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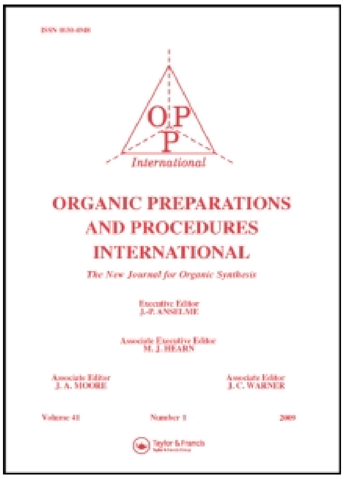

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A SHORT SYNTHESIS OF (±)-α-CHAMIGRENE

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A SHORT SYNTHESIS OF (±)-α-CHAMIGRENE

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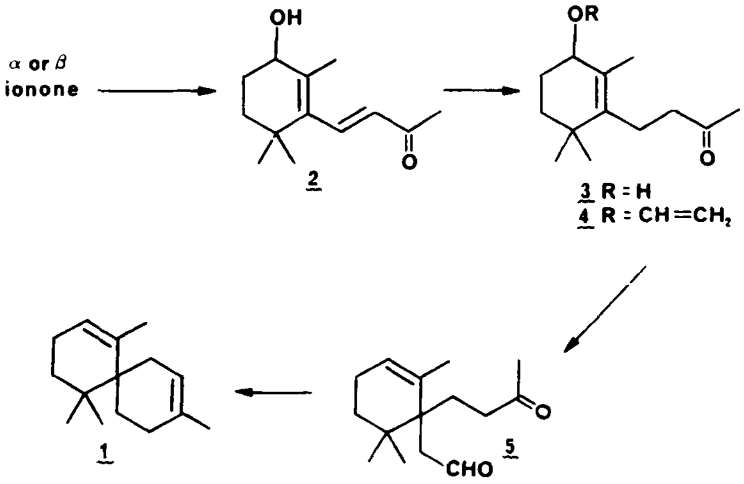
The spirocyclic sesquiterpene α-chamigrene (1) has inspired a fair amount of synthetic work since its isolation in 1968.[1] In connection with our interest in the total synthesis of the more complex diterpene forskolin,[2] we had the occasion to prepare the known alcohol 2 from β-ionone. During this study, it occurred to us that this simple, easily prepared[3] compound might also serve as an advanced precursor to 1, potentially in optically active form.



Selective reduction of the disubstituted olefin in 2 was carried out with NaTeH,[4] furnishing 3[5] in nearly quantitative yield. Transvinylation[6] then gave 4[5] (83%), which underwent smooth Claisen rearrangement (boiling decalin, 90 min., 60%) despite the considerable steric congestion attending

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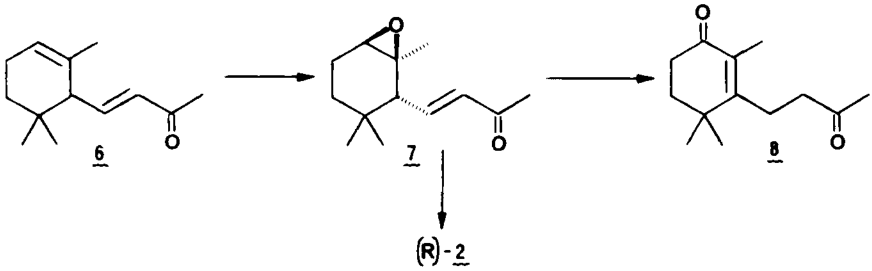
product development. It is worthy of note that neither the Johnson nor Eschenmoser variants of the Claisen rearrangement gave acceptable yields of the desired products (the ester or amide, respectively, corresponding to 5) even though the heteroatom substitution in these systems would be expected on electronic grounds to lower the activation energy for rearrangement.[7]

Application of McMurry's Ti^0 carbonyl coupling methodology[8] to 5 afforded 1, identical in all spectral properties except optical rotation to natural chamigrene.[9] The above sequence should be adaptable to the non-racemic synthesis of 1, as α-ionone (6) has been resolved[10] and transfer of chirality should be possible in the epoxidation/isomerization steps[11] (6 → 2). Experimentally, we have found that base catalyzed isomerization of racemic α-ionone oxide does indeed give a reasonable yield of 2 accompanied by a small amount of diketone 8.[12] Prolonged treatment with base results in the formation of 8 as the major product.



EXPERIMENTAL SECTION

IR spectra were recorded in CCl_4 solution with a Perkin-Elmer 298 instrument. ^1H NMR spectra were obtained with a Varian XL-200 spectrometer in $CDCl_3$ solution with Me_4Si and/or $CHCl_3$ as internal standard. Wh/2 denotes signal width at half height. The ^{13}C spectrum was obtained using an IBM WP-100SY instrument operating at 25 MHz. Mass spectral data (70 e.v.) was collected with a Hewlett-Packard 5987A instrument. Dimethoxyethane (DME) was dried by distillation from potassium. Microanalyses were performed by Robertson Laboratory, Madison, NJ. The term "standard extractive workup" refers to the following set of operations: partitioning of the reaction mixture between H_2O and ether, washing the organic phase with brine, drying ($MgSO_4$), filtering, and evaporating the solvent. Flash chromatography was performed with the solvents indicated, using Merck silica gel 60, 230-400 mesh, as adsorbent.

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Preparation of 3.- To a suspension of sodium hydroden telluride,[4] prepared by stirring tellurium powder (1.64 g, 12.9 mmol) with $NaBH_4$ (1.13 g, 29.7 mmol) in 50 mL of ethanol for 2 hrs at 25° under N_2, was added a solution of 2 (1.10 g, 5.28 mmol) in 5 mL of ethanol. The mixture was stirred for 7 hrs, then filtered through Celite. Evaporation of the solvent followed by standard extractive workup gave 1.03 g (93%) of pure 3.[5]
IR: 3610, 3480, 2940, 1710, 1360, 1240, 1160 cm^{-1}. ^1H NMR: δ 3.90 (t, J = 5 Hz, 1H), 2.54-2.39 (m, 2H), 2.25-2.10 (m, 2H), 2.05 (s, 3H), 1.86-1.43 (m, 3H), 1.60 (s, 3H), 1.32-1.02 (m, 2H), 0.92 (s, 3H), 0.85 (s, 3H). MS, m/e (relative intensity): 210 (M^+, 0.5), 152 (100), 139 (28), 124 (31), 111 (83), 109 (34).

Preparation of 4.- Alcohol 3 (230 mg, 1.09 mmol) was combined with 10 mL of ethyl vinyl ether and 175 mg (0.55 mmol) of $Hg(OAc)_2$. The solution was heated at reflux for 19 hrs during which time three 30 mg increments of $Hg(OAc)_2$ were added. The mixture was cooled and submitted to standard extractive workup. Flash chromatography (hexane/ethyl acetate, 2:1) afforded 213 mg (83%) of 4.[5]
IR: 2960, 1715, 1630, 1355, 1185, 1040 cm^{-1}. ^1H NMR: δ 6.29 (dd, J = 14.2, 6.6 Hz, 1H), 4.32 (dd, J = 14.2, 1.5 Hz, 1H), 4.02 (m, 1H), 4.00 (dd, J = 1.5, 6.6 Hz, 1H), 2.57-2.42 (m, 2H), 2.32-2.17 (m, 2H), 2.07 (s, 3H), 1.91-1.44 (m, 3H), 1.58 (s, 3H), 1.32-1.07 (m, 1H), 0.94 (s, 3H), 0.88 (s, 3H). MS, m/e (relative intensity): 193 (32), 175 (45), 133 (100), 119 (48), 107 (60), 91 (65), 79 (54), 55 (38).

Preparation of 5.- Vinyl ether 4 (100 mg, 0.423 mmol) in 5 mL decalin was heated at reflux under N_2 for 1.5 hr. After evaporation of the solvent, flash chromatography (hexane/ethyl acetate, 1:4) gave 60 mg (60%) of 5.
IR: 2965, 2740, 1715, 1445, 1365, 1355, 1240, 1165 cm^{-1}. ^1H NMR: δ 9.69 (dd, J = 8, 4 Hz, 1H), 5.68 (broad s, $W_{h/2}$ = 9 Hz, 1H), 2.54-2.37 (m, 3H), 2.26 (dd, J = 4, 14 Hz, 1H), 2.08 (s, 3H), 2.02-1.90 (m, 2H), 1.64 (m, 3H),

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1.57-1.40 (m, 2H), 1.23-1.10 (m, 2H), 0.85 (s, 3H), 0.81 (s, 3H). MS, m/e (relative intensity): 236 (M^+, 7), 218 (5), 203 (9), 192 (100), 176 (53), 175 (42), 166 (63), 165 (47).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24

Found: C, 76.35; H, 9.96.

Preparation of (±)-α-Chamigrene (1).- Titanium trichloride (5.01 g, 32.5 mmol), 4.90 g of 95:5 Zn-Cu couple (purchased from Alfa) and 110 mL DME were combined in a flame dried, argon purged 3-necked 500 mL round bottomed flask equipped with a reflux condenser, stirring bar, and rubber septum caps. The suspension was heated at reflux for 1 hr with magnetic stirring. A solution of ketoaldehyde 5 (680 mg, 2.88 mmol) in 20 mL DME was then added to the boiling suspension via syringe pump over the course of 25 hrs. Heating was continued for 14 hrs after the addition was complete. The reaction mixture was then cooled, filtered through Celite, and most of the solvent was removed by careful distillation. The residue was taken up in pentane and washed with H_2O to remove the remaining DME. Flash chromatography (pentane) of the residue obtained upon evaporation of the organic phase yielded 1 (267 mg, 45%).

IR: 2960, 2925, 1450, 1380, 1370, 1090, 1070, 945, 835 cm^{-1}. ^1H NMR: δ 5.50 (s, $W_{h/2}$ = 9 Hz, 1H), 5.36 (s, $W_{h/2}$ = 11 Hz, 1H), 1.95 (m, 6H), 1.81 (m, 2H), 1.64 (s, 6H), 1.24 (m, 2H), 0.88 (s, 3H), 0.82 (s, 3H). ^{13}C NMR, fully decoupled, ($CDCl_3$): δ 140.54, 133.87, 122.91, 122.46, 40.99, 36.16, 33.14, 30.74, 29.29, 29.17, 25.09, 23.55, 23.26, 23.11, 23.07. MS, m/e (relative intensity): 204 (M^+, 9), 148 (4), 136 (87), 121 (100), 105 (28), 93 (61), 91 (54).

Base-catalyzed Isomerization of α-Ionone oxide. Preparation of 2 and 8.- α-Ionone oxide 7[11] (6.82 g, 32.7 mmol) was combined in 90 mL of DME along with 5.0 g (32.7 mmol) of 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU). The solution was heated at reflux for 20 hrs under N_2. After removal of the

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solvent in vacuo, standard extractive workup (Et_2O, 2N HCl) followed by flash chromatography (hexane/ethyl acetate, 1:1) gave, in order of elution, 2.66 g of recovered 7, 0.142 g of 8,[12] and 3.59 g of 2 (53%; 86% based on recovered 7). Longer periods at reflux resulted in disappearance of 7 and led to increased yields of 8 at the expense of 2. ^1H NMR of 8: δ 2.58-2.29 (m, 6H), 2.11 (s, 3H), 1.76-1.64 (m, 2H), 1.63 (s, 3H), 1.07 (s, 6H).

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