(19) A complete summary of this investigation, with full experimental details, is found in the Ph.D. dissertation of P. G. Harris, Clemson University, 1977.
(20) The position of this equilibrium is the same as that reported by Ziegler (ref 10) for a very similar ketone.
(21) R. C. Cambie, K. P. Mathai, and A. W. Misseu, *Aust. J. Chem.*, **25**, 1253 (1972).
(22) The use of olefin **7**, prepared from podocarpic acid, was briefly considered, but rejected on two grounds. First, podocarpic acid is relatively costly and difficult to obtain in quantity, and second, the preparation of acid **4**, the precursor of olefin **7**, is a multistep sequence, with a mediocre overall yield.
(23) S. W. Pelletier and D. C. Herald, *Chem. Commun.*, 10 (1971).
(24) J. W. Huffman and P. G. Harris, *Synth. Commun.*, **7**, 137 (1977).
(25) B. M. Trost and M. Preckel, *J. Am. Chem. Soc.*, **95**, 7862 (1973). This procedure also leads to the conversion of ketones of the type of **6** and **9** to the 4β-carboxylic acids.
(26) J. P. Tresco, J. L. Fourrey, J. Polonsky, and E. Wenkert, *Tetrahedron Lett.*, 895 (1973).
(27) M. Kitadani, A. Yoshikoshi, Y. Kitahara, J. Campello, J. D. McChesney, D. J. Watts, and E. Wenkert, *Chem. Pharm. Bull.*, **18**, 402 (1970).
(28) G. Stork and A. Burgstahler, *J. Am. Chem. Soc.*, **73**, 3544 (1951).
(29) All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates, using a Perkin-Elmer Model 137 spectrophotometer, and are reported in microns. Ultraviolet spectra were taken in 95% ethanol (unless otherwise stated), using a Perkin-Elmer Model 202 spectrophotometer, and are reported as λ_{max} in nanometers (log ϵ). Nuclear magnetic resonance spectra were obtained on either a Varian Associates A-60 or a Perkin-Elmer Hitachi Model R-24 nuclear magnetic resonance spectrometer using deuteriochloroform as a solvent and are reported in parts per million relative to tetramethylsilane (δ). Gas–liquid chromatography was carried out on an F and M Model 810 analytical gas chromatograph using a hydrogen flame detector with helium as the carrier gas. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.
(30) W. E. Bachmann and N. L. Wendler, *J. Am. Chem. Soc.*, **68**, 2580 (1946).
(31) G. H. Schroeter, H. Muller, and J. Y. S. Huang, *Ber.*, **62**, 645 (1929).
(32) This alcohol was prepared by the sodium borohydride reduction of ketone **12**. The physical properties were in agreement with those reported in ref 15.
(33) J. W. Huffman, *J. Org. Chem.*, **35**, 3154 (1970).

Synthesis of 2-Alkylcyclopentenones. Jasmone, Dihydrojasmone, and a Prostaglandin Precursor

Peter Bakuzis* and Marinalva L. F. Bakuzis

Departamento de Química, Universidade de Brasília, Brasília, D.F., 70.000, Brazil

Received December 27, 1976

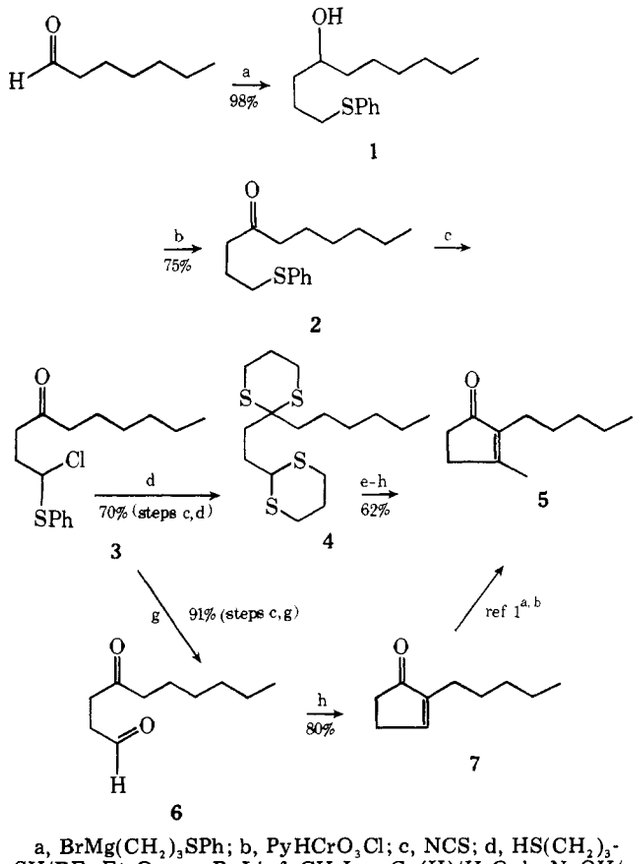
Jasmone (**15**), dihydrojasmone (**5**), and 2-(6-carboxyhexyl)cyclopent-2-en-1-one (**10**) were prepared in several steps from acyclic precursors. Thus, levulinic acid was transformed into a sulfide which was oxidized with *N*-chlorosuccinimide and hydrolyzed to the diketo aldehyde **13**. A chemoselective Wittig reaction, followed by base-catalyzed cyclization, gave jasmone (**15**). Similarly, **5** was prepared from heptanal, while **10** was prepared from azelaic acid monomethyl ester.

2-Alkylcyclopentenones are important intermediates in the preparation of natural products such as jasmones,[1] prostaglandins,[2] steroids,[3] and triterpenes.[4] One method of preparing such compounds is the base-catalyzed cyclization[5] of 1,4-dicarbonyl[6] compounds. While there are many methods of preparing 1,4-diketones,[6a] there are relatively few methods for preparing γ-keto aldehydes.[6b,c] We would like to report a simple sequence of reactions, from readily available starting materials, that permits the synthesis of the 1,4-dicarbonyl precursors of the title compounds.

Grignard reagents prepared from β-halo acetals are known to be unstable,[7] although they have been used for the preparation of alcohols[8] and ketones.[6b] Grignard and lithium reagents prepared from protected bromopropanols and butanols are useful for the preparation of alcohols, ketones, functional homologations, and 1,4-additions to unsaturated systems.[9] However, the preparation of both of these reagents by inexperienced workers is not easy, and the latter reagents are prepared from expensive starting materials. Recently, we showed that Grignard reagents prepared from bromoalkyl phenyl sulfides (easily prepared from the readily available dibromo alkanes) can be used for functional homologations.[10] In this report we present our results on the application of these compounds to the preparation of carbonyl compounds.

While the two sequences outlined in Scheme I for the preparation of dihydrojasmone are longer than the best present method,[11] they illustrate some of the potential of the $PhS(CH_2)_nMgBr$ reagents. Hydroxy sulfide **1**, prepared from heptanal in near-quantitative yields, was oxidized selectively to the carbonyl compound **2** with pyridinium chlorochromate.[12] The key intermediate **3**, prepared by oxidation of **2** with *N*-chlorosuccinimide,[10,13] was transformed into the dithiane **4** and then, by the usual methods[14] of alkylation, hydrolysis, and cyclization, into dihydrojasmone (**5**). Alter-

Scheme I

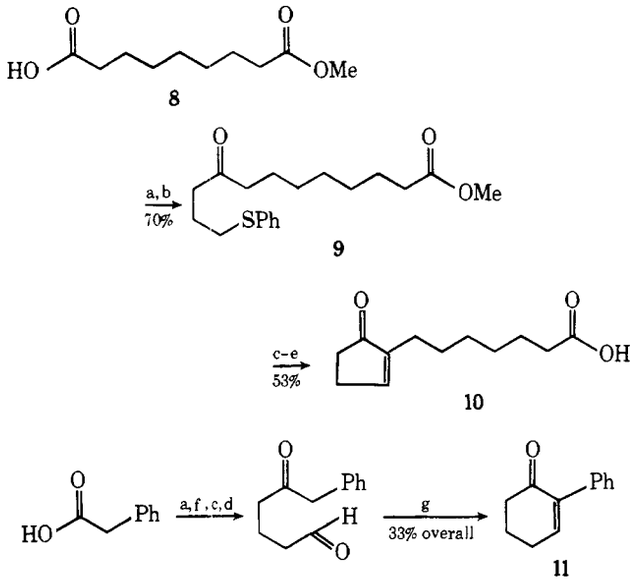


a, $BrMg(CH_2)_3SPh$; b, $PyHCrO_3Cl$; c, NCS; d, $HS(CH_2)_3SH/BF_3 \cdot Et_2O$; e, *n*-BuLi; f, CH_3I; g, Cu(II)/H_2O; h, NaOH/H_2O/Δ.

nately, the chloro sulfide **3** could be hydrolyzed[10,13,15] to keto aldehyde **6**[6b,16] and cyclized[16] to 2-pentylcyclopentenone (**7**). Cyclopentenone **7** has been transformed[1a,b] into dihydrojasmone.

Scheme II shows additional applications of the method for

Scheme II

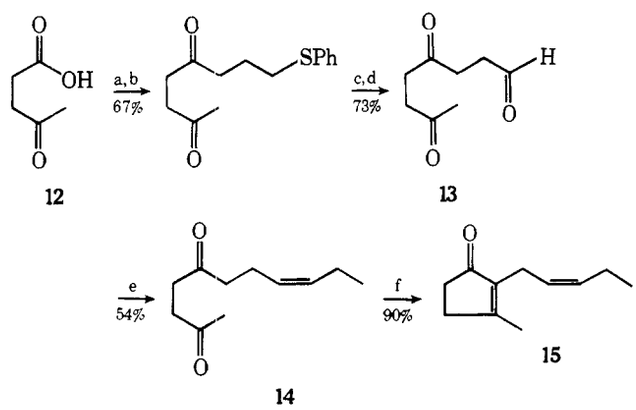


a, *t*-BuCOCl/NEt_3; b, $BrMg(CH_2)_3SPh$; c, NCS; d, Cu(II)/H_2O; e, $NaOH/H_2O/\Delta$; f, $BrMg(CH_2)_4SPh$; g, $NaOH/H_2O$/room temp

synthesis of 2-alkylcycloalkenones. Thus, cyclopentenone **10**,[17] an important intermediate[2] in the synthesis of prostaglandins, was prepared in 37% overall yield from the commercially available azelate **8**. The key intermediate **9** was prepared in a one-pot sequence via the mixed anhydride[11] formed from pivaloyl chloride. Similarly, phenylacetic acid was transformed into 2-phenylcyclohexenone (**11**)[18] in 33% overall yield. (For an additional example of the preparation of a keto sulfide, 7-phenylthio-3-heptanone, see the Experimental Section.)

Scheme III outlines the synthesis of *cis*-jasmone (**15**). Thus, levulinic acid (**12**) was transformed into the diketo aldehyde

Scheme III



a, *t*-BuCOCl/NEt_3; b, $BrMg(CH_2)_3SPh$; c, NCS; d, Cu(II)/H_2O; e, $Ph_3P{=}CHCH_2CH_3$; f, $NaOH/H_2O/\Delta$

13 in 49% overall yield by a sequence of reactions similar to that discussed in Scheme II. A chemoselective Wittig reaction transformed tricarbonyl compound **13** into the key intermediate **14**[19] in 54% yield without requiring protection of the two ketone groups. The stereochemistry of the double bond was assigned cis (>90%) in analogy to known[9e,19b,c] reactions under comparable conditions.[20] Confirmation of this assignment came from the spectra of the cyclized product, *cis*-jasmone (**15**), which showed no absorption in the infrared at 10.32 μ, characteristic of *trans*-jasmone.[21]

Experimental Section

All reactions were run under an atmosphere of N_2. THF was freshly distilled from $LiAlH_4$. Chlorinations of sulfides were found to give erratic results, even when reagent grade CCl_4 was used as solvent. However, reproducible results were obtained by purifying reagent grade CCl_4 by washing with concentrated H_2SO_4, aqueous base, and H_2O, drying over Na_2SO_4, and distilling. The crude chloro sulfides and the derived aldehydes were unstable and thus used immediately after preparation.

Procedure for the Preparation of γ-and δ-Keto Sulfides. Methyl 9-Oxo-12-phenylthiododecanoate (9). To a solution of 1.60 g (7.9 mmol) of azelaic acid monomethyl ester (**8**) in 15 mL of THF at −15 °C was added 1.15 mL (8.3 mmol) of NEt_3 and 1.03 mL (8.4 mmol) of pivaloyl chloride. After stirring at −15 °C for 1 h, the suspension was filtered and the precipitate was washed with 15 mL of THF. To the combined liquid phases, at −78 °C, was added, dropwise, a Grignard solution prepared from 0.19 g (7.8 mmol) of magnesium and 2.28 g (9.8 mmol) of 3-bromopropyl phenyl sulfide[10] in 17 mL of THF. After stirring at −78 °C for 20 min, the solution was allowed to come to room temperature, hydrolyzed with 10% NH_4Cl, and extracted with ether. The organic layer was washed with 10% NaOH and H_2O and dried over Na_2SO_4. The crude product was chromatographed on 90 g of silica gel, 1% ethanol in benzene eluting 1.86 g (70%) of methyl 9-oxo-12-phenylthiododecanoate (**9**). An analytical sample was prepared by bulb-to-bulb distillation: IR (neat) 5.78, 5.82, 6.3, 6.98, 8.52, 13.53, 14.49 μ; ^1H NMR (CCl_4) δ 7.21 (m, 5 H), 3.6 (s, 3 H), 2.88 (t, J = 7 Hz, 2 H). Anal. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.39. Found: C, 67.74; H, 8.39.

The ketones could also be prepared without filtration of the precipitated HCl·NEt_3. In these cases, the original quantity of THF was doubled.

7-Phenylthio-3-heptanone. From 40.8 mmol of propanoic acid and 40.8 mmol of 4-bromobutyl phenyl sulfide[10] a 61% yield of pure keto sulfide was obtained: IR (neat) 5.83, 6.3, 13.53, 14.50 μ; ^1H NMR (CCl_4) δ 7.20 (m, 5 H), 3.0–2.7 (m, 2 H), 2.5–2.0 (m, 4 H), 1.9–1.4 (m, 4 H), 0.97 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.18; H, 8.03.

6-Phenylthio-1-phenyl-2-hexanone. From 20 mmol of phenylacetic acid and 20 mmol of 4-bromobutyl phenyl sulfide a 65% yield of pure keto sulfide was obtained: IR (neat) 5.82, 6.3, 13.5, 14.3, 14.5 μ; ^1H NMR (CCl_4) δ 7.17 (m, 10 H), 3.53 (s, 2 H), 2.76 (t, J = 7 Hz, 2 H), 2.33 (t, J = 7 Hz, 2 H), 1.79–1.42 (m, 4 H). Anal. Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09. Found: C, 75.76; H, 6.93.

8-Phenylthio-2,5-octadione. From 50 mmol of levulinic acid (**12**), 50 mmol of Mg, and 83 mmol of 3-bromopropyl phenyl sulfide a 67% yield of pure diketo sulfide was obtained: IR (neat) 7.83, 6.3, 13.5, 14.5 μ; ^1H NMR (CCl_4) δ 7.24 (m, 5 H), 2.89 (t, J = 7 Hz, 2 H), 2.55 (s, 4 H), 2.09 (s, 3 H); mol wt, 250.1033 (calcd for $C_{14}H_{18}O_2S$, 250.1027).

Preparation of 1-Phenylthio-4-decanone (2). This compound could be prepared from heptanoic acid and 3-bromopropyl phenyl sulfide, but separation from by-products was difficult and therefore the following two-step procedure was developed. To a Grignard solution at room temperature, prepared from 0.64 g of magnesium and 7.7 g of 3-bromopropyl phenyl sulfide in 50 mL of diethyl ether, was added, dropwise, 2.28 g of *n*-heptanal. After stirring for 2 h, the mixture was hydrolyzed with dilute HCl, and the organic layer was washed with water and dried over Na_2SO_4. The crude product was chromatographed on 300 g of silica gel, benzene eluting 0.16 g of heptanal and 8% ether/benzene eluting 4.86 g of 1-phenylthio-4-decanol (**1**) (98%, based on unrecovered heptanal). An analytical sample was prepared by bulb-to-bulb distillation, the sample crystallizing upon cooling: mp 41.5–42.5 °C; IR (neat) 2.95, 6.29, 13.57, 14.5 μ; ^1H NMR (CCl_4) δ 7.22 (m, 5 H), 3.25–3.69 (m, 1 H), 2.9 (t, J = 6.5 Hz, 2 H). Anal. Calcd for $C_{16}H_{26}OS$: C, 72.12; H, 9.84. Found: C, 72.30; H, 9.63.

A mixture of 2.78 g of the alcohol **1**, prepared above and 3.55 g of pyridinium chlorochromate[12] in 50 mL of CH_2Cl_2 was stirred at room temperature for 2 h. After dilution with 50 mL of ether, the mixture was filtered and the filtrate was washed with 10% NaOH solution, 4% HCl solution, and water and dried over Na_2SO_4. The crude product was chromatographed on 75 g of silica gel, elution with benzene giving 2.08 g (75%) of 1-phenylthio-4-decanone (**2**). Continued elution with 8% ether/benzene gave 0.52 g of starting alcohol (**1**). An analytical sample of the ketone was prepared by bulb-to-bulb distillation, the sampling crystallizing upon cooling: mp 33–34 °C; IR (neat) 5.83, 6.29,

13.55, 14.5 μ; ^{1}H NMR (CCl_4) δ 7.2 (m, 5 H), 2.86 (t, J = 7 Hz, 2 H). Anal. Calcd for $C_{16}H_{24}OS$: C, 72.67; H, 9.15. Found: C, 72.62; H, 8.92.

Procedure for the Transformation of γ- and δ-Keto Sulfides into 2-Alkylcycloalkenones. 2-(6-Carboxyhexyl)cyclopent-2-en-1-one (10). A mixture of 484 mg of methyl 9-oxo-12-phenylthiododecanoate (**9**) and 210 mg of NCS in 10 mL of CCl_4 was stirred of 0 °C for 4 h. After the mixture was filtered and the solvent removed, the residue was refluxed for 15 min in a mixture of 450 mg of CuO, 450 mg of $CuCl_2$·$2H_2O$, 0.2 mL of H_2O, and 10 mL of acetone. After cooling rapidly, the mixture was diluted with 50 mL of benzene and filtered, and the filtrate was dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on 30 g of silica gel using 2% ethanol/benzene as eluent to give 292 mg (84%) of methyl 9,12-dioxododecanoate: IR (neat) 3.62, 5.74, 5.82 μ; ^{1}H NMR (CCl_4) δ 9.73 (s, 1 H), 3.59 (s, 3 H), 2.65 (s, 4 H).

Cyclization and hydrolysis of this unstable oil was carried out immediately after isolation. Thus, 829 mg of the oil in 15 mL of EtOH was added, over 25 min, to a degassed solution of 700 mL of 1% NaOH at 75 °C. After stirring for an additional 15 min, the solution was cooled, acidified with concentrated HCl, saturated with NaCl, and extracted with ether (3 × 120 mL). The crude product was chromatographed on 25 g of silica gel, 15–25% ether/benzene eluting 451 mg (63%) of the acid (**10**):[17] IR (neat) 5.85, 6.12 μ; ^{1}H NMR (CCl_4) δ 9.21 (s, 1 H), 7.32 (m, 1 H), 2.8–1.9 (m, 8 H), 1.9–1.1 (m, 8 H).

2-Pentylcyclopentenone (7). From 10 mmol of 1-phenylthio-4-decanone (**2**) and 11 mmol of NCS in 70 mL of CCl_4, at room temperature for 2 h, followed by hydrolysis and column chromatography as above, was obtained a 91% yield of 4-oxodecanal (**6**):[6b,16] IR (neat) 3.65, 5.80, 5.83 μ; ^{1}H NMR (CCl_4) δ 9.75 (s, 1 H), 2.65 (s, 4 H), 2.43 (t, J = 6.5 Hz, 2 H). Cyclization[16] of the keto aldehyde gave 2-pentyl-2-cyclopentenone (**7**):[16] IR (neat) 5.86, 6.10 μ; ^{1}H NMR (CCl_4) δ 7.20 (m, 1 H).

2-Phenylcyclohexenone (11). From 2.6 mmol of 6-phenylthio-1-phenyl-2-hexanone and 3.4 mmol of NCS in 12 mL of CCl_4, at room temperature for 2 h, followed by hydrolysis as above, was obtained an ether solution of crude keto aldehyde which was not isolated. The ethereal layer was washed with 10% HCl solution and then shaken with a 10% NaOH solution until the organic phase became colorless (in a few minutes). After drying and removal of solvent, the residue was chromatographed on 15 g of silica gel, 1:1 petroleum ether/benzene eluting 1.3 mmol (50%) of 2-phenylcyclohexenone (**11**):[18] mp 93.5–94.5 °C (lit.[18] 93–94 °C); IR (KBr) 6.0, 6.21 μ; ^{1}H NMR (CCl_4) δ 7.24 (s, 5 H), 6.92 (t, J = 3.5 Hz, 1 H).

Preparation of Dihydrojasmone (5). A mixture of 1.145 g of 1-phenylthio-4-decanone (**2**) and 0.735 g of NCS, in 30 mL of CCl_4, was stirred at room temperature for 3 h. After filtration and removal of the solvent, the residue was dissolved in 15 mL of CH_2Cl_2 and to this solution, at 0 °C, was added 2.65 mL of 1,3-propanedithiol and 0.25 mL of BF_3·Et_2O. After 5 min, the cooling bath was removed and the mixture was stirred overnight at room temperature and then diluted with ether and poured onto ice. The organic phase was washed three times with 10% NaOH solution and once with brine, and dried over Na_2SO_4. After removal of solvent, the residue was chromatographed on 60 g of silica gel, 1:1 petroleum ether/benzene eluting 1.06 g (70%) of 2-[2-(1,3-dithian-2-yl)ethyl]-2-hexyl-1,3-dithiane (**4**). An analytical sample was prepared by bulb-to-bulb distillation: IR (neat) 6.90, 7.05, 7.86, 8.08, 11.0, 12.46 μ; ^{1}H NMR (CCl_4) δ 3.96 (t, J = 6 Hz, 1 H), 3.2–2.4 (m, 8 H). Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.80; H, 8.62. Found: C, 54.79; H, 8.42.

To a solution of 0.56 g of the above dithiane in 5 mL of THF, at −15 °C, was added, via syringe, 2 mL of 1.3 M n-BuLi in hexane. After stirring for 1 h, the solution was cooled to −78 °C and 0.5 mL of CH_3I was added dropwise, After 1 h, the mixture was allowed to come to room temperature slowly, kept at this temperature for 0.5 h, and then diluted with ether. The ethereal solution was washed with water and dried over Na_2SO_4 and solvent was removed. The residue was chromatographed on 30 g of silica gel, 1:1 petroleum ether/benzene eluting 0.55 g (95%) of 2-[2-(2-methyl-1,3-dithian-2-yl)ethyl]-2-hexyl-1,3-dithiane:[14] IR (neat) 6.88, 7.04, 7.85, 10.99, 12.65 μ; ^{1}H NMR (CCl_4) δ 3.3–2.4 (m, 8 H), 2.04 (s, 4 H), 1.52 (s, 3H).

A mixture of 0.21 g of the above di-dithiane, 0.41 g of $CuCl_2$·$2H_2O$, 0.38 g of CuO, 0.1 mL of H_2O, and 10 mL of acetone was refluxed for 2 h. After cooling, the mixture was diluted with 50 mL of benzene and filtered, and the filtrate was dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on 15 g of silica gel, 1% ethanol/benzene eluting 0.080 g (72%) of 5-oxo-2-undecanone:[1,22] IR (neat) 5.8 μ; ^{1}H NMR (CCl_4) δ 2.58 (s, 4 H), 2.37 (t, J = 6.5 Hz, 2 H), 2.11 (s, 3 H). Dihydrojasmone (**5**)[1] was prepared in the usual way[1] by base-catalyzed cyclization of the diketone (90% yield): IR (neat) 5.88, 6.07 μ; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H).

Preparation of Jasmone (15). A mixture of 263 mg of 8-phenylthio-2,5-octadione and 155 mg of NCS in 10 mL of CCl_4 at −20 °C was stirred for 4 h. After filtration and removal of the solvent, the residue was hydrolyzed by refluxing, for 15 min, with 360 mg of $CuCl_2$·$2H_2O$, 335 mg of CuO, 0.2 mL of H_2O, and 10 mL of acetone. After cooling, the mixture was diluted with 100 mL of benzene and filtered, and the filtrate was dried over Na_2SO_4. After removal of solvent, the residue was chromatographed on 15 g of silica gel, 1.5% ethanol/benzene eluting 28 mg of starting sulfide and 3% ethanol/benzene eluting 107 mg (73%) of 4,7-dioxooctanal (**13**): unstable oil; IR (neat) 3.60, 5.83 μ; ^{1}H NMR (CCl_4) δ 9.65 (s, 1 H), 2.67 (s, 4 H), 2.63 (s, 4 H), 2.10 (s, 3 H).

To a suspension of 770 mg of n-propyltriphenylphosphonium bromide in 25 mL of toluene at room temperature was added, dropwise, 1.4 mL of 1.5 M n-butyllithium in hexane. After stirring for 1 h, the bright red suspension was cooled to −50 °C and to it was added, dropwise, 270 mg of diketo aldehyde **13**, prepared as above, in 2 mL of toluene. After the resulting black-brown suspension was sistirred at −45 to −50 °C for 20 min, the temperature was raised to −15 °C, and the suspension was stirred for 1 h and then allowed to come to room temperature and left overnight. The crude mixture was chromatographed on 30 g of silica gel, benzene eluting 171 mg (54%) of *cis*-8-undecene-2,5-dione (**14**):[19] IR (neat) 5.82 μ (no absorption at 10.3 μ); ^{1}H NMR (CCl_4) δ 5.25 (m, 2 H), 2.57 (s, 4 H), 2.09 (s, 3 H), 0.95 (t, J = 7.5 Hz, 3 H). ^{1}H NMR spectra in $CDCl_3$ at 100 MHz and in benzene at 60 MHz gave no evidence for the presence of the trans isomer. Cyclization of the enedione under the usual conditions[19] gave *cis*-jasmone (**15**):[19] IR (neat) 5.87, 6.05 μ (no absorption[21] at 10.3 μ); ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 2 H), 2.95 (t, J = 5 Hz, 2 H), 2.07 (s, 3 H), 0.98 (t, J = 7.5 Hz, 3 H).

Acknowledgment. We would like to thank Professor Baker of CPPN, Rio de Janeiro, for spectral determinations. The partial support of this work by CNPq and CAPES is gratefully acknowledged.

Registry No.—**1**, 62358-93-4; **2**, 62358-94-5; **4**, 62358-95-6; **5**, 1128-08-1; **6**, 43160-78-7; **7**, 25564-22-1; **8**, 2104-19-0; **9**, 62358-96-7; **10**, 5239-43-0; **11**, 4556-09-6; **12**, 123-76-2; **13**, 62358-97-8; **14**, 4868-21-7; **15**, 4907-07-7; 3-bromopropyl phenyl sulfide, 3238-98-0; 7-phenylthio-3-heptanone, 62358-98-9; propanoic acid, 79-09-4; 4-bromobutyl phenyl sulfide, 17742-54-0; 6-phenylthio-1-phenyl-2-hexanone, 62358-99-0; phenylacetic acid, 103-82-2; 8-phenylthio-2,5-octadione, 62359-00-6; heptanal, 111-71-7; methyl 9,12-dioxododecanoate 50266-44-9; 1,3-propanedithiol, 109-80-8; 2-[2-(2-methyl-1,3-dithian-2-yl)ethyl]-2-hexyl-1,3-dithiane, 62414-94-2; 5-oxo-2-undecanone, 7018-92-0.

References and Notes

(1) For reviews see R. A. Ellison, *Synthesis*, 397 (1973); T. L. Ho, *Synth. Commun.*, **4**, 265 (1974). For recent applications of 2-alkylcyclopentenones in the synthesis of jasmones see (a) U. Ravid and R. Ikan, *J. Org. Chem.*, **39**, 2637 (1974); (b) T. Shono, M. Okawa, and I. Nishiguchi, *J. Am. Chem. Soc.*, **97**, 6144 (1975).

(2) U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products", Vol. I, J. Ap Simon, Ed., Wiley, New York, N.Y., 1973, pp 81–142. For recent synthesis of prostanoids involving 2-alkylcyclopentenones as intermediates see C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *J. Am. Chem. Soc.*, **97**, 857 (1975), and references cited therein; J. F. Bagli and T. Bogri, *J. Org. Chem.*, **37**, 2132 (1972); *Tetrahedron Lett.*, 3815 (1972); F. S. Alvarez and D. Wren, *ibid.*, 569 (1973); P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413; F. Kienzle, G. W. Holland, J. L. Jernow, S. Kwoh, and P. Rosen, *ibid.*, **38**, 3440 (1973); J. G. Miller, W. Kurz, K. G. Untsch, and G. Stork, *J. Am. Chem. Soc.*, **96**, 6774 (1974); C. H. Sih, J. B. Heather, R. Soot, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *ibid.*, **97**, 865 (1975); K. F. Bernady, J. F. Poletto, and M. J. Weiss, *Tetrahedron Lett.*, 765 (1975); G. Stork, C. Kowalski, and G. Garcia, *J. Am. Chem. Soc.*, **97**, 3258 (1975); P. W. Collins, E. Z. Dajani, M. S. Bruhn, C. H. Brown, J. R. Palmer, and R. Pappo, *Tetrahedron Lett.*, 4217 (1975); M. Bruhn, C. H. Brown, P. W. Collins, J. R. Palmer, E. Z. Dajani, and R. Pappo, *ibid.*, 235 (1976); J. A. Noguez, and L. A. Maldonado, *Synth. Commun.*, **6**, 39 (1976); V. L. Melnivoka, A. E. Grigorev, and K. K. Pivnitskii, *Zh. Obshch. Khim.*, **46**, 1425 (1976); G. Traverso and D. Pirello, *Farmaco, Ed. Sci.*, **31**, 305 (1976).

(3) W. S. Johnson, *Angew. Chem., Int. Ed. Engl.*, **15**, 9 (1976); W. S. Johnson and G. E. DuBois, *J. Am. Chem., Soc.*, **98**, 1038 (1976); W. S. Johnson, S. Escher, and B. W. Metcalf, *ibid.*, **98**, 1039 (1976); and references cited therein.

(4) R. E. Ireland, P. Bey, K.-F. Cheng, R. J. Czarny, J.-F. Moser, and R. I. Trust, *J. Org. Chem.*, **40**, 1000 (1975).

(5) B. M. McCurry and R. K. Singh, *J. Org. Chem.*, **39**, 2316, 2317 (1974).

(6) (a) G. Rio and A. L. Nawrocka, *Bull. Soc. Chim. Fr.*, 317 (1976); (b) J. C. Stowell, *J. Org. Chem.*, **41**, 560 (1976); (c) references cited therein.

(7) C. Feugeas, *Bull. Soc. Chim. Fr.*, 2568 (1963).
(8) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969); H. J. J. Loozen, E. G. Godefroi, and J. S. M. M. Besters, *ibid.*, **40**, 892 (1975), and references cited therein.
(9) (a) P. E. Eaton and R. H. Mueller, *J. Am. Chem. Soc.*, 94, 1014 (1972); (b) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972); (c) J. Tufariello and E. J. Trybulski, *ibid.*, **39**, 3378 (1974); (d) R. J. Anderson, V. L. Corbin, G. Cotterrell, G. R. Cox, C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.*, **97**, 1197 (1975); (e) R. J. Anderson and C. A. Henrick, *ibid.*, **97**, 4327 (1975).
(10) P. Bakuzis, M. L. F. Bakuzis, C. C. Fortes, and R. Santos, *J. Org. Chem.*, **41**, 2769 (1976).
(11) M. Araki and T. Mukaiyama, *Chem. Lett.*, 666 (1974).
(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(13) P. Bakuzis, O. S. Campos, and M. L. F. Bakuzis, *J. Org. Chem.*, **41**, 3261 (1976).
(14) R. A. Ellison and W. D. Woessner, *J. Chem. Soc., Chem. Commun.*, 529 (1972).
(15) For the hydrolysis of chloro sulfides in the presence of mercury salts see P. G. Gassman and R. H. Drewes, *J. Am. Chem. Soc.*, **96**, 3002 (1974); A. J. Mura, G. Majestick, P. A. Grieco, and T. Cohen, *Tetrahedron Lett.*, 4437 (1975).
(16) (a) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 4446 (1973); (b) K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1397 (1975); (c) T. Nakai, F. Wada, and M. Okawara, *ibid.*, 1531 (1975).
(17) For recent synthesis of acid **10** and its esters see ref 16b and references cited therein; J.- B. Wiel and F. Rouessac, *J. Chem. Soc., Chem. Commun.*, 180 (1975); A. S. C. P. Rao, U. R. Nayak, and S. Dev, *Synthesis*, 608 (1975).
(18) S. Danishefsky and P. Cain, *J. Org. Chem.*, **40**, 3606 (1975); P. L. Fuchs, *ibid.*, **41**, 2935 (1976). For a one-pot synthesis of 2-alkylcyclohexenones (but not aryl-) see D. F. Taber, *ibid.*, **41**, 2649 (1976).
(19) (a) G. Büchi and Wüest, *J. Org. Chem.*, **31**, 977 (1966); (b) L. Crombie, P. Hemesley, and G. Pattenden, *J. Chem. Soc. C*, 1024 (1969); (c) A. J. Birch, K. S. Keogh, and V. R. Mamdapur, *Aust. J. Chem.*, **26**, 2671 (1973). For a recent synthesis see H. Stetter and H. Kuhlmann, *Synthesis*, 397 (1975).
(20) We found it unnecessary to prepare the Wittig reagent in NH_3 and then replace the solvent with benzene.[19b,c] Rather, the reagent could be prepared in situ in toluene and utilized at low temperature. Analogous observations have been made (ref 9e and references cited therein).
(21) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 869 (1952).
(22) T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).

Factors Governing the Relative Stabilities of the C/D Cis and Trans Ring Junctures in Δ^8-11-Keto Steroids

Donald G. Patterson and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

Young Yuh and Norman L. Allinger*

Department of Chemistry, University of Georgia, Athens, Georgia 30601

Received December 20, 1976

Pure 14α and 14β epimers of Δ^8-11-keto steroids with different 17β-alkyl groups were prepared and the position of their base-catalyzed equilibrium established by gas-liquid phase chromatography. In contrast to 15-keto steroids, where the nature of the 17β substituents crucially affects the cis/trans hydrindanone equilibrium, the 14β (C/D cis) isomer is greatly favored in the present series irrespective of the nature of the C-17 substituent. Using a previously described force-field method, the energies and conformations of the cis and trans isomers of the Δ^8-11-keto steroids were calculated and found to be in reasonable agreement with the experimentally established values.

One of the most interesting problems in steroid conformational analysis lies in the variation of the relative stabilities of the cis and trans (C/D) ring juncture, notably in steroidal hydrindanone systems.[1] Numerous variations observed in these systems led to a whole series of explanations.[1,2] A detailed experimental study using optical rotatory dispersion measurements of 17β-alkyl-5α,14ξ-androstan-15-ones[3] and a subsequent theoretical study using a force-field method[4] were in good agreement.[5] The data generated by this force-field method made it possible to understand the exact nature of the interactions which led to the observed energy differences.[5]

In the 8-methylhydrindane system the cis compound is the more stable one.[2a,5,6] The greater stability of the cis compound can be applied to steroid systems[2a] and Dreiding[7] summarized examples showing trans to cis isomerization of the C/D rings. Most of these compounds had either an isolated or aromatic double bond between C-8 and C-9. Djerassi and co-workers were able to isomerize a Δ^8-11-ketone in the sapogenin series from the 14α to the 14β epimer[8] and Eardley et al.[9] were able to effect a similar change with a Δ^8-11-ketone possessing a 17β-C_9H_{19} substituent.

The object of the present study was to investigate the base-catalyzed equilibration of 17β-alkyl-Δ^8-5α,14ξ-androsten-11-ones, in order to determine what role the size of the 17β-alkyl substituent plays in the relative stabilities of the cis and trans (C/D) ring juncture. In addition, theoretical calculations using the 1973 force-field method[10] were carried out in order to provide insight into the nature of the interactions involved. The results of the experimental study (Table I) are in accord with the theoretical predictions.

Synthesis of Δ^8-11-Keto Steroids. The synthesis of the various Δ^8-11-keto steroids is depicted in Scheme I. Hydrogenation (W-5 Raney nickel) of $\Delta^{5,7}$-cholestadien-3β-ol benzoate (**1**) gave in nearly quantitative yield the known[11] alkene **2**, which upon mercuric acetate oxidation in acetic acid afforded in 69% yield the known[12] $\Delta^{7,9(11)}$-5α-cholestadien-3β-ol benzoate (**3**). Oxidation at 0 °C with *m*-chloroperbenzoic acid gave the known[13] monoepoxide **4**, which was smoothly rearranged in the presence of boron trifluoride etherate to give a 74% yield of Δ^8-5α-cholesten-3β-ol-11-one benzoate (**5**). Owing to the facile alkaline isomerization at C-14, the benzoate **5** was saponified under mild conditions[8] to give the corresponding alcohol **6** which could be acetylated under normal conditions to give the known[14] Δ^8-5α-cholesten-3β-ol-11-one acetate (**6a**). Alternatively, saponification (5% methanolic KOH) of the benzoate **5** afforded in 83% yield the C-14 epimeric alcohol Δ^8-5α,14β-cholesten-3β-ol-11-one (**7**). Base-catalyzed equilibration of pure Δ^8-5α,14α (**6**) and Δ^8-5α,14β (**7**) gave an equilibrium mixture (see Table I) consisting of 96–97% of the 14β (**7**) and 3–4% of the 14α (**6**) epimers.

The versatile starting material Δ^{16}-5α-pregnene-11,20-dion-3β-ol acetate (**8**)[15,16] was chosen for the desired Δ^8-11-one compounds in the androstane and pregnane series. Beckmann rearrangement[17] of the oxime **9** gave 64% of 5α-androstane-11,17-dion-3β-ol acetate (**10**). Saponification to **11** followed