Tandem Cope–Claisen Rearrangement in the Synthesis of Steroids: Stork's Keto Acid

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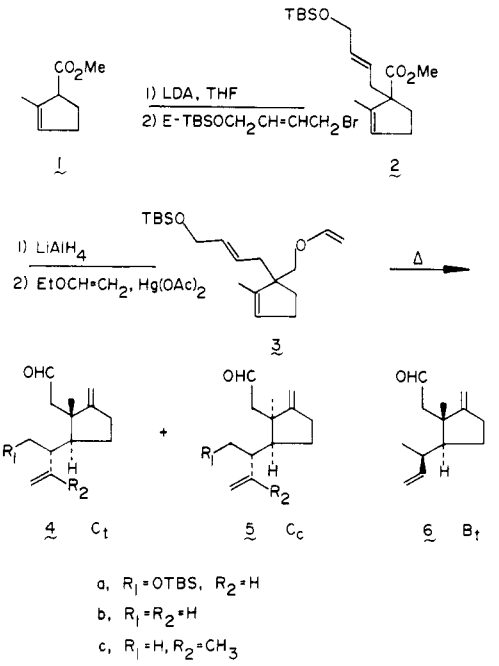
The tandem Cope–Claisen rearrangement of triene **3** affords aldehydes **4a** and **5a** (4/1 ratio) upon thermolysis at 300 °C. Aldehyde **4a** is subjected to intramolecular alkylation leading to Stork's keto acid **15**, an important intermediate in the synthesis of corticosteroids.

Conventional wisdom argues that functionalized polycyclic compounds are constructed by manipulating functionality and stereochemistry on a preexisting ring system. Our studies on the tandem Cope–Claisen[1] and related sigmatropic rearrangements[2] have demonstrated that acyclic diastereoselection and subsequent ring formation is a viable alternative to this time-honored strategy. We present in this paper a tandem Cope–Claisen-based construction of Stork's keto acid **15**,[3] a key intermediate in the synthesis of corticosteroids, that stereoselectively controls the C-8, C-13, and C-14 stereochemistry (steroid numbering) and utilizes a Cope-Claisen substrate which is more highly functionalized than substances employed in early studies.

Scheme I outlines the preparation and thermolysis of oxygenated vinyl ether **3**. The allylic bromide employed in the alkylation of ester **1** was prepared by monosilylation of (*E*)-2-butene-1,4-diol[4] with *tert*-butyldimethylsilyl chloride[5] followed by mesylation[6] and displacement with lithium bromide in acetone. The ratio of aldehydes **4a**/**5a** proved to be temperature dependent. At 250 °C the ratio was 83/17, requiring 12 h for the disappearance of starting material. This temperature proved impractical since the aldehydes could not sustain prolonged exposure to elevated temperatures. While a temperature of 360 °C afforded a 75/25 ratio (2.5 min), the more practical conditions of 300 °C for 30 min gave rise to an 80/20 ratio of diastereomers. The initial stereochemical assignments for aldehydes **4a** and **5a** were based upon the similar ratio of products obtained for the rearrangement of **3** (TBSO = H).[1a] In addition, a comparison of the ^{1}H NMR chemical shifts of the aldehyde proton and the angular methyl group of **4a** and **5a** correlated well with the shifts for the same signals of the C_t (chair-Cope, trans-Claisen) isomer **4b** and C_c (chair-Cope, cis-Claisen) isomer **5b** (Table I). Experience has shown that isomers of stereochemistry **6** only arise under special conditions.[1]

A previous application of olefinic aldehydes **4b** and **4c** in the formation of the pseudoguaianolide ring system and the synthesis of aromatin and confertin depended upon the functionalization of the side-chain olefin! In the present instance, ring formation is initiated between the oxygen-bearing carbons of **4a**, leaving the vinyl group for subsequent elaboration. Several modes of intramolecular alkylation using acyl anion equivalents were explored.

Scheme I



Dithiane **7a**, prepared by sequential thioketalization (Fieser conditions),[7] desilylation (n-Bu_4NF), mesylation (CH_3SO_2Cl, Et_3N), and displacement (LiBr, acetone), gave only a product of elimination, diene **8a**, upon treatment

with LDA in THF. Although 2-alkyldithianes have a pK_a on the order of magnitude of diisopropylamine[8] and efficient kinetic conversion to the dithiane anion would not be expected, such intramolecular alkylations have been realized.[9] Alternatively, a kinetically more acidic acyl anion equivalent was employed. The protected cyanohydrin **7b** was prepared from aldehyde **4a** (NaCN, HOAc, EtOH; $EtOCH{=}CH_2$, *p*-TsOH; TsCl, pyr) as a mixture of diastereomers. While LDA was once again ineffective as a base, potassium hexamethyldisilazane in THF afforded a 4/1 mixture of two compounds in 76% yield after acid

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(3) (a) Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.*, **1981**, *103*, 4948. (b) Stork, G.; Sherman, D. H. *Ibid.* **1982**, *104*, 3758.
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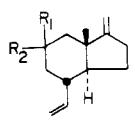
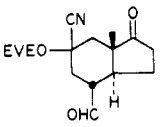
Table I. Chemical Shift Correlation of Aldehydes 4-6

	4a	5a	4b	5b	6
CH_3	1.03	1.26	1.08	1.31	1.02
CHO	9.68 (t, J = 2.8 Hz)	9.69 (t, J = 3.3 Hz)	9.67 (t, J = 3.0 Hz)	9.72 (t, J = 3.0 Hz)	9.64 (dd, J = 4.2, 0.2 Hz)

hydrolysis and brief exposure to base. The major component was the desired ketone **9b** (IR 1715 cm^{-1}) while the



9a, R_1 = CN, R_2 = OEVE
b, R_1, R_2 = O



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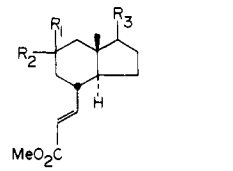
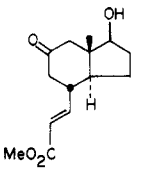
minor component was the aldehyde **8c** (IR 1720 cm^{-1}; ^1H NMR 9.73 (1 H, J = 2.7 Hz, CHO), 6.60–4.70 (m, 7 H, vinyl)). However, when sodium hexamethyldisilazane in refluxing THF was employed as the condensing agent, only the products of ring closure, protected cyanohydrins **9a**, were obtained in 82% yield.[10,11]

The cyanohydrin acetal served not only as an efficient acyl anion equivalent but also as an appropriate protecting group for the cyclohexanone carbonyl during subsequent manipulations of the olefin functionality. Ozonolysis[12] of bis-olefin **9a** afforded unstable keto aldehyde **10** which underwent selective olefination[13] of the aldehyde with (carbomethoxymethylene)triphenylphosphorane. The anticipated *trans*-olefin was confirmed by the magnitude (J = 15.7 Hz) of the vinylic coupling constant. Reduction of the cyclopentanone carbonyl with lithium aluminum tri-*tert*-butoxy hydride in THF afforded the alcohol **11b**,[14] completing the manipulation of the two carbonyl functions.

Exposure of the masked ketone function was accomplished by sequential treatment of the cyanohydrin acetal **11b** with 5% aqueous hydrochloric acid and methanolic



11a, R_1 = CN, R_2 = OEVE, R_3 = O
b, R_1 = CN, R_2 = OEVE, R_3 = β-OH



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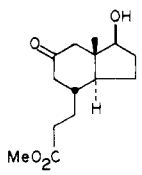
potassium carbonate. The final steps of the sequence were accomplished in 89% overall yield. Thus, hydrogenation of unsaturated ester **12** (Pd/C) afforded keto ester **13** in near quantitative yield. Subsequent silylation of the



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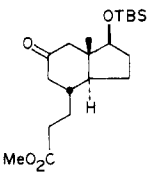

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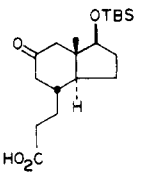

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hydroxyl group with *tert*-butyldimethylsilyl chloride[5] and saponification of the ester afforded keto acid **15** (mp 135–136 °C (cyclohexane) [lit.[15] mp 118–120 °C; antipode, lit.[3] mp 140–142 °C]. The ^1H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were identical with a sample of the optically active, synthetic acid.

Experimental Section[16]

(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-buten-1-ol. To a mixture of (*E*)-2-butene-1,4-diol (1.00 g, 11.0 mmol), triethylamine (1.60 mL, 11.0 mmol), and 4-(dimethylamino)pyridine (56.0 mg, 0.50 mmol) in 10 mL of DMF was added a solution of 1.10 g (7.30 mmol) of *tert*-butyldimethylsilyl chloride in 5 mL of DMF by a syringe pump at 40 °C under a nitrogen atmosphere over a period of 20 h. The reaction mixture was stirred at this temperature until a constant amount of starting diol remained (checked by GC analysis). The solution was then diluted with water (20 mL) containing 1.0 g of sodium bicarbonate, extracted with ether (3 × 50 mL), and washed 3 times with 5% HCl, once with sodium bicarbonate, and once with saturated brine. The organic portion was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (16% EtOAc/hexane) afforded 0.91 g (62%) of the (*E*)-monosilyloxy alcohol as a colorless oil: bp 68–70 °C (0.1 torr); ^1H NMR ($CDCl_3$, 90 MHz) δ 5.80 (m, 2 H), 4.15 (m, 4 H), 1.50 (m, 1 H, OH), 0.90 (s, 9 H); 0.06 (s, 6 H).

(*E*)-1-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-butene. To a mixture of 1.00 g (5.00 mmol) of monosilyloxy alcohol (vide supra), triethylamine (2.20 mL, 15.0 mmol), and 4-(dimethylamino)pyridine (22.0 mg, 0.20 mmol) in 20 mL of CH_2Cl_2 was added a solution of 1.04 g (10.0 mmol) of methanesulfonyl chloride in 5 mL of methylene chloride dropwise at 0 °C under a nitrogen atmosphere over a period of 10 min. After 1 h the reaction mixture was taken up in ether (100 mL) and washed successively with ice water, 5% HCl, saturated sodium bicarbonate, and brine. The solution was dried over $MgSO_4$ and concentrated in vacuo to give the mesylate [^1H NMR at δ 3.0 (s, 3 H)] as a light yellow oil. A

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(15) A sample of racemic acid **15** provided by Professor Snider (Brandeis University), when recrystallized from cyclohexane, had the same melting point and mixture melting point and a ^1H NMR spectrum identical with keto acid **15** prepared in this work. Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364.

(16) Reagents were used as received unless otherwise noted. Hexane, dimethyl sulfide (DMS), dimethylformamide (DMF), ethyl vinyl ether, methylene chloride, pyridine, and triethylamine (Et_3N) were distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl under nitrogen. *n*-Butyllithium was titrated according to the method of Kofron and Baclawski.[17] Flash chromatography was carried out on silica gel 60 (230–400 mesh) by using the apparatus discribed by Still.[18] Melting points (mp) were obtained on a Fisher-Johns apparatus and are corrected. Infrared spectra (IR) were recorded on a Beckmann Model 4250, a Perkin-Elmer 710B, a Nicolet Series 7000 fourier transform, or a Nicolet 5 SK fourier transform spectrometer. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker HX-500 (500 MHz), a Bruker HX-270 (270 MHz), a JEOL FX-900 (90 MHz), or a Varian EM-360 (60 MHz) spectrometer. ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker HX-500 (125.7 MHz) spectrometer. Mass spectra (GC/MS) were recorded on the Hewlett Packard 5985 GC/MS system containing a 2% OV-101 column (3 ft × $^1/_4$ in.) on Chromosorb WHP 100/200 and operated at 70 eV in the electron-impact (EI) mode unless otherwise indicated. Microanalyses were performed by Atlantic Microlab. Inc., Atlanta, GA. Thermolyses were carried out in Pyrex tubes (20 mL/1-mm thickness; 100 mL/1.5-mm thickness), which were washed with a solution of sodium bicarbonate, water, and acetone and then dried in an oven at 120 °C for several days. Tubes were flushed with nitrogen and samples were put into the tubes as neat liquids or as solutions in hexane, which was removed under vacuum. The tubes were evacuated (0.05–0.005 torr), sealed, and heated in a temperature-controlled molten salt bath. The salt (mp 142 °C) is a mixture of 40% sodium nitrite, 7% sodium nitrate, and 53% potassium nitrate and commercially available as Du Pont Hitec.

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solution of the mesylate in 30 mL of reagent-grade acetone containing 1.30 g (15.0 mmol) of anhydrous lithium bromide was refluxed for 2.5 h. The resulting solid was filtered, and the filtrate was carefully concentrated in vacuo. The oily residue was extracted with ether, washed with saturated aqueous sodium thiosulfite, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (2% EtOAc/hexane) afforded 0.79 g (60%) of bromide as an oil: bp 76–80 °C (0.25 torr); ^1H NMR ($CDCl_3$, 90 MHz) δ 5.88 (m, 2 H), 4.20 (m, 2 H), 3.95 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H).

Ester 2. Alkylation[1a] of 1.82 g of ester 1 afforded, after flash chromatography (2.5% EtOAc/hexane), 2.80 g (80%) of ester **2** as a colorless oil: bp 115 °C (0.1 torr); R_f 0.73 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$, 270 MHz) δ 5.54 (m, 3 H), 4.11 (dd, J = 4.7, 1.1 Hz, 2 H), 3.67 (s, 3 H), 2.70–1.80 (m, 6 H), 1.67 (dd, J = 3.5, 2.0 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.58; H, 9.97.

Reduction of Ester 2. Ester **2**[1a] (2.6 g, 8.0 mmol) was reduced with $LiAlH_4$ (0.6 g, 16.0 mmol) in ether, affording the corresponding alcohol as a colorless oil: bp 117–119 °C (0.2 torr); R_f 0.36 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.55 (m, 3 H), 4.11 (d, J = 4.1 Hz, 2 H), 3.51 (d, J = 10.6 Hz, 1 H_A), 3.39 (d, J = 10.6 Hz, 1 H_B), 2.30–1.80 (m, 6 H), 1.61 (dd, J = 3.7, 2.0 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H), hydroxyl proton was not observed. Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.93; H, 10.92.

Vinyl ether 3 was prepared as previously described:[1a] colorless oil; bp 110–120 °C (0.5 torr); R_f 0.85 (20% EtOAc/hexane); GC/MS, m/e (relative intensity) 322 (M^+, 0.1), 265 (2), 147 (20), 93 (100); ^1H NMR ($CDCl_3$, 270 MHz) δ 6.50 (dd, J = 14.3, 6.8 Hz, 1 H), 5.57 (m, 2 H), 5.41 (m, 1 H), 4.13 (dd, J = 14.3, 2.0 Hz, 1 H), 4.10 (d, J = 3.7 Hz, 2 H), 3.94 (dd, J = 6.8, 2.0 Hz, 1 H), 3.53 (d, J = 8.0 Hz, 1 H_A), 3.49 (d, J = 8.0 Hz, 1 H_B), 2.25–1.80 (m, 6 H), 1.63 (dd, J = 3.7, 2.1 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H). Anal. Calcd for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.63. Found: C, 70.83; H, 10.65.

Thermolysis of Vinyl Ether 3. Aldehydes 4a (C_t) and 5a (C_c). A sample of vinyl ether **3** (320 mg, 1.0 mmol) was thermolyzed in a 100-mL pyrolysis tube[15] at 300 ± 2 °C for 30 min to afford a mixture of aldehydes **4a** and **5a** in the ratio of 4:1 (determined by ^1H NMR integration of the tertiary methyl singlets at δ 1.03 and 1.26, respectively). Flash chromatography (3% EtOAc/hexane) afforded 190 mg (60%) of **4a** (C_t) and 45 mg (14%) of **5a** (C_c) as colorless oils.

4a: R_f 0.67 (20% EtOAc/hexane); GC/MS(CI), m/e (relative intensity) 323 (M^+ + 1, 1.3), 265 (6), 191 (21), 173 (49), 147 (100); IR (neat) 3066, 2951, 2923, 2891, 2852, 2730, 1720, 1645, 1466, 1251, 1095, 833, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.68 (t, J = 2.8 Hz, 1 H), 5.70 (m, 1 H), 5.10–4.75 (m, 4 H), 3.59 (dd, J = 9.8, 5.3 Hz, 1 H_A), 3.55 (dd, J = 9.8, 6.2 Hz, 1 H_B), 2.58 (dd, J = 16.0, 2.8 Hz, 1 H_A), 2.51 (d, J = 16.0, 2.8 Hz, 1 H_B), 2.50–1.65 (m, 6 H), 1.03 (s, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H). Anal. Calcd for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.63. Found: C, 70.78; H, 10.64.

5a: R_f 0.60 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.69 (t, J = 3.3 Hz, 1 H), 5.75 (m, 1 H), 5.06–4.75 (m, 4 H), 3.54 (dd, J = 5.9, 2.7 Hz, 2 H), 2.60–1.70 (m, 8 H), 1.26 (s, 3 H), 0.87 (s, 9 H), 0.02 (s, 6 H). Anal. Calcd for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.63. Found: C, 70.78; H, 10.66.

Tosylate 7b. Caution: THIS REACTION MUST BE DONE IN A WELL-VENTILATED Hood!!! To a suspension of sodium cyanide (7.2 g, 147 mmol) in 150 mL of absolute ethanol was added 12.6 g (210 mmol) of glacial acetic acid dropwise at room temperature. After 100 min, a solution of aldehyde **4a** (2.0 g, 6.2 mmol) in 15 mL of absolute ethanol was added and the solution was allowed to stir at room temperature for 4 h. The reaction mixture was taken up in ether and washed twice with water. The aqueous layers were combined and extracted with ether. The combined ethereal portions were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a cyanohydrin [IR (neat) 3540, 2240 cm^{-1}]. To a solution of the crude cyanohydrin containing 23.0 mg (0.12 mmol) of p-toluenesulfonic acid monohydrate in 75 mL of ether was added 2 mL (20.0 mmol) of ethyl vinyl ether dropwise at 0 °C under a nitrogen atmosphere. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 30 min. The mixture was taken up in ether, washed twice with saturated aqueous potassium carbonate solution and once with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (5% EtOAc/hexane) afforded 2.1 g (82%) of the acetal cyanohydrin of **4a** as a mixture of diastereomers: R_f 0.65, 0.68 (20% EtOAc/hexane); IR (neat) 3067, 2232, 1643, 1467, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.66 (m, 1 H), 5.05–4.30 (m, 6 H), 3.60 (m, 4 H), 2.40–1.40 (m, 8 H), 1.36–1.00 (m, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H). Anal. Calcd for $C_{24}H_{43}NO_3Si$: C, 68.36; H, 10.28. Found: C, 68.35; H, 10.31.

To a solution of 2.00 g (4.75 mmol) of the above cyanohydrin in 50 mL of THF was added 7.20 mL (7.20 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF in one portion at room temperature under an atmosphere of nitrogen. After 2 h, the reaction mixture was taken up in ethyl acetate and washed with brine, saturated sodium bicarbonate, and brine. The organic portion was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (25% EtOAc/hexane) afforded 1.43 g (98%) of the alcohols as a mixture of diastereomers: R_f 0.17, 0.20 (20% EtOAc/hexane); IR (neat) 3416 (br), 2230, 1542, 1380, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 5.90–5.50 (m, 1 H), 5.20–4.20 (m, 6 H), 3.59 (m, 4 H), 2.50–1.50 (m, 8 H), 1.37–1.00 (m, 9 H), hydroxyl proton was not observed. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51. Found: C, 70.08; H, 9.52.

To a solution of 1.43 g (4.65 mmol) of the alcohols in 30 mL of pyridine was added 1.33 g (7.00 mmol) of recrystallized p-toluenesulfonyl chloride at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was then kept in a refrigerator for 3 days at 5–10 °C. The mixture was poured into ice–water, extracted with ether, and washed twice with cold 5% HCl, once with saturated sodium bicarbonate, and once with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (9% EtOAc/hexane) afforded 2.14 g (100%) of tosylate **7b** as a mixture of diastereomers: R_f 0.26, 0.32 (20% EtOAc/hexane): ^1H NMR ($CDCl_3$, 270 MHz) δ 7.78 (d, J = 8.2 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 5.70–5.30 (m, 1 H), 5.10–4.30 (m, 6 H), 4.00 (m, 2 H), 3.52 (m, 2 H), 2.44 (s, 3 H), 2.50–1.50 (m, 8 H), 1.30–0.90 (m, 9 H). Anal. Calcd for $C_{26}H_{35}NO_5S$: C, 65.05; H, 7.64. Found: C, 65.23; H, 7.65.

Cyclization of Tosylate 7b: Diene 9a. To a solution of 952 mg (5.20 mmol) of sodium bis(trimethysilyl)amide (Aldrich) in 60 mL of THF was added a solution of 800 mg (1.74 mmol) of tosylate **7b** in 10 mL of THF dropwise at room temperature over a period of 8 min under an atmosphere of nitrogen. The organic phase was washed twice with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (5% EtOAc/hexane) afforded 410 mg (82%) of cyclized diene **9a** as a colorless oil: R_f 0.83 (20% EtOAc/hexane); IR (neat) 3068, 2230, 1652, 1380 cm^{-1}; GC/MS (CI), m/e (relative intensity) 290 (M^+ + 1, 5), 200 (13), 191 (7), 73 (100); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.65 (m, 1 H), 5.20–5.00 (m, 3 H), 4.63 (m, 2 H),3.75–3.53 (m, 2 H), 2.60–1.50 (m, 10 H), 1.40–0.95 (m, 9 H). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40. Found: C, 74.56; H, 9.43.

Keto Aldehyde 10. To a suspension of sodium carbonate (500 mg) in 8 mL of absolute methanol and 15 mL of methylene chloride was added 230 mg (0.80 mmol) of diene **9a**. The solution was cooled to −70 °C in a dry ice bath and ozone was passed through the solution until the solution turned blue (4 min). The solution was flushed with nitrogen over a period of 15 min. Dimethyl sulfide (0.5 mL) was added to the solution and the solution was stirred for 4 h while slowly warming to room temperature. Volatile components were removed in vacuo and the residue was filtered through a Florisil (10 g) column with ethyl acetate. Concentration of the eluate in vacuo gave 231 mg (99%) of crude keto aldehyde **10** as a colorless oil. The crude material was used for the next reaction without further purification. Analytical samples were prepared by flash chromatography (50% EtOAc/hexane): R_f 0.47 (50% EtOAc/hexane); IR (neat) 2730, 2246, 1740, 1725, 1450, 1380 cm^{-1}; GC/MS(CI), m/e (relative intensity) 294 (M^+ + 1, 3.3), 204 (18), 73 (100); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.77 (d, J = 1.5 Hz, 1 H), 5.10 (q, J = 5.3 Hz, 1 H), 3.54 (m, 2 H), 2.80–1.50 (m, 10 H), 1.40–1.00 (m, 6 H), 1.20 (s, 3 H).

Unsaturated Ester 11a. A solution of 185 mg (0.63 mmol) of keto aldehyde **10** and 221 mg (0.66 mmol) of (carbomethoxymethylene)triphenylphosphorane in 13 mL of methylene chloride was stirred at room temperature for 17 h under a nitrogen at-

mosphere. Water was added and the mixture was extracted with ether and washed twice with water. Flash chromatography (50% EtOAc/hexane) afforded 220 mg (99%) of unsaturated ester **11a** as a colorless oil: R_f 0.57 (50% EtOAc/hexane); IR (neat) 2226, 1741, 1724, 1657, 1438 cm^{-1}; GC/MS, *m/e* (relative intensity) 250 (74), 218 (29), 173 (24), 93 (70), 67 (100); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.79 (dd, J = 15.7, 8.2 Hz, 1 H), 5.92 (d, J = 15.7 Hz, 1 H), 5.15 (q, J = 5.2 Hz, 1 H), 3.74 (s, 3 H), 3.60 (m, 2 H), 2.75–1.50 (m, 10 H), 1.38–1.18 (m, 6 H), 1.19 (s, 3 H).

Keto Alcohol 12. To a solution of 100 mg (0.29 mmol) of ketone **11a** in 4 mL of THF was added a solution of 220 mg (0.87 mmol) of lithium hydridotri-*tert*-butoxyaluminate (Alfa) in 1.5 mL of THF dropwise at −75 °C over a period of 10 min under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 2.5 h and at 0 °C for 3 h. The mixture was poured into a cold dilute acetic acid extracted with ether and washed with saturated sodium bicarbonate and water. The organic portion was dried over $MgSO_4$ and concentrated in vacuo to give a mixture of diastereomeric alcohols **11b** [R_f 0.37, 0.29 (50% EtOAc/hexane)] in quantitative yield. The mixture of the crude alcohols in 2 mL of ether, 2 mL of methanol, and 0.5 mL of 5% HCl was stirred at room temperature for 50 min. The solution was extracted with ethyl acetate and concentrated in vacuo. To the residue was added 4 mL of absolute methanol and 150 mg of finely ground anhydrous potassium carbonate and the mixture was stirred at room temperature for 30 min. The mixture was taken up in ethyl acetate, washed successively with 5% HCl, saturated sodium bicarbonate solution, and brine, dried over $MgSO_4$, and concentrated in vacuo to give 64 mg (89%) of keto alcohol **12** as a colorless oil: R_f 0.23 (50% EtOAc/hexane); IR (neat) 3437 (br), 1728, 1716, 1650, 1456 cm^{-1}; GC/MS, *m/e* (relative intensity) 252 (M^+, 20), 193 (15), 180 (53), 149 (40), 113 (90), 81 (100); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.75 (dd, J = 15.6, 7.5 Hz, 1 H), 5.79 (d, J = 15.6 Hz, 1 H), 3.90 (br t, J = 8.7 Hz, 1 H), 3.71 (s, 3 H), 2.60–1.20 (m, 10 H), 0.76 (d, J = 0.5 Hz, 3 H), hydroxyl proton was not observed.

Ester 13. A solution of 62.0 mg (0.25 mmol) of unsaturated ester **12** and 10.0 mg of 10% Pd/C in 4 mL of ethyl acetate was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 30 min. The reaction mixture was filtered through a Celite (10 g) pad with ethyl acetate and the filtrate through a Celite (10 g) pad with ethyl acetate and the filtrate was concentrated in vacuo to give 61.0 mg (98%) of pure ester **13** as a colorless oil: R_f 0.14 (50% EtOAc/hexane); IR (neat) 3460 (br), 1735, 1710, 1435 cm^{-1}; GC/MS, *m/e* (relative intensity) 254 (M^+, 13), 223 (11), 180 (100), 149 (36), 121 (44), 109 (31); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.86 (br t, J = 8.6 Hz, 1 H), 3.67 (s, 3 H), 2.50–1.30 (m, 14 H), 0.71 (s, 3 H), hydroxyl proton was not observed. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.86; H, 8.77.

Keto Acid 15. To a solution of 40.0 mg (0.16 mmol) of ester **13** and 44.0 mg (0.64 mmol) of imidazole in 1.5 mL of DMF was added a solution of *tert*-butyldimethysilyl chloride in 0.7 mL of DMF dropwise at room temperature under a nitrogen atmosphere over a period of 5 min. The solution was stirred for 17.5 h at this temperature and then poured into water. The solution was extracted 8 times with pentane, washed successively with 5% HCl saturated sodium bicarbonate, and brine. The pentane solution was dried over $MgSO_4$ and concentrated in vacuo to give 57.0 mg of silyl ether **14** as a colorless oil. An analytical sample was prepared by flash chromatography (20% EtOAc/hexane): R_f 0.48 (25% EtOAc/hexane); IR (neat) 1739, 1712, 1252 cm^{-1}; GC/MS(CI) *m/e* (relative intensity) 369 (M^+ + 1, 100), 353 (37), 337 (94); ^1H NMR ($CDCl_3$, 90 MHz) δ 3.77 (br t, J = 8.5 Hz, 1 H), 3.65 (s, 3 H), 2.50–1.30 (m, 14 H), 0.85 (s, 9 H), 0.67 (s, 3 H), 0.01 (s, 6 H).

The crude product was dissolved in 5 mL of methanol and was added to 0.5 mL of 5% aqueous potassium hydroxide solution at room temperature. The solution was stirred at this temperature for 4 h and then neutralized with 5% HCl. The reaction mixture was extracted 3 times with methylene chloride, dried over $MgSO_4$, and concentrated in vacuo to give 50.0 mg (91%) of acid **15** as a crystalline solid. Recrystallization gave material of mp 135–136 °C (cyclohexane; lit.[15] mp 118–120 °C, EtOAc); R_f 0.40 (50% EtOAc/hexane); IR ($CHCl_3$) 2957, 2929, 2856, 1706, 1470, 1420, 1137, 1096, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (br t, J = 8.5 Hz, 1 H), 2.50–1.35 (m, 14 H), 0.86 (s, 9 H), 0.68 (s, 3 H), 0.00 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 210.9, 178.3, 80.1, 53.3, 48.4, 46.9, 46.2, 35.9, 31.1, 29.3, 25.8, 23.2, 18.0, 12.2, −4.5, −4.9.

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Registry No. (±)-**1**, 83747-57-3; (±)-**2**, 91202-50-5; (±)-**2** alcohol, 91202-51-6; (±)-**3**, 91202-52-7; (±)-**4a**, 91202-53-8; **4a** cyanohydrin, 91202-54-9; **4a** acetal cyanohydrin, 91202-55-0; (±)-**4b**, 91237-59-1; (±)-**5a**, 91237-60-4; (±)-**5b**, 91237-61-5; (±)-**6**, 91237-62-6; (±)-**7a**, 91202-56-1; **7b**, 91202-57-2; **7b** alcohol, 91202-58-3; (±)-**8a**, 91202-59-4; (±)-**8c**, 91202-60-7; **9a**, 91202-61-8; (±)-**9b**, 91202-62-9; **10**, 91202-63-0; **11a**, 91202-64-1; **11b**, 91202-65-2; (±)-**12**, 91202-66-3; (±)-**13**, 91202-67-4; (±)-**14**, 91202-68-5; (±)-**15**, 91237-63-7; (*E*)-2-butene-1,4-diol, 821-11-4; *tert*-butyldimethylsilyl chloride, 18162-48-6; (*E*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-buten-1-ol, 91202-69-6; (*E*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-buten-1-ol mesylate, 91202-70-9; (*E*)-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-butene, 91202-71-0; $MeO_2CCH{=}PPh_3$, 2605-67-6.

An Efficient Construction of Germacrane Skeleton via the Substituted (Phenylthio)acetonitriles: The Synthesis of (−)-Dihydrogermacrene D†

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An efficient cyclization procedure using intramolecular alkylation of a substituted acetonitrile was developed for the preparation of medium cyclic systems. A synthesis of (−)-dihydrogermacrene D, a sesquiterpene derivative with a 10-membered ring, was achieved via this route.

(−)-Germacrene D (**1**), one of typical germacrane sesquiterpenes which have been recognized as both biogenetic and synthetic precursors to a variety of sesquiterpene families,[1] was first isolated from *Pseudotsuga japnonica* by Hirose and co-workers in 1969.[2] Since then, this labile compound has been detected widely in plants, especially

† Synthesis of medium Cyclic and Macrocyclic Compounds. Part 5, Part 4, T. Kitahara and K. Mori, *Tetrahedron*, in press.

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