A Biomimetic Approach to Taxol: Stereoselective Synthesis of a 12-Membered Ring Ene-Epoxide

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Abstract. The stereoselective synthesis of a taxol intermediate via a biomimetic route is described. Aldol condensation of γ-butyrolactone and citral derivatives generated three stereogenic centers at positions C1, C2, and C11 corresponding to taxol. Intramolecular alkylation of the cyanohydrin ether efficiently formed the 12-membered ring system in which stereoselective reduction, followed by directed epoxidation, afforded the key intermediate epoxide.

INTRODUCTION

Taxol **1** (Fig. 1), isolated from pacific yew, is an anticancer agent found to be active against breast and ovarian cancers. The structure was determined in 1971,[1] and since then numerous efforts have been made to synthesize taxol. Four successful syntheses have been reported.[2–5] The most problematic point in the synthesis of taxol is the formation of the four tightly constrained rings that bear multiple oxygen functions. The (3,8)-*trans* stereochemistry at the B/C ring junction is a particular challenge.

Cyclization of geranylgeranyl diphosphate has been proposed[6] as a biosynthetic route of taxol (Scheme 1), requiring (i) cyclization of geranylgeranyl diphosphate between C1 and C2; (ii) ring closure via *re*-face attack at C11; (iii) deprotonation to the $\Delta^{11(12)}$-alkene; (iv) transannular cyclization promoted by protonation at C7 to generate the B/C ring and (3,8)-*trans* stereogenic centers; (v) deprotonation at C5 leading to taxa-4(5),11(12)-diene.[7] We have focused our attention on this biomimetic approach to taxol,[8] and now we describe the stereoselective synthesis of a key intermediate, the ene-oxide **2**.

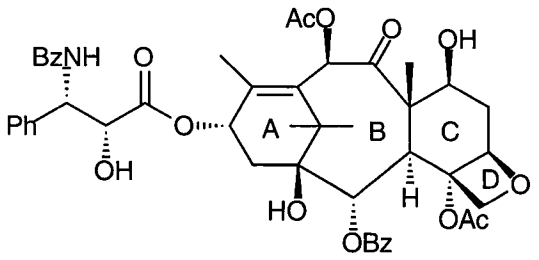
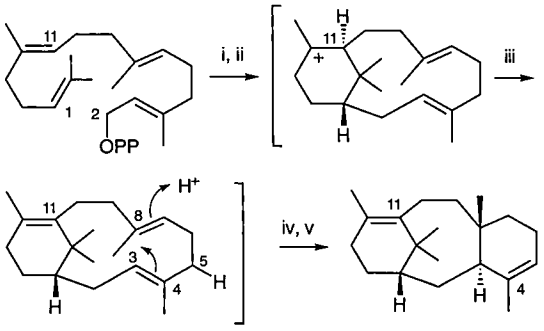


Fig. 1. Taxol **1**.



Scheme 1

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RESULTS AND DISCUSSION

Our strategy for the synthesis of taxol is shown in retrosynthetic fashion in Scheme 2. Epoxide **2** is an attractive target intermediate from which acid-catalyzed cyclization between C3 and C8 could generate the B/C ring junction and stereogenic centers at positions C3, C7, and C8. Deprotonation of the resulting carbocation at C4 will lead to either a 4(5)- or 4(20)-alkenic moiety and allow formation of the D ring. The lactone could be used as a precursor of A ring. It was considered that the stereochemistry at positions C1 and C11 will affect the conformation of **2** and control the stereochemistry of the transannular cyclization.

We have undertaken a conformational search of (1,11)-*trans* **2a** and (1,11)-*cis* **2b** by Monte Carlo methods using molecular mechanics (MM2)[9] as encapsulated in MacroModel.[10] The global minimum of **2a** and **2b** is shown in Fig. 2. The other conformers of **2a** within a 3 kcal/mol window of the global minimum had the protective groups at positions C2, C9, and C14 in varying orientations; however, the ring conformations were the same as for the global minimum. The calculation showed that the distance between the desired cyclization sites (C3 and C8) is 4.27 Å in the global minimum conformation, and therefore transannular cyclization to the desired (3,8)-*trans* stereochemistry could be expected to occur. Conformational analysis of **2b** with (1,11)-*cis* stereochemistry showed that the global minimum (Fig. 2) would favor a (3,8)-*cis* formation. For both structures the conformational analysis is of the ground state. However, the transition state derived from the strained conformer **2b** is expected to be less favored than from the lower energy form **2a**.

The 12-membered ring of compound **2a** is constructed by intramolecular alkylation[11] of the cyanohydrin ether **4**, and the stereogenic centers at positions C7, C8, and C9 are formed by stereoselective reduction of **3**, followed by epoxidation. All stereogenic centers in **4** are prepared by aldol condensation of lactone **5** and the citral derivative **6**. A computational modeling of the boron enolate transition state[12] in this aldol reaction showed that transition state A* is preferable (>1.2 kcal / mol) to B*, C*, and D* (Fig. 3), suggesting that the desired stereochemistries at positions C1, C2, and C11, will be generated in the aldol reaction.

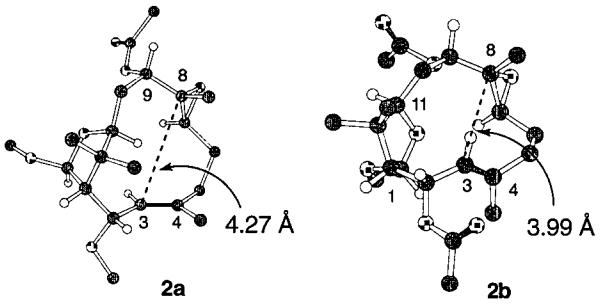
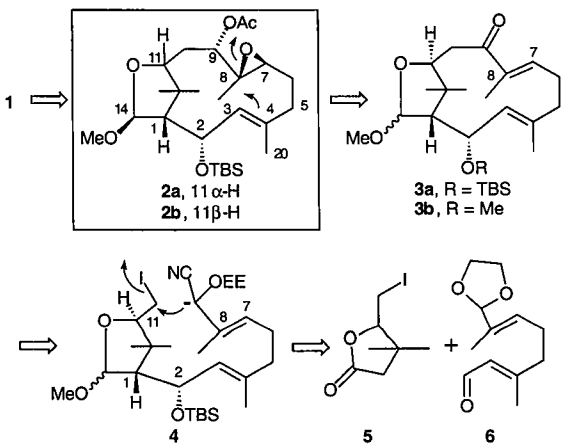


Fig. 2. Global conformers of **2a** and **2b**.

The lactone **5** was prepared from prenol (Scheme 3) by Johnson–Claisen rearrangement ($MeC(OMe)_3$, cat. heptanoic acid, 80%), hydrolysis of ester (NaOH, EtOH), and iodolactonization (I_2, KI, $NaHCO_3$, 99% in 2 steps). The citral derivative **6** was obtained from geranyl acetate; allylic oxidation (SeO_2; MnO_2, 42%), acetalization (ethylene glycol, H^+), hydrolysis of the acetate (K_2CO_3, MeOH), and oxidation (MnO_2, 57% yield in 3 steps). The aldol reaction between **5** and **6** was carried out in THF at –78 °C using lithium diisopropyl amide. Isomer **7** was isolated as the only product, in 83% yield, and HPLC showed the stereoselectivity of the aldol reaction is >95% in agreement with the calculation. For the calculation, boron was used as a countercation instead of lithium; however, it is suspected that the reaction would proceed via a twist-boat transition state of the E-enolate.[13]

Protection of the secondary alcohol **7** (TBSCl, imidazole, DMF, 96%) was followed by reduction of the lactone with diisobutylaluminum hydride in toluene to give the corresponding lactol, which was immediately protected (MeOH, *p*-TsOH, 0 °C) and treated with acid (1N HCl, MeOH) in situ to give enal **8** as a 74 : 26 mixture of diastereomers in 64% overall yield. The mixture **8** was used without separation. Treatment with TMS(CN) in the presence of a catalytic amount of 18-crown-6 KCN, followed by acid treatment (1N HCl) in situ gave a cyanohydrin, which was protected as an ethoxyethyl ether, to give the cyanohydrin ether **4** in 91% overall yield. Intramolecular alkylation of **4** pro-



Scheme 2

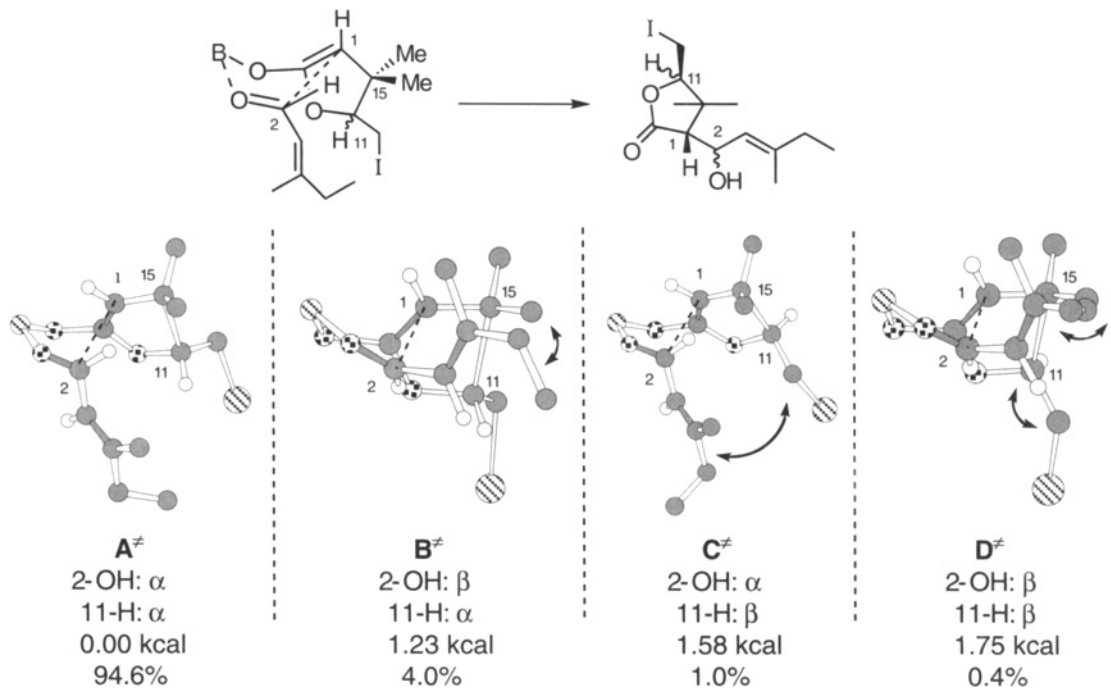
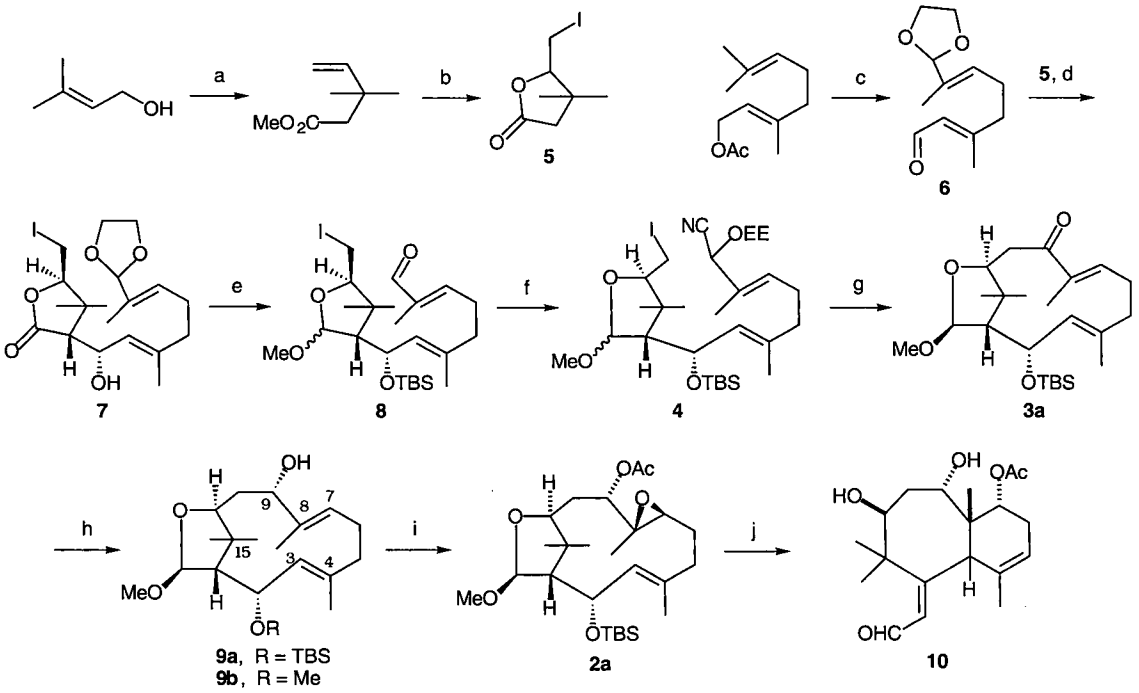


Fig. 3. MM2 transition structure model of aldol condensation.



a) $MeC(OMe)_3$, heptanoic acid, 180 °C, 80%; b) NaOH, EtOH; I_2, KI, $NaHCO_3$, 99%; c) SeO_2, salicylic acid, TBHP, CH_2Cl_2 MnO_2, PhH, CH_2Cl_2 42% in 2 steps; cat. *p*-TsOH, ethylene glycol; K_2CO_3, MeOH; MnO_2, PhH, CH_2Cl_2, 57% in 3 steps; d) LDA, -78 °C, THF, 83%; e) TBSCl, imidazole, DMF, 96%; DIBAL, toluene, -78 °C; *p*-TsOH, MeOH; 1 N HCl, 64%; f) TMS(CN), cat. 18-crown-6 KCN; 1 N HCl, THF; cat. *p*-TsOH, ethyl vinyl ether, 91% overall yield; g) $LiN(TMS)_2$, THF, reflux; cat. pyridinium *p*-toluenesulfonate, MeOH; 2% aq. NaOH, ether, 82% from **4**; h) $NaBH_4$, EtOH, quant.; i) cat. $VO(acac)_2$, TBHP, PhH; Ac_2O, Py, 87% in 2 steps; j) $BF_3{\cdot}Et_2O$, PhH, 0 °C, 35%.

Scheme 3

ceeded smoothly by adding a solution of **4** in THF to a base solution of lithium hexamethyldisilazide dropwise over 6 h under reflux. Deprotection of the ethoxyethyl group with acid and treatment with base gave the desired cyclic enone **3a** in 82% overall yield, and HPLC analysis showed that only one isomer **3a** was obtained. The diastereomers based on the stereochemistry of methoxy group underwent isomerization under the methanolysis of the ethoxyethyl ether avoiding steric hindrance of the α-methoxy group in the bicyclic system.

There are two ways to effect epoxidation of the C7-C8 alkene in **3a**, namely nucleophilic epoxidation of the enone or directed epoxidation after reduction of ketone at C9. We considered both possibilities and modeled the reactions by conformational analysis using molecular mechanics (MM2). A conformational search, (Monte Carlo MM2) of the methyl ether **3b** (TBS was replaced with a methyl group in **3a**) gave a global minimum as depicted in Fig. 4. Based on the assumption of a peripheral attack[14] of the reagent on the enone, nucleophilic epoxidation of the alkene moiety would introduce the epoxide with the stereochemistry at C7 opposite to that required. On the other hand, reduction of the ketone is predicted to occur stereoselectively from the α-face, leading to allylic alcohol **9b**. A conformational analysis of **9b** carried out in the same manner suggested the hydroxy-directed epoxidation would proceed from the β-face to give the epoxide with the required stereochemistry as in **2a**.

Reduction of **3a** with sodium borohydride in ethanol gave **9a** in quantitative yield (Scheme 3). Directed epoxidation was carried out by a catalytic amount of $VO(acac)_2$ with *t*-BuOOH in benzene, and acetylation of the secondary alcohol gave acetate **2a** in 87% yield. The structure of acetate **2a** was unambiguously determined by X-ray crystallography (Fig. 5) and was in good agreement with that predicted in the MM2 calculation shown in Fig. 2. This result demonstrates the value of MM2 calculations.

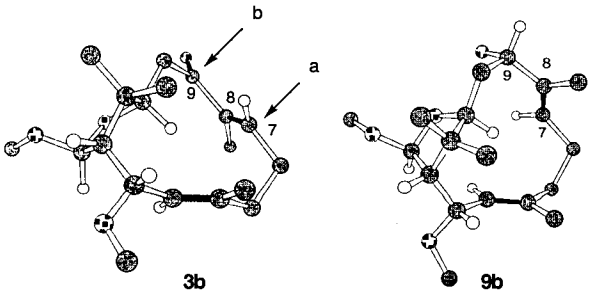


Fig. 4. Global conformers of **3b** and **9b**.

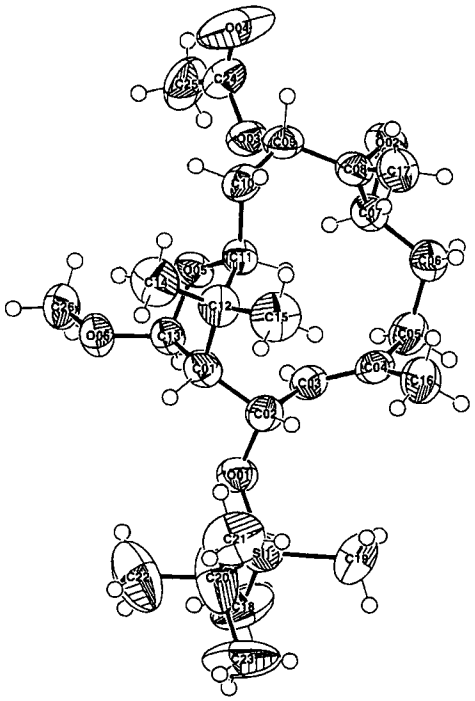


Fig. 5. X-ray crystal structure of **2a**.

Our first attempt of acid-catalyzed cyclization involved adding of $BF_3 \cdot Et_2O$ to a benzene solution of **2a** at 0 °C. The product **10** was isolated by HPLC in 35% yield and its structure was determined by analyzing the ^1H COSY spectra. The expected cyclization resulted in the formation of the C-ring system. However, the elimination of the TBS group at the C-2 position induced the rearrangement of the C1-C15 bond leading to a bicyclo[5.4.0]undecene skeleton with opening of the acetal moiety forming an unsaturated aldehyde.

EXPERIMENTAL SECTION

*Aldol Reaction of **5** and **6** to Alcohol **7***

To a solution of diisopropylamine (2.0 mL, 14.3 mmol) in dry THF (20 mL) cooled to 0 °C was added dropwise a hexane solution of butyllithium (1.66 N, 8.0 mL) under argon. After 30 min, the solution was cooled to –78 °C. Then a solution of the lactone **5** (2.4 g, 9.5 mmol) in dry THF (20 mL) was added dropwise to this solution. Stirring was continued for 1 h at the same temperature. To this reaction mixture was added dropwise enal **6** (2.0 g, 9.5 mmol) in dry THF (20 mL), and the mixture was stirred for 20 min. The reaction mixture was poured into a cold saturated ammonium chloride solution with vigorous stirring, and the aqueous solution was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (elution with hexane : ethyl acetate, 4 : 1) to afford the alcohol **7**

(3.66 g, 7.9 mmol, 83% yield). HPLC (SI-60-5, 7.5 ϕ × 300 mm, elution with 6% 2-propanol in hexane, 2.80 mL/min) retention time 11 min. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.55 (t, 1H, J = 7.0 Hz), 5.28 (d, 1H, J = 9.2 Hz), 5.10 (s, 1H), 4.70–4.62 (m, 1H), 4.37 (dd, 1H, J = 4.1, 9.2 Hz), 4.03–3.87 (m, 4H), 3.33–3.14 (m, 2H), 2.61 (d, 1H, J = 4.9 Hz), 2.24–2.08 (m, 4H), 1.73 (s, 3H), 1.59 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 175.7, 140.0, 133.3, 130.8, 125.2, 107.7, 87.5, 66.8, 65.5, 57.1, 42.3, 38.6, 31.6, 25.3, 23.7, 22.3, 16.6, 14.2, 10.1; IR(neat) 3456, 2962, 1766, 1468, 1371, 1226, 1117, 1068, 990, 757 cm^{-1}.

Enal 8

To a solution of the alcohol **7** (17.0 g, 36.7 mmol) and imidazole (3.7 g, 61.6 mmol) in dry DMF (100 mL) was added *t*-butyldimethylsilyl chloride (7.7 g, 51.4 mmol) at 0 °C under argon. After being stirred for 12 h, the reaction mixture was diluted with ethyl acetate and poured into ice-cooled 1 N hydrochloric acid. The aqueous solution was extracted with ethyl acetate, and the combined organic extracts were washed with aqueous sodium bicarbonate solution and brine, and then dried over magnesium sulfate. After removal of solvent, the residue was chromatographed on silica gel (elution with hexane : ethyl acetate, 8 : 1) to give the TBS ether (20.3 g, 35.2 mmol, 96%).

To a solution of the above lactone (19.0 g, 32.8 mmol) in dry toluene (200 mL) at –78 °C was added dropwise DIBAL in toluene (2.0 N, 20 mL, 40 mmol) under argon. After being stirred for 15 min., the reaction mixture was poured into an ice-cooled 1 N HCl solution with vigorous stirring. The mixture was extracted with ethyl acetate, and the extract was washed with aqueous sodium bicarbonate solution and brine, then dried over magnesium sulfate. After removal of solvent, the residual crude lactol was used for the next reaction without further purification.

To a solution of the lactol (18.5 g) in dry methanol (60 mL) was added a catalytic amount of *p*-toluenesulfonic acid at 0 °C. The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was poured into a cold 1 N hydrochloric acid solution with vigorous stirring. The aqueous solution was extracted with ethyl acetate, and the extract was washed with aqueous sodium bicarbonate solution and brine and dried over magnesium sulfate. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel (elution with hexane : ethyl acetate, 8 : 1) to give the aldehyde **8** (12.1 g, 22.0 mmol, 64% from lactone).

HPLC (SI-60-5, 7.5 ϕ × 300 mm, elution with 6.5% ethyl acetate in hexane, 3.02 mL/min), retention time 5.5 min (major diastereomer) and 6.5 min (minor diastereomer).

major diastereomer: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.39 (s, 1H), 6.49 (t, 1H, J = 7.6 Hz), 5.10 (t, 1H, J = 9.7 Hz), 4.63–4.52 (m, 1H), 4.49 (d, 1H, J = 4.5 Hz), 4.00 (dd, 1H, J = 4.1, 9.5 Hz), 3.30–3.12 (m, 2H), 3.18 (s, 3H), 2.48–2.34 (m, 1H), 2.20–1.85 (m, 4H), 1.76 (s, 3H), 1.71 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); IR (neat) 2924, 1727, 1687, 1634, 1465, 1384, 1359, 1253, 1049, 835, 774 cm^{-1}; minor diastereomer: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.39 (s, 1H), 6.49 (t, 1H, J = 7.3 Hz), 5.21 (d, 1H, J = 8.4 Hz), 4.54-4.61 (m, 1H), 4.46 (d, 1H, J = 4.6 Hz), 3.85 (dd, 1H, J = 3.5, 10.8 Hz), 3.29-3.45 (m, 2H), 3.36 (s, 3H), 2.42–2.50 (m, 1H), 2.00–2.21 (m, 4H), 1.76 (s, 3H), 1.73 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).

Cyanohydrin Ether 4

A mixture of the aldehyde **8** (4.5 g, 8.2 mmol) and a catalytic amount of 18-crown-6 KCN complex was cooled to 0 °C. To the mixture was added trimethylsilyl cyanide (1.6 g, 16.4 mmol). The reaction mixture was stirred for 2 h at room temperature. Then to this mixture was added 1 N HCl (2 mL) and THF (20 mL) at 0 °C. After being stirred for 30 min at the same temperature, the reaction mixture was poured into brine. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried over magnesium sulfate. After removal of solvent, the residual crude cyanohydrin was used for the next reaction without further purification.

To a solution of the cyanohydrin and a catalytic amount of *p*-toluenesulfonic acid in dry benzene (50 mL) was added ethyl vinyl ether (0.86 mL, 9 mmol) at 0 °C under argon. After being stirred for 40 min, the reaction mixture was quenched with triethylamine at the same temperature. The mixture was poured into a cold saturated sodium bicarbonate solution. The aqueous solution was extracted with ethyl acetate, and the combined organic extracts were washed with brine and dried over magnesium sulfate. After removal of solvent, the residue was chromatographed on silica gel (elution with hexane : ethyl acetate, 8 : 1) to give the protected cyanohydrin ether **4** (5.0 g, 7.5 mmol, 91% from aldehyde **8**).

^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.50 (br, 1H), 5.30–4.41 (m, 6H), 4.18–2.99 (m, 4H), 3.36 (s, 3H), 2.20–2.10 (m, 5H), 1.77 (s, 3H), 1.59 (s, 3H), 1.42–1.17 (m, 12H), 0.87 (s, 9H),0.03 (s, 3H), 0.00 (s, 3H); IR (neat) 2924, 1727, 1687, 1462, 1385, 1253, 1054, 835, 775 cm^{-1}.

Intramolecular Alkylation of 4

A solution of 1,1,1,3,3,3-hexamethyldisilazane (8.9 g, 55.2 mmol) in dry THF (150 mL) was placed in a three-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a dropping funnel. To the solution was added dropwise butyllithium (1.69 N, 24 mL) at 0 °C, and the mixture was stirred for 0.5 h at the same temperature under argon. A solution of the protected cyanohydrin ether **4** (1.79 g, 2.76 mmol) in dry THF (30 mL) was added dropwise to this flask over 6 h at reflux. Cooling to room temperature, the reaction mixture was poured into a cold saturated ammonium chloride solution with vigorous stirring. The aqueous solution was extracted with ethyl acetate, and the organic extracts were washed with brine and dried over magnesium sulfate. After removal of solvent, the residue was treated with a catalytic amount of pyridinium *p*-toluenesulfonate in methanol (20 mL) at room temperature. After being stirred for 12 h, the reaction mixture was poured into a cold saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the extract was washed with brine, then dried over magnesium sulfate. After removal of the solvent, the residue was treated with 2% aqueous sodium hydroxide solution (5 mL) in

ether (15 mL). After stirring for 2 h at 0 °C, the reaction mixture was quenched with cold 1 N hydrochloric acid. The aqueous solution was extracted with ethyl acetate, and the organic extracts were washed with a saturated sodium bicarbonate solution and brine, then dried over magnesium sulfate. After removal of solvent, the residue was chromatographed on silica gel (elution with hexane : ethyl acetate, 8 : 1) to give the enone **3a** (950 mg, 2.25 mmol, 82% from **4**).

HPLC (SI-60-5, 7.5 ϕ × 300 mm, elution with 7% ethyl acetate in hexane, 2.80 mL/min), retention time 19.5 min.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.08 (t, 1H, *J* = 9.5 Hz), 5.34 (d, 1H, *J* = 10.4 Hz), 5.14 (t, 1H, *J* = 8.6 Hz), 5.04 (s, 1H), 4.45 (dd, 1H, *J* = 4.3, 10.4 Hz), 3.37 (s, 3H), 2.88–2.30 (m, 6H), 1.97 (d, 1H, *J* = 4.3 Hz), 1.72 (s, 3H), 1.66 (s, 3H), 1.01 (s, 3H), 0.86 (s, 9H), 0.70 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); IR (neat) 2948, 2952, 1670, 1468, 1385, 1252, 1055, 836, 775 cm^{-1}.

Reduction of ***3a***

To a solution of the enone **3a** (600 mg, 1.42 mmol) in ethanol (14 mL) was added sodium borohydride (54 mg) at 0 °C. After being stirred for 30 min at the same temperature, the reaction mixture was carefully quenched with 1 N hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic extract was washed with a saturated sodium bicarbonate solution and brine, then dried over magnesium sulfate. After removal of solvent, the residue was purified by column chromatography on silica gel (elution with hexane : ethyl acetate, 8 : 1) to give the allylic alcohol **9a** (495 mg, 1.16 mmol, 82%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.36 (d, 1H, *J* = 10.6 Hz), 5.22 (d, 1H, *J* = 10.6 Hz), 5.04 (s, 1H), 4.42 (dd, 1H, *J* = 3.0, 10.6 Hz), 4.27 (d, 1H, *J* = 9.9 Hz), 4.29–4.25 (br, 1H), 3.35 (s, 3H), 2.49–1.85 (m, 6H), 1.97 (d, 1H, *J* = 3.0 Hz), 1.64 (s, 3H), 1.62 (s, 3H), 1.03 (s, 3H), 0.85 (s, 9H), 0.77 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 134.8, 128.8, 125.1, 105.3, 81.6, 74.9, 66.9, 62.7, 60.4, 55.2, 41.1, 39.1, 29.0, 25.8, 22.9, 20.3, 18.0, 16.7, 14.4, 14.2; IR (neat) 2914, 1662, 1514, 1469, 1442, 1385, 1250, 1203, 1042, 950, 903, 838, 775, 732 cm^{-1}.

Epoxidation of ***9a*** *and Acetylation*

To a solution of the allylic alcohol **9a** (127 mg, 0.3 mmol) and a catalytic amount of vanadyl acetylacetonate in benzene (4 mL) was added *t*-butylhydroperoxide (70% in water, 0.06 mL, 0.4 mmol) at room temperature. After being stirred for 2.5 h at the same temperature, the reaction mixture was quenched by an addition of an aqueous solution of sodium thiosulfate. The aqueous layer was extracted with ethyl acetate. The organic extracts were washed with a saturated solution of sodium bicarbonate and brine, then dried over magnesium sulfate. After removal of the solvent, the residual crude epoxy-alcohol was treated with acetic anhydride (0.1 mL, 1.0 mmol), pyridine (0.15 mL, 1.8 mmol), and methylene chloride (2 mL) at 0 °C under argon. After being stirred for 12 h at room temperature, the reaction mixture was poured into a cold 1 N solution of hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the organic extracts were washed with a saturated solution of sodium bicarbonate and brine, then dried over magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography (elution with hexane : ethyl acetate, 4 : 1) to afford the desired epoxy acetate **2a** (125 mg, 0.26 mmol, 87% from the allylic alcohol **9a**) as a white crystal, whose structure was determined by X-ray crystal structure analysis.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.44 (d, 1H, *J* = 10.0 Hz), 5.13 (t, 1H, *J* = 3.0 Hz), 5.05 (s, 1H), 4.46 (dd, 1H, *J* = 3.3, 10.0 Hz), 4.06 (d, 1H, *J* = 9.5 Hz), 3.33 (s, 3H), 3.15 (d, 1H, *J* = 9.7 Hz), 2.42–1.87 (m, 7H), 2.05 (s, 3H), 1.66 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.87 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); IR (neat) 2928, 2825, 1739, 1468, 1369, 1250, 1229, 1123, 1065, 834, 782 cm^{-1}; mp 139.5–140.5 °C; crystal dimension: 0.55*0.35*0.20 mm^3, crystal system: triclinic, space group: P -1, unit cell dimenstions and volume: *a* =10.961 (1) Å *b* =13.382 (1) Å *c* =10.618 (2) Å, α =108.26 (1)° β =99.50 (1)° γ =100.54 (1)° V =1412.2 (4) Å^3, ρ_{calcd}: 1.136 g/cm^3, $2\theta_{max}$: 120°, radiation: Cu Kα, wavelength: 1.54178 Å, scan mode: 2θ/ω, temperature of measurement: room temperature, no. of measured and independent reflections: 4141, no. of reflections included in the refinement : 3290, σ limits: 3, whether and how Lorentzian polarization and absorption corrections were performed (μ, min./max. transmission): Lorentzian polarization; method of structure solution and program: direct method SIR92; method of refinement and program: full-matrix least squares; no. of parameters: 347; treatment of H atoms: located on Fourier-difference maps and refined, R: 0.0967, wR: 0.1083 ($w = \exp(15.00\sin^2\theta/\lambda^2)/\sigma^2(Fo)$), whether refined against |F| or |F^2|: |F|, residual electron density: 1.553 e/Å^3, the databank at which the detailed results are deposited: CSD.

Acid-Catalyzed Cyclization of ***2a***

To a solution of the acetate 2a (26.6 mg, 0.057 mmol) in dry benzene (2.0 mL) at 0 °C was added dropwise boron trifluoride etherate (0.53 N, 2.18 mL, 1.46 mmol) in dry benzene under argon. After stirring for 10 min at 0 °C, the reaction mixture was poured into a cold saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried over magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel to give the cyclized product **10** (7.0 mg, 0.020 mmol, 35% yield).

HPLC (SI-60-5, 7.5 ϕ × 300 mm, elution with 10% 2-propanol in hexane, 2.96 mL / min), retention time 17 min; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.99 (d, 1H, *J* = 7.9 Hz), 5.87 (d, 1H, *J* = 7.9 Hz), 5.46 (d, 1H, *J* = 5.3 Hz), 5.01 (dd, 1H, *J* = 10.2, 2.6 Hz), 3.83 (d, 1H, *J* = 3.3 Hz), 3.75 (dd, 1H, *J* = 11.9, 4.0 Hz), 2.56 (s, 1H), 2.35–1.72 (m, 4H), 2.07 (s, 3H), 1.56 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H); IR (neat) 3456, 2962, 1735, 1666, 1369, 1233, 1019 cm^{-1}.

CONCLUSION

We have demonstrated the stereoselective aldol condensation of **5** and **6** generating three stereogenic centers at positions C1, C2, and C11, and intramolecular alkylation of the cyanohydrin ether **4** efficiently formed the bicyclic system **3a**. Stereoselective reduction followed

by directed epoxidation afforded the epoxide **2a**. Further studies of transannular cyclizations in **2a** are underway in our laboratory.

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