ORGANIC LETTERS

2013
Vol. 15, No. 7
1556–1559

Biomimetic Synthesis of Zeylanone and Zeylanone Epoxide by Dimerization of 2-Methyl-1,4-naphthoquinone

Sayako Maruo,[†] Kazuyuki Nishio,[†] Takahiro Sasamori,[‡] Norihiro Tokitoh,[‡] Kouji Kuramochi,*[,†] and Kazunori Tsubaki[†]

Graduate School for Life and Environmental Sciences, Kyoto Prefectural University, 1-5 Shimogamo Hangi-cho, Sakyo-ku, Kyoto 606-8522, Japan, and Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

kuramoch@kpu.ac.jp

Received February 4, 2013

ABSTRACT

A biomimetic synthesis of zeylanone and zeylanone epoxide, which are natural dimeric naphthoquinones, has been accomplished starting from plumbagin, a natural monomeric naphthoquinone. The key features of our synthesis are cascade intermolecular and intramolecular Michael reactions, followed by epoxidation of the resultant hydroquinone with molecular oxygen.

Zeylanone (**1**) was originally isolated from the evergreen shrub *Plumbago zeylanica* in 1979 by Sankaram et al. (Figure 1).[1] Although the structure of **1** was confirmed from detailed NMR studies carried out by Gu et al.,[2] the relative configurations at positions C-5a and C-12a in zeylanone remain undefined. The specific rotation value of 0 (*c* 1.5%, $CHCl_3$) for natural zeylanone indicates that the natural product was isolated as a racemic mixture. This compound shows cytotoxic activities against cancer cell lines, as well as antibacterial and antifungal activities.[2] Recently, zeylanone epoxide (**2**) was isolated from the stem bark of *Diospyros anisandra*.[3] The *syn* relationship between the methyl group at C-5a and H-12a in **2** was determined by NOESY correlations. However, the stereochemical relationship between the methyl group at C-5a and the epoxide remains unknown. The structurally related dimeric naphthoquinones juglorescein (**3**) and juglocombin A (**4**) were isolated from *Streptomyces* strains GW4184 and 815.[4]

It has been proposed that the biosynthetic pathways of both **1** and **2** may involve the dimerization of plumbagin (**5**) (Scheme 1).[1,3] Sequential intermolecular and intramolecular Michael reactions of **5**, followed by oxidation of the resulting hydroquinone, would give **1** or **2**.

We report herein the first synthesis of **1** and **2** based on the proposed biosynthetic pathway, as well as determination of the relative configurations of natural zeylanone and zeylanone epoxide. We also obtained optically pure (+)- and (−)-zeylanone and determined their absolute configurations.

Vitamin K_3 (**6**), 2-methyl-1,4-naphthoquinone, was used as a model substrate for developing the key dimerization step (Scheme 2). Treatment of **6** with lithium hexamethyldisilazide (LHMDS) (0.5 equiv) in THF at −78 °C led to its decomposition. We tested several other bases (NaHMDS, KHMDS, LDA, NaH, *t*-BuOK, and DBU) but were unable to detect formation of the hydroquinone **7**. We also quenched the reaction by the addition of TBSCl in an attempt to trap any **7** that was generated. However, none of the desired product **8** was obtained. We therefore concluded that the

[†] Kyoto Prefectural University
[‡] Kyoto University

(1) Sankaram, A. V. B.; Rao, A. S. *Tetrahedron* **1979**, *35*, 1777.
(2) Gu, J.-Q.; Graf, T. N.; Lee, D.; Chai, H.-B.; Mi, Q.; Kardono, L. B. S.; Setyowati, F. M.; Ismail, R.; Riswan, S.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Swanson, S. M.; Kroll, D. J.; Falkinham, J. O., III.; Wall, M. E.; Wani, M. C.; Kinghorn, A. D.; Oberlies, N. H. *J. Nat. Prod.* **2004**, *67*, 1156.
(3) Uc-Cachón, A. H.; Molina-Salinas, G. M.; Said-Fernández, S.; Méndez-González, M.; Cáceres-Farfán, M.; Borges-Argáez, R. *Nat. Prod. Res.* **2013**10.1080/14786419.2012.718770.
(4) Lessmann, H.; Maskey, R. P.; Fotso, S.; Lackner, H.; Laatsch, H. *Z. Naturforsch., B: J. Chem. Sci.* **2005**, *60*, 189.

10.1021/ol400335s © 2013 American Chemical Society
Published on Web 03/25/2013

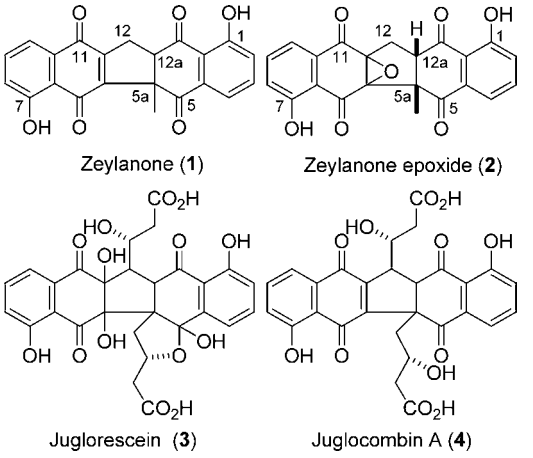
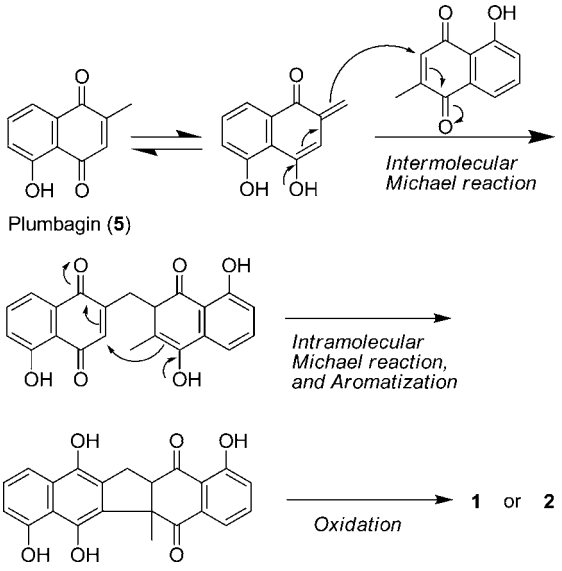
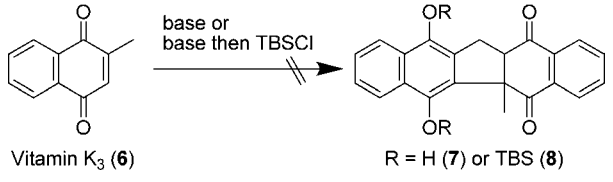


Figure 1. Structures of zeylanone and its related dimeric naphthoquinones. Selected carbon atoms are labeled using IUPAC numbering.

Scheme 1. Proposed Biosynthesis of Zeylanone (**1**) and Zeylanone Epoxide (**2**)

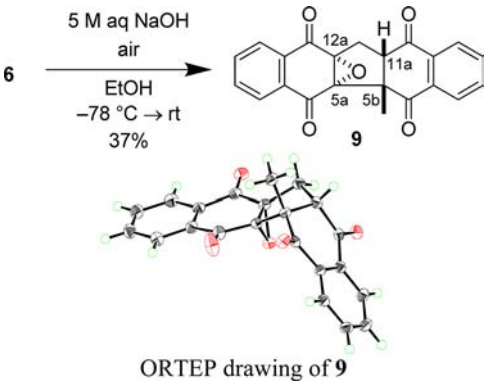


Scheme 2. Attempts to Obtain Hydroquinone Intermediates



proposed synthesis failed as a result of preferential decomposition of **6** or **7**.

Scheme 3. Formation of Epoxide **9**[a]



[a] Selected carbon atoms are labeled using IUPAC numbering.

We found that treatment of **6** with 5 M NaOH in EtOH under an aerobic atmosphere afforded a dimeric epoxide **9** in 37% yield (Scheme 3).[5] The structure of **9** was unambiguously determined by X-ray crystallography (see Supporting Information). A *cis* relationship between H-11a and the methyl group at C-5b, and an *anti* relationship between the methyl group and the epoxide were indicated. The formation of **9** is explained by generation of hydroquinone **7** and its subsequent epoxidation with molecular oxygen under basic conditions.[6]

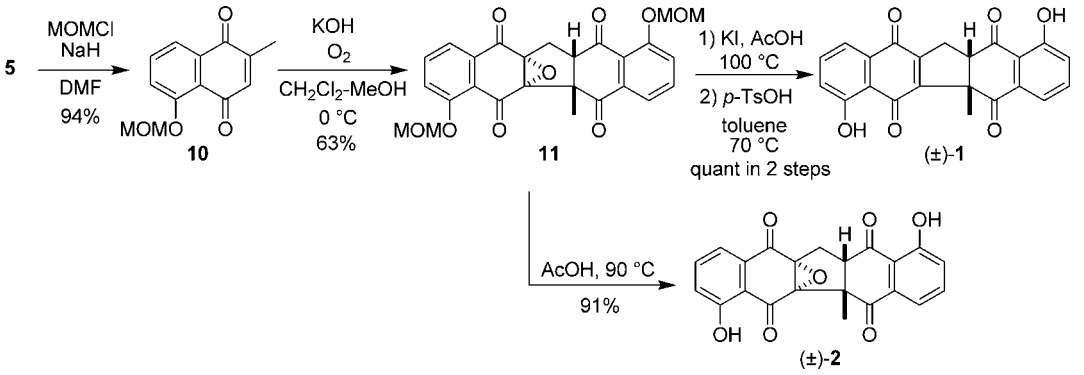
The synthesis of zeylanone and zeylanone epoxide is shown in Scheme 4. Because plumbagin (**5**) decomposed under basic conditions for dimerization, the hydroxyl group of **5** was protected as a methoxymethyl ether to give **10**. Dimerization of **10** with KOH in CH_2Cl_2–MeOH under an oxygen atmosphere afforded the dimer **11** in 63% yield. Treatment of **11** with KI in acetic acid, followed by *p*-toluenesulfonic acid, gave (±)-**1** in quantitative yield in two steps. The spectral data (UV, IR, ^{1}H and ^{13}C NMR, and MS) for synthetic (±)-**1** were in agreement with those reported for natural **1**.[1,2] Deprotection of the methoxymethyl group in **11** with acetic acid gave zeylanone epoxide [(±)-**2**]. The spectral data (IR, ^{1}H and ^{13}C NMR, and MS) for synthetic (±)-**2** were in agreement with those reported for natural **2**.[3] On the basis of the X-ray structure of **9**, a *cis* relationship between the methyl group at C-5a and H-12a was established in (±)-**1** and (±)-**2**. In addition, an *anti* relationship between the epoxide and the methyl group in (±)-**2** was determined.

(5) Baxter et al. reported similar dimerization reactions of 2-ethyl- and 2-alkyl-1,4-naphthoquinone using *N*-methylcyclohexylamine as a base. However, they reported that treatment of 6 with *N*-methylcyclohexylamine afforded pentacene-5,7:12,14-diquinone, see: (a) Baxter, I.; Cameron, D. W.; Titman, R. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2046. (b) Baxter, I.; Cameron, D. W.; Sanders, J. K. M.; Titman, R. B. *J. Chem. Soc. C* **1971**, 1253.

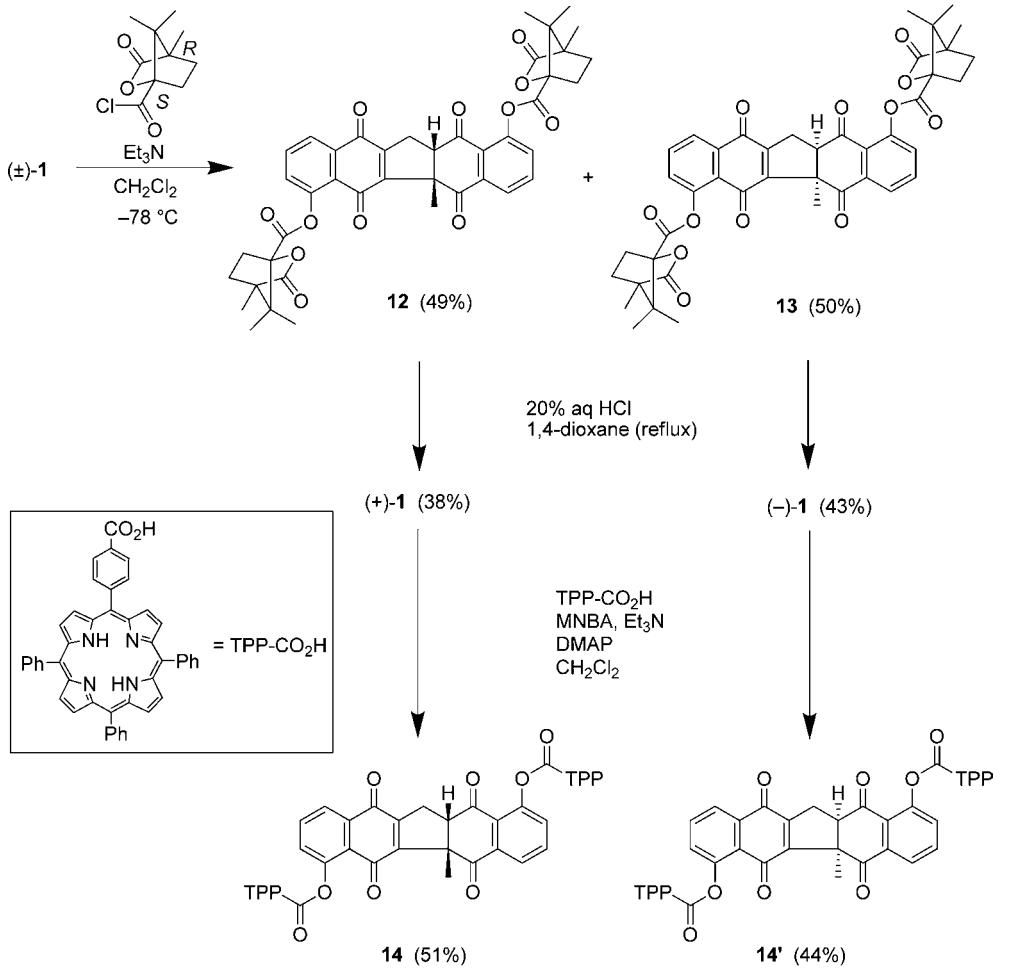
(6) (a) Dowd, P.; Ham, S. W.; Geib, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 7734. (b) Dowd, P.; Ham, S. W.; Hershline, R. *J. Am. Chem. Soc.* **1992**, *114*, 7613. (c) Ham, S. W.; Yoo, J. S. *Chem. Commun.* **1997**, 929.

(7) (a) Matile, S.; Berova, N.; Nakanishi, K.; Novkova, S.; Philipova, I.; Blagoev, B. *J. Am. Chem. Soc.* **1995**, *117*, 7021. (b) Matille, S.; Berova, N.; Nakanishi, K.; Fleischhauer, J.; Woody, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 5198.

Scheme 4. Synthesis of (±)-Zeylanone (**1**) and Zeylanone Epoxide (**2**)



Scheme 5. Optical Resolution of (±)-Zeylanone (**1**), and Preparation of Chiral Tetraphenylporphyrin Derivatives **14** and **14′**



We prepared both enantiomers of zeylanone, and determined their absolute configurations using the exciton-coupled circular dichroic method[7] (Scheme 5 and Figure 2). Esterification of (±)-**1** with (1*S*,4*R*)-camphanic chloride afforded two diastereomers **12** and **13**, which were separated by HPLC. Hydrolysis of **12** and **13** under acidic conditions

(8) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286.

(9) The absolute configurations of (+)- and (−)-**1** were confirmed by comparison of TDDFT-B3LYP/6-31G(d,p)-calculated CD spectra with experimentally determined spectra (see Supporting Information).

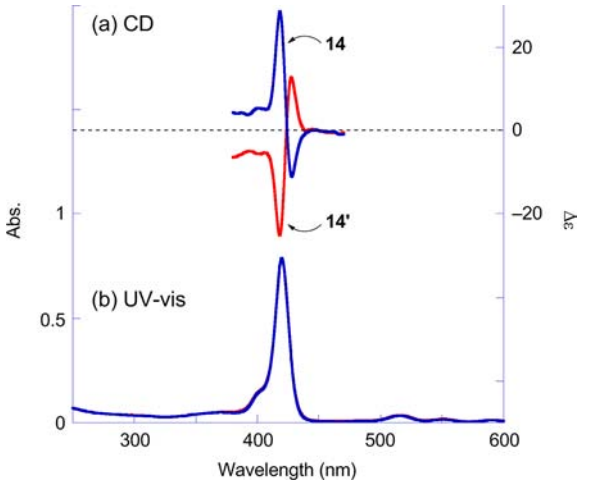


Figure 2. CD (a) and UV (b) spectra of **14** and **14′**.Conditions: $CHCl_3$, 1×10^{-6} M, 25 °C, light path length = (a) 5 mm, (b) = 10 mm.

gave (+)-**1** and (−)-**1**, respectively. The specific rotations of (+)-**1** and (−)-**1** were +507.3 and −508.1 (*c* 0.42, $CHCl_3$), respectively. Both (+)-**1** and (−)-**1** were condensed with tetraphenylporphyrincarboxylic acid (TPP-CO_2H) by 2-methyl-6-nitrobenzoic anhydride (MNBA)[8] and triethylamine to afford **14** and **14′**, respectively. The CD and UV spectra of **14** and **14′** are shown in Figure 2. The CD spectra of **14** and **14′** exhibited split Cotton effects as a result of the chiral exciton couplings between the two TPP groups. The negative exciton chirality ($\Delta\varepsilon$ −11.0 at 428 nm and +28.6 at 419 nm) of **14** led to the assignment to (+)-**1** and **14** of the 5a*S*,12a*S* configuration (Figure 3a). The positive exciton chirality ($\Delta\varepsilon$ +12.8 at 428 nm and −25.0 at 419 nm) of **14′** led to the assignment to (−)-**1** and **14′** of the 5a*R*,12a*R* configuration (Figure 3b).[9]

In summary, we have successfully developed a dimerization of 2-methyl-1,4-naphthoquinone via sequential intermolecular and intramolecular Michael reactions. Using

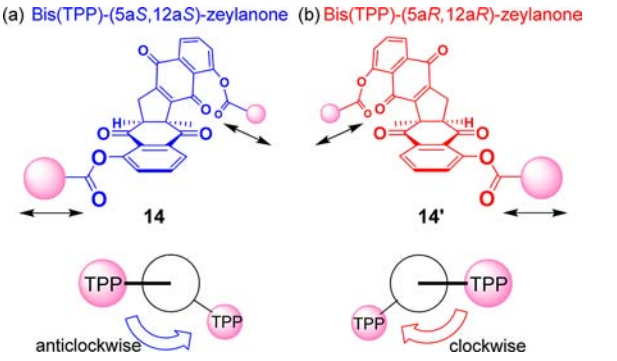


Figure 3. Determination of absolute configurations of **14** and **14′**.

these reactions, we accomplished the first synthesis of zeylanone and zeylanone epoxide, dimeric natural naphthoquinones, and confirmed their relative configurations. Zeylanone was obtained in a four-step sequence, with an overall yield of 59%, starting from plumbagin. Zeylanone epoxide was synthesized in three steps, with an overall yield of 54%. We prepared both enantiomers of zeylanone and determined their absolute configurations. Further synthetic studies toward related natural products are currently ongoing in our laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Challenging Exploratory Research (23659013). We are grateful to Prof. Takeo Kawabata (Kyoto University), Prof. Fumio Sugawara, Dr. Toshifumi Takeuchi, and Dr. Shinji Kamisuki (Tokyo University of Science) for assistance with HRMS and specific rotation measurements.

Supporting Information Available. Detailed experimental procedures, characterization data, ^1H and ^{13}C NMR spectra, X-ray crystallographic data, and calculated and experimental CD spectra of (+)- and (−)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.