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Two novel α-tocopheroids from the aerial roots of *Ficus microcarpa*

Yi-Ming Chiang and Yueh-Hsiung Kuo*

Department of Chemistry, National Taiwan University, Taipei, Taiwan, Republic of China

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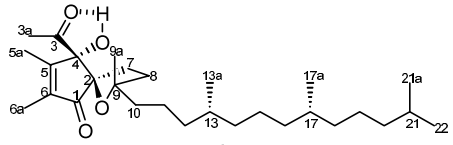
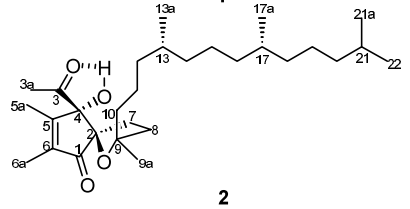
Abstract—Two novel α-tocopheroids, namely α-tocospiros A (**1**) and B (**2**), together with α-tocopherol (**3**) were isolated from the aerial roots of *Ficus microcarpa*. Their structures were elucidated by spectral methods. Under basic conditions, compounds **1** and **2** were obtained from α-tocoquinon-2,3-oxide (**6a** and **6b**) via a highly stereoselective nucleophilic addition reaction. Reaction and biotransformation mechanisms of **1** and **2** are proposed. © 2003 Elsevier Science Ltd. All rights reserved.

Ficus microcarpa L. f. (Moraceae) is a popular ornamental plant in Taiwan. Phytochemical studies of this plant have led to the identification of triterpenoids from the leaves,[1] fruits,[2] bark,[3] and aerial roots.[4] In the present study, two novel α-tocopheroids, α-tocospiros A (**1**) and B (**2**), which are unique compounds, each containing two five-membered rings in a spiro form, were isolated from the aerial roots of this plant. In order to confirm the assigned structures, compounds **1** and **2** were synthesized from commercially available α-tocopherol (**7**). Products having a spirofused bicyclic carbon skeleton are not unprecedented in α-tocopheroid chemistry. Oxidation of the model compound 2,2,5,7,8-pentamethylchroman-6-ol with superoxide ions in an aprotic solvent has been reported[5] to give rise, inter alia, to the ring-contracted products **4** and **5**. However, the highly stereoselective nucleophilic addition reaction that generated the two stereocenters under basic conditions with high yield in a short time are unprecedented in α-tocopheroid chemistry. The structural elucidation of α-tocospiros A (**1**) and B (**2**) and the possible mechanism of the highly stereoselective nucleophilic addition reaction are reported here.

α-Tocospiro A (**1**) was isolated as a colorless oil; its molecular formula $C_{29}H_{50}O_4$ was established through ^{13}C NMR and HREIMS data and represents five indices of hydrogen deficiency (IHD). The IR spectrum of **1** showed absorptions for hydroxyl (3434 cm^{-1}), five-membered ring conjugated carbonyl (1718 cm^{-1}), and alkenyl (1655 cm^{-1}) groups. The ^1H NMR[6] spectrum exhibited signals for one singlet methyl group [δ_H 1.02 (H_3-9a)], four doublet methyl groups [δ_H 0.81 (3H, d, $J=6.4$ Hz, H_3-17a), 0.82 (3H, d, $J=7.6$ Hz, H_3-13a), 0.83 (6H, d, $J=6.8$ Hz, H_3-21a and H_3-22)], two vinyl methyl groups [δ_H 1.79 (H_3-5a), 1.81 (H_3-6a)], an acetyl group [δ_H 1.99 (H_3-3a)], four methylene protons [δ_H 1.67 (1H, dt, $J=11.6$, 6.8 Hz, H_β-8), 1.87 (1H, dt, $J=11.6$, 6.8 Hz, H_α-8); δ_H 1.76 (1H, dt, $J=12.4$, 6.8 Hz, H_α-7), 2.40 (1H, dt, $J=12.4$, 6.8 Hz, H_β-7)], and a low-field exchangeable hydroxyl proton [δ_H 4.70 (s)].



1



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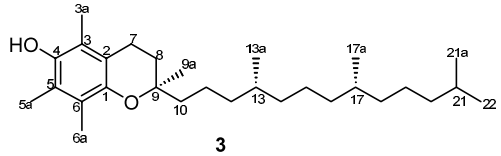

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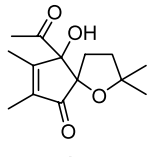

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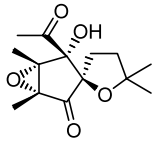

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* Corresponding author. Tel.: 886-2-23638146; fax: 886-2-23636359; e-mail: yhkuo@ccms.ntu.edu.tw

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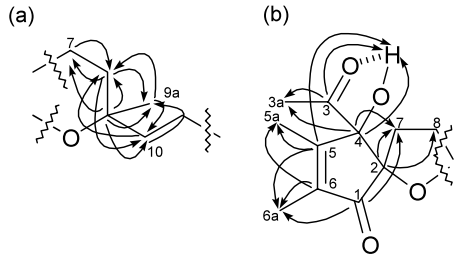


Figure 1. Selected HMBC correlations of **1**.

The ^{13}C NMR and DEPT data[6] showed eight CH_3, eleven CH_2, three CH, and seven C including three oxygen-bearing carbons [δ_C 87.0 (C-9), 89.1 (C-4), and 92.2 (C-2)], two olefinic carbons [δ_C 139.3 (C-6) and 163.0 (C-5)], and two carbonyl carbons [δ_C 204.9 (C-1) and 207.1 (C-3)]. α-Tocopherol (**3**), isolated from the same source, had similar ^1H and ^{13}C NMR data as **1** on its side-chain (C-12 to C-22).[7] From the molecular formula and the above evidence, compound **1** was considered to be a α-tocopherol-related compound. In fact, long range ^{13}C–^1H correlations (HMBC) confirmed α-tocopherol-related partial structure (Fig. 1a), the long-range ^{13}C–^1H correlations were observed as C-1/H_3-6a, H_2-7; C-2/H_2-7, H_2-8; C-3/H_3-3a, OH; C-4/H_3-3a, H_2-7, OH; C-5/H_3-5a, H_3-6a, OH; and C-6/H_3-5a, H_3-6a, respectively, and indicated a 4-acetyl-4-hydroxy-2,3-dimethylcyclopentenone moiety (Fig. 1b). The hydroxyl proton presented at δ_H 4.70 (s) was ascribed as having a hydrogen bond with the acetyl group. The UV absorption data at λ_{max} 234.5 nm was consistent with this partial structure.[8] The presence of these features suggested that **1** was a spiro compound of two five-membered rings. Mass fragments confirmed the assigned structure (Fig. 2).

Compound **1** has five stereocenters occurring in two distantly separated portions of the molecule (C-2, C-4, and C-9; C-13 and C-17). For the spiro moiety, the relative stereochemistry and preferred conformation was assigned on the basis of the NOESY spectrum. NOESY correlations (Fig. 3) for OH/H_3-5a, H_β-7, H_3-9a; H_β-7/H_3-9a; and H_α-8/H_2-10 established the relative stereochemistry of the spiro moiety.

α-Tocospiro B (**2**) was considered to be an isomer of **1** on the basis of mass, ^1H, and ^{13}C NMR spectra.[6] The major difference between **1** and **2** in ^1H NMR spectrum concerned the H_3-9a signal (δ_H1.02 in **1**, δ_H1.29 in **2**). This suggested that compounds **1** and **2** were epimers.

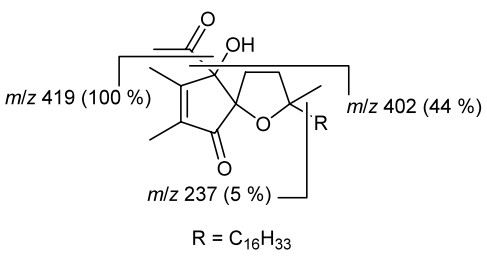


Figure 2. Mass fragments of **1**.

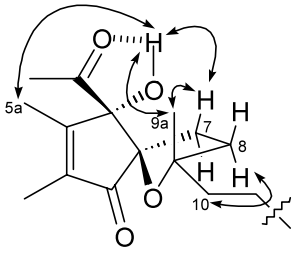


Figure 3. Selected NOESY correlations of **1**.

The relative stereochemistry of the spiro moiety in **2** was also assigned on the basis of a NOESY experiment. NOESY correlations (Fig. 4) for OH/H_3-5a, H_β-7, H_2-

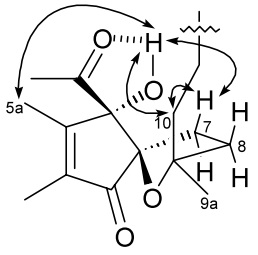
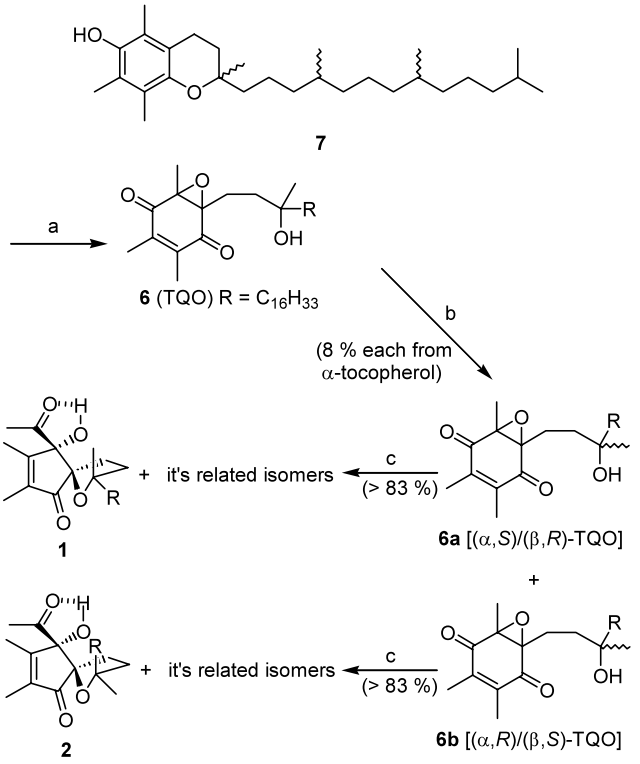
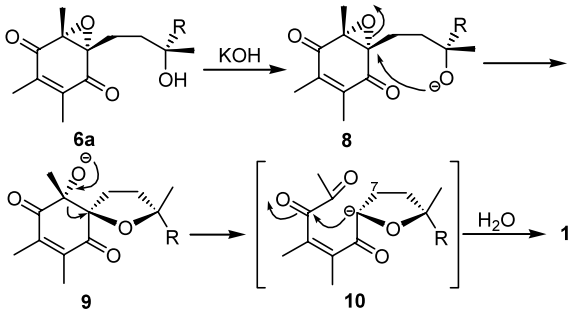


Figure 4. Selected NOESY correlations of **2**.



Scheme 1. Synthesis of **1** and **2** from α-Tocopherol. (a) See Ref. 7; (b) HPLC separation; (c) KOH, MeCN, trace H_2O, rt, 25 min.

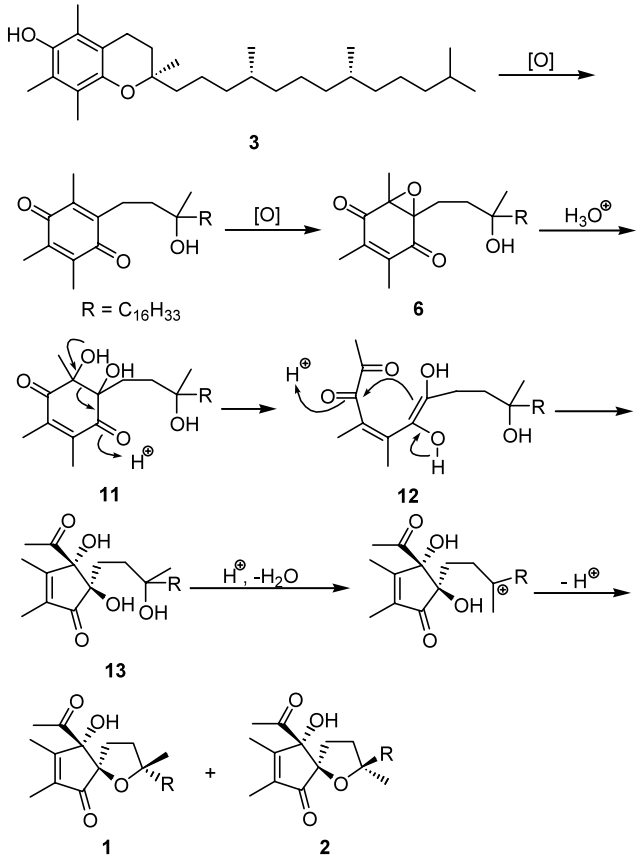


Scheme 2. Proposed reaction mechanism.

10 and H_{α}-7/H_2-10 established the relative stereochemistry of the spiro moiety in **2**.

In order to confirm the assigned structures of compounds **1** and **2**, α-tocoquinon-2,3-oxide (TQO, **6**) was prepared from commercially available α-tocopherol (**7**) by a procedure reported by Grams[9] (Scheme 1). After normal phase HPLC separation, TQO (**6**) was separated into two groups of isomers, **6a** (mixture of α-epoxy, 9*S* and β-epoxy, 9*R*) and **6b** (mixture of α-epoxy, 9*R* and β-epoxy, 9*S*), with an 8% yield of each from α-tocopherol. Although these two sets of isomers were separated successfully, their ^{1}H and ^{13}C NMR were quite similar so their relative configuration could not be determined. The ^{1}H NMR data of **6a** and **6b** were both similar to the reported data in the literature.[10] After treatment with KOH in acetonitrile, compound **1** and its related isomers were obtained from **6a** with a yield of more than 83%. Under the same conditions, compound **2** and its related isomers were obtained from **6b**. The observations described above reveal that the transformation from **6a** to **1** and **6b** to **2** are highly stereoselective that generates two chiral centers in one reaction. The proposed reaction mechanism is given in Scheme 2. Briefly, the alkoxide ion (**8**), generated by KOH attacks the epoxide to become a spiro anion (**9**). After ring opening, intermediate **10** is produced. This carbanion **10**, attacks the C-4 carbonyl immediately. The highly stereoselection could be explained by the steric effect. In intermediate **10**, CH_2-7 is a larger group than an oxygen atom, therefore, the acetyl group should be located in the same face as oxygen atom. After cyclization, compounds **1** and **2** were produced from **6a** and **6b**, respectively. Based on this mechanism, we determined the relative structures of **6a** and **6b**, which are (α,*S*)/(β,*R*)-TQO and (α,*R*)/(β,*S*)-TQO, respectively.

The biotransformation of **1** and **2** was proposed from α-tocopherol (**3**), and the pathway was sketched as in Scheme 3. α-Tocoquinon-2,3-oxide (**6**) yielded triol **11** via enzymatic hydrolysis of the epoxide, with **11** being converted to **12** under acidic conditions. Compound **13** was obtained from **12** via aldol condensation using the same stereoselective reaction as used for the transformations from **6a** to **1** and **6b** to **2**. Under acidic conditions, compound **13** was converted into **1** and **2**. The configuration of C-13 and C-17 in **1** and **2** must be the same as in α-tocopherol (**3**) which was isolated from the same source.



Scheme 3. Proposed biogenetic pathway for the formation of **1** and **2**.

Acknowledgements

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6. **α-Tocospiro A (1)**: Colorless oil; $[\alpha]_D^{24}$ +130.5 ($CHCl_3$, *c* 1.6); EIMS *m*/*z* (rel. intensity): 462 (M^+, 8), 419 (100), 402 (44), 237 (5), 137 (14), 95 (20), 69 (26), 55 (34); HREIMS *m*/*z*: 462.3715 (calcd for $C_{29}H_{50}O_4$: 462.3711); IR ν_{max}: 3434, 1718, 1655, 1379, 1367, 1240, 1190, 1162, 1081, 1004, 903, 744, 641, 588 cm^{-1}; UV λ_{max} (log ε) (MeOH) 234.5 (3.87) nm; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (3H, d, $J=6.4$ Hz, H_3-17a), 0.82 (3H, d, $J=7.6$ Hz, H_3-13a), 0.83 (6H, d, $J=6.8$ Hz, H_3-21a, H_3-22), 1.02 (3H, s, H_3-9a), 1.58 (2H, dd, $J=8.4$, 7.2 Hz, H_2-10), 1.67 (1H, dt, $J=11.6$, 6.8 Hz, H_β-8), 1.76 (1H, dt, $J=12.4$, 6.8 Hz, H_α-7), 1.79 (3H, s, H_3-5a), 1.81 (3H, s, H_3-6a), 1.87 (1H, dt, $J=11.6$, 6.8 Hz, H_α-8), 1.99 (3H, s, H_3-3a), 2.40 (1H, dt, $J=12.4$, 6.8 Hz, H_β-7), 4.70 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7 (C-6a, q), 11.8 (C-5a, q), 19.7 (C-13a, q), 19.7 (C-17a, q), 22.4 (C-11, t), 22.6 (C-22, q), 22.7 (C-21a, q), 24.5 (C-19, t), 24.8 (C-3a, q), 24.8 (C-15, t), 25.4 (C-9a, q), 28.0 (C-21, d), 32.7 (C-17, d), 32.8 (C-7, t), 32.8 (C-13, d), 36.2 (C-8, t), 37.3, 37.5, 37.5 (C-18, t; C-14, t; C-16, t), 37.5 (C-12, t), 39.3 (C-20, t), 41.5 (C-10, t), 87.0 (C-9, s), 89.1 (C-4, s), 92.2 (C-2, s), 139.3 (C-6, s), 163.0 (C-5, s), 204.9 (C-1, s), 207.1 (C-3, s). **α-Tocospiro B (2)**: colorless oil; $[\alpha]_D^{24}$ −107.3 ($CHCl_3$, *c* 0.4); EIMS *m*/*z* (rel. intensity): 462 (M^+, 3), 419 (100), 402 (34), 237 (5), 137 (20), 95 (8), 69 (16), 55 (18); HREIMS *m*/*z*: 462.3716 (calcd for $C_{29}H_{50}O_4$: 462.3711); IR ν_{max}: 3434, 1716, 1654, 1379, 1368, 1240, 1166, 1082, 1021, 900, 735, 643, 591 cm^{-1}; UV λ_{max} (log ε) (MeOH) 235.0 (3.91) nm; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (3H, d, $J=6.4$ Hz, H_3-17a), 0.82 (3H, d, $J=7.2$ Hz, H_3-13a), 0.84 (6H, d, $J=6.4$ Hz, H_3-21a, H_3-22), 1.29 (3H, s, H_3-9a), 1.72–1.78 (2H, m, H_2-8), 1.80 (3H, s, H_3-5a), 1.82 (3H, s, H_3-6a), 1.85 (1H, dt, $J=12.4$, 8.4 Hz, H_α-7), 2.00 (3H, s, H_3-3a), 2.34 (1H, dt, $J=12.4$, 5.6 Hz, H_β-7), 4.67 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7 (C-6a, q), 11.8 (C-5a, q), 19.6, 19.7 (C-17a, q; C-13a, q), 22.4 (C-11, t), 22.6 (C-22, q), 22.7 (C-21a, q), 24.5 (C-19, t), 24.8 (C-3a, q), 24.8 (C-15, t), 25.4 (C-9a, q), 28.0 (C-21, d), 32.7 (C-17, d), 32.8 (C-13, d), 33.4 (C-7, t), 36.8 (C-8, t), 37.3, 37.4, 37.4 (C-18, t; C-14, t; C-16, t), 37.4 (C-12, t), 39.3 (C-20, t), 42.1 (C-10, t), 87.2 (C-9, s), 89.4 (C-4, s), 92.6 (C-2, s), 139.5 (C-6, s), 163.2 (C-5, s), 205.1 (C-1, s), 207.0 (C-3, s). **α-Tocopherol (3)**: Yellow oil; IR ν_{max}: 3484, 3021, 1380, 1264, 1215, 1161, 1114, 1088, 920 cm^{-1}; $[\alpha]_D^{24}$ +7.6 ($CHCl_3$, *c* 0.7); EIMS *m*/*z* (rel. intensity): 430 (M^+, 100), 205 (15), 165 (97), 69 (36).
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