

Construction of the ABC Ring System of Taxanes via Stereoselective One-Pot Three-Component Coupling and Intramolecular Alkylation of a Protected Cyanohydrin Ether

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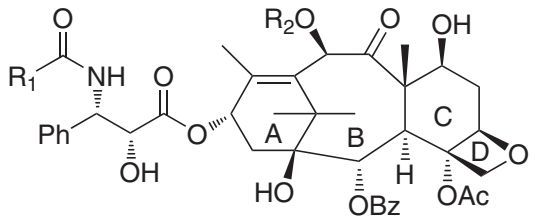
Construction of the ABC ring system of taxanes via one-pot three-component coupling and intramolecular alkylation is accomplished. The 1,4-addition of a protected cyanohydrin ether to 2-methyl-2-cyclohexenone and subsequent addition of the resulting enolate to formaldehyde proceeded stereoselectively to provide the AC ring in 90% yield. The stereoselective reduction of the 2-keto group was achieved by using hydroxy-directed hydride reduction with $LiAlH_4$. The intramolecular alkylation of the protected cyanohydrin ether furnished the ABC ring system of taxanes in 43% yield.

The taxanes paclitaxel (**1**) and docetaxel (**2**) are highly potent agents in the treatment of breast, ovarian, lung, head, and neck cancers (Figure 1).[1] Inspired by the potent biological activity, in addition to the synthetic challenges offered by the structure,[2–7] our group has focused on the total synthesis of this natural product. We have already reported an efficient method for the construction of A, B, and C rings.[8–11] In addition, we have also reported a formal total synthesis of paclitaxel (**1**) via the stereoselective coupling of the highly functionalized A and C rings and the intramolecular alkylation of the protected cyanohydrin ether.[12] However, the preparation of the highly functionalized C ring was laborious in this case. Recently, we have reported the stereoselective one-pot three-component coupling[13–17] of protected cyanohydrin ether **8** with 2-methyl-2-cyclohexenone (**7**), and formaldehyde to provide the desired AC ring system of taxanes in high yield (Scheme 1).[18] Here we wish to report the construction of the ABC ring system of taxanes via the stereoselective one-pot three-component coupling and the intramolecular cyclization of the protected cyanohydrin ether.

Our synthetic strategy to construct the ABC ring system of taxanes is shown in Scheme 1. The intramolecular alkylation of the protected cyanohydrin ether **4** is the crucial step in the construction of the highly strained 8-membered ring. We planned to introduce the protected cyanohydrin ether group at the 10-position via the oxidation of the $\Delta^{10,(11)}$ double-bond of the diene **5**. The protected tetraol **5** could be obtained from **6** by stereoselective reductions of the 7-keto group[18] and the 2-keto group which is derived from the protected cyanohydrin ether group, followed by the stereoselective oxidation of the $\Delta^{1,(14)}$ double-bond. The second key step is the stereoselective one-pot three-component coupling of the protected cyanohydrin ether **8** with 2-methyl-2-cyclohexenone (**7**) and formaldehyde.[18] The coupling reaction could introduce the *trans*-stereochemistry between C(3) H and C(8) methyl. The triene **8** should be readily accessible from the A ring **9**.[19]



R_1 = Ph, R_2 = Ac: Paclitaxel (1)
R_1 = O*t*-Bu, R_2= H: Docetaxel (2)

Figure 1. Structures of paclitaxel and docetaxel.

Treatment of the chloronitrile **9**[19] with DBU afforded triene **10** (Scheme 2). Reduction of nitrile **10** to the corresponding aldehyde and subsequent formation of a protected cyanohydrin afforded the desired compound **8** in 95% yield from **9**. The key reaction, stereoselective one-pot three-component coupling, was carried out to provide the desired coupling product **6** in 90% yield. Stereoselective reduction of the ketone at the 7-position in **6**, followed by conversion of the cyanohydrin ether at the 2-position into the corresponding ketone provided **12** as a single diastereomer.[18] The relative stereochemistry at the 3-, 4-, 7-, and 8-positions was determined to be the desired configuration based on the NOE observation of benzylidene acetal **13** derived from the diol **12** (Scheme 3).[18]

We prepared the ketone **14** to examine the effect of a protecting group at the 9-OH group on the stereoselective reduction of the 2-keto group (Scheme 3). Several reducing reagents were examined in the reduction of ketones **13** and **14** (Table 1). Ketone **13**, containing benzylidene acetal protection on the 7-OH and 9-OH groups, was reduced with $LiAlH_4$ (Entry 1) or $LiBH_4$ (Entry 4) to afford alcohol **15**β, whereas no reaction occurred with $NaBH_4$ (Entry 2) or $Zn(BH_4)_2$ (Entry 3). The stereochemistry of the 2-OH group was speculated to be the undesired β-configuration based on the coupling constant

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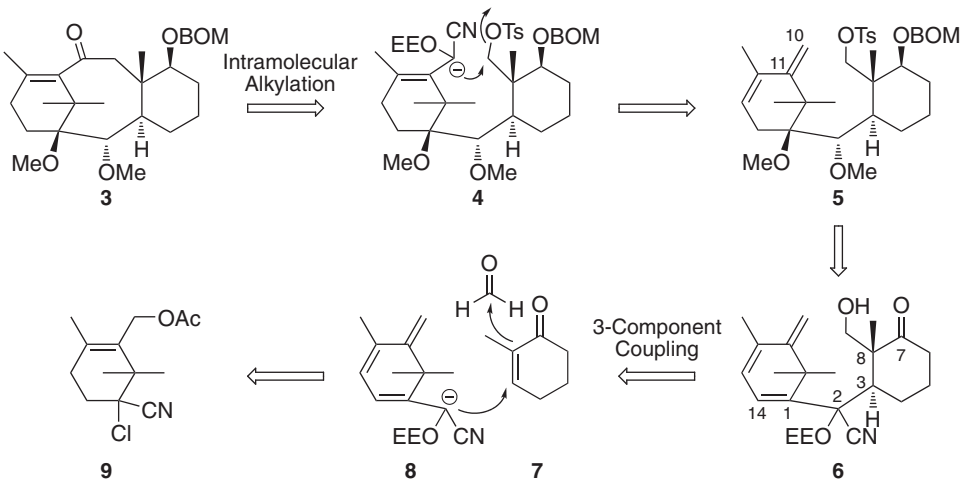
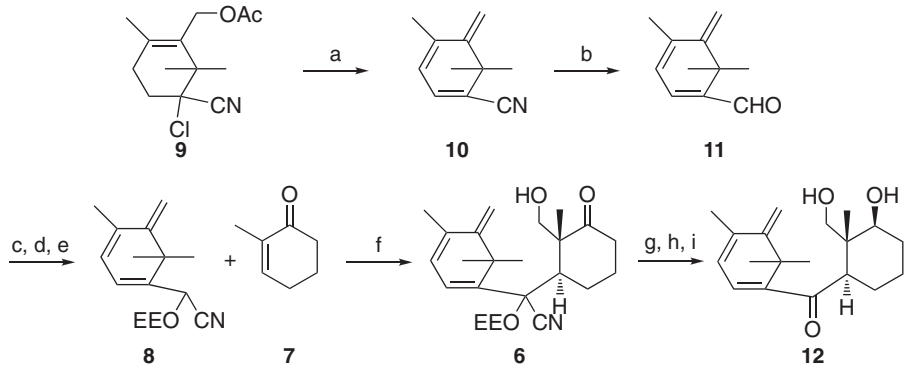
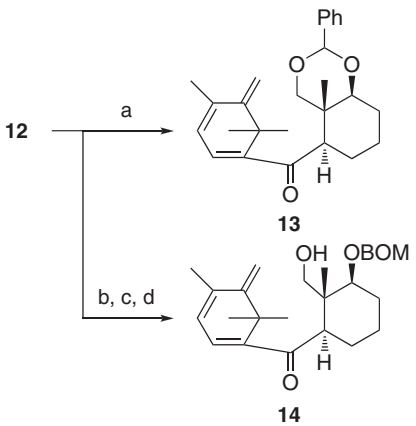


Scheme 1. Synthetic strategy for the ABC ring system of taxanes.



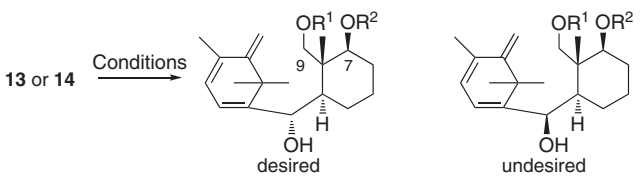
Scheme 2. Preparation of the AC ring **12**. (a) DBU, benzene, reflux, quant; (b) *i*-Bu_2AlH, toluene, −78 °C, quant; (c) TMSCN, KCN·DC-18-Cr-6; (d) 1 M HCl, THF; (e) EVE, CSA, CH_2Cl_2, 0 °C, 3 steps 95%; (f) *i*-Pr_2NLi, THF then HCHO, −78 °C, 90%; (g) $NaBH_4$, MeOH; (h) $CuSO_4$, $MeOH/H_2O$; (i) 1 M NaOH aq. Et_2O, 3 steps 61%.



Scheme 3. Preparation of ketones **13** and **14**. (a) PhCH-$(OMe)_2$, CSA, CH_2Cl_2, 52%; (b) TBSCl, imidazole, CH_2Cl_2; (c) BOMCl, *i*-Pr_2NEt, CH_2Cl_2; (d) TBAF, THF, 3 steps 47%.

(9.9 Hz) of H2 and H3. Calculation of coupling constants by Carplus equation based on conformational analysis using MM2 (MacroModel 6.0, Monte Carlo) suggested $J_{2,3} = 0.5$ Hz for **15α** and $J_{2,3} = 10.0$ Hz for **15β**. On the other hand, the reduction of ketone **14**, containing a free hydroxy group at the

Table 1. Reduction of the Ketones **13** and **14** with Several Kinds of Reducing Reagents



15α: $R^1 = R^2$ = -CH(Ph)- **15β**: $R^1 = R^2$ = -CH(Ph)-
16α: R^1 = H, R^2 = BOM **16β**: R^1 = H, R^2 = BOM

Entry	Substrate	Reagent	Solvent	Temperature /°C	Product (yield/%)
1	**13**	$LiAlH_4$	Et_2O	−78	**15β** (64)
2	**13**	$NaBH_4$	MeOH	0	n.r.
3	**13**	$Zn(BH_4)_2$	Et_2O	−78 to 0	n.r.
4	**13**	$LiBH_4$	Et_2O	−78 to 0	**15β**
5	**14**	$LiAlH_4$	Et_2O	−78	**16α** (59)
6	**14**	$Zn(BH_4)_2$	Et_2O	−78 to 0	n.r.
7	**14**	$LiBH_4$	Et_2O	−78 to 0	decomposed

9-position, afforded the desired isomer, **16α** (Entry 5). It is conceivable that hydride approached from the sterically less hindered Si face in the case of ketone **13** containing protection on the 9-OH group (Figure 2). On the other hand, hydroxy-

directed hydride reduction from the Re-face would take place in the case of ketone **14** containing a free hydroxy group at the 9-position.

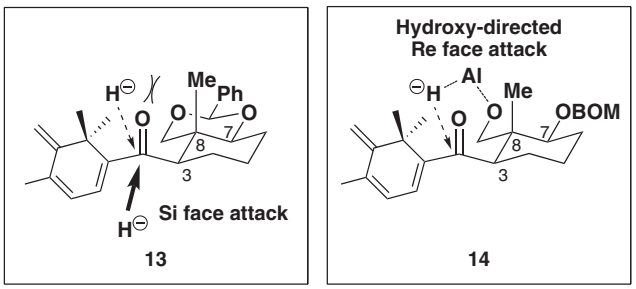
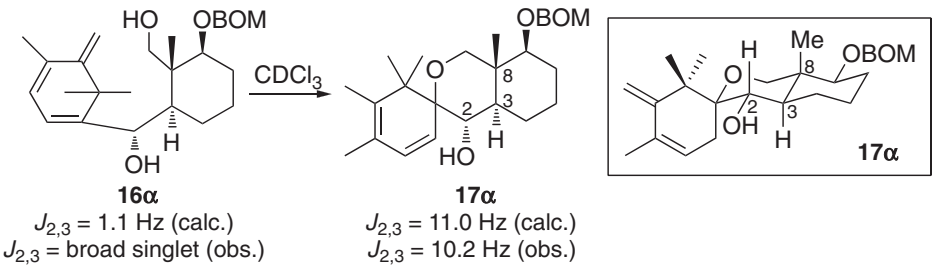


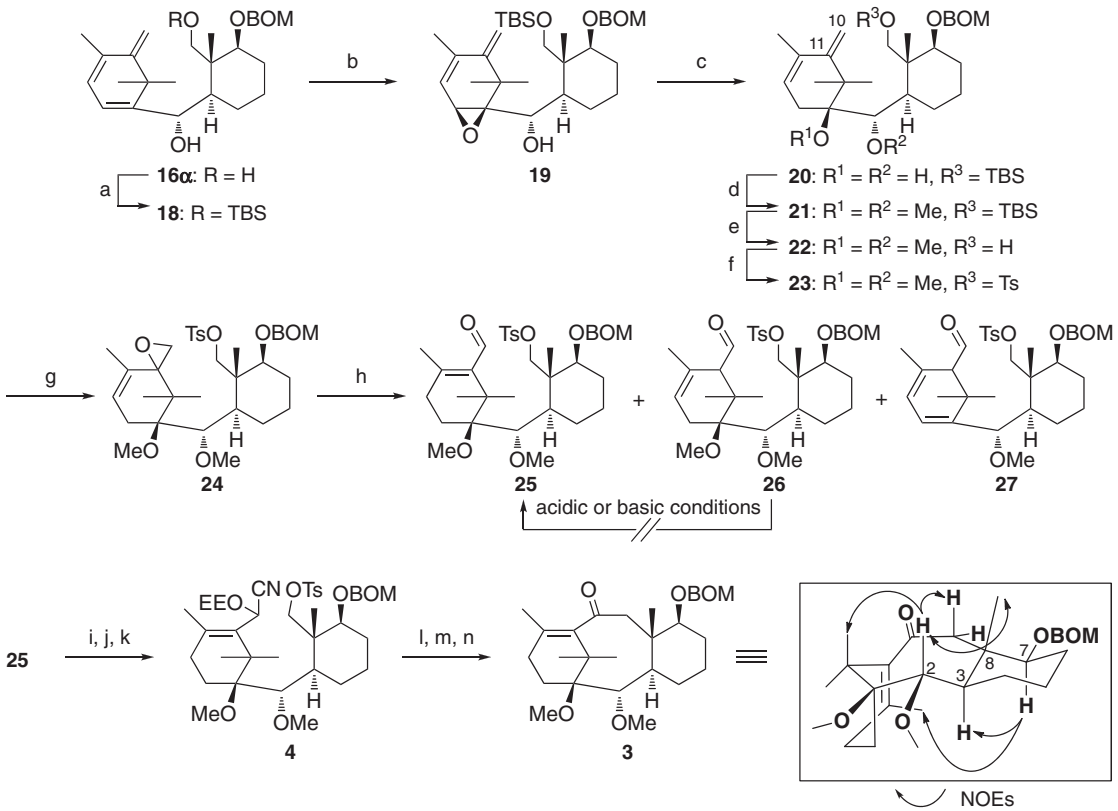
Figure 2. Proposed mechanism in the stereoselective reduction of the ketones **13** and **14**.

Unexpectedly, intramolecular etherification of the alcohol **16α** occurred in $CDCl_3$ (Scheme 4). Stereochemistry of the 2-OH group was speculated to be desired α-configuration based on the coupling constant (10.2 Hz) of H2 and H3. Calculation of coupling constants by Carplus equation based on conformational analysis using MM2 (MacroModel 6.0, Monte Carlo) suggested $J_{2,3} = 1.1$ Hz for **16α** and $J_{2,3} = 11.0$ Hz for **17α**. The observed J values were small for **16α** and 10.2 Hz for **17α**. These comparisons also supported the above speculations.

Construction of the ABC ring **3** was performed as follows (Scheme 5). Protection of the primary hydroxy group in **16α** with a TBS group afforded the corresponding silyl ether **18**. Hydroxy-directed stereoselective epoxidation, regioselective ring opening of the epoxide with $LiAlH_4$,[12] protection of diol **20** with methyl groups, followed by conversion of the TBS group to a Ts group provided **23**. The epoxidation of $\Delta^{10,(11)}$



Scheme 4. Stereochemical assignment of the 2-OH group in **17α**.



Scheme 5. Construction of the ABC ring **3**. (a) TBSCl, imidazole, CH_2Cl_2, quant; (b) $VO(acac)_2$, TBHP, benzene, 4 °C; (c) $LiAlH_4$, Et_2O, 0 °C; (d) NaH, MeI, THF; (e) TBAF, THF; (f) TsCl, DMAP, Δ, 5 steps 31%; (g) dimethyldioxirane, CH_2Cl_2, 72%; (h) *p*-TsOH, benzene, 75% (**25**:**26**:**27** = 4:3:3); (i) TMSCN, KCN•DC-18-Cr-6; (j) HCl, THF; (k) EVE, CSA, CH_2Cl_2, 0 °C, 3 steps 83%; (l) $LiN(TMS)_2$ dioxane, Δ, 43%; (m) CSA, MeOH; (n) NaOH, Et_2O, 2 steps 42%.

double-bond and subsequent treatment of the diene monoepoxide with *p*-TsOH afforded the desired enal **25** with undesired aldehydes **26** and **27** in 75% combined yield (**25**:**26**:**27** = 4:3:3).[20–22] The β,γ-unsaturated aldehyde **26** could not be converted to the desired enal **25** in either acidic (CSA in MeOH) or basic (DBU in CH_2Cl_2) conditions. The enal **25** was converted to the protected cyanohydrin ether **4**. The crucial step, the intramolecular alkylation of the protected cyanohydrin ether was carried out.[12] Treatment of **4** with $LiN(TMS)_2$ in refluxing dioxane for 7 h afforded the desired cyclization product in 43% yield. Hydrolysis of the cyanohydrin furnished the desired ABC ring **3**. The stereochemistry of compound **3** was confirmed by NOE experiments (Scheme 5).

In conclusion, we developed an efficient synthetic route for **3**. One-pot stereoselective three-component coupling of the protected cyanohydrin ether **8** with 2-methyl-2-cyclohexenone (**7**) and formaldehyde afforded the desired coupling product **6** in 90% yield. The stereoselective reduction of the 2-keto group was achieved by hydroxy-directed hydride reduction with $LiAlH_4$. The crucial intramolecular cyclization of the protected cyanohydrin ether **4** afforded the desired ABC ring **3** in 43% yield. This synthetic strategy allowed us to construct the ABC ring system of taxanes from structurally simple A and C rings.

Experimental

General Procedures. ^{1}H NMR spectra were recorded on a JEOL Model EX-270 (270 MHz) instrument in the indicated solvent. Chemical shifts were recorded in parts per million (ppm) relative to Me_4Si (0.0 ppm) or chloroform (7.26 ppm) as an internal standard. NMR multiplicities were reported using the following abbreviations. s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, *J*: coupling constant in Hertz. ^{13}C NMR spectra were recorded on a JEOL Model EX-270 (67.8 MHz). Chemical shifts were recorded in a part per million (ppm) relative to chloroform (77.1 ppm) as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum One. Only the strongest and/or structurally important signals were reported as the IR data given in cm^{-1}. The reactions were monitored by thin layer chromatography (TLC) carried out on Merck precoated TLC plates (60F-254) with indicator. Visualization of the spots was UV-light and 5% *p*-anisaldehyde/sulfuric acid/ethanol solution, phosphomolybdic acid/ethanol solution, ceric sulfate/water solution or iodine. Column chromatography separations were performed using silica gel (Merk silicagel). Flash column chromatography separations were performed using silica gel (KANTO, Silica Gel 60N, spherical, neutral, 40–100 μm). ESI-TOF mass spectra were measured with P. E. Biosystems TK-3500 Biospectrometry Workstation. All reactions were carried out under an argon atmosphere in dried glassware unless otherwise noted. Dry THF, dry hexane, dry benzene, dry Et_2O, and dry dioxane were distilled from sodium wire containing a catalytic amount of benzophenone, dry CH_2Cl_2 was distilled from P_2O_5. Dry *i*-Pr_2NH, dry pyridine and dry $(TMS)_2NH$ were distilled from CaH_2. Dry acetone was distilled from $CaSO_4$ (DRIERITE™). Dry MeOH was distilled from $Mg(OMe)_2$. All reagents were purchased at highest commercial quality and used as received unless otherwise noted.

Nitrile 10. To a solution of chloronitrile **9** (19.6 g, 76.7 mmol) in benzene (100 mL) was added DBU (23.0 mL, 153 mmol) at room temperature under an argon atmosphere. The reaction mixture was heated to reflux. After being stirred under reflux for 10 h, the reaction mixture was poured into water and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 10% Et_2O in hexane) to give the nitrile **10** (18.6 g, 76.7 mmol, quant) as a pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.59 (d, $J = 6.3$ Hz, 1H), 5.85 (d, $J = 6.3$ Hz, 1H), 5.38 (brs, 1H), 5.32 (d, $J = 2.0$ Hz, 1H), 1.98 (s, 3H), 1.35 (s, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 151.2, 139.0, 135.5, 119.8, 119.7, 118.9, 114.0, 38.3, 30.6, 20.0. IR (neat): 2966, 2202, 1560, 1459, 1408, 1361, 897, 840 cm^{-1}.

Aldehyde 11. To a solution of nitrile **10** (12.2 g, 76.7 mmol) in toluene (70 mL) was added dropwise *i*-Bu_2AlH (100 mL, 1.01 M in toluene, 100 mmol) at −78 °C. After being stirred at the same temperature for 3 h, the reaction mixture was carefully quenched with saturated aqueous Na_2SO_4 solution and 1 M HCl aqueous solution. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 10% Et_2O in hexane) to give the aldehyde **11** (16.0 g, 76.7 mmol, quant) as a pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 9.32 (s, 1H), 6.67 (d, $J =$ 6.3 Hz, 1H), 6.05 (d, $J = 6.3$ Hz, 1H), 5.33 (brs, 2H), 2.01 (s, 3H), 1.43 (s, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 192.3, 154.7, 146.0, 143.1, 141.7, 120.9, 112.5, 38.7, 29.9, 20.3. IR (neat): 2962, 2706, 1674, 1559, 1233, 1131 cm^{-1}.

Protected Cyanohydrin 8. To the enal **11** (16.0 g, 76.7 mmol) was added TMSCN (12.5 mL, 92.1 mmol) and a catalytic amount of DC-18-crown-6 KCN complex at 0 °C under an argon atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was diluted with THF (20 mL) and 1 M HCl was carefully added at 0 °C (Caution: HCN is generated). After being stirred at the same temperature for 30 min, the reaction mixture was diluted with Et_2O and washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a mixture of the crude cyanohydrin and CSA (178 mg, 0.77 mmol) in CH_2Cl_2 (20 mL) was added dropwise ethyl vinyl ether (8.80 mL, 92.1 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 10% Et_2O in hexane) to give the protected cyanohydrin **8** (9.0 g, 3 steps 95%) as a yellow oil.

Three-Component Coupling of Protected Cyanohydrin Ether 8 with 2-Methyl-2-cyclohexenone (7) and Formaldehyde. To a solution of *i*-Pr_2NH (0.98 mL, 7.5 mmol) in dry THF (40 mL) was added *n*-BuLi (4.50 mL, 1.65 M in hexane, 7.40 mmol) at 0 °C under argon. After being stirred at 0 °C for

1 h, to the mixture was added dropwise a solution of the protected cyanohydrin **8** (1.31 g, 5.00 mmol, azeotropically dried with toluene) in dry THF (10 mL) at −78 °C over 30 min. After being stirred at −78 °C for 2 h, a solution of 2-methyl-2-cyclohexenone (**7**) (500 mg, 4.50 mmol) in dry THF (10 mL) was added dropwise to the reaction mixture at −78 °C over 10 min. After stirring at −78 °C for 30 min, formaldehyde (50 mL, ca. 0.1 M in THF, 5.0 mmol)[23] was added to the reaction mixture at −78 °C. Then the mixture was poured into ice-cooled saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 70% EtOAc in hexane) to give the coupling product **6** (1.65 g, 90%) as a colorless oil.

Trienone 12. To a solution of the ketone **6** (1.65 g, 4.10 mmol) in MeOH (20 mL) was added $NaBH_4$ (500 mg, 12.5 mmol) at 0 °C under argon. After being stirred at room temperature for 1 h, the reaction mixture was poured into aqueous 1 M HCl solution and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the crude protected cyanohydrin in MeOH (30 mL) and H_2O (10 mL) was added a catalytic amount of copper(II) sulfate. After being stirred at 40–50 °C for 2 h, the reaction mixture was poured into brine and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the crude cyanohydrin in Et_2O (10 mL) was added 0.5 M NaOH aqueous solution at 0 °C. After being stirred at room temperature for 30 min, the mixture was poured into brine and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 70% EtOAc in hexane) to give the trienone **12** (760 mg, 3 steps 61%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.83 (d, $J = 6.3$ Hz, 1H), 5.88 (d, $J = 6.3$ Hz, 1H), 5.23 (s, 1H), 5.20 (s, 1H), 3.65 (dd, $J = 3.6$, 10.2 Hz, 1H), 3.57 (d, $J = 10.9$ Hz, 1H), 3.36 (d, $J = 10.9$ Hz, 1H), 3.04 (dd, $J = 3.6$, 11.2 Hz, 1H), 1.97 (s, 3H), 1.80–1.20 (m, 6H), 1.42 (s, 3H), 1.36 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 203.6, 155.6, 146.8, 140.1, 131.6, 120.4, 111.4, 74.9, 69.6, 47.2, 44.0, 43.0, 41.0, 30.1, 29.9, 28.2, 25.0, 24.8, 23.6, 22.6, 20.3. IR (neat): 3384, 2928, 2862, 1711, 1648, 1558, 1444, 1379, 1237, 1129, 1053 cm^{-1}. HRMS (ESI-TOF): calcd for $[C_{19}H_{29}O_3 + H]^+$ 305.2111, found: 305.2110.

Benzylidene Acetal 13. To a mixture of diol **12** (750 mg, 2.46 mmol) and a catalytic amount of CSA in CH_2Cl_2 (10 mL) was added benzaldehyde dimethylacetal (0.44 mL, 3.0 mmol) at 0 °C under argon. After being stirred at room temperature for 24 h, the mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 5% EtOAc in hexane) to give the benzylidene acetal **13** (500 mg, 52%) as a colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ 7.58–7.27 (m, 5H), 6.71 (d, $J = 6.3$ Hz, 1H), 5.90 (d, $J = 6.3$ Hz, 1H), 5.54 (s, 1H), 5.24 (d, $J = 1.3$ Hz, 1H), 5.22 (s, 1H), 3.87 (d, $J = 10.9$ Hz, 1H), 3.65 (d, $J = 10.9$ Hz, 1H), 3.61 (dd, $J = 4.6$, 10.9 Hz, 1H), 2.92 (dd, $J = 3.3$, 12.2 Hz, 1H), 2.00 (d, $J = 1.3$ Hz, 3H), 2.00–1.20 (m, 6H), 1.44 (s, 3H), 1.38 (s, 6H), 1.26 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 201.7, 155.2, 146.6, 140.2, 138.4, 131.2, 128.9, 128.3, 126.2, 120.0, 111.6, 102.6, 84.3, 78.9, 48.8, 41.1, 37.7, 31.5, 26.3, 26.0, 23.8, 23.1, 20.2, 11.8. IR (neat): 3020, 2949, 2862, 1655, 1560 cm^{-1}.

Alcohol 14. To a mixture of diol **12** (624 mg, 2.05 mmol) and imidazole (600 mg, 8.81 mmol) in dry CH_2Cl_2 (20 mL) was added TBSCl (620 mg, 4.11 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo and passed through a short pad of silica gel (5% EtOAc in hexane). After removal of the solvent, the residue was used for the next reaction without further purification. To a solution of alcohol and *i*-Pr_2NEt (3.0 mL, 17.7 mmol) in dry CH_2Cl_2 (20 mL) was added BOMCl (1.2 mL, 8.7 mmol) at room temperature under an argon atmosphere. After being stirred at 40 °C for 17 h, the reaction was quenched by addition of MeOH (1.40 mL, 34.5 mmol). The mixture was poured into ice-cooled saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo and passed through a short pad of silica gel (3% EtOAc in hexane). The residue was used for the next reaction without further purification.

To a solution of the TBS ether in dry THF (30 mL) was added TBAF$\cdot n$H$_2$O (4.2 g, 16.1 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 22 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 20% EtOAc in hexane) to give the alcohol **14** (408 mg, 47%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.36–7.29 (m, 5H), 7.03 (d, $J = 6.4$ Hz, 1H), 5.91 (d, $J = 6.4$ Hz, 1H), 5.23 (d, $J = 1.7$ Hz, 1H), 5.20 (brs, 1H), 4.78 (dd, $J = 6.8$, 15.3 Hz, 2H), 4.70 (d, $J = 12.1$ Hz, 1H), 4.58 (d, $J = 12.1$ Hz, 1H), 3.62 (dd, $J = 4.0$, 11.9 Hz, 1H), 3.61 (d, $J = 11.9$ Hz, 1H), 3.20 (d, $J = 11.9$ Hz, 1H), 3.27–3.15 (m, 1H), 1.97 (s, 3H), 1.57 (s, 3H), 1.44 (s, 3H), 1.81–1.20 (m, 6H), 0.90 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 203.4, 155.8, 146.9, 139.6, 137.4, 132.0, 128.7, 128.0, 127.9, 120.8, 111.1, 94.2, 78.8, 70.4, 65.6, 46.7, 43.6, 40.9, 35.5, 29.3, 29.1, 26.8, 25.2, 23.7, 20.3, 11.1. IR (neat): 3510, 3033, 2941, 1652, 1563, 1497, 1471, 1455 cm^{-1}.

Allylic Alcohol 15β. To a solution of ketone **13** (52.5 mg, 0.134 mmol) in dry Et_2O (3.0 mL) was added $LiAlH_4$ (10.2 mg, 0.270 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 30 min, the reaction was quenched by slow addition of a saturated aqueous solution of Na_2SO_4. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 10% EtOAc in hexane) to give the

allylic alcohol **15β** (33.8 mg, 64%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.60–7.30 (m, 5H), 6.01 (d, $J = 6.3$ Hz, 1H), 5.81 (d, $J = 6.3$ Hz, 1H), 5.58 (s, 1H), 5.18 (s, 1H), 5.15 (d, $J = 1.7$ Hz, 1H), 4.68 (d, $J = 11.6$ Hz, 1H), 4.20 (d, $J = 9.9$ Hz, 1H), 3.77 (d, $J = 11.6$ Hz, 1H), 3.61 (dd, $J = 4.3$, 10.9 Hz, 1H), 1.92 (s, 3H), 1.80–1.20 (m, 7H), 1.34 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 155.0, 150.1, 139.0, 132.3, 128.9, 128.4, 126.4, 121.1, 119.0, 110.0, 102.3, 84.7, 80.0, 47.3, 40.6, 38.6, 30.2, 27.0, 26.9, 25.6, 23.7, 19.8, 11.6. IR (neat): 3481, 2942, 2861, 1584, 1456 cm^{-1}.

Diol 16α. To a solution of ketone **14** (500 mg, 1.18 mmol) in dry Et_2O (2.0 mL) was added $LiAlH_4$ (100 mL, ca. 0.1 M in Et_2O, 10 mmol) at −78 °C under an argon atmosphere. After being stirred at the same temperature for 5 h, the reaction was quenched by slow addition of 1 M NaOH aqueous solution. The mixture was diluted with saturated aqueous potassium sodium tartrate and EtOAc. After being stirred at room temperature for 1 h, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was used for the next reaction without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.36–7.29 (m, 5H), 6.02 (d, $J = 6.1$ Hz, 1H), 5.83 (d, $J = 6.1$ Hz, 1H), 5.13 (d, $J = 1.7$ Hz, 1H), 5.11 (s, 1H), 4.81 (d, $J = 6.6$ Hz, 1H), 4.80–4.75 (brs, 1H), 4.75 (d, $J = 6.6$ Hz, 1H), 4.72 (d, $J = 12.1$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 3.76 (d, $J = 11.7$ Hz, 1H), 3.70 (d, $J = 11.7$ Hz, 1H), 3.56 (dd, $J = 3.8$, 11.4 Hz, 1H), 1.93 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.80–1.20 (m, 7H), 0.96 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 156.3, 150.5, 137.5, 131.6, 128.7, 128.0, 127.9, 121.4, 119.4, 109.0, 94.1, 80.1, 70.5, 69.1, 65.0, 44.0, 42.0, 40.6, 28.4, 27.6, 27.0, 23.4, 20.0, 18.2, 12.5. IR (neat): 3469, 2941, 2872, 1596, 1454, 1383 cm^{-1}.

Tricyclic Ether 17α. The alcohol **16α** (1.0 mg, 2.3 μmol) was dissolved in $CDCl_3$ (3 mL, pH ca. 4.0). After 30 min, formation of ether **17α** was observed by NMR. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 6.00 (d, $J = 9.9$ Hz, 1H), 5.90 (d, $J = 9.9$ Hz, 1H), 4.78 (d, $J = 6.9$ Hz, 1H), 4.63 (d, $J = 6.9$ Hz, 1H), 4.58 (dd, $J = 11.9$, 15.8 Hz, 2H), 3.83 (d, $J = 10.9$ Hz, 1H), 3.66 (d, $J = 11.4$ Hz, 1H), 3.54 (d, $J = 11.4$ Hz, 1H), 3.32 (dd, $J = 4.13$, 11.4 Hz, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 1.83–0.80 (m, 7H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 138.7, 137.9, 132.5, 128.5, 127.9, 127.7, 123.4, 120.0, 92.8, 80.4, 79.9, 70.4, 69.7, 69.5, 44.3, 42.9, 40.8, 29.8, 26.4, 23.7, 21.5, 20.7, 20.1, 18.1, 13.4, 11.1. IR (neat): 3557, 3032, 2933, 2863, 1740, 1596, 1497 cm^{-1}.

TBS Ether 18. To a mixture of diol **16α** (172 mg, 0.403 mmol) and imidazole (165 mg, 2.42 mmol) in dry CH_2Cl_2 (6 mL) was added TBSCl (182 mg, 1.21 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 7% EtOAc in hexane) to give the TBS ether **18** (218 mg, quant) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 6.06 (d, $J = 5.9$ Hz, 1H), 5.85 (d, $J = 5.9$ Hz, 1H), 5.10 (s, 2H), 4.81 (brs, 1H), 4.87 (d, $J = 6.9$ Hz, 1H), 4.81 (d, $J = 6.9$ Hz, 1H), 4.71 (d, $J = 11.7$ Hz, 1H), 4.54 (d, $J = 11.7$ Hz, 1H), 3.64 (s, 2H), 3.56 (dd, $J = 3.5$, 8.7 Hz, 1H), 1.94 (s, 3H), 1.80–1.20 (m, 7H), 1.21 (s, 3H), 1.19 (s, 3H), 1.07 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 156.6, 149.4, 138.0, 131.2, 128.5, 127.9, 127.7, 121.7, 119.8, 108.5, 95.5, 80.0, 70.5, 70.0, 69.7, 66.4, 44.1, 41.6, 40.7, 29.3, 27.8, 27.5, 26.3, 26.2, 26.1, 25.7, 22.0, 20.0, 19.0, 18.4, −5.31, −5.34. IR (neat): 3460, 3032, 2930, 1584, 1498, 1472, 1387, 1255, 1149 cm^{-1}.

Epoxide 19. To a mixture of allylic alcohol **18** (101 mg, 0.190 mmol) and TBHP (0.12 mL, 5 M in decane, 0.60 mmol) in dry benzene (3.0 mL) was added vanadyl acetoacetonate (3.1 mg, 9.0 μmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 2 h, the reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 5% EtOAc in hexane) to give the epoxide **19** (97 mg, 93%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 5.82 (brs, 1H), 5.08 (d, $J = 1.7$ Hz, 1H), 5.03 (brs, 1H), 4.85 (d, $J = 6.9$ Hz, 1H), 4.81 (d, $J = 6.9$ Hz, 1H), 4.74 (d, $J = 11.9$ Hz, 1H), 4.45 (d, $J = 11.9$ Hz, 1H), 4.43 (brs, 1H), 3.71 (d, $J = 9.9$ Hz, 1H), 3.60 (d, $J = 9.9$ Hz, 1H), 3.53 (dd, $J = 4.3$, 11.7 Hz, 1H), 3.48 (d, $J = 4.3$ Hz, 1H), 2.10–1.20 (m, 7H), 1.88 (s, 3H), 1.55 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 0.92 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 153.3, 139.9, 138.2, 128.5, 127.9, 119.5, 108.8, 95.5, 81.0, 69.4, 67.4, 66.7, 64.1, 53.8, 46.3, 44.4, 40.8, 39.1, 31.1, 28.6, 26.8, 26.4, 21.9, 21.0, 20.5, 18.4, 14.2, 12.4, 11.6, −5.2, −5.4. IR (neat): 3509, 3033, 2930, 1679, 1648, 1472, 1389, 1362, 1254 cm^{-1}.

Diol 20. To a solution of epoxide **19** (202 mg, 0.360 mmol, azeotropically dried with toluene) in dry Et_2O (1.0 mL) was added $LiAlH_4$ (16 mL, 0.1 M in Et_2O, 1.6 mmol) at −78 °C under an argon atmosphere. After being stirred at 0 °C for 1.5 h, the reaction was quenched by addition of 1 M NaOH aqueous solution. The mixture was diluted with saturated aqueous potassium sodium tartrate and chloroform. The mixture was stirred at room temperature for 2 h and the aqueous layer was extracted with chloroform. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue (270 mg) was purified by flash chromatography to give the diol **20** (58.7 mg, 50%) as a white solid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 5.48 (brs, 1H), 5.13 (s, 1H), 5.11 (s, 1H), 4.88 (d, $J = 6.9$ Hz, 1H), 4.78 (d, $J = 6.9$ Hz, 1H), 4.69 (d, $J = 11.9$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 3.91 (d, $J = 5.9$ Hz, 1H), 3.60–3.50 (m, 3H), 2.40–1.40 (m, 9H), 1.84 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 156.2, 137.9, 132.3, 128.5, 128.5, 127.9, 127.8, 127.7, 127.6, 123.1, 110.0, 95.1, 79.9, 69.7, 69.4, 68.9, 65.9, 45.1, 43.5, 39.3, 34.3, 31.7, 26.1, 22.7, 20.8, 20.3, 18.3, 14.2, −5.3, −5.5. IR (neat): 3509, 2954, 2930, 2883, 2858, 1679, 1610, 1472, 1388, 1362, 1254, 1149, 1107 cm^{-1}.

Dimethyl Ether 21. To a suspension of sodium hydride (101 mg, 55% dispersion in mineral oil, 4.20 mmol), washed with dry hexane (5 mL × 3 times) in dry THF (0.5 mL), was

added dropwise a solution of the diol **20** (58.7 mg, 0.110 mmol) in dry THF (3.0 mL) at 0 °C under an argon atmosphere. After being stirred for 30 min, methyl iodide (0.69 mL, 1.1 mmol) was added to the mixture at 0 °C. After being stirred at room temperature for 7 h, the reaction was quenched by addition of MeOH. The mixture was poured into saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the dimethyl ether **21** (50.8 mg, 79%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 5.52 (brs, 1H), 5.01 (s, 1H), 4.93 (s, 1H), 4.81 (d, $J = 6.9$ Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.52 (d, $J = 11.9$ Hz, 1H), 3.89 (brs, 1H), 3.65 (d, $J = 10.2$ Hz, 1H), 3.48 (d, $J = 10.2$ Hz, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 3.20–3.10 (m, 1H), 2.70–2.40 (m, 2H), 2.00–1.20 (m, 7H), 1.83 (s, 3H), 1.24 (s, 3H), 1.08 (s, 3H), 0.92 (s, 9H), 0.89 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 154.8, 138.2, 132.0, 127.8, 124.3, 106.5, 94.6, 85.2, 83.4, 81.0, 69.6, 67.2, 60.6, 53.2, 44.4, 44.2, 31.7, 28.3, 26.3, 24.2, 23.3, 22.7, 18.5, 14.2, 10.9, −5.1, −5.4. IR (neat): 2931, 1605, 1472, 1377, 1255, 1102 cm^{-1}.

Alcohol 22. To a solution of the TBS ether **21** (24.8 mg, 40.0 μmol) in THF (1.0 mL) was added TBAF$\cdot n$H$_2$O (110 mg, 0.400 mmol) at room temperature under an argon atmosphere. After being stirred at 50 °C for 10 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the alcohol **22** (17.4 mg, 87%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 5.59 (brs, 1H), 5.04 (brs, 1H), 4.95 (brs, 1H), 4.82 (d, $J = 6.6$ Hz, 1H), 4.78 (d, $J = 6.6$ Hz, 1H), 4.63 (s, 2H), 3.65–3.25 (m, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.24 (brs, 1H), 2.80–2.60 (m, 1H), 2.50–2.30 (m, 1H), 2.10–1.40 (m, 7H), 1.84 (d, $J = 1.3$ Hz, 3H), 1.21 (s, 3H), 1.13 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 154.9, 137.9, 132.2, 128.5, 128.0, 127.8, 124.1, 106.8, 94.0, 85.2, 83.6, 79.8, 69.9, 65.4, 61.0, 53.2, 44.3, 43.8, 40.6, 31.7, 27.0, 23.9, 23.3, 22.7, 20.3, 14.2, 11.3. IR (neat): 3494, 2942, 2828, 2244, 1605, 1471, 1455, 1380 cm^{-1}.

Tosylate 23. To a mixture of alcohol **22** (17.4 mg, 37.0 μmol) and DMAP (460 mg, 3.75 mmol) in dry chloroform (filtrated through alumina, 1.0 mL) was added TsCl (373 mg, 1.95 mmol) at room temperature under an argon atmosphere. The reaction mixture was heated to reflux. After being stirred under reflux for 12 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the tosylate **23** (35.3 mg, 96%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.79 (d, $J = 8.3$ Hz, 2H), 7.40–7.20 (m, 7H), 5.45 (brs, 1H), 4.92 (s, 1H), 4.88 (s, 1H), 4.62 (d, $J = 11.9$ Hz, 1H), 4.53 (d, $J = 6.9$ Hz, 1H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.40 (d, $J = 11.9$ Hz, 1H), 4.12 (d, $J = 9.9$ Hz, 1H), 3.94 (d, $J = 9.9$ Hz, 1H), 3.39 (brs, 1H), 3.37 (s, 6H), 3.22 (dd, $J = 11.6$, 4.3 Hz, 1H), 2.60–2.40 (m, 2H), 2.41 (s, 3H), 2.10–1.20 (m, 7H), 1.80 (d, $J = 1.0$ Hz, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 153.7, 144.8, 138.1, 133.3, 132.1, 129.8, 128.5, 128.4, 128.2, 127.8, 127.7, 107.3, 95.2, 85.2, 83.5, 80.5, 72.0, 69.5, 61.0, 53.3, 44.2, 43.5, 42.7, 28.6, 26.8, 23.7, 23.1, 21.7, 20.2, 11.1. IR (neat): 2935, 2829, 1739, 1658, 1600, 1496, 1464, 1455, 1367, 1242, 1149, 1100, 1044 cm^{-1}. HRMS (ESI-TOF): calcd for $[C_{36}H_{50}O_7S + Na]^+$ 649.3169, found: 649.3167.

Epoxide 24. To a solution of diene **23** (68.0 mg, 0.106 mmol) in dry CH_2Cl_2 (2.0 mL) was added dimethyldioxirane (1.5 mL, ca. 0.1 M in acetone, 0.15 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 3 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography to give the epoxide **24** (50 mg, 72%) as a colorless oil.

Enal 25. To a solution of the epoxide **24** (50 mg, 78 μmol) in dry benzene (2.0 mL) was added a catalytic amount of *p*-TsOH at 0 °C under an argon atmosphere. After being stirred at the same temperature for 13 h, the mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentration in vacuo. The residue was purified by flash chromatography to give the enal **25** (15 mg, 30%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 10.1 (s, 1H), 7.75 (d, $J = 8.2$ Hz, 2H), 7.40–7.20 (m, 7H), 4.63 (d, $J = 12.2$ Hz, 1H), 4.46 (brs, 2H), 4.40 (d, $J = 12.2$ Hz, 1H), 4.17 (d, $J = 9.9$ Hz, 1H), 3.95 (d, $J = 9.9$ Hz, 1H), 3.56 (brs, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.40–3.30 (m, 1H), 2.41 (s, 3H), 2.40–2.10 (m, 2H), 2.06 (s, 3H), 1.90–1.10 (m, 9H), 1.30 (s, 3H), 1.26 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 193.0, 151.7, 145.1, 139.9, 138.1, 133.0, 129.9, 128.5, 128.2, 127.8, 127.7, 95.3, 83.0, 81.5, 80.3, 71.7, 69.5, 59.9, 53.0, 43.8, 42.6, 42.5, 33.0, 28.7, 24.5, 23.5, 22.7, 22.1, 21.7, 19.2, 11.1. IR (neat): 2927, 1672, 1599, 1455, 1364, 1177 cm^{-1}.

Protected Cyanohydrin 4. To enal **25** (15 mg, 20 μmol) was added TMSCN (0.50 mL, 4.9 mmol) and a catalytic amount of KCN–DC-18-crown-6 complex at 0 °C under an argon atmosphere. The mixture was stirred at the same temperature for 30 min. The reaction mixture was diluted with THF (2.0 mL), and then 1 M HCl was added at 0 °C (Caution: HCN is generated). After being stirred at the same temperature for 30 min, the reaction mixture was diluted with Et_2O and washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a mixture of cyanohydrin and a catalytic amount of CSA in dry CH_2Cl_2 (2.0 mL) was added ethyl vinyl ether (0.1 mL, 1.0 mmol) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 25% Et_2O in hexane) to give the protected cyanohydrin **4** (13 mg, 3 steps 83%) as a yellow oil.

MS (ESI-TOF): calcd for $[C_{41}H_{59}O_9SN + NH_4]^+$ 759.4, found: 759.4.

ABC Ring 3. To a solution of $(TMS)_2NH$ (0.6 mL, 2.90 mmol) in dry dioxane (2.0 mL) was added *n*-BuLi (1.80 mL, 1.57 M in hexane, 2.80 mmol) at 0 °C and stirred at room temperature for 30 min under an argon atmosphere. A solution of the protected cyanohydrin **4** (45 mg, 60 μmol, azeotropically dried with toluene) in dry dioxane (3.0 mL) was added dropwise to the lithiated mixture under reflux over 2 h. After being stirred under reflux for 5 h, the reaction mixture was poured into ice-cooled saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the cyclized product (15 mg, 27 μmol, 43%) as a brown oil.

To a solution of the protected cyanohydrin (15 mg, 0.027 mmol) in MeOH (2.0 mL) was added a catalytic amount of CSA. After being stirred at 0 °C for 4 h, the reaction mixture was poured into brine and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the crude cyanohydrin in Et_2O (2.0 mL) was added 0.5 M NaOH aqueous solution (1.0 mL) at 0 °C. After being stirred at room temperature for 3 h, the mixture was poured into brine and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the ABC ring **3** (5.5 mg, 2 steps 42%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 4.88 (d, $J = 6.9$ Hz, 1H), 4.81 (d, $J = 6.9$ Hz, 1H), 4.70 (d, $J = 11.9$ Hz, 1H), 4.63 (d, $J = 11.9$ Hz, 1H), 3.51 (s, 3H), 3.43 (s, 3H), 3.38 (d, $J = 4.6$ Hz, 1H), 3.06 (dd, $J = 11.2$, 4.6 Hz, 1H), 2.90 (d, $J = 11.4$ Hz, 1H), 2.80–2.60 (m, 1H), 2.49 (d, $J = 11.4$ Hz, 1H), 2.10–0.80 (m, 10H), 1.70 (s, 3H), 1.26 (s, 3H), 1.08 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 204.2, 147.3, 138.3, 137.6, 128.4, 128.0, 127.6, 95.0, 85.4, 83.6, 81.6, 69.8, 60.5, 53.9, 50.4, 45.5, 43.6, 40.6, 32.1, 29.8, 28.6, 27.5, 24.6, 23.5, 23.4, 21.7, 19.9, 16.2. IR (neat): 2929, 1733, 1675, 1621, 1119, 1041 cm^{-1}. HRMS (ESI-TOF): calcd for $[C_{29}H_{42}O_5 + Na]^+$ 493.2924, found: 493.2923.

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