Stereocontrolled Syntheses of Carotenoid Oxidative Metabolites, (−)-Loliolide, (−)-Xanthoxin, and Their Stereoisomers

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We achieved the stereocontrolled syntheses of (−)-loliolide, (−)-xanthoxin, and their stereoisomers from (+)- or (−)-3-alkoxy-6-hydroxymethyl-1,1,5-trimethylcyclohexene through the corresponding *syn* and *anti*-epoxides, respectively, which were obtained by utilizing the highly diastereoselective Sharpless asymmetric epoxidation or mCPBA oxidation.

Most of the oxidative metabolites of the carotenoids possess an eleven, thirteen, or fifteen carbon skeleton. Among them, loliolide[1] and xanthoxin[2] in addition to abscisic acid,[3] have been paid much attention because of their interesting biological activities. (−)-Loliolide (**1a**), which has been detected in many higher plants and marine mollusks, are well-known to have immunosuppressive, germination inhibitory, and repellent activities.[4] Its C-5 stereoisomer (carotenoid numbering), (+)-epiloliolide (**1b**), was also isolated from various sources, which was found to show comparable cytotoxicity to (−)-loliolide.[5] (−)-Xanthoxin (**2**) has been proposed as a precursor of (+)-abscisic acid,[6] which is the primary plant hormone controlling many biological plant processes such as acceleration of abscission, induction of dormancy, and inhibition of rooting, and it shows similar biological activities to abscisic acid. Although a number of synthetic efforts of these terpenoids and their derivatives including the racemic form have been reported,[7,8] only a few report controlled their stereochemistry. In particular, controlling the relative stereochemistry between the C-3 and C-5 asymmetric carbons has remained as one of the essential unsolved subjects in the synthesis of carotenoids and their oxidative metabolites.

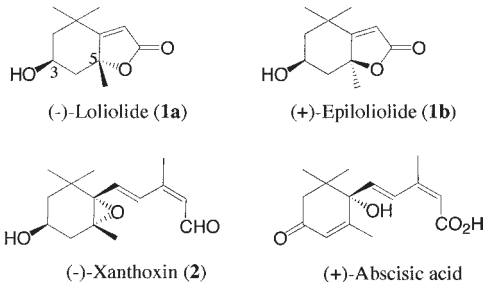
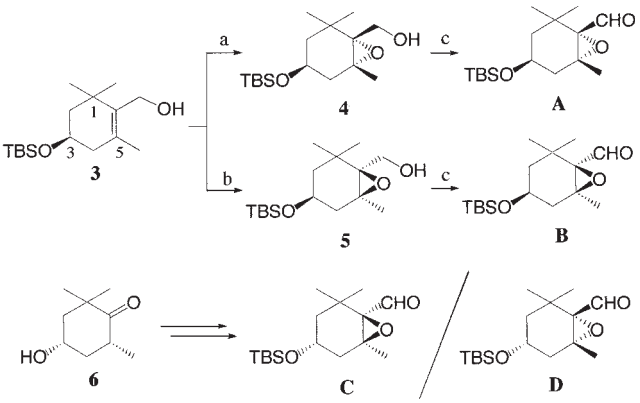


Figure 1.

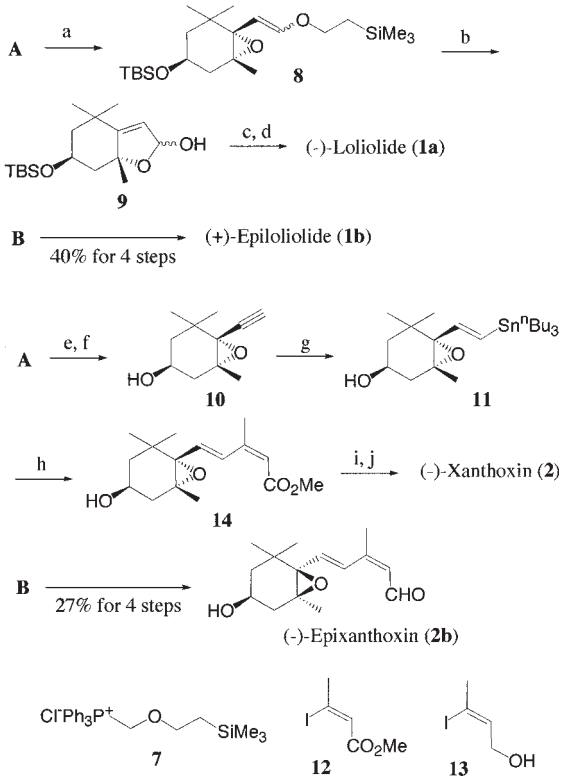
Recently, during the course of our synthetic study of the polyfunctional carotenoid, peridinin,[9] we achieved the stereoselective synthesis of the optically active epoxyaldehyde derivative **A**, which would be applicable for the syntheses of carotenoids and the related natural products as a common chiral intermediate. Herein, we disclose the stereocontrolled preparation of all its stereoisomers, **B**, **C**, and **D**, and the efficient total syntheses of (−)-loliolide (**1a**), (−)-xanthoxin (**2**), and their stereoisomers.

The desirable high diastereoselectivity was achieved by finding the precise reaction conditions for the Sharpless asymmetric epoxidation[10] of **3**.[9] Thus, it was essential that all reagents and solvents must be freshly distilled, the use of the strict equivalent of the reagents was required ((−)-diethyl-D-tartrate (0.3 eq.), $Ti(O^iPr)_4$ (0.2 eq.), and *tert*-butylhydroperoxide (2.0 eq.)), and the reaction temperature (−20 °C) was controlled. Under these precise reaction conditions, we obtained the desired *anti*-epoxide **4** in 99% yield and 92% de (Scheme 1).[11] Meanwhile, the epoxidation of **3** with mCPBA surprisingly produced the *syn*-epoxide **5** with high diastereoselectivity (94% de). The epoxides **4** and **5** were then transformed into the corresponding aldehydes **A** and **B** by the Swern oxidation, respectively.[12] Furthermore, aldehydes **C** and **D** were stereoselectively obtained from the (3*S*)-hydroxy ketone **6** by the same procedure.



Scheme 1. Reagents and condition: a) (−)-diethyl-D-tartrate, $Ti(O^iPr)_4$, 1.5 M TBHP in toluene, MS 4 Å, CH_2Cl_2, −20 °C, 30 min, 99%, 92% de; b) mCPBA, CH_2Cl_2, rt, 1 h, 90%, 94% de; c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 40 min; Et_3N, 10 min, 100%.

We then examined the efficient synthesis of (−)-loliolide from the epoxyaldehyde **A**. After several trials, we succeeded in the stereoselective synthesis of (−)-loliolide *via* the Wittig olefination with (trimethylsilyl)ethoxymethyltriphenylphosphonium bromide **7**.[13] Thus, the Wittig reaction of **A** with **7** yielded the corresponding olefin **8** as a mixture of stereoisomers (Scheme 2). The acid treatment of the obtained crude olefin **8** produced the lactol **9**, which was oxidized with MnO_2 and then treated with TBAF to produce (−)-loliolide (**1a**) in 37% yield from **A**. The spectral and physical data of the synthesized (−)-loliolide were in good agreement with those already reported.[14] The aldehydes **B**–**D** were also transformed into (+)-epiloliolide (**1b**; 40% yield from **B**) and their enantiomers by the same procedure, respectively. This is a new and efficient route for the synthesis of optically active loliolide.



Scheme 2. Reagents and conditions: a) **7**, ^{t}BuOK, ether, rt, 1 h; b) 1N HCl aq., THF, rt, 5 min; c) MnO_2, ether, rt, 2 h, 49% for 3 steps; d) TBAF, THF, rt, 2 h, 76%; e) $ClCH_2P^+Ph_3Cl^-$, ^{n}BuLi, THF, −30 °C, 3 h; f) ^{t}BuOK, DMSO, rt, 20 min, 53% for 2 steps; g) ^{n}Bu$_3$SnH, $PdCl_2(PPh_3)_2$, THF, rt, 10 min; h) **12**, $PdCl_2(CH_3CN)_2$, CuI, DMF, 50 °C, 20 h, 64% for 2 steps; i) $LiAlH_4$, THF, −25 °C, 10 min, 83%; j) MnO_2, ether, rt, 5 h, 92%.

Next, we examined the stereocontrolled synthesis of (−)-xanthoxin and its stereoisomers. Thus, an acetylene derivative **10**, which was obtained from the epoxyaldehyde **A**[9] was regio- and stereoselectively transformed into (*E*)-vinylstannane **11** by the Pd-catalyzed hydrostannylation (Scheme 2). The Stille coupling of **11** with an ester **12**[15] in the presence of catalytic amounts of $PdCl_2(CH_3CN)_2$ and CuI in DMF smoothly proceeded, and the corresponding coupling product **14** was obtained in 64% yield in 2 steps under complete retention of its stereochemistry. The reaction of **11** with alcohol **13** unfortunately gave a complex mixture due to the decomposition of the coupling product. The synthesis of (−)-xanthoxin (**2**) was achieved by the hydride reduction of **14** followed by MnO_2 oxidation of the resulting allyl alcohol moiety. The spectral and physical data of the synthesized (−)-xanthoxin were in good agreement with those already reported.[16] Furthermore, the aldehyde **B–D** was transformed into the corresponding stereoisomers of (−)-xanthoxin ((−)-epixanthoxin; 26% yield form **B**) by the same procedure. The utilization of the Pd-catalyzed coupling thus demonstrated is a new approach for the synthesis of xanthoxin and related compounds.

In conclusion, we achieved the efficient stereocontrolled syntheses of (−)-loliolide, (−)-xanthoxin, and their stereoisomers. This is the first example that the stereochemistry in the every stereoisomers of these oxidized metabolites has been satisfactorily controlled. Our future interest is in the relationship between the stereochemistry of our synthesized carotenoid metabolites and their biological activities.

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11 In the Sharpless epoxidation of **3** with (+)-diethyl-L-tartrate, the precise reaction conditions applied in the case of (−)-diethyl-D-tartrate were not needed, and the corresponding *syn*-epoxide **5** was obtained in 90–95% de under reported conditions.[10]

12 Data for **A**: $[\alpha]_D^{22}$ −76.84 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 3.85 (m, 1H), 2.24 (ddd, 1H, J = 14.6, 5.4, 1.2 Hz), 1.71 (dd, 1H, J = 14.9, 7.6 Hz), 1.49 (ddd, 1H, J = 13.2, 3.4, 1.2 Hz), 1.38 (s, 3H), 1.28 (dd, 1H, J = 13.2, 9.0 Hz), 1.28 (s, 3H), 1.07 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.40, 72.25, 66.13, 64.19, 46.28, 40.78, 33.55, 27.99, 26.21, 25.78, 20.59, 18.01, −4.79, −4.84. Data for **B**: $[\alpha]_D^{25}$ +21.58 (*c* 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 3.85 (m, 1H), 2.06 (ddd, 1H, J = 14.9, 7.6, 1.5 Hz), 1.88 (dd, 1H, J = 14.9, 9.0 Hz), 1.55 (dd, 1H, J = 12.4, 12.4 Hz), 1.36 (s, 3H), 1.31 (s, 3H), 1.16 (ddd, 1H, J = 12.7, 4.2, 1.5 Hz), 1.07 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.58, 73.02, 64.82, 63.54, 43.91, 39.59, 34.02, 26.33, 25.75, 23.96, 21.59, 18.02, −4.66, −4.72.

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14 Data for (−)-loliolide (**1a**): mp 150.5–151.5 °C; $[\alpha]_D^{21}$ −103.13 (*c* 0.79, $CHCl_3$); IR (KBr, cm^{-1}) 3436, 2978, 2924, 1734, 1721, 1620; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.33 (m, 1H), 2.48 (ddd, 1H, J = 13.9, 2.9, 2.9 Hz), 2.25 (brm, 1H), 2.00 (ddd, 1H, J = 14.4, 2.4, 2.4 Hz), 1.79 (s, 3H), 1.78 (dd, 1H, J = 13.9, 4.2 Hz), 1.52 (dd, 1H, J = 14.6, 3.7 Hz), 1.48 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.90, 172.15, 112.64, 86.99, 66.54, 47.17, 45.52, 35.93, 30.58, 26.90, 26.39; *Anal*. Found: C, 67.01; H, 8.22%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

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16 Data for (−)-xanthoxin (**2**): mp 90.0–91.0 °C; $[\alpha]_D^{21}$ −53.30 (*c* 0.88, $CHCl_3$); IR (KBr, cm^{-1}) 3501, 2932, 1659, 1628, 1588; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (d, 1H, J = 8.3 Hz), 7.19 (d, 1H, J = 15.4 Hz), 6.37 (d, 1H, J = 15.4 Hz), 5.85 (d, 1H, J = 7.8 Hz), 3.88 (m, 1H), 2.38 (ddd, 1H, J = 14.4, 5.2, 1.5 Hz), 2.08 (d, 3H, J = 0.6 Hz), 1.60–1.70 (m, 2H), 1.25 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.39, 153.27, 134.60, 128.95, 127.78, 70.02, 67.28, 63.87, 46.70, 40.64, 35.14, 29.37, 24.95, 21.07, 19.88; *Anal*. Found: C, 71.98; H, 8.93%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.