Total Synthesis of (±)-Aiphanol, a Novel Cyclooxygenase-inhibitory Stilbenolignan

Atsuhito Kuboki,* Toru Yamamoto, and Susumu Ohira*
Department of Biochemistry, Okayama University of Science, 1-1 Ridai-cho, Okayama 700-0005

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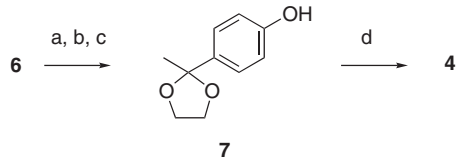
(±)-Aiphanol has been stereoselectively synthesized through IBX-mediated *o*-quinone formation, and through [4+2] cycloaddition of the *o*-quinone and cinnamyl alcohol unit.

Aiphanol (**1**), a novel stilbenolignan, which has recently been isolated from the seeds of *Aiphanes aculeata* Willd (Arecaceae) possesses significant inhibitory activity toward cyclooxygenases-1 and -2.[1] Compound **1** demonstrated the IC_{50} value of 1.9 μM toward cyclooxyganase-1 and of 9.9 μM toward cyclooxyganase-2. Compound **1** has a stilbenolignan skeleton in which a stilbene unit is bridged with a phenylpropane moiety by 1,4-dioxane. Total synthesis of **1** has not yet been communicated in the literature, and we wish to report here the results of our research, which culminated in a total synthesis of Aiphanol **1**.

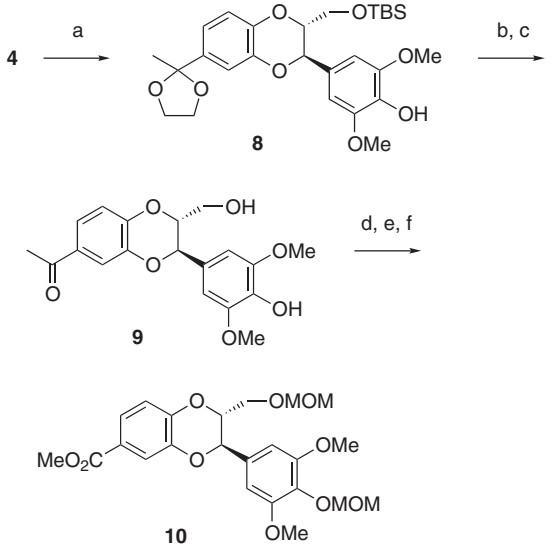
In the retrosynthetic analysis (Figure 1), the stilbene moiety of **1** would be obtained from aldehyde **2** and phosphonium salt **3** by Wittig olefination. The 1,4-benzodioxane skeleton might be available via a [4+2] cycloaddition of cinnamyl alcohol **5** and *o*-quinone **4**. Compound **4** would be prepared from 4-hydroxyacetophenone (**6**) by regioselective oxidation with IBX (*o*-iodoxybenzoic acid).[2] Similar strategy was previously developed by Pan et al. in synthesis of (±)-Sinaiticin.[3]

Our synthesis of **4** commenced with subjection of the inexpensive **6** to sequential silylation, acetal protection, and desilylation to give phenol **7** in 71% overall yield. Treatment of **7** in a solution of DMSO[4] with IBX for 0.5 h at room temperature provided the desired *o*-quinone **4** in 90% yield. Interestingly, *o*-quinone could not be obtained from methyl 4-hydroxycinnamate, methyl 4-hydroxybenzoate, or 4-hydroxybenzonitrile by IBX-mediated phenol oxidation. It is suggested that a quaternary carbon at the benzilic position of substrates is required for the stability of the resultant *o*-quinone.[5]



Scheme 1. (a) TBSCl, imidazole, DMF, rt, 1 h (95%); (b) ethylene glycol, PTSA, benzene, reflux, 2.5 h (75%); (c) TBAF, THF, rt, 1 h (quant.); (d) IBX, DMSO, rt, 0.5 h (90%).

[4+2] cycloaddition of **4** and **5**, which was prepared from sinapyl alcohol[6] protected by TBS group, was completed within 0.5 h at room temperature to afford the desired 1,4-benzodioxane **8** in 69% yield. In the cycloaddition, no regioisomer of **8** could be detected.[7,8] In addition, both free phenol and protection of the primary alcohol of **5** were necessary for successful cycloaddition. Acetal group of **8** was removed under acidic con-



Scheme 2. (a) **5**, acetone–benzene, rt, 0.5 h (69%); (b) AcCl, MeOH, rt, overnight [88% (*trans/cis* = 2/1)]; (c) K_2CO_3, DMF, 50 °C, 3 h [57% (*trans* only)]; (d) MOMCl, $^iPr_2NEt$, CH_2Cl_2, rt, 2 h (97%); (e) KI, H_2O, NaOH, 1,2-dimethoxymethane, rt, 0.5 h; (f) MeI, K_2CO_3, DMF, rt, 3 h (69% in 2 steps).

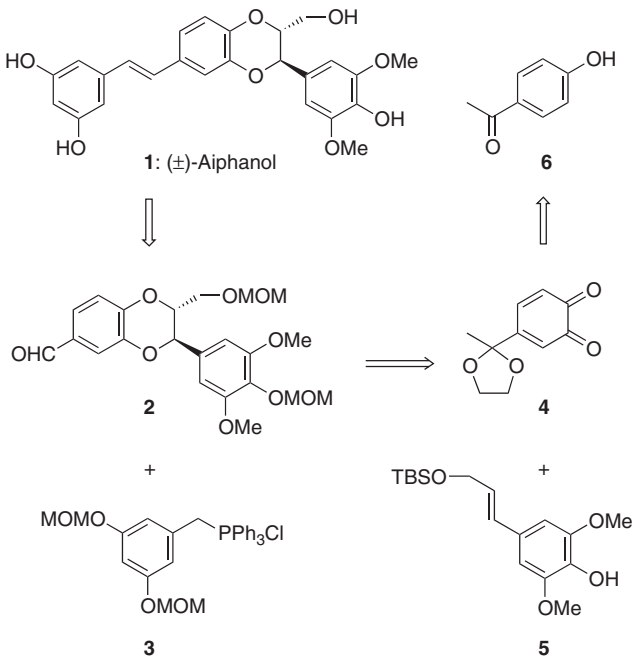
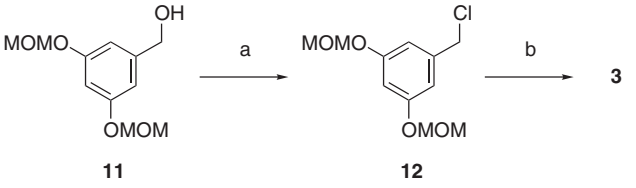


Figure 1.

ditions to give ketone **9** in 88% yield. The diastereoselectivity of the cycloaddition was determined as *trans/cis* = 2/1 by ^{1}H NMR analysis of ketone **9**. This geometric mixture was treated under basic conditions reported by Pan[3] et al. to convert it to trans isomer in 57% yield. The isomerization necessitated deprotection of the acetal group of **8**. The resultant acetophenone **9** was protected by MOM group and converted to methyl ester **10** by sequential iodoform reaction and esterification in 69% yield.

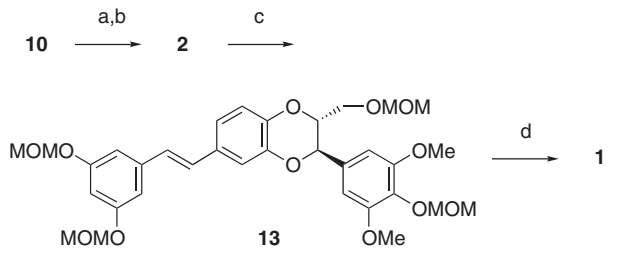
The next step was construction of a stilbene skeleton by Wittig olefination using phosphonium **3**, which was prepared from benzyl alcohol **11**[9] in the 2 steps described below. Alcohol **11** was converted to benzyl chloride **12** with methanesulfonyl chloride and triethylamine in 95% yield. Chloride **12** was treated with triphenylphosphine to afford **3** in 38% yield.



Scheme 3. (a) MsCl, Et_3N, CH_2Cl_2, rt, overnight (95%); (b) Ph_3P, toluene, reflux, overnight (38%).

Ester **10** was converted to benzaldehyde **2** by sequential reduction with $LiAlH_4$ and oxidation with Dess-Martin periodinane. Aldehyde **2** was treated with **3** in the presence of cesium fluoride in toluene under reflux conditions[10] to give protected Aiphanol **13** as *E*/*Z* diastereomeric mixture in 59% yield from **10**. The whole MOM group of **13** was removed under acidic conditions to afford Aiphanol **1** as a mixture of diastereomers in 65% yield. The ratio was determined as *E*/*Z* = 7/1 by ^{1}H NMR analysis. Finally, the remaining *Z*-isomer of **1** was separated by HPLC to give pure (±)-Aiphanol **1**. The spectral data (^{1}H, ^{13}C NMR) of the synthetic **1**[11] were in good accordance with those already reported.[1]

In conclusion, the first total synthesis of (±)-Aiphanol was achieved using a convergent strategy (14 steps from **6**, 5.8% overall yield) which included regioselective oxidation of phenol to *o*-quinone with IBX and the [4+2] cycloaddition of resultant *o*-quinone and cinnamyl alcohol as key steps. We also developed a synthetic procedure for key intermediate **2**, which was useful for the synthesis of a variety of benzodioxane neolignans and flavonolignans. Further refinement of the synthetic scheme and preparation of an optically active form will be reported in due course.



Scheme 4. (a) $LiAlH_4$, THF, rt, 1 h (94%); (b) Dess-Martin periodinane, CH_2Cl_2, rt, 0.5 h; (c) **3**, CsF, toluene, reflux, 4 h (64% in 2 steps); (d) AcCl, MeOH, rt, overnight [65% (*E*/*Z* = 7/1)].

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References and Notes

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4 When DMF or $CHCl_3$ was used as solvent following the reported procedure,[2] the oxidation was decelerated markedly.
5 4-tert-Butylphenol, 4-isopropylphenol, 4-ethylphenol, and 4-methylphenol were subjected to the oxidation, respectively. Although corresponding *o*-quinone could be detected by TLC or ^{1}H NMR in all cases, *o*-quinone could be only isolated from 4-tert-butylphenol.
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11 Data for Aiphanol **1**: ^{1}H NMR (500 MHz, acetone-d_6) δ 7.10 (1H, d, *J* = 2.1 Hz), 7.05 (1H, dd, *J* = 8.5, 2.1 Hz), 6.98 (1H, d, *J* = 16.2 Hz), 6.91 (1H, d, *J* = 16.2 Hz), 6.87 (1H, d, *J* = 8.5 Hz), 6.80 (2H, s), 6.52 (1H, d, *J* = 2.1 Hz), 6.24 (1H, dd, *J* = 2.1, 2.1 Hz), 4.93 (1H, d, *J* = 7.9 Hz), 4.10 (1H, ddd, *J* = 7.9, 4.3, 2.4 Hz), 4.06 (1H, dd, *J* = 6.7, 4.9 Hz), 3.81 (6H, s), 3.70 (1H, ddd, *J* = 12.2, 4.9, 2.4 Hz), 3.50 (1H, ddd, *J* = 12.2, 6.7, 4.3 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.1, 149.7, 146.0, 145.4, 141.6, 138.2, 132.8, 129.7, 129.1, 129.0, 121.9, 118.7, 116.4, 108.8, 106.7, 103.8, 80.6, 78.5, 62.8, 57.6.

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