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Synthesis and Stereochemical Assignments for Goniobutenolides A and B

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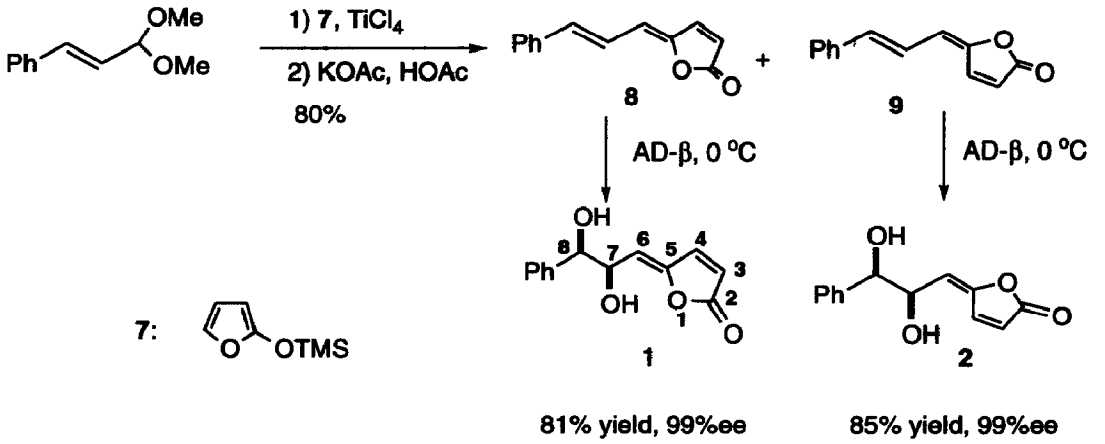
Abstract: *Goniobutenolides A and B and their C-7 epimers are stereoselectively synthesized using osmium-catalyzed asymmetric dihydroxylation (AD) as the key transformation. The relative and absolute stereochemistry of the natural goniobutenolides A and B are assigned with reference to the spectral data and optical rotations from the literature.*

A group of styryllactones has been isolated from ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas[1] of which many have been synthesized due to their interesting structures and biological activities.[2] Among these lactones, goniobutenolides A and B are marginally cytotoxic against human tumor cells. The structures **1** and **2** (or their enantiomers) were proposed based on extensive NMR studies. The *threo* relationship of the two vicinal hydroxyls prompted us to synthesize these lactones to demonstrate the synthetic utility of the selective asymmetric dihydroxylation (AD) of conjugated dienes and polyenes[3] and to establish the absolute configurations of these natural products.

As outlined in Scheme I, construction of the diol lactones was realized in three steps in greater than 60% overall yields. Mukaiyama coupling of cinnamyl aldehyde dimethyl acetal with trimethylsiloxyfuran **7** followed by refluxing the aldol adduct in glacial acetic acid in the presence of KOAc gave a mixture of the *E*- and *Z*-trienes (1:1 ratio) in 85% combined yield.[4,5] The *E*- and *Z*-isomers (**8** and **9**), whose stereochemistry was established by NOE experiments, were readily separated by flash chromatography. Dihydroxylation of each of the trienes under standard AD conditions[3,6] gave the corresponding diol regioselectively in over 80% yields and 99% ee.[7] However, the spectral data (^{1}H-NMR and ^{13}C-NMR) for **1** and **2** did not corresponded to that for either of the natural goniobutenolides A or B. Since the spectral data for both **1** and **2** appeared totally in agreement with the assigned structures, we concluded that the 7,8-dihydroxyl must have the *erythro* instead of the *threo* relationship.

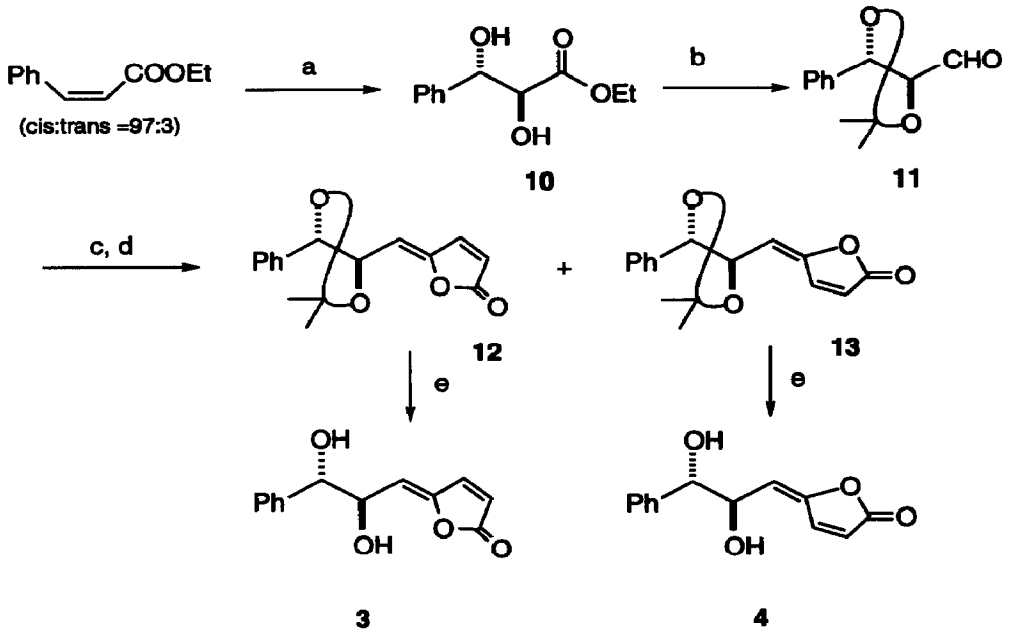
Scheme I



To confirm this speculation, the *erythro* goniobutenolides **3** and **4** were synthesized (Scheme II). AD of *cis*-ethyl cinnamate using the DHQ-IND ligand furnished the *erythro* diol *(2S,3S)*-**10** in 82% yield and 63%ee.[8,9] The enantiomeric diol (*i.e., ent*-**10**) was obtained in 75% yield and 78% ee when DHQD-IND was used as the chiral ligand. The *(2S,3S)*-diol (**10**) was chosen for the following transformations. Compound **10** was protected as its acetonide, and the protected diol ester was cleanly reduced to the aldehyde **11** using 1.2 equivalents of Dibal-H in methylene chloride at –78 °C. The butenolides **12** and **13** were formed following an aldol and elimination procedure.[5] Dienes **12** and **13** were separated by flash chromatography and treated with dilute HCl in THF to give the target molecules **3** (pale yellow oil, $[\alpha]_D^{22}$ –49.2; c 0.25, $CHCl_3$) and **4** (white crystals, $[\alpha]_D^{22}$ +15.5; c 0.20, $CHCl_3$), respectively. The ee values of **3** and **4** were both 64% as determined by direct HPLC analysis on a Chiralcel OF column[10] indicating that no racemization occurred during the above transformations. The spectral data for the synthetic goniobutenolides **3** and **4** are identical to those reported except for the opposite signs of rotation [The reported values for goniobutenolide A and B are +82.0 (c 0.25, in $CHCl_3$) and –36.5 (c 0.20, in $CHCl_3$), respectively]. Therefore, the absolute configurations of the natural goniobutenolides A and B is as shown in **5** and **6**, respectively.

In conclusion, the relative and absolute stereochemistries of the natural goniobutenolides A and B have been established, and the concise syntheses of the C-7 epimers (**1** and **2**) of the goniobutenolides highlight the effectiveness of the AD process for selective oxidation of polyenes.

Scheme 2



a, AD/DHQ-IND, 0 °C, 82% y, 63% ee; b, i) $Me_2C(OMe)_2$, PPTS (cat); ii) Dibal-H, CH_2Cl_2, -78 °C,89%; c, 7, BF_3-Et_2O, 85%; d, Et_3N, Ac_2O, 84%; e, 1N HCl, 1:1 (v/v) H_2O/THF, 85 -91%.

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4. It is interesting to note that directly coupling of cinnamyl aldehyde with the furyl ether under similar conditions gave exclusively the Michael addition product in almost quantitative yield.
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7. 1: $[\alpha]_D^{22}$ –246.5 (c 1.1, EtOH). The ee value was 99%, which was determined by direct analysis on a Chiralcel OB column (HPLC): 20% IPA/HEX, 1mL/min, (*S,S*) 22.6min, (*R, R*) 29.8min. ^{1}H NMR (400 MHz, $CDCl_3$), *δ*: 2.92 (2H, s), 4.65 (1H, d, *J* = 6.3 Hz), 4.83 (1H, dd, *J* = 8.5, 6.3 Hz), 5.29 (1H, d, *J* = 8.5 Hz), 6.12 (1H, d, *J* = 5.4 Hz), 7.24-7.35 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$), *δ*: 71.23, 77.03, 113.56, 120.59, 126.75, 128.38, 128.47, 139.40, 143.60, 150.13, 169.0. 2: $[\alpha]_D^{22}$ +95.5 (c 1.0, EtOH). The ee value was 99%, which was determined by directly analysis on a Chiralcel OJ column (HPLC): 30% IPA/HEX , 0.8mL/min, (*S, S*) 18.3min, (*R,R*) 13.1min. ^{1}H NMR: (400 MHz, $CDCl_3$), *δ*: 2.70 (2H, s), 4.52 (1H, t, *J* = 7.4 Hz), 4.58 (1H, d, *J* = 7.7 Hz), 5.56 (1H, dd, *J* = 7.3, 1.6 Hz), 6.07 (1H, dd, *J* = 5.6, 1.7 Hz), 7.25-7.33 (5H, m), 7.49 (1H, d, *J* = 5.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), *δ*: 73.26, 77.81, 112.49, 121.08, 122.80, 126.79, 128.73, 139.15, 140.91, 145.70, 151.56.
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9. The ee value of the diol ester **10** was determined by direct HPLC analysis on a Chiralcel OJ column: 10% IPA/HEX, 0.8 mL/min, (*S,S*) 19.5 min, (*R,R*) 23.9 min.
10. The ee value for **3** and **4** were determined by direct HPLC analysis on a Chiralcel OF column. **3**: 20% IPA/HEX, 1 mL/min, (*S,S*) 26.8 min, (*R,R*) 33.5 min. **4**: 20% IPA/HEX, 1 mL/min, (*S,S*) 28.7 min, (*R,R*) 41.1 min.

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