Total Synthesis of the Tricyclic Sesquiterpene (±)-Ceratopicanol. An Illustration of the Holosynthon Concept

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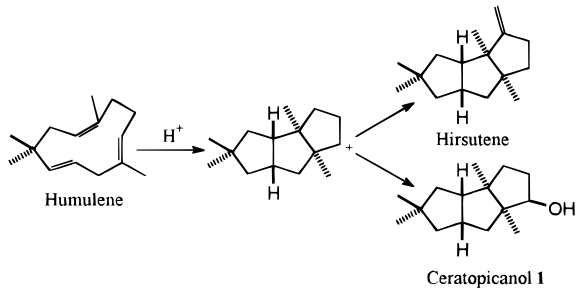
In 1988, Hansen and Abraham[1] reported the isolation from the fungus *Ceratocystis Piceae* Ha 4/82 of (+)-ceratopicanol (**1**), a novel triquinane sesquiterpene. They also elucidated its chemical structure. The uncommon presence of two vicinal bridgehead quaternary carbons among the five contiguous chiral centers, on a *cis*,*anti*,*cis*-triquinane framework makes **1** an attractive synthetic challenge.

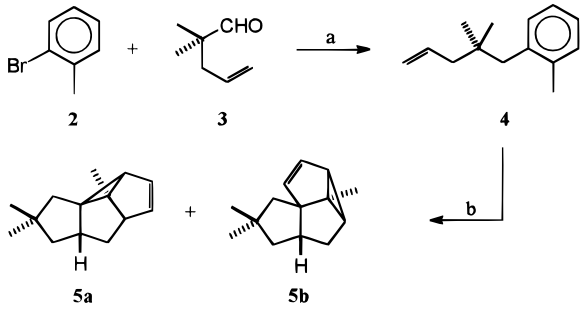
In 1991, Mehta and Karra described the first synthesis of (−)-ceratopicanol, the enantiomer of the natural product, also establishing the absolute configuration of the natural product.[2] Their approach started from the cheap (*R*)-(+)-limonene and involved 19 steps. In 1995, Clive and Magnuson[3] reported a 21 step approach of this target important in biogenetic theory because of its relation with hirsutene and related natural products.[4]



We propose in this paper the total synthesis of racemic (±)-ceratopicanol using seven steps, the key one being an intramolecular meta photocycloaddition of the phenylpentene derivative **4** which constitutes a typical holosynthon.[5]

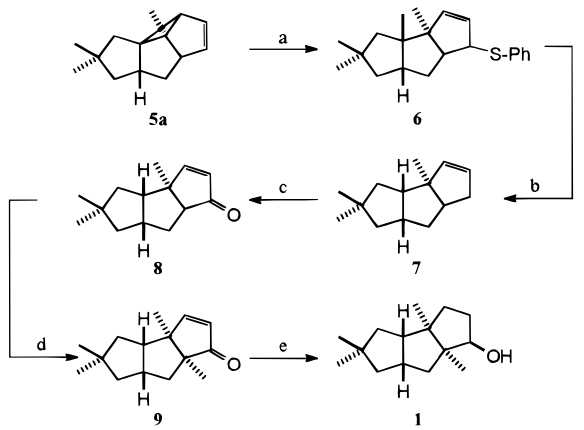
The irradiation of aromatics in the presence of alkenes provides [2 + 2], [3 + 2], and [4 + 2] cycloadducts.[6] These reactions act as efficient synthetic tools, and their utility was recently illustrated by Pete[7] and by Wender[8] in the preparation of several complex molecules. Especially, the [3 + 2] photoaddition process, or meta photocycloaddition, can achieve, in one operation, the building of three rings and up to six stereogenic centers.[9]

Scheme 1. Preparation of Holosynthon 4 and Irradiation Step[a]



[a] Key: (a) Li; Li/NH_3 (liquid); NH_4Cl; 98%; (b) *hν* 254 nm, cyclohexane; 72% (**5a**/**5b** = 2/1).

Scheme 2. Functionalization of the Photoisomer 5a to Ceratopicanol 1[a]



[a] Key: (a) PhSH, neat, 100 °C, ultrasound; 97%; (b) Li, NH_3 (liquid), −78 °C; 80%; (c) CrO_3−DMP, 25 °C; 60%; (d) LDA, −78 °C; MeI; 97%; (e) $NaBH_4$, EtOH, 25 °C; 60%.

The irradiation of the substituted 5-phenylpentene **4** at 254 nm yields efficiently the triquinane skeleton. As a result, the one-step building of the tricyclic framework greatly simplifies the total synthesis of (±)-ceratopicanol (**1**). The intramolecular meta photocycloaddition of **4** led to compounds **5a** and **5b** (2:1)[10] (72% yield), confirming that this type of reaction is most successful with molecules bearing three atoms between arene and alkene.[9] Before this irradiation step, **4** was quantitatively obtained in a one-pot experiment according to the method performed by Hall for related compounds,[11] starting from commercially available materials: 2-bromotoluene (**2**) and 2,2-dimethyl-4-pentenal (**3**) (Scheme 1).

Purification on silica gel yielded the strained photoadducts **5a**, which, by treatment with thiophenol[12] followed by reductive desulfuration,[12] easily underwent cyclopropane ring opening via 1,5-free-radical addition. We isolated **7**; then, allylic oxidation with chromic anhydride and 3,5-dimethylpyrazole (DMP) complex[13,14] yielded the unsaturated ketone **8**. The latter was then alkylated by lithium diisopropylamide and methyl iodide, leading to the enone **9** with 97% yield (Scheme 2).

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(3) Clive, D. L. J.; Magnuson, S. R. *Tetrahedron Lett.* **1995**, *36*, 15.
(4) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* **1981**, *64*, 1347.
(5) Holosynthon: structural entity specifically designed to make possible a great change in complexity or similarity (between this structural entity and its successor) when a one-pot reaction or a set of reactions are applied to it. (a) Barone, R.; Chanon, M. In *Computer Aids to Chemistry*; Vernin, G., Chanon, M., Eds.; Horwood: Chichester, 1986; p 69. (b) Barberis, F.; Barone, R.; Arbelot, M.; Baldy, A.; Chanon, M. *J. Chem. Inf. Comput. Sci.* **1995**, *34*, 467. (c) Lacourcelle, C.; Poite, J. C.; Baldy, A.; Jaud, J.; Negrel, J. C.; Chanon, M. *Acta Chem. Scand.* **1993**, *47*, 92. (d) See also a special issue: *Chem. Rev.* **1996**, *96*, 1.
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(8) (a) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688. (b) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445. (c) Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805. (d) Wender, P. A.;Von Geldern, T. W.; Levine, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 4858. (e) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1990**, *31*, 2520.
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(10) The angular isomer **5b** could be recycled by irradiation to produce a mixture of angular and linear isomers.
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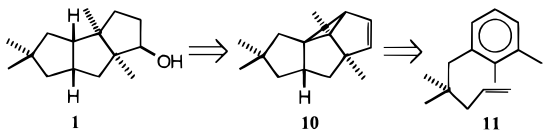
The last step to obtain (±)-ceratopicanol with the appropriate stereochemistry was reduction of **9**. Mehta previously showed with a carbonyl analogue that use of $NaBH_4$ at −20 °C provided the expected product with 87% yield.[2] In our case, the unsaturated bond and the carbonyl system were completely reduced at room temperature, and the target molecule was formed in 60% yield.

Our final (±)-ceratopicanol sample displayed satisfactory 400 MHz ^1H NMR ($CDCl_3$) and 100 MHz ^{13}C NMR ($CDCl_3$) spectra, in agreement with that reported in the literature.[1,2] The other spectroscopic data, IR spectrum, and elemental analysis are fully in accord with the molecular structure.

Our first approach to provide the target brought the intermediate **10** in a very low yield from photocyclization of precursor **11**.

The presence of the methyl group in position 3 on the aromatic ring is probably responsible for this lack of reactivity,[9,15] since the arene−olefin **4**, similar to **11**, provided the expected photoadduct.



1 **10** **11**

To conclude, this work underlines the synthetic potential of the meta photocycloaddition, as already showed by Wender[8] and as stressed by Cornelisse in his review.[9] In our application of this concept, we performed the total stereoselective synthesis of (±)-ceratopicanol with only seven steps and an overall yield of 19%, owing to the one-step photochemical construction of the skeleton of the target product.

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Supporting Information Available: Experimental procedures and characterization data for all synthesized compounds (5 pages).

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