JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Total Synthesis of Laetevirenol A

Young Lok Choi,[†,‡] Bum Tae Kim,[†] and Jung-Nyoung Heo[†,§,*]

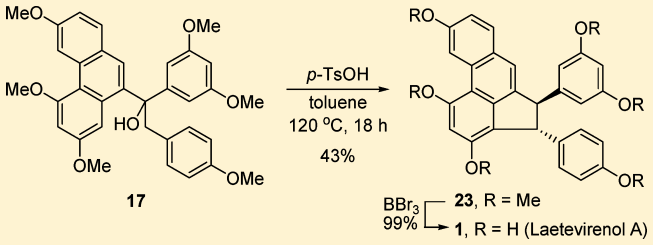
[†]Medicinal Chemistry Research Center, Korea Research Institute of Chemical Technology, 141 Gajeong-ro, Daejeon 305-600, Korea

[‡]Department of Chemistry, Korea University, 145 Anam-ro, Seoul 105-600, Korea

[§]Graduate School of New Drug Discovery and Development, Chungnam National University, 99 Daehak-ro, Daejeon 305-764, Korea

Supporting Information

ABSTRACT: The first complete synthesis of laetevirenol A was performed in nine steps via intramolecular Friedel–Crafts alkylation in a *trans*-selective manner. The key phenanthrene intermediate was synthesized by a one-pot Suzuki–Miyaura coupling and an aldol condensation cascade reaction.



Laetevirenol A (**1**) was isolated from the roots and stems of *Parthenocissus laetevirens*, along with laetevirenol B (**2**)–E, by Pan et al. in 2008 (Figure 1).[1] Laetevirenol A displayed strong antioxidant activities, most likely due to the presence of a phenanthrene moiety acting as a free-radical scavenger. Structurally, laetevirenol A belongs to a large and diverse family of polyphenol compounds that includes resveratrol (**3**)-based natural products such as quadranglularin A (**4**),[2] parthenocissin A (**5**),[3] and pauciflorol F (**6**).[4] Members of this family of resveratrol oligomers possess a wide range of biological activities including antitumor,[5] antioxidant,[6] anti-inflammatory,[7] anti-HIV,[8] antifungal,[9] and neuroprotective activities.[10]

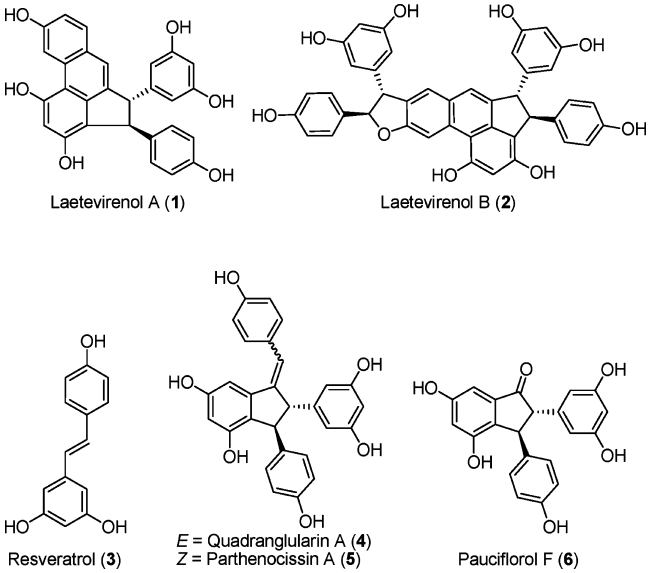
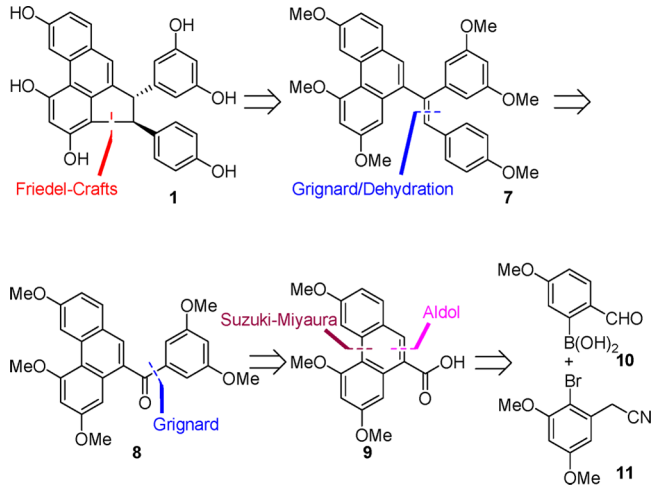


Figure 1. Representative molecules of resveratrol-based oligomers.

The complex molecular diversity of resveratrol oligomers has attracted considerable attention from organic and medicinal chemists. Recently, Snyder et al. developed an elegant strategy that allowed them to access several molecules of resveratrol oligomers via a programmable process. The process was initiated from a simple, common intermediate.[11] Thereafter, Nicolaou and Chen's group reported the synthesis of hopeahainol A and hopeanol by employing an intramolecular Friedel–Crafts alkylation.[12]

Our synthetic strategy began with the retrosynthetic analysis of laetevirenol A (**1**) to a triaryl-substituted olefin intermediate, **7** (Scheme 1). At this late stage of cyclization, the Friedel–Crafts alkylation would be appropriate to provide trans stereochemistry to laetevirenol A.[13,14] Consequently, it was anticipated that the triaryl-substituted olefin **7** could be obtained through a Grignard addition of ketone **8**, followed

Scheme 1. Retrosynthetic Analysis for Laetevirenol A



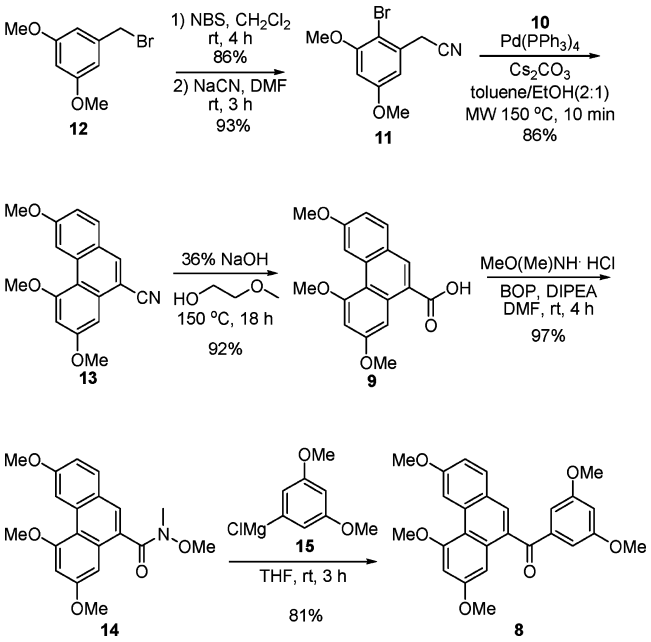
Received: July 4, 2012
Published: September 4, 2012

   dx.doi.org/10.1021/jo301345a | J. Org. Chem. 2012, 77, 8762–8767

by acid-catalyzed dehydration. Furthermore, ketone **8** could, in turn, be prepared from phenanthrene carboxylic acid through a Grignard reaction. Phenanthrene **9** was expected to be easily obtained using our previously performed method, a one-pot Suzuki–Miyaura coupling/aldol condensation cascade reaction of phenylacetonitrile **11** with 2-formylphenylboronic acid **10**.[15]

For the preparation of phenanthrene **9**, a one-pot Suzuki–Miyaura coupling/aldol condensation cascade reaction was employed. The substrate for this reaction, phenylacetonitrile **11**, was easily prepared by bromination of benzyl bromide **12**[16,11c] with NBS, followed by cyanation with NaCN in DMF (Scheme 2).[17] Based on the original procedure reported by our

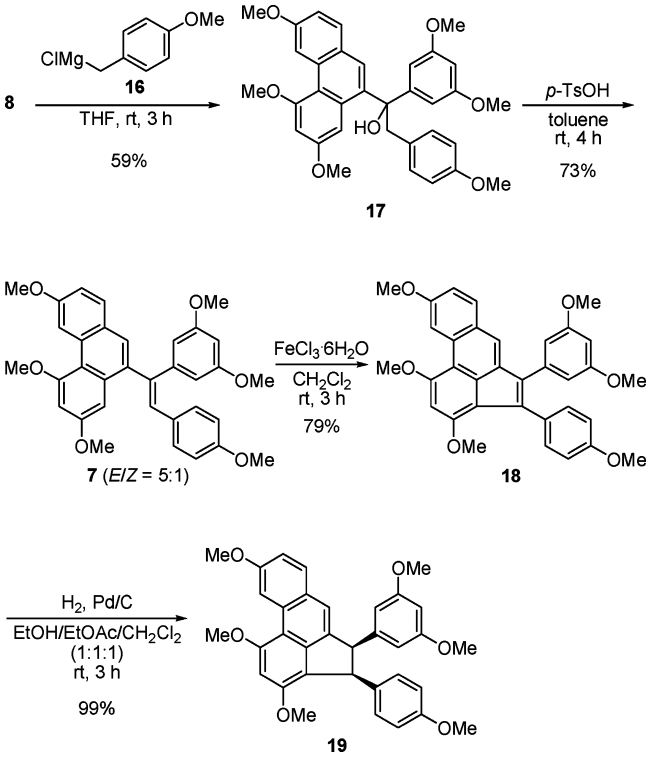
Scheme 2. Synthesis of Phenanthrene Ketone 8



group,[15a] the one-pot reaction of **11** with 2-formylphenylboronic acid **10** under microwave irradiation easily produced the phenanthrene **13** in 86% yield. Hydrolysis of the phenanthrene nitrile **13** in basic conditions produced the corresponding acid **9** in excellent yield,[18] which was subsequently converted into the Weinreb amide **14** in 97% yield. The Grignard addition of **14** with phenylmagnesium chloride **15** was then carried out to afford the ketone **8** in 81% yield.

Next, ketone **8** was subjected to the Grignard addition with benzylmagnesium chloride **16** to give the expected tertiary alcohol **17** in 59% yield (Scheme 3).[19] Dehydration of the tertiary alcohol **17** with *p*-TsOH in toluene at room temperature afforded a triaryl-substituted olefin **7** in 73% yield with an *E*/*Z* ratio of 5:1.[20] Other Brønsted acids, including HCl, CSA, and TFA, proved to be less effective, resulting in an *E*/*Z* ratio of ∼1:1. With access to olefin **7** established, our efforts turned to implementing the key intramolecular Friedel–Crafts alkylations. A small screening of Lewis acids revealed that exposure of olefin **7** to $FeCl_3$ promoted intramolecular oxidative cyclohydrogenation to provide a fully conjugated acephenanthrylene **18** in good yield.[21,22] Thus, we envisioned that further elaboration of **18** by catalytic hydrogenation would provide the *cis* stereoisomer of laetevirenol A. Indeed, exposing **18** to the standard palladium-

Scheme 3. Synthesis of *Cis*-Isomer 19

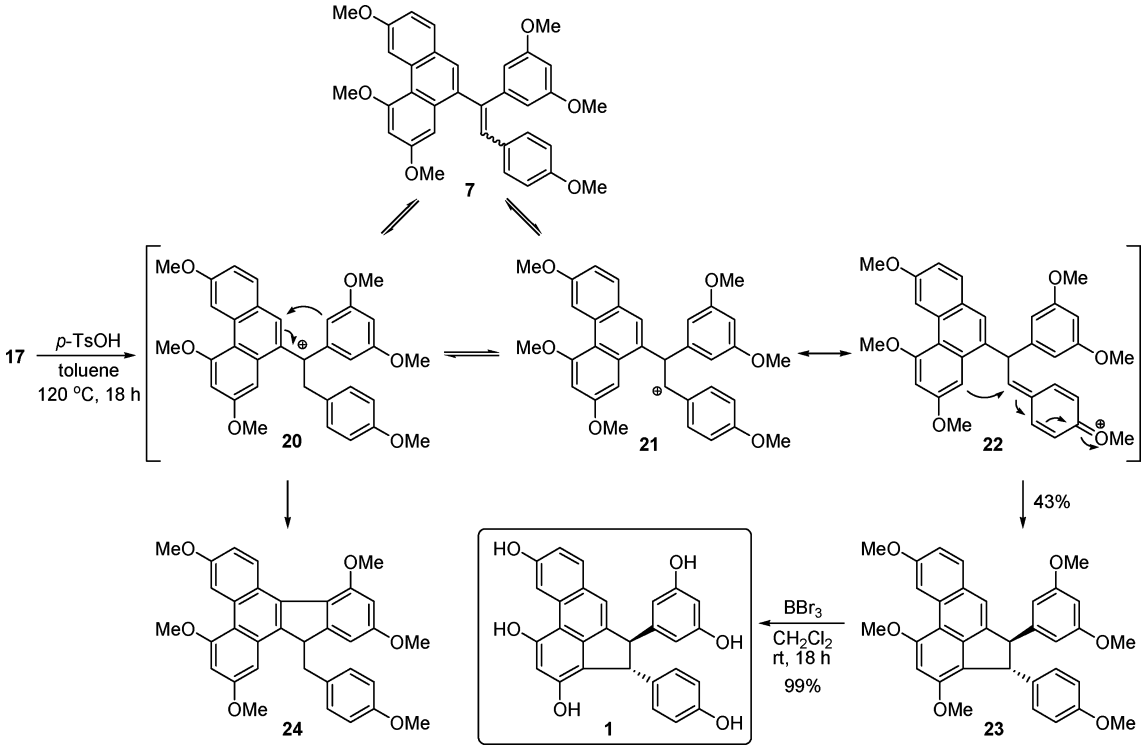


catalyzed hydrogenation conditions led to the desired cis derivative **19** in quantitative yield.[23]

Given these findings, we then hypothesized that it might be possible to find Friedel–Crafts reaction conditions to generate the quinone methide **22**, which could be a stabilized resonance form of the secondary benzylic cabocation **21** to produce the desired trans stereoisomer **23** (Scheme 4). After investigating numerous reaction conditions, we were pleased to find that the one-pot dehydration/Friedel–Crafts alkylation of **17** with *p*-TsOH in toluene at elevated temperature (120 °C). The desired *trans*-cyclized product **23** was obtained as a single isomer. However, the product was synthesized in moderate yield (43%), along with **18** and **24**. At higher temperatures, we believe that carbocations **20** and **21** may rapidly equilibrate via a 1,2-hydride shift or interconversion through olefin intermediate **7** due to the significant contribution of quinone methide **22** for the stabilization of **21**. When olefin **7** (*E*/*Z* = 1.7:1) was treated with *p*-TsOH, a mixture of cyclized products **23** and **24** was obtained in a 2.5:1 ratio. We believe that this observation supports the hypothesis that the interconversion between **20** and **21** proceeds through olefin **7**. Finally, global demethylation of **23** using BBr_3 in CH_2Cl_2 provided laetevirenol A (**1**) in quantitative yield. The spectroscopic data of the synthetic laetevirenol A were identical to those reported for the natural product.[1] In the case in which the strong Brønsted acid TfOH is used, the 9*H*-indeno[2,1-*l*]phenanthrene **24** could be exclusively obtained in 74% yield, probably through the tertiary carbocation **20**.[24] Interestingly, the Friedel–Crafts cyclization of **17** seems to depend upon the pK_a value of the Brønsted acids.[25] When methanesulfonic acid (pK_a = −0.6) or *p*-TsOH (pK_a = −2.8) was used, the reaction provided a mixture of **23**/**24** in 1.4:1 or 5.3:1 ratio, respectively. Therefore, the much higher value of TfOH (pK_a = −14.0) perhaps resulted in significant stabilization of carbocation **20**.

dx.doi.org/10.1021/jo301345a | J. Org. Chem. 2012, 77, 8762–8767

Scheme 4. Synthesis of Laetevirenol A (1)



In summary, we have successfully achieved the first complete synthesis of laetevirenol A in nine steps, starting from the commercially available benzyl bromide **12**, in an overall 12% yield. The intramolecular Friedel–Crafts alkylation was employed as the final key step. The synthesis of the phenanthrene ketone intermediate **8** involves a Grignard addition and a one-pot Suzuki–Miyaura coupling/aldol condensation reaction. Notably, this route makes it possible to access the *cis*-isomer **19** and indeno[2,1-*l*]phenanthrene **24** of laetevirenol A natural product analogues. Our strategy can be considered as a simple and rapid synthesis of this family of interesting natural products.

EXPERIMENTAL SECTION

2-Bromo-1-(bromomethyl)-3,5-dimethoxybenzene. To a solution of 1-(bromomethyl)-3,5-dimethoxybenzene **12** (2.0 g, 8.7 mmol) in CH_2Cl_2 (26 mL) at 0 °C was added NBS (1.53 g, 8.7 mmol) in several portions. The solution was gradually warmed to room temperature and stirred for 4 h. The reaction mixture was quenched with saturated NaS_2O_3 solution and extracted with CH_2Cl_2. The organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to afford 2-bromo-1-(bromomethyl)-3,5-dimethoxybenzene (2.3 g, 86%) as a white solid: ^{1}H NMR (300 MHz, CDCl3) δ 6.63 (1H, d, J = 2.7 Hz), 6.44 (1H, d, J = 2.5 Hz), 4.60 (2H, s), 3.87 (3H, s), 3.82 (3H, s); ^{13}C NMR (75 MHz, CDCl3) δ 159.9, 157.3, 138.7, 107.3, 105.2, 100.2, 56.6, 55.8, 34.0; MS (EI) *m*/*z* 307 (M^+, 7), 229 (72), 135 (77); HRMS (EI) calcd for $C_9H_{10}Br_2O_2$ [M^+] 307.9048, found 307.9048.

2-(2-Bromo-3,5-dimethoxyphenyl)acetonitrile (11). To a solution of 2-bromo-1-(bromomethyl)-3,5-dimethoxybenzene (26.0 g, 84 mmol) in DMF (138 mL) was added sodium cyanide (12.33 g, 252 mmol). The resulting mixture was stirred at rt for 3 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford phenylacetonitrile **11** (20.0 g, 93%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (1H, d, *J* = 2.7 Hz), 6.47 (1H, d, *J* = 2.7 Hz), 3.89 (3H, s), 3.84 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 157.2, 131.6, 117.1, 105.9, 103.9, 99.4, 56.4, 55.7, 25.3; MS (EI) *m*/*z* 255 (M^+, 100), 212 (18), 146 (19); HRMS (EI) calcd for $C_{10}H_{10}BrNO_2$ [M^++2] 256.9874, found 256.9856.

3,5,7-Trimethoxyphenanthrene-9-carbonitrile (13). To a thick-walled microwave vial were added phenylacetonitrile **11** (256 mg, 1.0 mmol), (2-formyl-5-methoxyphenyl)boronic acid **10** (198 mg, 1.1 mmol), $Pd(PPh_3)_4$ (46 mg, 4 mol %), and Cs_2CO_3 (978 mg, 3.0 mmol) sequentially. The mixture was suspended in toluene/EtOH (4 mL/2 mL). Then, the reaction vial was sealed, placed into a microwave reactor, and irradiated at 150 °C for 10 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford phenanthrene **13** (252 mg, 86%) as a white solid: mp 201–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (1H, d, *J* = 2.5 Hz), 8.18 (1H, s), 7.80 (1H, d, *J* = 8.7 Hz), 7.30 (1H, d, *J* = 2.5 Hz), 7.23 (1H, dd, *J* = 8.7, 2.5 Hz), 6.83 (1H, d, *J* = 2.5 Hz), 4.12 (3H, s), 4.01 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 160.4, 159.7, 137.0, 133.9, 133.1, 130.8, 124.4, 119.1, 116.0, 115.4, 109.8, 106.2, 100.6, 98.9, 56.13, 55.8, 55.5; MS (EI) *m*/*z* 293 (M^+, 17), 277 (17), 234 (10), 198 (6); HRMS (EI) calcd for $C_{18}H_{15}NO_3$ [M^+] 293.1052, found 293.1053.

3,5,7-Trimethoxyphenanthrene-9-carboxylic Acid (9). A solution of 3,5,7-trimethoxyphenanthrene-9-carbonitrile **13** (700 mg, 2.4 mmol) in a mixture of 36% aq NaOH solution (7 mL) and 2-methoxyethanol (21 mL) was heated at 150 °C for 18 h. Upon cooling, the solution was acidified with 6 N HCl solution and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Trituration of the crude product with Et_2O gave the carboxylic acid **9** (683 mg, 92%) as a white solid: mp 227–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (1H, d, *J* = 2.5 Hz), 8.66 (1H, s), 8.34 (1H, d, *J* = 2.6 Hz), 7.87 (1H, d, *J* = 8.7 Hz), 7.21 (1H, dd, *J* = 8.8, 2.5 Hz), 6.83 (1H, d, *J* = 2.6 Hz), 4.12 (3H, s), 4.02 (3H, s), 4.01 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.5, 160.2, 160.1, 159.0, 133.7, 133.3, 133.1,

dx.doi.org/10.1021/jo301345a | J. Org. Chem. 2012, 77, 8762–8767

131.8, 124.4, 124.0, 115.6, 115.3, 109.6, 100.4, 99.5, 56.5, 55.6 (2); MS (EI) *m/z* 312 (M^+, 100), 279 (6), 210 (8), 139 (6); HRMS (EI) calcd for $C_{18}H_{16}O_5$ [M^+] 312.0998, found 312.0992.

***N*,3,5,7-Tetramethoxy-*N*-methylphenanthrene-9-carboxamide (14).** A solution of carboxylic acid **9** (633 mg, 2.03 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (218 mg, 2.23 mmol), BOP (1.08 g, 2.44 mmol), and DIPEA (1.1 mL, 8.12 mmol) in DMF (6 mL) was stirred at 25 °C for 4 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (30% EtOAc/hexanes) to afford Weinreb amide **14** (702 mg, 97%) as a white solid: mp 126−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (1H, d, J = 2.6 Hz), 7.77 (1H, d, J = 8.7 Hz), 7.70 (1H, s), 7.19 (1H, dd, J = 8.7, 2.6 Hz), 6.93 (1H, d, J = 2.5 Hz), 6.78 (1H, d, J = 2.5 Hz), 4.11 (3H, s), 4.00 (3H, s), 3.93 (3H, s), 3.62 (3H, s), 3.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 158.9, 158.7, 132.2, 132.1, 130.0, 129.1, 127.1, 124.9, 115.6, 115.2, 109.6, 99.5, 98.5, 61.3, 55.9, 55.4, 55.3; MS (EI) *m/z* 355 (M^+, 2), 295 (100), 252 (24); HRMS (EI) calcd for $C_{20}H_{21}NO_5$ [M^+] 355.1420, found 355.1437.

(3,5-Dimethoxyphenyl)(3,5,7-trimethoxyphenanthren-9-yl)-methanone (8). To a solution of Weinreb amide **14** (100 mg, 0.3 mmol) in THF (1 mL) at 0 °C was added a solution of (3,5-dimethoxyphenyl)magnesium chloride **15** (1.4 mL, 1.4 mmol, 1 M in THF). The reaction mixture was allowed to warm at 25 °C and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 10 mL). The extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford ketone **8** (105 mg, 81%) as a white solid: mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (1H, d, J = 2.5 Hz), 7.80 (1H, s), 7.74 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 2.5 Hz), 7.18 (1H, dd, J = 8.8, 2.5 Hz), 7.05 (2H, d, J = 2.3 Hz), 6.80 (1H, d, J = 2.5 Hz), 6.70 (1H, t, J = 2.3 Hz), 4.12 (3H, s), 4.01 (3H, s), 3.84 (3H, s), 3.79 (6H s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 160.7, 160.1, 159.7, 158.7, 140.9, 133.2, 133.1, 132.0, 131.8, 130.8, 124.2, 115.9, 115.3, 109.6, 108.0, 105.7, 99.8, 99.5, 55.9, 55.6, 55.35, 55.30; MS (EI) *m/z* 432 (M^+, 100), 373 (11), 295 (17), 252 (7); HRMS (EI) calcd for $C_{26}H_{24}O_6$ [M^+] 432.1573, found 432.1570.

1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-1-(3,5,7-trimethoxyphenanthren-9-yl)ethanol (17). To a solution of ketone **8** (100 mg, 0.2 mmol) in THF (1 mL) at 0 °C was added a solution of (4-methoxybenzyl)magnesium chloride **16** (2 mL, 0.5 mmol, 0.25 M in THF). The reaction mixture was allowed to warm gradually to 25 °C and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 15 mL). The organic extracts were washed with H_2O and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give alcohol **17** (75 mg, 59%) as a white solid: mp 183−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (1H, d, J = 2.6 Hz), 8.06 (1H, s), 7.80 (1H, d, J = 8.7 Hz), 7.30−7.24 (1H, m), 7.20 (1H, dd, J = 8.7, 2.6 Hz), 6.70 (4H, s), 6.65 (1H, d, J = 2.5 Hz), 6.39 (2H, d, J = 2.3 Hz), 6.27 (1H, t, J = 2.3 Hz), 4.05 (3H, s), 4.00 (3H, s), 3.85 (1H, d, J = 12.8 Hz), 3.74 (3H, s), 3.65 (1H, d, J = 12.7 Hz), 3.60 (6H, s), 3.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 160.2, 158.6, 158.6, 149.3, 136.0, 132.2, 131.8, 130.3, 128.0, 127.2, 125.4, 117.0, 115.0, 113.3, 109.6, 104.8, 101.7, 99.0, 98.8, 78.5, 77.4, 55.9, 55.4, 55.4, 55.3; MS (EI) *m/z* 554 (M^+, 1), 433 (59), 295 (27), 252 (8), 165 (100), 137 (19), 121 (44); HRMS (EI) calcd for $C_{34}H_{34}O_7$ [M^+] 554.2305, found 554.2305.

(*E*)-10-(1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-vinyl)-2,4,6-trimethoxyphenanthrene (7*E*). To a solution of alcohol **17** (84 mg, 0.156 mmol) in toluene (1.5 mL) was added *p*-TsOH·$6H_2O$ (13 mg, 0.8 mmol) and the mixture stirred at rt for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 10 mL). The extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative HPLC using an XTerra C18 OBD (5 μm) column (30% H_2O/ACN, 40 mL/min) to afford olefin **7*E*** (50 mg, 61%) as a yellow solid (retention time = 15.0 min): mp 202−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (1H, d, J = 2.5 Hz), 7.78 (1H, d, J = 8.8 Hz), 7.76 (1H, s,), 7.21−7.17 (3H, m), 7.07 (1H, d, J = 2.5 Hz), 6.85 (1H, s), 6.77 (2H, dd, J = 8.8, 2.0 Hz), 6.67 (1H, d, J = 2.5 Hz), 6.47 (2H, d, J = 2.3 Hz), 6.30 (1H, t, J = 2.3 Hz), 4.07 (3H, s), 4.00 (3H, s), 3.80 (3H, s), 3.67 (3H, s), 3.58 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 160.1, 158.6, 158.2, 157.8, 142.7, 141.0, 137.7, 134.8, 131.5, 130.9, 130.6, 129.9, 129.7, 129.6, 126.0, 115.8, 114.8, 113.5, 109.6, 107.9, 100.6, 99.5, 98.9, 55.8, 55.3, 55.2 (2), 55.1; MS (EI) *m/z* 534 (M^+, 100), 401 (29), 295 (16); HRMS (EI) calcd for $C_{34}H_{32}O_6$ [M^+] 536.2199, found 536.2188.

(*Z*)-10-(1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-vinyl)-2,4,6-trimethoxyphenanthrene (7*Z*). The product (10 mg, 12%) was obtained by the above prep HPLC (retention time = 10.5 min): mp 235−236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (1H, d, J = 2.6 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.57 (1H, s), 7.23 (1H, s), 7.16 (1H, dd, J = 8.7, 2.6 Hz), 6.99 (1H, d, J = 2.5 Hz), 6.94 (2H, dd, J = 6.8, 1.9 Hz), 6.72 (1H, d, J = 2.5 Hz), 6.57 (2H, d, J = 2.3 Hz), 6.53 (2H, dd, J = 6.8, 2.1 Hz), 6.35 (1H, t, J = 2.3 Hz), 4.12 (3H, s), 4.01 (3H, s), 3.69 (6H, s), 3.67 (3H, s), 3.64 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 160.2, 158.5, 158.3, 158.2, 145.6, 138.9, 134.8, 133.4, 131.5, 130.5, 129.8, 129.72, 129.67, 126.4, 116.0, 114.7, 113.6, 109.5, 105.1, 99.7, 99.1, 98.9, 55.8, 55.3 (2), 55.2, 55.1; MS (EI) *m/z* 536 (M^+, 95), 505 (57), 214 (51), 108 (100); HRMS (EI) calcd for $C_{34}H_{32}O_6$ [M^+] 536.2199, found 536.2199.

5-(3,5-Dimethoxyphenyl)-1,3,9-trimethoxy-4-(4-methoxyphenyl)acephenanthrylene (18). To a solution of olefin **7*E*** (8 mg, 0.015 mmol) in CH_2Cl_2 (0.7 mL) at rt was added $FeCl_3$·$6H_2O$ (8 mg, 0.03 mmol) and stirred for 3 h. The reaction mixture was treated with H2O (10 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give acephenanthrylene **18** (6.3 mg, 79%) as a yellow solid: mp 137−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, d, J = 2.7 Hz), 8.09 (1 H, s), 7.91 (1H, d, J = 8.8 Hz), 7.40 (2H, d, J = 8.7 Hz), 7.20 (1H, dd, J = 8.8, 2.7 Hz), 6.85 (2H, d, J = 8.7 Hz), 6.72 (1H, s), 6.53 (2H, d, J = 2.3 Hz), 6.39 (1H, t, J = 2.3 Hz), 4.22 (3H, s), 4.03 (3H, s), 3.86 (3H, s), 3.84 (3H, s), 3.68 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 160.5, 159.3, 158.6, 156.1, 139.0, 138.0, 135.3, 133.4, 132.3, 131.9, 131.8, 129.3, 127.9, 126.6, 117.3, 114.8, 112.9, 112.3, 109.5, 108.7, 99.1, 95.7, 56.30, 59.28, 55.5, 55.4; MS (EI) *m/z* 534 (M^+, 100), 519 (22), 284 (16); HRMS (EI) calcd for $C_{34}H_{30}O_6$ [M^+] 534.2042, found 534.2039.

***cis*-5-(3,5-Dimethoxyphenyl)-1,3,9-trimethoxy-4-(4-methoxyphenyl)-4,5-dihydroacephenanthrylene (19).** To a solution of acephenanthrylene **18** (20 mg, 0.037 mmol) in a mixture of EtOAc/EtOH/CH_2Cl_2 (0.6 mL/0.6 mL/0.6 mL) was added 10% Pd/C (20 mg, 10 wt %). The resulting suspension was stirred at rt for 3 h under an atmosphere of hydrogen (balloon). The reaction mixture was filtered through a short Celite pad and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford *cis*-dihydroacephenanthrylene **19** (18 mg, 99%) as a white solid: mp 182−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, d, J = 2.6 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.23 (1H, s), 7.15 (1H, dd, J = 8.7, 2.7 Hz), 6.85 (1H, s), 6.51−6.37 (5H, m), 6.19 (1H, t, J = 2.4 Hz), 6.09 (2H, d, J = 2.3 Hz), 5.16−5.04 (2H, m), 4.20 (3H, s), 4.02 (3H, s), 3.83 (3H, s), 3.64 (3H, s), 3.55 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 159.1, 157.85, 157.82, 154.3, 142.7, 141.7, 141.5, 134.0, 130.5, 129.6, 129.5, 128.5, 122.5, 122.0, 114.4, 112.9, 112.8, 109.8, 108.4, 99.0, 97.4, 56.8, 56.5, 56.3, 55.6, 55.3, 55.2, 52.7; MS (EI) *m/z* 536 (M^+, 100), 505 (11), 428 (18); HRMS (EI) calcd for $C_{34}H_{32}O_6$ [M^+] 536.2199, found 536.2183.

***trans*-5-(3,5-Dimethoxyphenyl)-1,3,9-trimethoxy-4-(4-methoxyphenyl)-4,5-dihydroacephenanthrylene (23).** To a solution of alcohol **17** (277 mg, 0.5 mmol) in toluene (10 mL) was added *p*-TsOH·$6H_2O$ (95 mg, 0.5 mmol). The resulting mixture was sealed and stirred at 120 °C for 18 h. After being cooled to room

dx.doi.org/10.1021/jo301345a | J. Org. Chem. 2012, 77, 8762−8767

temperature, the mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford the desired *trans* isomer **23** (115 mg, 43%) as a white solid: mp 179−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (1H, d, J = 2.6 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.14 (1H, dd, J = 8.7, 2.6 Hz), 6.99 (2H, d, J = 8.4 Hz), 6.80 (2H, d, J = 4.0 Hz), 6.78 (1H, d, J = 5.9 Hz), 6.34 (1H, t, J = 2.3 Hz), 6.28 (2H, d, J = 2.3 Hz), 4.72 (1H, d, J = 3.7 Hz), 4.46 (1H, d, J = 2.7 Hz), 4.17 (3H, s), 4.01 (3H, s), 3.78 (3H, s), 3.76 (3H, s), 3.70 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 158.9, 158.0, 157.7, 154.1, 148.04, 142.0, 141.0, 137.9, 130.4, 129.4, 128.4, 128.1, 122.5, 122.0, 114.3, 113.7, 112.8, 109.6, 105.9, 98.25, 97.4, 77.4, 77.2, 77.0, 76.6, 61.1, 57.3, 56.3, 56.2, 55.4, 55.3 (2), 55.2; MS (EI) m/z 536 (M^+, 100), 505 (55), 488 (16); HRMS (EI) calcd for $C_{34}H_{32}O_6$ [M^+] 536.2199, found 536.2197.

Laetevirenol A (1). To a solution of *trans*-dihydroacephenanthrylene **23** (20 mg, 0.037 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added a solution of BBr_3 (745 μL, 0.75 mmol, 1 M in CH_2Cl_2). The reaction mixture was stirred at 25 °C for 24 h and quenched with MeOH. The resulting mixture was diluted with EtOAc (50 mL), washed with brine, and dried over $MgSO_4$. The solution was concentrated in vacuo and purified by silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford laetevirenol A (18 mg, 99%) as a yellow solid: mp 143−144 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.37 (1H, s), 8.93 (1H, d, J = 2.5 Hz), 8.44 (1H, s), 8.13 (1H, s), 8.09 (2H, s), 7.96 (1H, s), 7.64 (1H, d, J = 8.6 Hz), 7.17 (1H, d, J = 1.3 Hz), 7.03 (1H, dd, J = 8.5, 2.5 Hz), 6.89 (2H, d, J = 8.5 Hz), 6.79 (1H, s), 6.71 (2H, d, J = 8.5 Hz), 6.20 (1H, d, J = 2.1 Hz), 6.10 (2H, d, J = 2.3 Hz), 4.63 (1H, d, J = 3.0 Hz), 4.28 (1H, dd, J = 3.2, 1.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.5, 156.9, 156.6, 156.1, 152.5, 149.6, 142.6, 142.4, 137.5, 132.1, 129.9, 128.8, 128.1, 122.1, 120.0, 115.9, 115.3, 112.5, 111.7, 106.6, 104.9, 101.5, 62.0, 57.8; MS (EI) m/z 451 (M^+, 1), 167 (23), 149 (100); HRMS (EI) calcd for $C_{28}H_{19}O_6$ [M^+] 451.1182, found 451.1178.

3,5,7,11,13-Pentamethoxy-9-(4-methoxybenzyl)-9*H*-indeno[2,1-*l*]phenanthrene (24). To a solution of alcohol **17** (277 mg, 0.5 mmol) in toluene (10 mL) at room temperature was added TfOH (44 μL, 0.5 mmol). The reaction mixture was sealed and stirred at 120 °C for 18 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (3 × 100 mL). The extracts were washed with H_2O and brine and dried over $MgSO_4$. The mixture was concentrated in vacuo and purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford 9*H*-indeno[1,2-*l*]phenanthrene **24** (199 mg, 74%) as a white solid: mp 96−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (1H, d, J = 9.3 Hz), 9.19 (1H, d, J = 2.7 Hz), 7.21 (1H, dd, J = 9.3, 2.8 Hz), 7.14 (1H, d, J = 2.4 Hz), 6.94 (2H, d, J = 8.6 Hz), 6.75 (1H, d, J = 2.4 Hz), 6.72 (2H, d, J = 8.6 Hz), 6.54 (1H, d, J = 2.2 Hz), 6.27 (1H, d, J = 2.1 Hz), 4.43 (1H, dd, J = 9.0, 3.6 Hz), 4.13 (3H, s), 4.03 (3H, s), 4.02 (3H, s), 3.93 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.69−3.65 (1H, m), 2.64 (1H, dd, J = 13.9, 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 159.5, 158.4, 158.2, 157.2, 155.0, 152.7, 138.4, 137.2, 133.0, 132.4, 131.5, 130.6, 129.9, 123.8, 122.8, 115.3, 113.5, 113.4, 109.6, 103.0, 99.3, 98.1, 98.0, 56.4, 56.1, 55.5, 55.5, 55.4, 55.3, 49.9, 39.9; MS (EI) m/z 536 (M^+, 100), 505 (11), 428 (18); HRMS (EI) calcd for $C_{34}H_{32}O_6$ [M^+] 536.2199, found 536.2188.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for compounds **7**−**9**, **11**−**14**, **17**−**19**, **23**, **24**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: heojn@krict.re.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by the KRICT and Ministry of Knowledge Economy, Korea is gratefully acknowledged.

■ DEDICATION

This work is dedicated to Prof. William R. Roush on the occasion of his 60th birthday.

■ REFERENCES

(1) He, S.; Wu, B.; Pan, Y.; Jiang, L. *J. Org. Chem.* **2008**, *73*, 5233.

(2) (a) Adesanya, S. A.; Nia, R.; Martin, M.-T.; Boukamcha, N.; Montagnac, A.; Pais, M. *J. Nat. Prod.* **1999**, *62*, 1694. (b) Li, W.; Li, H.; Li, Y.; Hou, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609.

(3) (a) Tanaka, T.; Iinuma, M.; Murata, H. *Phytochemistry* **1998**, *48*, 1045. (b) Kim, H. J.; Saleem, M.; Seo, S. H.; Jin, C.; Lee, Y. S. *Planta Med.* **2005**, *71*, 973.

(4) (a) Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.-i.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932. (b) Lee, B. H.; Choi, Y. L.; Shin, S.; Heo, J.-N. *J. Org. Chem.* **2011**, *76*, 6611. (c) Yang, Y.; Philips, D.; Pan, S. *J. Org. Chem.* **2011**, *76*, 1902. (d) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450. (e) Bo, C.; Lu, J.-P.; Xie, X.-G.; She, X.-G.; Pan, X.-F. *Chin. J. Org. Chem.* **2006**, *26*, 1300.

(5) (a) Li, L.; Henry, G. E.; Seeram, N. P. *J. Agric. Food. Chem.* **2009**, *57*, 7282. (b) Ito, T.; Akao, Y.; Yi, H.; Ohguchi, K.; Matsumoto, K.; Tanaka, T.; Iinuma, M.; Nozawa, Y. *Carcinogenesis* **2003**, *24*, 1489. (c) Ohguchi, K.; Tanaka, T.; Ito, T.; Iinuma, M.; Matsumoto, K.; Akao, Y.; Nozawa, Y. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1587. (d) Ohyama, M.; Tanaka, T.; Ito, T.; Iinuma, M.; Bastow, K. F.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3057.

(6) Kim, H. J.; Chang, E, J.; Cho, S. H.; Chung, S. K.; Park, H. D.; Choi, S. W. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1990.

(7) Huang, K. S.; Lin, M.; Yu, L. N.; Kong, M. *Tetrahedron* **2000**, *56*, 1321.

(8) Dai, J. R.; Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 351.

(9) (a) Bala, A. E.; Kollmann, A.; Ducrot, P.-H.; Majira, A.; Kerhoas, L.; Delorme, R.; Einhorn, J. *Pestic. Sci.* **1999**, *55*, 218. (b) Sotheeswaran, S.; Pasupathy, V. *Phytochemistry* **1993**, *32*, 1083.

(10) (a) Choi, C. W.; Choi, Y. H.; Cha, M.-R.; Kim, Y. S.; Yon, G. H.; Hong, K. S.; Park, W.-K.; Kim, Y. H.; Ryu, S. Y. *Planta Med.* **2011**, *77*, 374. (b) Jang, M. H.; Piao, X. L.; Kim, J. M.; Kwon, S. W.; Park, J. H. *Phytother. Res.* **2008**, *22*, 544.

(11) (a) Snyder, S. A.; Gollner, A.; Chiriac, M. I. *Nature* **2011**, *474*, 461. (b) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186. (c) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753. (d) Snyder, S. A.; Wright, N. E.; Pflueger, J. J.; Breazzano, S. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 8629. (e) Snyder, S. A.; Thomas, S. B.; Mayer, A. C.; Breazzano, S. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 4080.

(12) (a) Nicolaou, K. C.; Wu, T. R.; Kang, Q.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3440. (b) Nicolaou, K. C.; Kang, Q.; Wu, T. R.; Lim, C. S.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 7540.

(13) For reviews, see: (a) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley: New York, 1973. (b) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 293−339.

(14) For representative recent examples of intramolecular Friedel−Crafts cyclization, see: (a) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9447. (b) Sun, B.-F.; Hong, R.; Kang, Y.-B.; Dong, L. *J. Am. Chem. Soc.* **2009**, *131*, 10384. (c) Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 5820. (d) Zhang, Z.-W.; Li, W.-D. Z. *Org. Lett.* **2010**, *12*, 1649.

(15) (a) Kim, Y. H.; Lee, H.; Kim, Y. J.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2008**, *73*, 495. (b) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett.* **2008**, *10*, 3543. (c) Choi, Y. L.; Yu, C.-M.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2009**, *74*, 3948. (d) Goh, Y.-H.; Kim, G.; Kim, B. T.; Heo, J.-N. *Heterocycles* **2010**, *80*, 669.
(16) Compound **12** is commercially available. It can also be readily prepared from the corresponding benzyl alcohol by following the literature procedure. See ref 11c.
(17) Molander, G. A.; Pack, S. K. *Tetrahedron* **2003**, *59*, 10581.
(18) Magnus, P.; Morris, J. C.; Lynch, V. *Synthesis* **1997**, 506.
(19) Suzuki, K.; Kobayashi, T.; Nishikawa, T.; Hori, Y.; Hagiwara, T. EP 1,167,372, 2002.
(20) The *E*/*Z* isomers of **7** were separated by preparative HPLC, and the relative stereochemistry was identified by NOE experiments. For details, see the Supporting Information.
(21) Other transition-metal-based Lewis acids such as $Bi(OTf)_3$, $Sc(OTf)_3$, AgOTf, and $Yb(OTf)_3$ proved less efficient.
(22) (a) Jeffrey, J. L.; Sarpong, R. *Tetrahedron Lett.* **2009**, *50*, 1969. (b) Levi, Z. U.; Tilley, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 11012. (c) Feng, X.; Wu, J.; Enkelmann, V.; Mullen, K. *Org. Lett.* **2006**, *8*, 1145.
(23) All attempts for global demethylation of **19** with BBr_3 or BCl_3 failed to afford the *cis*-laetevirenol A isomer.
(24) Compound **24** is highly unstable at ambient conditions and readily decomposed to a mixture of unknown compounds.
(25) (a) Ordwell, F. B. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Guthrie, J. P. *Can. J. Chem.* **2009**, *30*, 799.