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Expeditious Syntheses of (±)-5-Oxosilphiperfol-6-ene and (±)-Silphiperfol-6-ene

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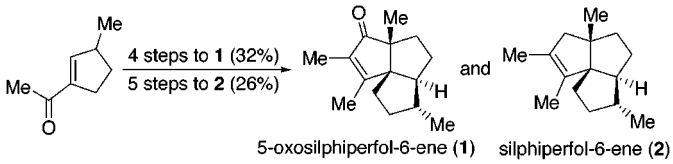
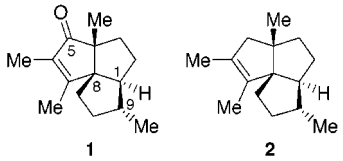
ABSTRACT



Stereocontrolled syntheses of 5-oxosilphiperfol-6-ene (1) and silphiperfol-6-ene (2) have been accomplished in four and five steps, with overall yields of 32% and 26%, respectively, from 1-acetyl-3-methylcyclopentene. The strategy features two pivotal reactions: (a) a Diels–Alder reaction between 1,3-dimethylcyclopentadiene and 1-acetyl-3-methylcyclopentene, which proceeds with remarkable regio-, endo-, and diastereofacial selectivities, and (b) an intramolecular Paterno–Büchi reaction to snap together the triquinane framework.

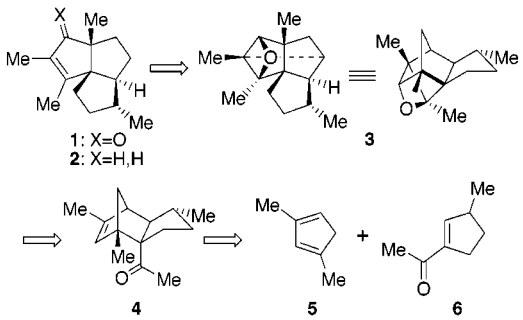
With three fused five-membered rings and four chiral centers, including two that are quaternary, 5-oxosiphiperfol-6-ene[1a] (**1**) and silphiperfol-6-ene[1b] (**2**) represent formidable targets for total synthesis.[2] The challenge posed by these natural



products has been taken on by others, and creative solutions have been described.[3,4] We report here highly expeditious syntheses of these compounds, using a strategy that is convergent and stereocontrolled.

Our interest in the development of concise syntheses of complex molecules has spurred us to explore a unique photocycloaddition−fragmentation strategy to di- and triquinane frameworks.[5,6] The strategy exploits the strain and dense complexity that is achieved through the intramolecular Paterno−Büchi reaction of 5-acyl-2-norbornenes and appeared particularly well suited for the synthesis of triquinanes **1** and **2**, as is evident from the retrosynthetic analysis in Scheme 1. The complete carbon skeleton of the natural product is present in oxetane **3**, the Paterno−Büchi product

Scheme 1



(1) (a) Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 2399−2403. (b) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259−265.

(2) Recent review on triquinanes: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719.

(3) Total syntheses of **1**: (a) Demuth, M.; Hinsken, W. *Helv. Chim. Acta* **1988**, *71*, 569−576. (b) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707−3712. (c) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, *63*, 2699−2704.

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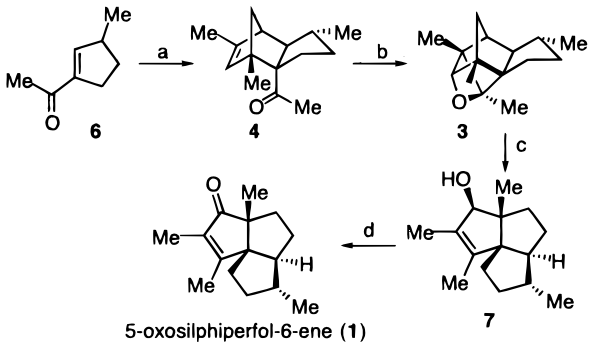
of norbornene **4**. Critical to the success of the whole strategy was the Diels−Alder reaction between 1,3-dimethylcyclopentadiene (**5**) and enone **6**. There were stringent requirements for this cycloaddition, which puts in place all the carbons of the natural product: *it had to proceed with good regio-, endo-, and diastereofacial selectivities*.[7]

The required enone, 1-acetyl-3-methylcylopentene[8] (**6**), was readily prepared on a multigram scale by a simple, one-pot procedure. Ozonolysis of 1,3-dimethylcyclohexene followed by intramolecular aldol condensation of the resultant keto aldehyde afforded **6** in 77% yield. The critical Diels−Alder reaction (Scheme 2) between enone **6** and diene **5** was

Scheme 2

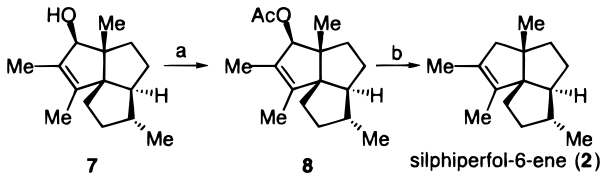


(a) **5**, Eu(FOD)$_3$ (10 mol%), toluene, 80 °C, 36 h, 84%. (b) hν, Corex, 19 h, 79%. (c) LiDBB, THF, -78 °C to 10 °C, 35 h, 57%, along with 10% reovered **3**. (d) PDC, DMF, rt, 24 h, 84%.

carried out at 80 °C using 10 mol % Eu(fod)$_3$ and proceeded with remarkable selectivity.[9] Of the eight possible isomers, the desired "endo-α-methyl" cycloadduct **4** was formed in high yield as by far the major product.[10] Irradiation of **4** using Corex-filtered light gave oxetane **3** (79%), the reductive fragmentation[6g] of which unraveled the cage to produce allylic alcohol **7** (57%), a common intermediate to natural products **1** and **2**. Oxidation of **7** with PDC gave 5-oxo-siphiperfol-6-ene (**1**) in 84% yield.[11]

Silphiperfol-6-ene (**2**) was synthesized by reductive deoxygenation of allylic alcohol **7** (Scheme 3). Since direct

Scheme 3



(a) Ac_2O, Py, DMAP, 0 °C, 20 min, 96%. (b) Li, ethylenediamine, 10 °C, 10 min, 71%, and 15% of recovered **7**.

reductive deoxygenation (e.g., $NaBH_4-CF_3CO_2H$) gave a mixture of alkene regioisomers, a two-step sequence was employed (Scheme 3). Alcohol **7** was first converted to acetate **8** using Ac_2O and a catalytic amount of DMAP (96%). Reduction of **8** with lithium in ethylenediamine afforded silphiperfol-6-ene (**2**) in 71% yield (84% based on recovered **7**).[11]

In conclusion, the present work provides a compelling demonstration of the Paterno−Büchi/reductive fragmentation strategy for complex molecule synthesis. Triquinane natural products **1** and **2** were synthesized by a convergent strategy from the readily available enone **6** in just four and five steps, respectively, using a route that afforded the highest overall yields reported to date for these compounds.

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

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(4) Formal and total syntheses of **2**: (a) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690−6693. (b) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1985**, *26*, 5987−5990. (c) Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106−1107. (d) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663−5676. (e) Dickson, J. K., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1440−1443. (f) Vo, N. H.; Snider, B. B. *J. Org. Chem.* **1994**, *59*, 5419−5423. (g) Reference 3b.

(5) Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 2613−2614.

(6) (a) Rawal, V. H.; Dufour, C.; Eschbach, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1797−1798. (b) Rawal, V. H.; Dufour, C.; Iwasa, S. *Tetrahedron Lett*. **1995**, *36*, 19−22. (c) Rawal, V. H.; Fabré, A.; Iwasa, S. *Tetrahedron Lett*. **1995**, *36*, 6851−6854. (d) Rawal, V. H.; Eschbach, A.; Dufour, C.; Iwasa, S. *Pure Appl. Chem*. **1996**, *68*, 675−678. (e) Dufour, C.; Iwasa, S.; Fabré, A.; Rawal, V. H. *Tetrahedron Lett*. **1996**, *37*, 7867−7870. (f) Dvorak, C. A.; Rawal, V. H. *Chem. Commun*. **1997**, 2381−2382. (g) Dvorak, C. A.; Dufour, C.; Iwasa, S.; Rawal, V. H. *J. Org. Chem*. **1998**, *63*, 5302−5303.

(7) Prior to our studies, there were no reports on the use of enone **6** in a Diels−Alder reaction and only two on diene **5**. See: (a) Ford, W. T. *J. Org. Chem.* **1971**, *36*, 3979−3987. (b) Stammen, B.; Berlage, U.; Kindermann, R.; Kaiser, M.; Gunther, B.; Sheldrick, W. S.; Welzel, P.; Roth, W. R. *J. Org. Chem*. **1992**, *57*, 6566−6575.

(8) Previously, this enone was prepared from 3-methylcyclohexanone in seven steps in 21% overall yield. See: Takeda, A.; Shinhama, K.; Tsuboi, S. *J. Org. Chem.* **1980**, *45*, 3125−3128.

(9) Diene **5** polymerized in the presence of common Lewis acids, even $ZnCl_2$ or $LiClO_4$. Although the thermal cycloaddition was successful, it proceeded more slowly and with lower selectivity.

(10) The product was isolated in 92% yield after chromatography and consisted of a (20:1):(1.4:1.0) ratio of (endo-α:*β*):(exo-α:*β*) diastereomers, the major product being the desired endo-α (**4**). The assigned structures are consistent with 2D NOE experiments. Further chromatographic purification gave the desired isomer contaminated with some exo isomers in 84% yield. This mixture was used in the next step, at which point the exo isomers are consumed through unproductive processes.

(11) All compounds discussed exhibited spectral properties consistent with the assigned structures (see Supporting Information). The spectral data for **1** and **2** were identical to those reported for the natural products (refs 3c, 1b,and 4).