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A Biomimetic Synthesis of Lucidene

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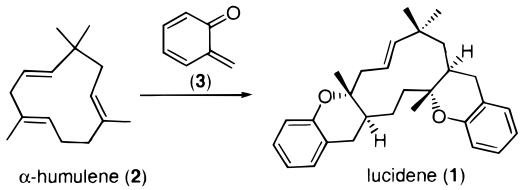
ABSTRACT



Lucidene (1) has been shown to be derived from α-humulene (2) and *o*-benzoquinone methide (3) generated under thermal conditions.

Lucidene (**1**) is a bis(benzopyranyl)sesquiterpene isolated from the root bark of *Uvaria Lucida* ssp. *lucida*[1] in racemic form (Figure 1). The co-isolation of α-humulene (**2**) from

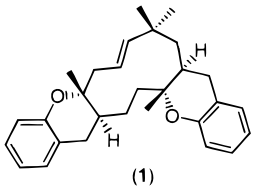


Figure 1. Structure of lucidene.

the same species led to speculation that lucidene is a double Diels−Alder reaction product of humulene (**2**) with two molecules of *o*-benzoquinone methide (**3**).[1] Such a postulate is attractive on the grounds that FMO theory would support the regiochemical and syn-stereochemical aspects[2] of such inverse demand hetero Diels−Alder processes and electronic factors would favor addition to the more electron rich trisubstituted double bonds at the expense of the more sterically hindered disubstituted double bond. It has also been reported that *trans* double bonds in medium sized rings show a higher reactivity than otherwise expected on account of steric strain.[3] The racemic nature of **1** would likewise be consistent with its production via a nonenzymatic route. A potential involvement of *o*-benzoquinone methide (**3**) as a Michael type acceptor to provide other natural products such as uvaretin, diuvaretin, and chamuvaretin from these plant species[1,4] is also supportive of a hetero Diels−Alder route to lucidene.

In the accompanying paper we have conducted studies toward a biomimetic synthesis of tropolone natural products, such as pycnidione (**4**), via a hetero Diels−Alder reaction of humulene (**2**) with a tropolone quinone methide (Figure 2). Although pycnidione (**4**) bears a close structural similarity

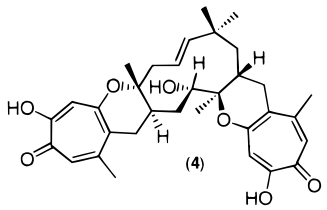


Figure 2. Structure of pycnidione.

to lucidene (**1**), it differs in that the postulated hetero Diels−Alder additions to humulene (**2**) would occur from the same face for lucidene (**1**) (methyls *cis*) but from opposite faces

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(1) Weenen, H.; Nkunya, H. H. *J. Org. Chem.* **1990**, *55*, 5107−5109.

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for pycnidione (**4**) (methyls *trans*). Pycnidione (**4**) is also isolated in enantiomerically pure form.

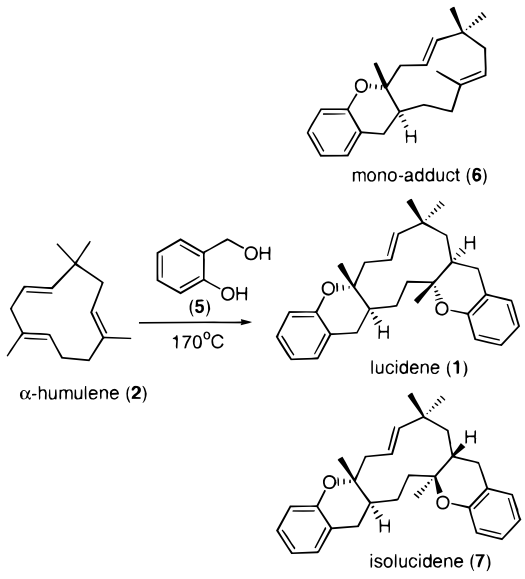
To offer experimental support to a biomimetic hetero Diels−Alder route to lucidene (**1**) and to investigate what level of regiochemical and stereochemical control could be achieved from such methodology, we investigated the thermal generation of *o*-benzoquinone methide (**3**) in the presence of humulene (**2**).

Hence thermolysis at 170 °C in a sealed tube of *o*-hydroxybenzyl alcohol[5] (**5**) (2.05 equiv) in the presence of humulene (**2**) gave three isolated products (**6**, **7**, and lucidene (**1**)) (Table 1) along with an uncharacterized base-soluble material (Scheme 1). The single monoaddition product (*E*)-(*E*)-5a,6,9,10,13,14,14a,15-octahydro-5a,9,9,12-tetramethylcycloundeca[*trans*-1,2-*b*]benzopyran[6,7] (**6**) was consistent with a syn-addition of *o*-benzoquinone methide (**3**) to the trisubstituted double bond situated furthest from the *gem*-dimethyl group of humulene (**2**). Separation of the other two products (ratio **1**:**7** = 2.5:1) required HPLC[8] and gave lucidene (**1**)[9] as the major product and a minor product assigned as isolucidene (**7**)[10] by spectral comparison to lucidene (**1**). A further reaction under similar conditions using 6 equiv of *o*-hydroxybenzyl alcohol (**5**) improved the overall yield of **1** and **7** (45%) but also gave evidence for the production of a small amount of triple *o*-benzoquinone methide adduct.[11]

Table 1. Yields of **1** and **7**

solvent	yield (%) of **6**	combined yield (%) of **7** and **1**
1,4-dioxane	23	4
MeCN:H_2O (1:1)	32	7
p-xylene	28	17

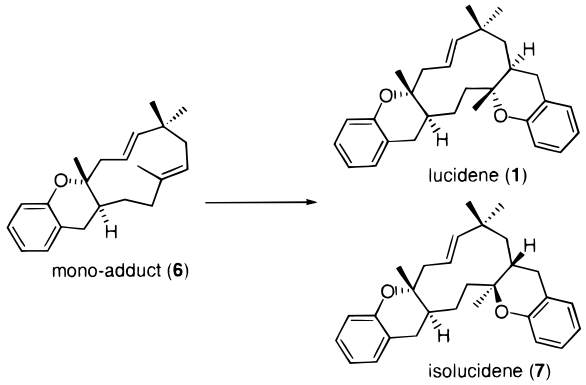
Scheme 1[a]



[a] Reagents and conditions: *o*-hydroxybenzyl alcohol (**5**) (2.05 equiv), 170 °C, sealed tube.

Exposure of monoadduct **6** to the reaction conditions (160 °C, 4 h, sealed tube) did not produce either of the other two potential monoadducts, and reexposure of **6** to *o*-hydroxybenzyl alcohol (**5**) under the reaction conditions (160 °C, 4 h, sealed tube) afforded a mixture of **1** and **7** in the same relative amounts as before (Scheme 2). The conformation of monoaddition adduct **6** in crystalline form is such that the approach of a second *o*-benzoquinone methide (**3**) moiety would be expected to lead preferentially to the natural diastereomer **1** as was observed (Figure 3).

Scheme 2[a]



[a] Reagents and conditions: *o*-hydroxybenzyl alcohol (**5**) (2.05 equiv), 160 °C, sealed tube.

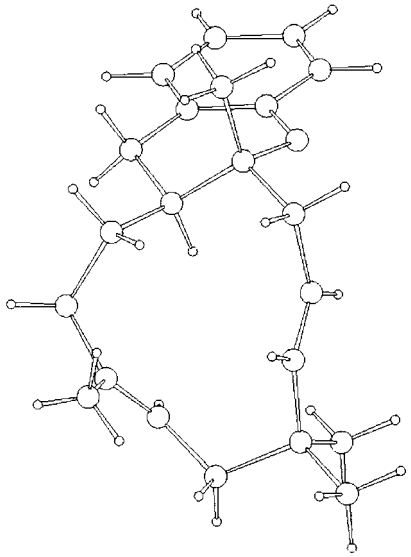


Figure 3. X-ray crystal structure of **6**.

In conclusion we have demonstrated that the naturally occurring diastereomer lucidene (**1**) is the favored bis-adduct

of humulene (**2**) with *o*-benzoquinone methide (**3**) generated under nonenzymatic conditions at elevated temperature. If in vivo, as is likely, *o*-benzoquinone methide is generated enzymatically at normal temperatures, then the racemic nature of biosynthesized lucidene (**1**) suggests nonenzymatic control in the subsequent cycloadditions. An intermediate *o*-benzoquinone methide monoadduct (**6**) has also been isolated en route to lucidene (**1**). This offers positive evidence that a similar route may be occurring to provide lucidene (**1**) biosynthetically.

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(2) A regiochemically controlled reaction of *o*-benzoquinone methide to (−)-alloaromadendrene to provide (−)-tanzanene has been reported, see: Paknikar, S. K.; Fondekar, K. P.; Mayer, R. *Nat. Prod. Lett.* **1996**, *8*, 253−256. For related Diels−Alder approaches employing functionalised *o*-quinone methides, see for example: Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696−6698. Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671−3672. Genisson, Y.; Tyler, P. C.; Young, R. N. *J. Am. Chem. Soc.* **1994**, *116*, 759−760.

(3) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Product Chemistry*; Academic Press: New York, 1974; Vol. 1, p 87.

(4) Lasswell, W. L.; Hufford, C. D. *J. Org. Chem.* **1977**, *42*, 1295−1302.

(5) This dehydration route to *o*-quinone methide (**3**) proved superior to others, see: Cunneen, J. I.; Farmer, E. H.; Koch, H. P. *J. Chem. Soc.* **1943**, 472−476.

(6) Melting point: 118 °C [from 40:60 petroleum ether].

(7) Structure was confirmed by single-crystal X-ray diffraction.

(8) Hypercil C_{18} using MeCN:H_2O (4:1).

(9) Melting point: 208−211 °C [lit.[1] mp 208−210 °C]; mass calcd 417.2794, found 417.2782; with spectral data (^{1}H, ^{13}C, IR) consistent with the reported data.[1]

(10) Melting point: 121 °C, mass calcd. 417.2794, found 417.2784.

(11) Mass spectrum: $[MH^+] = 523$.