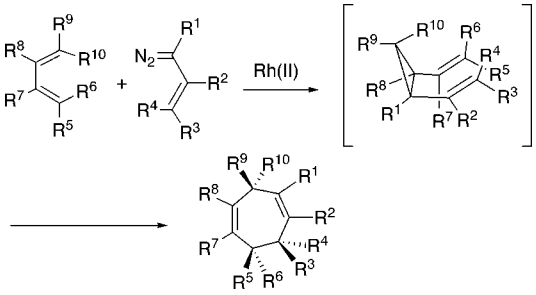
(±)-5-*epi*-10-*epi*-vibsanin E

A direct access to (±)-5-*epi*-10-*epi*-vibsanin E is described, based on three key cycloaddition steps, a rhodium-catalyzed [4 + 3] cycloaddition, a heteronuclear [4 + 2] cycloaddition, and a photochemically induced [4 + 2] cycloaddition.

A very effective method for the construction of seven-membered carbocycles is the [4 + 3] cycloaddition between rhodium-stabilized vinylcarbenoids and dienes.[1] The reaction is applicable to a wide range of dienes including heterocycles such as furans,[2] pyrroles,[3] pyridones,[4] and even benzene derivatives.[5] The mechanism of the [4 + 3] cycloaddition is a tandem cyclopropanation/Cope rearrangement, which ensures that the [4 + 3] cycloaddition is highly diastereoselective, capable of complete diastereocontrol at up to three stereogenic centers (Scheme 1).[1] Furthermore, chiral auxiliaries[6] and chiral catalysts[7] have been very effectively applied to render the reaction asymmetric.

The application of the [4 + 3] cycloaddition to the synthesis of natural products is limited.[8] In this paper, we describe the utilization of this methodology to the synthesis of the tricyclic core of vibsanin E (**1**),[9] which contains a highly functionalized cycloheptane ring. The most notable feature

Scheme 1



of the synthetic design is the use of three cycloaddition steps (Figure 1). The first is a [4 + 3] cycloaddition, which generates the cycloheptane core. This is followed by an intramolecular heteronuclear [4 + 2] cycloaddition to generate the other two rings. The two side chains are introduced by a photochemically induced [4 + 2] cycloaddition, followed by an oxidative cleavage.

(1) Davies, H. M. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Greenwich, CT, 1998; Vol. 5, pp 119−164.
(2) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.
(3) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.
(4) Davies, H. M. L.; Hodges, L. M. *J. Org. Chem.* **2002**, *67*, 5683.
(5) Davies, H. M. L.; Clark, T. J.; Kimmer, G. F. *J. Org. Chem.* **1991**, *56*, 6440.
(6) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468.
(7) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.
(8) (a) Davies, H. M. L.; Calvo, R. L.; Townsend, R. J.; Ren, P.; Churchill, R. M. *J. Org. Chem.* **2000**, *65*, 4261. (b) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2000**, *41*, 9021. (c) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1998**, *63*, 657. (d) Kende, A. S.; Smalley Jr., T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431.
(9) (a) Kawazu, K. *Agric. Biol. Chem.* **1980**, *44*, 1367. (b) Fukuyama, K.; Katsube, Y.; Kawazu, K. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1701 (c) Fukuyama, Y.; Minami, H.; Kagawa, M.; Kodama, M.; Kawazu, K. *J. Nat. Prod.* **1999**, *62*, 337.

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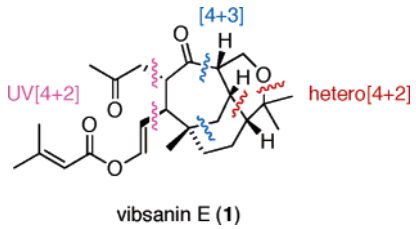
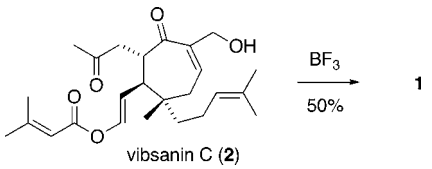


Figure 1. General synthetic strategy to **1**.

Vibsanin E is a member of a small family of diterpenes, whose occurrence to date is limited to only a few natural sources such as the plant *Viburnum awabuki*,[9c] the liverwort *Odontoschisma denudantum*,[10] and the plant *Viburnum odoratissimum*.[9a,b] Vibsanin E was isolated from the latter source in 1980,[9a] and its absolute configuration was established by X-ray crystallography the same year.[9b] To our knowledge, no total synthesis of vibsanin E has been reported, although a semi-synthesis has been achieved by the Lewis acid induced cyclization of vibsanin C (**2**) (Scheme 2).[9c] Model studies on an alternative strategy to the tricyclic

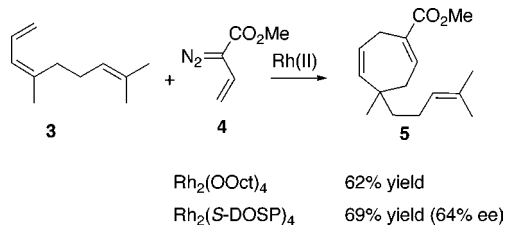
Scheme 2



core of vibsanin E have been recently reported.[11]

The first step of the synthesis is the rhodium-catalyzed [4 + 3] cycloaddition between the diene **3**[12] and the vinyldiazoacetate **4**[13] (Scheme 3). This reaction can be conducted

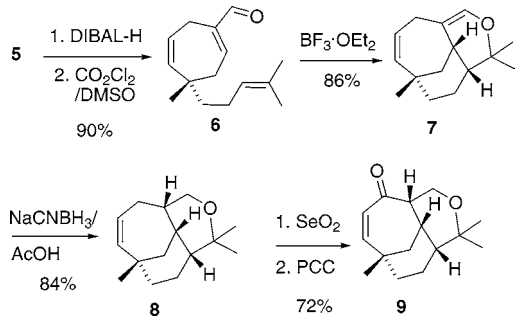
Scheme 3



on a 0.2 mol scale with 0.1 mol % of rhodium(II) octanoate to generate the cycloheptadiene **5** in 62% yield. This transformation demonstrates the selectivity of the vinylcarbenoid chemistry because **3** contains three double bonds and six allylic C−H sites, potentially susceptible to C−H insertion,[14] yet only the sterically most accessible double bond undergoes the initial cyclopropanation. This strategy would also be amenable for an enantioselective synthesis of vibsanin derivatives because when the [4 + 3] cycloaddition is catalyzed by the dirhodium tetraprolinate complex Rh_2-(*S*-DOSP)$_4$[15] (**5**) is formed in 64% ee.

The second stage of the synthesis is the conversion of the cycloheptadiene **5** to the tricyclic core **9** (Scheme 4).

Scheme 4



Reduction of the methyl ester in **5** by DIBAL-H followed by oxidation of the resulting alcohol under Swern conditions generates the aldehyde **6** in 90% yield for the two steps. The tricyclic core of vibsanin E (**7**) is readily obtained in 86% yield by a BF_3·OEt_2-assisted heteronuclear [4 + 2] cycloaddition of the aldehyde **6**. In addition, this transformation generates two new stereocenters with the desired relative configuration. A fourth stereocenter is introduced by reduction of the enol ether functionality in **7** with $NaCNBH_3$ under acidic conditions to furnish the alkene **8** in 84% yield. The protonation of the enol ether occurs from the convex face to generate a single diastereomer of **8**. Allylic oxidation[16] of **8** by selenium dioxide followed by PCC oxidation generates the conjugated ketone **9** in 72% yield for the two steps. All of the reactions in Scheme 4 can be conducted in reasonable amounts, resulting in the rapid synthesis of **9** on a 10 g scale.

The most obvious method to complete the synthesis of vibsanin E was by a tandem conjugate addition/alkylation strategy. Unfortunately, **9** is quite resistant to conjugate addition, and the only reaction that could be achieved was a dimethylcuprate induced reaction to form the ketone **10** (Scheme 5). X-ray crystallographic analysis of **10** confirmed that the methyl group was introduced from the desired convex face,[17] but due to the difficulty in conducting the con-

(10) Hashimoto, T.; Toyota, M.; Koyama, H.; Kikkawa, A.; Yoshida, M.; Tanaka, M.; Takaoka, S.; Asakawa, Y. *Tetrahedron Lett.* **1998**, *39*, 579

(11) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327.

(12) Leopold, E. J. *Org. Synth.* **1986**, *64*, 164.

(13) Davies, H. M. L.; Hougland, P. W.; Cantrell, W. R., Jr. *Synth. Commun.* **1992**, *22*, 971.

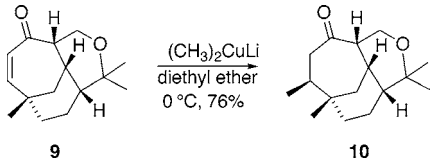
(14) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(15) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(16) Nicolaou, K. C.; Hwang, C. K.; Sorensen, E. J.; Clairborne, C. F. *Chem. Commun.* **1992**, 1117.

(17) The X-ray crystallographic data have been submitted to the Cambridge Structural Database [Kovalevskyi, A. Yu.; Coppens. P. 2004, CCDC No. 258973].

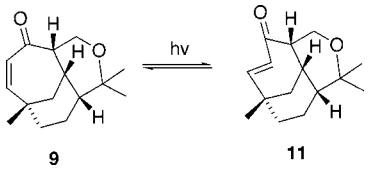
Scheme 5



jugate addition step, alternative strategies were examined. One possibility would be a Diels−Alder strategy, but all attempts at conducting thermal Diels−Alder reactions with **9** failed.

The limited reactivity of **9** was an indication that the system was too sterically crowded for effective functionalization. Therefore, an alternative strategy was needed to increase the reactivity of **9**. An intriguing possibility was to exploit the photochemical properties of **9** (Scheme 6). The

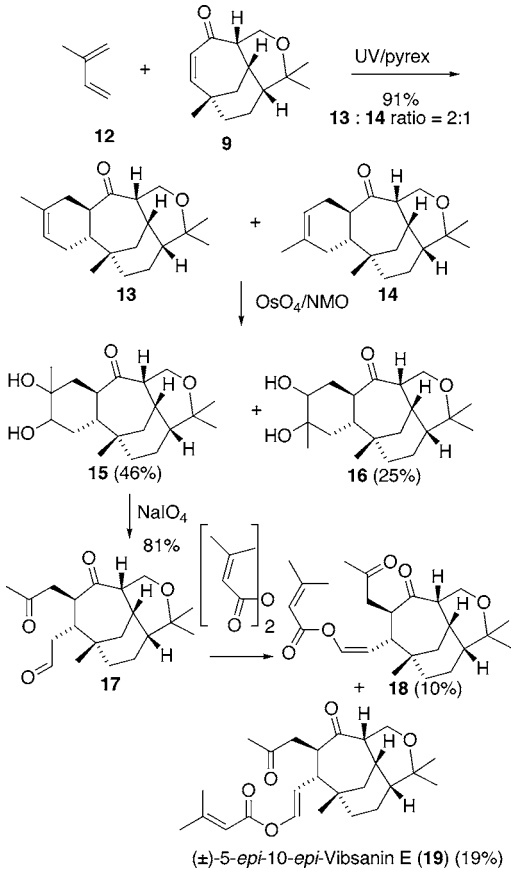
Scheme 6



photochemical isomerization of cis-cycloalkenones to trans-cycloalkenones is an established procedure,[18] and if such a reaction occurred with **9**, the corresponding trans cycloheptenone **11**, would be expected to be much more reactive than **9**. Furthermore, the [4 + 2] cycloaddition chemistry of **11** would be expected to form products with an *anti* stereochemical relationship across the enone.

To explore the photochemistry of **9**, its reaction with isoprene was examined under photolysis by Pyrex filtered light. When the enone **9** was dissolved in isoprene (**12**) and irradiated with UV light a very efficient reaction occurs giving the two alkene regioisomers **13** and **14** favoring **13** in a 2:1 ratio and in a combined yield of 91% (Scheme 7). Both **13** and **14** were trans fused, but unfortunately they were epimeric at C-5 and C-10 to the desired stereochemistry in vibsanin E. These two alkenes were separable by column chromatography but it was more convenient to treat the mixture of **13** and **14** with osmium tetroxide/*N*-methylmorpholine *N*-oxide and then separate the resulting diols **15** and **16**, which were obtained in 46% and 25% yield, respectively. To set the stage for the final manipulation of the side chains the diol **15** was cleaved by $NaIO_4$ to the keto-aldehyde **17**

Scheme 7



in 81% yield. The final step of the synthesis is selective acylation of the aldehyde functionality of **17** in the presence of the two ketone functionalities. This chemistry was achieved by employing 3,3-dimethylacrylic anhydride as the acylating agent in pyridine and with 4-pyrrolidinopyridine as the nucleophilic catalyst giving (±)-5-*epi*-10-*epi*-vibsanin E (**19**) in 19% yield and the *cis* isomer **18** in a 10% yield.

In conclusion, we have described a highly efficient approach for the construction of the tricyclic core of vibsanin E by a [4 + 3] cycloaddition followed by an intramolecular heteronuclear [4 + 2] cycloaddition. The photochemical isomerization of a cis cycloheptenone to a trans-cycloheptenone is a very effective method for activating the tricyclic core for further functionalization. The stereochemistry of the resulting [4 + 2] cycloaddition eventually leads to the synthesis of (±)-5-*epi*-10-*epi*-vibsanin E.

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Supporting Information Available: Spectroscopic data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1964**, *86*, 2087 (b) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051. (c) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1965**, *87*, 2052. (d) Eaton, P. A. *Acc. Chem. Res.* **1968**, *1*, 50. (e) Shinozaki, H.; Arai, S.; Tada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 821. (f) Hart, H.; Dunkelblum, E. *J. Am. Chem. Soc.* **1978**, *100*, 5141. (g) Mintas, M.; Schuster, D. I.; Willard, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 2305. (h) Mintas, M.; Schuster, D. I.; Willard, P. G. *Tetrahedron* **1988**, *44*, 6001. (i) Dorr, H.: Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 10229.