

# A New and Efficient Method for *o*-Quinone Methide Intermediate Generation: Application to the Biomimetic Synthesis of (±)-Alboatrin

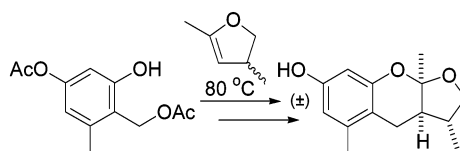
Raphaël Rodriguez, Robert M. Adlington, John E. Moses, Andrew Cowley, and Jack E. Baldwin\*

Chemistry Research Laboratory, University of Oxford, Mansfield Road,  
Oxford OX1 3TA, United Kingdom

jack.baldwin@chem.ox.ac.uk

Received August 2, 2004

## ABSTRACT



A new and efficient method for *o*-quinone methide intermediate generation from *o*-methyleneacetoxyphe- nols has been developed and applied to the biomimetic synthesis of (±)-Alboatrin.

*o*-Quinone methides are highly reactive, transient species, which have been applied as intermediates in the synthesis of several natural products.<sup>1,2</sup> Such compounds are known to react with nucleophiles in 1,4-Michael-type fashion and with a range of dienophiles to perform [4 + 2] cycloadditions. Over the years, many strategies have been established in order to generate *o*-quinone methides in situ. However, problems with such protocols often include undesirable high temperatures,<sup>1,3</sup> long reaction times,<sup>1,3,4</sup> the need for catalysis,<sup>1,5</sup> and acidic<sup>1</sup> or basic conditions,<sup>1,6b</sup> which can induce problematic side reactions such as dimerization. In addition, the *o*-quinone methide precursors necessary for use with

existing methodologies are often unstable and relatively inaccessible.<sup>1</sup>

Alboatrin (**1**) is a phytotoxic natural product reported in 1988 by Ichihara et al.<sup>7</sup> and later structurally corrected by Murphy et al.<sup>8</sup> The biosynthesis of **1** may be proposed to proceed through a hetero-Diels–Alder cycloaddition of an orcinol-derived *o*-quinone methide (**2**) and (*R*)-4,5-dihydro-2,4-dimethylfuran (**3**) (Figure 1).

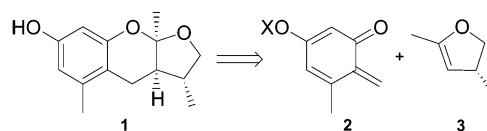


Figure 1. Biomimetic pathway to Alboatrin.

Indeed, Wilson et al. have made a similar connection and demonstrated in a recent study its feasibility as a major

(1) For a recent review, see: Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, 58, 5367.

(2) For example, see: (a) Baldwin, J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. *Org. Lett.* **1999**, 1, 1933. (b) Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Williams, A. J.; Watkin, D. J. *Org. Lett.* **1999**, 1, 1937. (c) Adlington, R. M.; Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett.* **2002**, 4, 3009.

(3) Katada, T.; Eguchi, S.; Esaki, T.; Sasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2649.

(4) Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycle* **2004**, 62, 445.

(5) Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *Chem. Commun.* **1999**, 691.

(6) (a) Loubinoux, B.; Tabbache, S.; Gerardin, P.; Miazimbakana, J. *Tetrahedron* **1988**, 44, 6055. (b) Loubinoux, B.; Miazimbakana, J.; Gerardin, P. *Tetrahedron Lett.* **1989**, 30, 1939.

pathway to the structurally related natural product Xyloketal D.<sup>4</sup>

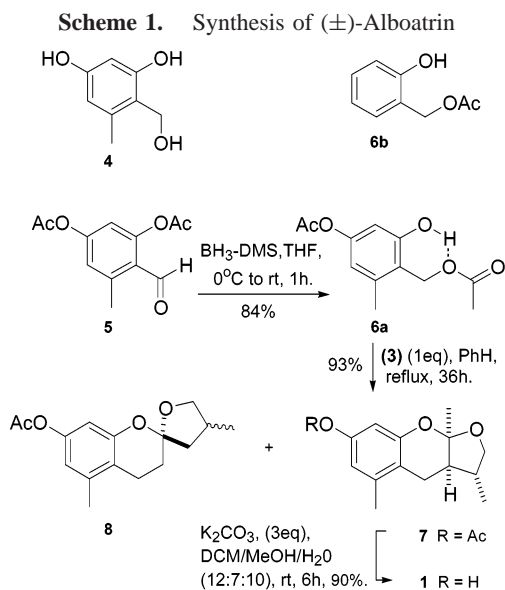
As part of our continuing efforts directed toward the biomimetic synthesis of complex natural products derived from functionalized *o*-quinone methides,<sup>2</sup> we became interested in developing methodology that would allow ready access to structures such as **1**.

Initially we considered that the most convenient procedure to allow the formation of the desired *o*-quinone methide would be dehydration of the corresponding hydroxymethyl-orninol derivative (**4**).<sup>2b</sup> However, upon reduction of the corresponding aldehydic precursor, compound **4** was found to be unstable and rapidly decomposed under the reaction conditions. To address this problem, we reasoned that suitable protection of the phenolic positions may prevent premature decomposition.

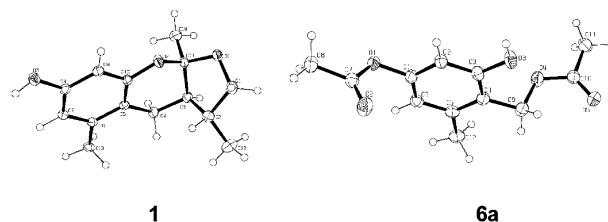
To this end, known diacetate **5**<sup>9</sup> was prepared, which we hoped could be reduced to its alcohol, so that such a compound might facilitate *o*-quinone methide formation under thermal conditions from an *o*-methyleneacetox-phenol (**6a**), itself generated via a transesterification mechanism. Although such *o*-methyleneacetox-phenols, e.g., **6b**, (Scheme 1), have been described in the literature, members of this

*o*-methyleneacetox-phenol (**6b**) from salicylaldehyde.<sup>6a</sup> Perhaps as a consequence, reports of potential *o*-methyleneacetox-phenols to serve as *o*-quinone methide synthons are limited to base-promoted chemistry, followed by in situ nucleophilic Michael addition.<sup>6b</sup> We have been unable to find reports of their use for *o*-quinone methide generation under purely thermal conditions.

In practice, the transfer of the phenolic acetate to the adjacent benzyl alcohol group occurred during the reduction of **5** with borane–DMS complex. Gratifyingly, this strategy permitted us to prepare and isolate a stable precursor (**6a**)<sup>10</sup> for the generation of the benzopyran core of **1** using the *o*-quinone methide pathway. Thus, simple heating of **6a** in the presence of (±)-4,5-dihydro-2,4-dimethylfuran afforded acetylalboatrins (**7**) as the major product (63% yield), acetyl-*epi*-alboatrins<sup>11</sup> (5% yield), and an inseparable mixture [3:2] of diastereoisomers (**8**)<sup>4</sup> (25% yield). Deacylation of **7** yielded the desired (±)-Alboatrins, for which spectral data was identical to the natural material [<sup>1</sup>H, <sup>13</sup>C].<sup>7,8</sup> The structure of **1** was also confirmed by X-ray analysis and was found to be in agreement with Murphy's proposal (Figure 2).<sup>12</sup>



class of compounds have been reported as being labile structures that “can be conserved for several days in dilute solution but polymerize rapidly as soon as they are pure”.<sup>6b</sup> Their reported synthesis is likewise unattractive; for example, Loubinoux has reported the need for a six-step synthesis of



**Figure 2.** X-ray structure of **1** and **6a**.

The proton NMR of **6a** displayed a sharp signal at 8.23 ppm, characteristic of a hydrogen bond between the phenolic OH and the benzylic acetate, which was confirmed by the X-ray crystal structure of **6a** (Figure 2).<sup>12</sup> This hydrogen bond may facilitate the elimination of acetic acid upon heating through a six-membered ring transition state, furnishing the *o*-quinone methide under relatively mild conditions.

The described methodology required no added acid, base, or catalyst for the formation of the hetero-Diels–Alder adduct, and the elimination of acetic acid was not found to be detrimental to the reaction.

To further demonstrate the versatility of this methodology, several benzopyran cores have been prepared with a range of dienophiles (Table 1). The reaction times, temperatures required, and yields obtained compare favorably with those

(7) Ichihara, A.; Nonaka, M.; Sakamura, S.; Sato, R.; Tajimi, A. *Chem. Lett.* **1988**, 27.

(8) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071.

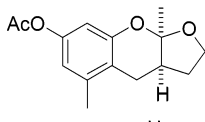
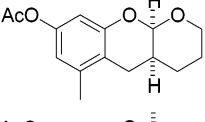
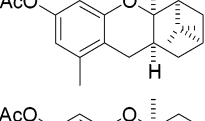
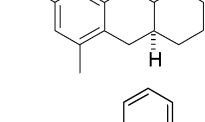
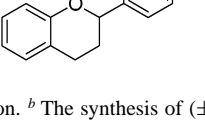
(9) Gruneiro, E. M.; Gros, E. G. *An. Asoc. Quim. Argent.* **1971**, 59, 259. We obtained **5** in two steps starting from orcinol: (a) POCl<sub>3</sub> (1 equiv), (DMF), –10 °C to room temperature, 2 h, 38%; (b) pyridine (2.2 equiv), AcCl (1.1 equiv), DCM, 0 °C then to room temperature, 2 h, AcCl (1.1 equiv), 0 °C then to room temperature, 2 h, 71%.

(10) Mp = 95–96 °C. Stable at room temperature for over 4 months.

(11) Deacylated to *epi*-alboatrins.<sup>8</sup>

(12) Atomic coordinates for **1** and **6a** are available upon request from the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition numbers: (**1**) CCDC 239364, (**6a**) CCDC 237660).

**Table 1.** *o*-Quinone Methide Hetero-Diels–Alder Cycloaddition Products

<i>o</i> -qms precursor	dienophile	temperature (°C)	time (hours)	yield (%) <sup>a</sup>	adduct
6a	(±)-4,5-dihydro-2,4-dimethylfuran ( <b>3</b> ) <sup>b</sup>	80	36	63	(±)-Acetylalboatrin ( <b>7</b> )
6a	4,5-dihydro-2-methylfuran	100	12	78 <sup>c</sup>	 ( <b>9</b> )
6a	3,4-dihydro-2 <i>H</i> -pyran	100	12	72 <sup>c</sup>	 ( <b>10</b> )
6a	(1 <i>R</i> )-(+)- $\alpha$ -pinene	140	12	30 <sup>c</sup>	 ( <b>11</b> )
6a	1-methylcyclohexene	140	12	60 <sup>c</sup>	 ( <b>12</b> )
6b <sup>d</sup>	styrene	100	12	79 <sup>c</sup>	 ( <b>13</b> )
(other <i>o</i> -quinone methide precursors)		(90)	6.5	64) <sup>13a</sup>	
		(60)	10.5	42) <sup>13a</sup>	
		(190)	2	68) <sup>13a</sup>	
		(90-110)	12	56) <sup>13b</sup>	

<sup>a</sup> Yields were calculated after column chromatography. Reactions were performed in a sealed tube under argon. <sup>b</sup> The synthesis of (±)-**3** is described in ref 4. <sup>c</sup> Dienophile used as solvent at 0.85 M. <sup>d</sup> Compound **6b** was prepared as a colorless oil by direct acetylation of commercially available 2-hydroxybenzyl alcohol [pyridine (1 equiv), AcCl (1 equiv), DCM, 0 °C to room temperature, 1 h, 89%], was used without further purification, and was stable for over 3 months at 0 °C.

described for other methods,<sup>1,4,13</sup> and the reaction can be performed on very hindered dienophiles such as  $\alpha$ -pinene.

In conclusion, we have demonstrated a new method for *o*-quinone methide generation from *o*-methylenacetoxyphe- nols, which has been applied to an efficient total synthesis of (±)-Alboatrin (**1**). This new method for *o*-quinone methide

generation compares favorably with existing alternatives in terms of conditions used, yields, and selectivity of desired products.

**Supporting Information Available:** Experimental procedures and NMR spectral data for all new compounds prepared. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048479D

(13) (a) Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1990**, *112*, 5341. (b) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 5282.