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Efficient Generation of *ortho*-Quinone Methide: Application to the Biomimetic Syntheses of (±)-Schefflone and Tocopherol Trimers

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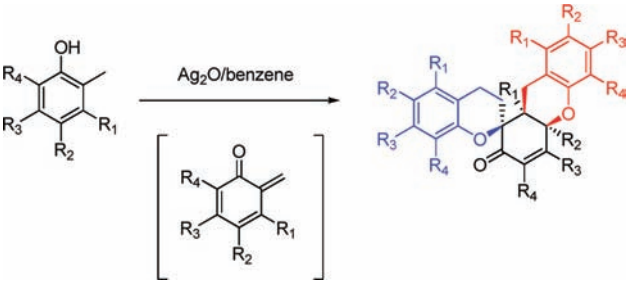
ABSTRACT



An efficient method using silver oxide-mediated oxidation for the synthesis of *ortho*-quinone methides has been developed and applied to the biomimetic syntheses of novel trimeric natural products, (±)-schefflone and tocopherol trimers. Further studies of the critical trimerization as well as substrate scope and limitations are also reported.

ortho-Quinone methides (*o*-QMs) are a class of important and versatile synthetic intermediates, which have been broadly utilized in the synthesis of complex natural products[1] as well as the development of new bioorthogonal "click" reactions.[2] Despite that many synthetic methodologies have been developed to access them, new methods for the efficient generation of highly reactive and functionalized *o*-QM intermediate under mild condition are particularly attractive.[3]

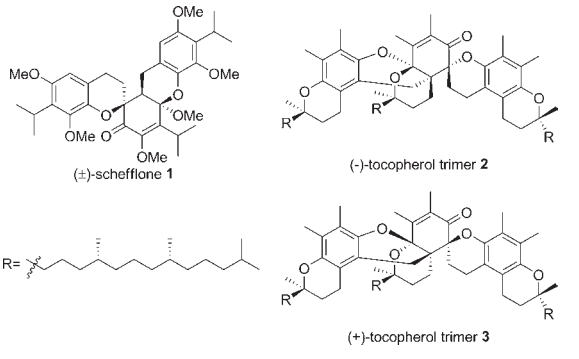


Figure 1. Structures of Trimeric Natural Products.

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(1) For selected recent total syntheses using an *o*-QM intermediate, see: (a) Green, J. C.; Jiminez-Alonso, S.; Brown, E. R.; Pettus, T. R. R. *Org. Lett.* **2011**, *13*, 5500. (b) Spence, J. T. J.; George, J. H. *Org. Lett.* **2011**, *13*, 5318. (c) Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. T. *Org. Lett.* **2010**, *12*, 1676. (d) Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350. (e) Batsomboon, P.; Phakhodee, W.; Ruchirawat, S.; Ploypradith, P. *J. Org. Chem.* **2009**, *74*, 4009. (f) Lumb, J. P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230.

(2) (a) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 15730. (b) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 5573. (c) Percivalle, C.; Rosa, A. L.; Verga, D.; Doria, F.; Mella, M.; Palumbo, M.; Antonio, M. D.; Freccero, M. *J. Org. Chem.* **2011**, *76*, 3096. (d) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 11892.

(3) For a recent review of *o*-QMs, see: (a) Ferreira, S. B.; Silva, F. C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocycl. Chem.* **2009**, *46*, 1080. (b) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367. For recent review of biomimetic total synthesis via *o*-QM intermediate, see: (c) Jackson, S. K.; Wu, K-L; Pettus, T. R. R. In *Biomimetic Organic Synthesis*; Poupon, E., Nay, B., Eds.; Wiley-VCH: Weinheim, 2011; Chapter 19.

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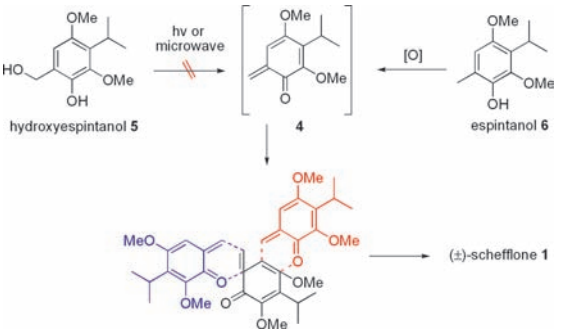
(±)-Schefflone **1**[4] and tocopherol trimers **2** and **3**[5] are structurally complex natural products which have the unique spiro-chroman-type trimeric skeleton (Figure 1). Biogenetically, these natural products could be derived from tandem hetero-Diels–Alder cycloadditions of the *o*-QM precursors. Although hetero-Diels–Alder dimerization or trimerization of *o*-QM was used for the synthesis of the spiro-chroman skeleton,[6] total synthesis of the trimeric natural products directly from the monomeric *o*-QM intermediate has rarely been reported thus far.[7] Herein, we report the biomimetic syntheses of (±)-schefflone and tocopherol trimers through silver oxide mediated *o*-QM formation. Further studies of the key trimerization as well as substrate scope and limitations are also described.

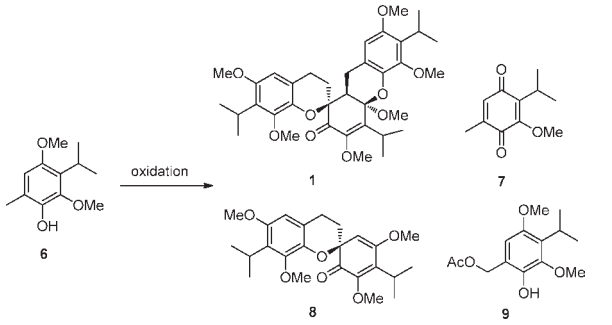
According to the biosynthetic hypothesis,[4] two tandem [4 + 2]-hetero-Diels–Alder cycloadditions of the *ortho*-quinone methide intermediate **4** generated from the naturally occurring monomer including hydroxyespintanol **5**[8] or espintanol **6**[9] may be responsible for the formation of homotrimer **1** (Scheme 1). Initial attempts to generate the desired *o*-QM **4** from hydroxyespintanol **5** under either hv or microwave conditions proved to be unsuccessful.[10] Therefore, we focused on the generation of *o*-QM **4** via oxidation of espintanol **6**.

Scheme 1. Synthetic Plan for (±)-Schefflone **1**



We first investigated a number of oxidants. As shown in Table 1, CAN (entry 1) and DDQ (entry 2) only afforded the byproduct quinone **7** in high yields, while $K_3Fe(CN)_6$ (entry 3) and MnO_2 (entry 4) provided the desired (±)-schefflone **1** in moderate yields. Synthetic **1** was confirmed to be identical to natural schefflone by ^1H and ^{13}C NMR as well as HRMS data.[11] To improve the yield, we further examined other oxidants. Interestingly, we found that by treating espintanol **6** with silver oxide[6,12] (entry 5) in benzene at room temperature (16 h), we could obtain trimeric (±)-schefflone **1** and dimer **8** in 72% and 8% yields, respectively. Further reaction screening using various Ag(I) salts (entries 6–10) revealed that Ag_2O was still the better oxidant for the efficient generation of *o*-QM and subsquent trimer and dimer formations. Notably, the use of AgOAc as an oxidant (entry 9) led to the production of acetate **9** in 40% yield, which was conceivably due to the Michael addition of the acetate anion to *o*-QM **4**.

Table 1. Optimization of the Oxidative Trimerization



		yield (%)[b]			
entry	reagents and conditions[a]	**1**	**7**	**8**	**9**
1	CAN, MeCN, 0 °C to rt, 2 h	–	98	–	–
2	DDQ, $MeNO_2$, rt, 1 h	–	98	–	–
3	$K_3Fe(CN)_6$, Benzene/2 M NaOH, rt, 16 h	68	–	–	–
4	MnO_2, Benzene, rt, 16 h	67	13	–	–
5	**Ag_2O, Benzene, rt, 16 h**	**72**	–	**8**	–
6	$AgSbF_6$, Benzene, rt, 24 h	–	40	–	–
7	AgOTf, Benzene, rt, 16 h	–	90	–	–
8	$AgNO_3$, Benzene, rt, 16 h	–	90	–	–
9	AgOAc, Benzene, rt, 16 h	–	30	–	40
10	Ag_2CO_3, Benzene, rt, 16 h	10	40	–	–

[a] $K_3Fe(CN)_6$ and MnO_2 were used in 3 equiv amounts, while other reagents were used in 1.2 equiv amounts. [b] Yield of isolated product.

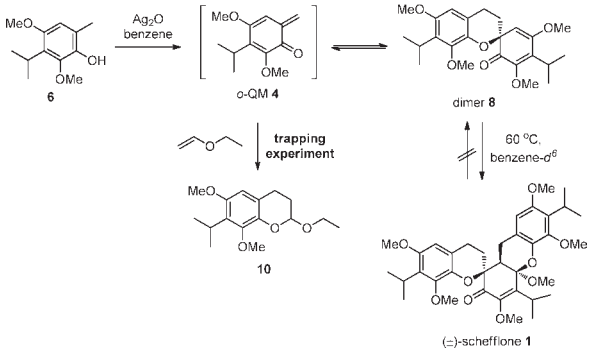
To understand the mechanism of the critical trimerization process promoted by Ag_2O, we designed and conducted several expriments (Scheme 2).[11] First, we used LC-MS to monitor the trimerization, which indicated

(4) Nkunya, M. H. H.; Jonker, S. A.; de Gelder, R.; Wachira, S. W.; Kihampaa, C. *Phytochemistry* **2004**, *65*, 399.
(5) Row, L. -C.; Ho, J. C.; Chen, C. M. *J. Nat. Prod.* **2007**, *70*, 1214.
(6) (a) Moore, R. F.; Waters, W. A. *J. Chem. Soc.* **1954**, 243. (b) Bolon, D. A. *J . Org. Chem.* **1970**, *35*, 715.
(7) For previous syntheses of tocopherol dimers and trimers, see: (a) Krol, E. S.; Escalante, D. D. J.; Liebler, D. C. *Lipids* **2001**, *36*, 49. (b) Schröder, H.; Netscher, T. *Magn. Reson. Chem.* **2001**, *39*, 701. (c) Yamauchi, R.; Kato, K.; Ueno, Y. *Lipids* **1988**, *23*, 779. (d) Nelan, D. R.; Robeson, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 2963.
(8) Ichimaru, M.; Nakatani, N.; Moriyasu, M.; Nishiyama, Y.; Kato, A.; Mathenge, S. G.; Juma, F. D.; ChaloMutiso, P. B. *J. Nat. Med.* **2010**, *64*, 75.
(9) For isolation of espintanol, see: (a) Hocquemiller, R.; Cortés, D.; Arango, G. J.; Myint, S. H.; Cave, A.; Angelo, A.; Muñoz, V.; Fournet, A. *J. Nat. Prod.* **1991**, *54*, 445. For total syntheses of espintanol, see: (b) Zúñiga, A. C.; Romero-Ortega, M.; José G. Avila Zárraga, J. G. A. *Synthesis* **2005**, *4*, 527. (c) Tomooka, C. S.; Liu, H.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 6009. (d) Söderberg, B. C.; Fields, S. L. *Org. Prep. Proced. Int.* **1996**, *28*, 221. (e) Wadsworth, D. J.; Losch, S. *Tetrahedron* **1994**, *50*, 8673. (f) Hocquemiller, R.; Cortés, D.; Arango, G. J.; Myint, S. H.; Cave, A.; Angelo, A.; Muñoz, V.; Fournet, A. *J. Nat. Prod.* **1991**, *54*, 445.
(10) (a) Bharate, S. B.; Singh, I. P. *Tetrahedron Lett.* **2006**, *47*, 7021. (b) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 717. Under Singh's condition we only obtained the hydroxyespintanol acetate **9**.

(11) See Supporting Information for details.
(12) (a) Jurd, L. *Tetrahedron* **1977**, *33*, 163. (b) Jurd, L.; Roitman, J. N. *Tetrahedron* **1978**, *34*, 57. (c) Jurd, L. *Aust. J. Chem.* **1978**, *31*, 347.

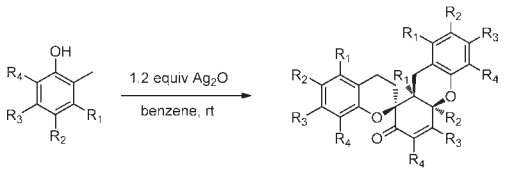
that in the first 15 min only dimer **8** was formed, and the reaction proceeded through the formation of trimer **1** until the ratio of dimer **8** to trimer **1** was not changed after 22 h. Second, we applied ^{1}H NMR experiments to study the interconversion between dimer **8** and trimer **1**. When dimer **8** was heated (benzene-d^6, 60 °C, 48 h), trimer **1** was formed; however, thermolysis of trimer **1** (benzene-d^6, 60 °C, 48 h) only led to the recovered starting material. Finally, we conducted the trapping experiment to confirm the existence of the highly reactive *o*-QM intermediate **4**. When excessive electron-rich dienophile ethyl vinyl ether was added into the reaction, chroman **10** was generated in almost quantative yield through [4 + 2]-hetero-Diels–Alder cycloaddtion.[13] These studies strongly suggest that the initial formation of dimer **8** from the highly reactive *o*-QM intermediate **4** is rapid and reversible, but the second [4 + 2]-hetero-Diels–Alder cycloaddtion of dimer **8** with *o*-QM **4** is irreversible to "lock" the structure and thus render trimer **1** as a major product.

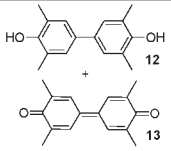
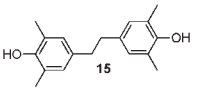
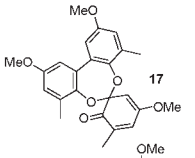
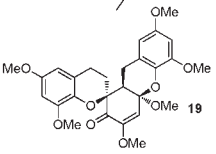
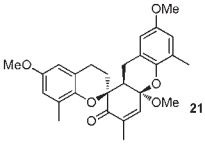
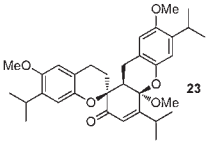
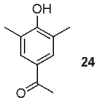
Scheme 2. Mechanistic Studies for the Trimerization



To gain insight into the substrate scope and limitations for the Ag_2O-promoted trimerization and understand the effect of substitution on the aromatic ring to the trimerization process, a number of phenol substrates were evaluated under this condition (Table 2). Oxidation of 2,6-dimethylphenol **11** (entry 1) which is not substituted at the *para* position to phenol exclusively led to the formation of biaryl coupled products phenol **12** and quinone **13**.[14] This result indicates that substitution at the *para* position to phenol is necessary for trimerization. Therefore, we decided to further test the *para*-substituted substrates. When 2,4,6-trimethylphenol **14** (entry 2) bearing a methyl group at the *para* position was treated with Ag_2O, dimer **15** was observed as a major product through a radical coupling process, which also confirms that the *para* substitution should not have α hydrogens.[6b] Next, we examined the effect of an electron-donating group at the *para* position. Oxidation of 2-methyl-4-methoxylphenol **16** (entry 3) afforded a spiroketal-type trimer **17** instead of the expected [4 + 2]-hetero-Diels–Alder trimer. This result might be rationalized by the initial formation of

Table 2. Substrate Scope and Limitations



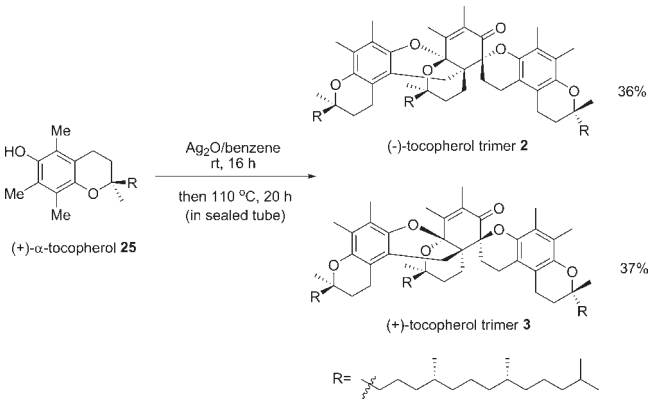
entry	phenols	products	yield (%)[a]
1[b]	 **11**	 **12** + **13**	56 42
2	 **14**	 **15**	20
3	 **16**	 **17**	56
4	 **18**	 **19**	58
5	 **20**	 **21**	92
6	 **22**	 **23**	11
7	 **24**	no reaction	

[a] Yield of isolated product. [b] Reaction condition: 1.2 equiv of Ag_2O, Et_2O, −78 °C to rt.

a biaryl coupled bisphenol intermediate through the more favored radical coupling process, followed by oxidative ketalization to furnish the spiroketal motif.[15] In contrast, oxidation of 2,4-dimethoxyl-6-methylphenol **18** (entry 4) smoothly generated the desired trimer **19** in 58% yield. Other related substrates **20** and **22** (entries 5 and 6) containing a methoxyl group at the *para* position all yielded the desired trimers **21** and **23**, respectively. However, oxidation of substrate **22** bearing only one *ortho* substitution showed a much lower yield (11%) than the di-*ortho* substituted substrate **20** (92%). Finally, we studied

(13) Bolon, D. A. *J . Org. Chem.* **1970**, *35*, 3666.
(14) Kneifel, H.; Poszich-Buscher, C.; Rittich, S.; Breimaier, E. *Angew. Chem., Int. Ed.* **1991**, *30*, 202.
(15) Bowman, D. F.; Hewgill, F. R.; Kennedy, B. R. *J. Chem. Soc. C* **1966**, *24*, 2274.

Scheme 3. Syntheses of Tocopherol Trimers



the effect of an electron-withdrawing group at the *para* postion. As shown in entry 7, the oxidation of 4-acetyl-2,6-dimethyl phenol **24** was sluggish and led to no reaction.

Based on the results from substrate scope and limitations, we envisioned that the fully substituted tocopherol **25** should be a suitable substrate for the Ag_2O-mediated trimerization. As expected, treatment of tocopherol **25** with Ag_2O in benzene smoothly afforded (−)-tocopherol trimer **2** (36%) and (+)-tocopherol trimer **3** (37%) (Scheme 3). All of these synthetic samples were identical to the previously reported natural products.[11]

In conclusion, an efficient method using Ag_2O mediated oxidation for the generation of *ortho*-quinone methide has been developed and applied to the biomimetic total syntheses of (±)-schefflone and tocopherol trimers. Further experiments provided mechanistic insight into the critical [4 + 2]-hetero-Diels–Alder trimerization. Studies of substrate scope and limitations also showed the substitution effects for successful trimerization. Applications of this methodology to produce other complex natural products are in progress and will be reported in due course.

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

Note Added after ASAP Publication. This article was published ASAP on November 2, 2011. Figure 1 and Scheme 1 have been updated. The corrected version was posted on November 11, 2011. Scheme 3, Figure 1, reference 7, and the Supporting Information were replaced on November 29, 2011.