Table I. ^{13}C Chemical Shifts of Darutigenol, Kirenol, and Related Compounds[a]

	3[d]	4[e]	8[f]	9[g]	1[b,h]	2[b,i]	6[b,j]	7[b,k]
C(1)	37.8	48.2	37.8	38.0	37.0	47.3	38.2	38.3
C(2)	26.9	63.8	17.5	17.6	27.2	64.1	17.8	17.8
C(3)	78.8	44.1	35.1	35.2	78.7	43.6	35.3	35.4
C(4)	38.7	40.2	37.3	37.4	38.8	40.2	37.2	37.2
C(5)	54.5	54.6	47.8	47.9	54.1	54.9	47.2	47.2
C(6)	19.4[c]	19.6	19.4[c]	19.1[c]	22.1	21.8	22.0	22.0
C(7)	38.1	38.3	39.2	39.5	35.8	36.0	34.9	34.9
C(8)	81.5	81.9	81.9	82.4	138.9	138.0	138.6	137.1
C(9)	54.5	55.3	54.6	54.9	50.4	50.6	50.3	50.3
C(10)	36.8	38.6	36.8	36.7	37.9	39.2	36.6	36.5
C(11)	19.1[c]	18.9	19.0[c]	19.2[c]	18.2	18.3	17.8	17.8
C(12)	32.9	32.8	33.0	39.1	31.7	31.6	31.5	30.7
C(13)	40.4	40.4	40.4	40.9	37.0	37.0	37.4	36.6
C(14)	54.8	54.7	55.0	52.0	127.4	128.1	127.0	127.7
C(15)	88.0	88.3	88.0	84.7	75.6	76.0	75.5	78.2
C(16)	61.2	61.0	61.2	64.2	63.1	63.0	62.7	62.7
C(17)	22.3	22.4	22.6	19.9	22.8	22.4	21.8	22.9
C(18)	28.5	27.2	71.6	71.7	28.3	27.3	70.8	70.8
C(19)	15.8	65.2	18.0	18.0	15.6	64.6	17.3	18.3
C(20)	14.8	16.7	15.4	15.4	14.6	16.4	14.7	15.1

[a] In ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] In 20:1 $CDCl_3$–CD_3OD (by volume). [c] Assignments in any vertical column may be interchanged. [d] Registry no. 5975-40-6. [e] Registry no. 68152-04-5. [f] Registry no. 68152-05-6. [g] Registry no. 68199-26-8. [h] Registry no. 5940-00-1. [i] Registry no. 52659-56-0. [j] Registry no. 68152-06-7. [k] Registry no. 68199-27-9.

Isokirenol (4). A solution of 110 mg of kirenol in 20 mL of dioxane and 50 mL of chloroform saturated with hydrogen chloride gas was kept at room temperature for 48 h. Workup as above and chromatography of the crude product, 100 mg, on silica gel, followed by elution with 12:1 chloroform–methanol, yielded 55 mg of solid and subsequently 25 mg of another solid which was not characterized. Crystallization of the first product from ethyl acetate afforded crystalline 4: mp 156–157 °C; ^1H NMR δ 0.93, 1.00, 1.03 (s, 3 each, Me_3), 3.3–4.0 (m, 3, H-2, H_2-19), 3.49, 3.59, 3.66, 3.76, 3.81, 3.89, 3.96 (7 lines, 3, H-15, H_2-16).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 80.10; H, 10.20.

Acknowledgment. The authors are indebted to Dr. A. Diara and Professor Takao Murakami for generous samples of darutigenol and kirenol, to Dr. I. R. Burfitt for early ^{13}C NMR determinations, to Professor H. Kagan for the Horeau test,[3] and to Mme. Z. Varon for technical assistance. P.C. acknowledges with gratitude receipt of a travel grant under the Senior Fulbright-Hays Program.

References and Notes

(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 61. For the previous paper see R. Goutarel, M. Pais, H. E. Gottlieb, and E. Wenkert, *Tetrahedron Lett.*, 1235 (1978).
(2) (a) A. Diara, C. Asselineau, P. Laszlo, and J. Pudles, *Bull. Soc. Chim. Fr.*, 99 (1963); (b) J. H. Kim, *Yakhak Hoeji*, **16**, 65 (1972) [*Chem. Abstr.*, **80**, 83511 (1974)]; (c) T. Murakami, T. Isa, and T. Satake, *Tetrahedron Lett.*, 4991 (1973) [cf. also L. Canonica, B. Rindone, C. Scolastico, K. D. Han, and J. H. Kim, *Tetrahedron Lett.*, 4801 (1969)]; (d) F. M. Panizo, B. Rodriguez, and S. Valverde, *An. Quim.*, **70**, 164 (1974) [*Chem. Abstr.*, **81**, 117061 (1974)], and references therein; (e) R. C. Cambie, I. R. Burfitt, T. E. Goodwin, and E. Wenkert, *J. Org. Chem.*, **40**, 3789 (1975).
(3) Application of Horeau's method of determination of the absolute configuration of chiral alcohols to the 3-keto derivative of darutigenol (1), kindly prepared by Mme. Z. Varon, under conditions of exhaustive acylation led to (−)-α-phenylbutyric acid in 6.1% optical yield. Whereas this implies an *S* configuration for C(15), the result is only tenuous in the absence of any knowledge regarding the effect of the neighboring hydroxymethyl group.
(4) (a) E. Wenkert and B. L. Buckwalter, *J. Am. Chem. Soc.*, **94**, 4367 (1972); (b) J. Polonsky, Z. Baskevitch, N. Cagnoli-Bellavita, P. Ceccherelli, B. L. Buckwalter, and E. Wenkert, *ibid.*, **94**, 4369 (1972).
(5) The fact of the triacetates of the pimaratriol epimers **6** and **7** also showing a distinct C(15) shift difference ($\Delta\delta$ = 2.2 ppm) indicates that the dissimilarity of rotamer preferences is not a consequence of the 15,16-diols existing in intramolecularly hydrogen-bonded ($\Delta^{8(14)} \rightarrow$ OH) form.

An Approach to 2,3-Disubstituted Cyclopentanones

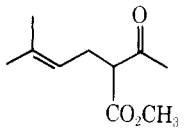
Barry M. Trost* and William C. Vladuchick

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received June 27, 1978

The general importance of cyclopentanones in natural products has led to the development of various methodology for such systems—especially based upon the conjugate addition of cuprates to enones.[1-3] We were specifically interested in the availability of 3-substituted-2-(carboalkoxy)cyclopentanones as a versatile building block for which such conjugate addition reactions are impractical—in part due to the lability of 2-(carboalkoxy)cyclopent-2-en-1-one.[4] We wish to report a new approach to such systems[5] and their utility on constructing 2,3-disubstituted cyclopentanones.

Scheme I summarizes the approach. The initial carbomethoxylation[6a] proceeds with high regioselectivity to give keto ester **1** producing only a very small amount (<5%) of alternate **2.** Separation of these positional isomers was unnecessary since the subsequent diazo transfer reaction[7] gave only diazo compound **3,** the product of reaction of **1.** The intramolecular cyclopropanations[8] to bicyclo[3.1.0]hexane **4** proceeded best with copper–bronze.

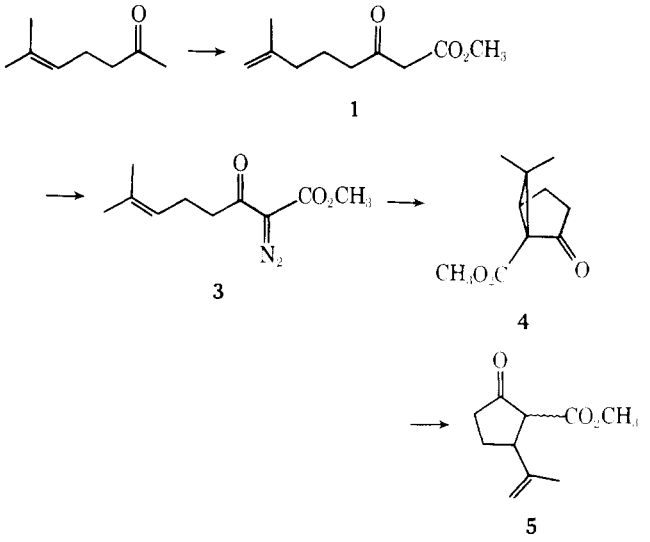


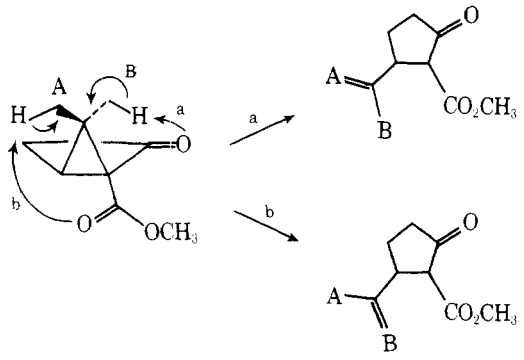
2

The key step is the thermolytic opening of the cyclopropyl ketone which is suggested to be a concerted proton transfer with cleavage of the cyclopropyl C–C bond.[9] Two possible pathways invoke participation of the ketone oxygen (path a) or the ester oxygen (path b). While the product is superficially the same, it does lead to a differentiation of the methyl carbons. Geometrically, path b appears better aligned; furthermore, if the initial proton–oxygen interaction involves the lone pairs on oxygen, only path b is feasible.

In this event, passing a hexane solution of cyclopropyl ketone **4** through a hot column heated at 350 °C smoothly gave keto ester **5.** The crude product was purified by extraction from the organic phase as the potassium enolate salt followed

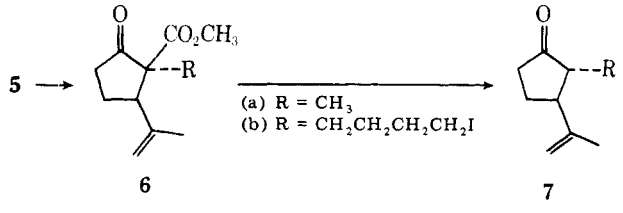
Scheme I. Synthesis of 3-Isopropenyl-2-(carbomethoxy)-cyclopentanone





by immediate acidification and back extraction with ether. Reaction and purification in this manner routinely gave 79% yields of **5**. The 3-isopropenyl substituent can serve as a protected form of a 3-acetyl substituent since the former can be subsequently oxidatively cleaved to the ketone.

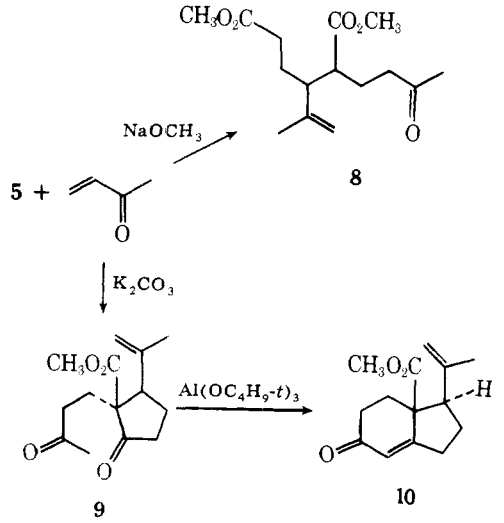
The alkylation of (carbomethoxy)cyclopentanone **5** was accomplished by addition of methyl iodide or 1,4-diiodobutane to a refluxing solution of **5** in benzene containing potas-



6 **7**

sium carbonate.[10] In each case, a single isomer seemed to be produced as indicated by NMR signals for one methyl group and one terminal methylene group. Although the stereochemical outcome of the alkylation was not established experimentally, the stereochemistry is anticipated as depicted on the basis of least hindered approach of the alkylating agent. Attempts to decarbomethoxylate **6a** in acidic media led to extensive decomposition; however, heating a solution of **6** in HMPA containing 2 equiv of tetramethylammonium acetate[11] at 110 °C led smoothly to **7a** in 72% yield.

In an attempt to condense **5** with methyl vinyl ketone utilizing sodium methoxide as base, keto diester **8** was isolated as a diastereomeric mixture. Such a compound results from a retro-Dieckmann cleavage of the desired cyclopentanone **9**. To preclude such a process, the Michael reaction was per-



8 **9** **10**

formed utilizing the nonnucleophilic base, potassium carbonate, which led to **9** in 80% yield. The structure was supported by the presence of three distinct carbonyl absorptions and absorptions for a terminal methylene group in the infrared spectrum. More importantly, **9** is a single stereoisomer as determined by chromatography and by a single set of proton NMR signals for the terminal methylene group and the three different methyl groups. To illustrate the utility of this approach for natural products of the steroid variety, **9** was cyclized to the tetrahydroindanone **10** with aluminum *tert*-butoxide.[12] Other bases led to decomposition or retro-Dieckmann cleavage, whereas acid induced aldol condensation led to decomposition and/or double bond rearrangement.

In summary, the sequence outlined above serves as a potential general entry into the 3-substituted 2-(carbomethoxy)-1-cyclopentanones. The presence of the β-keto ester functionality allows diversified structural elaboration including regiospecific alkylation at C(2) and C(5) (through dianion)[13] without the necessity of trapping a regiospecifically generated enolate. Furthermore, regiospecific Michael addition with traditional Michael acceptors is available which is generally not the case in simple enolate chemistry. An efficient decarbomethoxylation procedure has been demonstrated to complete the 2,3-disubstituted cyclopentanone synthesis. Reduction of the ketone and dehydration of the resultant β-hydroxy ester to the enoate can make available yet another versatile grouping for structural elaboration.

Experimental Section

All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were obtained as solutions in the indicated solvent on a Perkin-Elmer 267 spectrophotometer and are reported in reciprocal centimeters. NMR spectra were determined in the indicated solvent on a Jeolco MH-100 (100 MHz) instrument; chemical shifts are reported in ppm downfield from tetramethylsilane (Me_4Si). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; addition of b indicates a broadened pattern. Coupling constants are given in hertz. Mass spectra were recorded on an AEI-MS-902 high resolution mass spectrometer at ionizing voltage of 70 eV and an ionizing current of 100 mA unless otherwise specified. Boiling points are uncorrected. Thin-layer or preparative thick-layer (1.5 mm) plates were made of E. Merck AG Darmstadt silica gel PF-254 and activated by drying at 140 °C for 2 h. Eluting solvents are indicated in the text. Removal of material from the silica gel was accomplished by successive washings with ether or ethyl acetate.

In experiments requiring dry solvents, ether, tetrahydrofuran, dioxane, and dimethoxyethane were distilled from sodium benzophenone ketyl. Benzene, toluene, methylene chloride, dimethylformamide, triethylamine, xylene, hexane, and pyridine were distilled from calcium hydride. Methyl vinyl ketone was distilled from hydroquinone immediately before use. Apparatus for experiments requiring anhydrous conditions was dried by flaming in a stream of nitrogen.

Methyl 7-Methyl-3-oxo-6-octenoate (1). Sodium hydride oil dispersion (57%, 51.0 g (29.0 g), 1.2 mol) was washed twice with hexane and then suspended in dimethyl carbonate (108.0 g, 1.2 mol) and anhydrous ether (150 mL). To this stirred slurry at room temperature was added 6-methyl-5-hepten-2-one (75.7 g, 0.6 mol) dropwise over 5 h and then an additional 400 mL of anhydrous ether. After stirring at room temperature for 4 h, 50 mL of anhydrous methanol was added dropwise to quench the excess sodium hydride. Stirring was continued at room temperature until the hydrogen evolution subsided. Ice (~50 g) was added to the solution which was then acidified with cold (0 °C) aqueous 3 N hydrochloric acid to pH 5. The phases were separated and the aqueous portion was further acidified to pH 3 and extracted with ether (2 × 150 mL). The combined organic portions were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was distilled at reduced pressure to yield 66 g (60%) of methyl 7-methyl-3-oxo-6-octenoate as a clear colorless oil, bp 85–90 °C (0.6 mm) (lit.[6b] bp 129–31 °C (12 mm)), homogeneous by TLC.

1-Carbomethoxy-6,6-dimethyl-2-oxobicyclo[3.1.0]hexane (4). A solution of *p*-toluenesulfonyl azide (4.53 g, 23.0 mmol) in acetonitrile (8 mL) was added via syringe to a stirred solution of methyl 7-methyl-3-oxo-6-octenoate (4.23 g, 23.0 mmol) in anhydrous triethylamine (3.21 mL, 2.33 g, 23.0 mmol) and acetonitrile (30 mL). The resulting solution was stirred at room temperature for 10 h and then added to a separatory funnel containing 100 mL of ether and 100 mL of saturated aqueous ammonium chloride. The phases were separated

and the aqueous phase back-extracted with ether. The combined organic portions were washed with cold (0 °C) 4 N aqueous potassium hydroxide, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo to yield 4.76 g (99%) of methyl 2-diazo-7-methyl-3-oxo-6-octenoate (**3**) as an opaque off-white oil. The purity of the material obtained in this manner was sufficient to allow further reaction without purification: IR (CCl_4) 2120, 1725, 1660, 1375, 1305, 1055; NMR (100 MHz, CCl_4) δ 1.61 (3 H, s), 1.66 (3 H, s), 2.10–2.40 (2 H, m), 2.76 (2 H, t, J = 8 Hz), 3.76 (3 H, s), 4.96–5.20 (1 H, m).

A slurry of **3** (4.76 g, 22.7 mmol), copper–bronze powder (2.0 g), and toluene (100 mL) was refluxed for 1.5 h. The slurry was cooled, filtered through celite, and diluted with ether. The solution was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was distilled at reduced pressure to give 2.5 g (60%) of 1-(carbomethoxy)-6,6-dimethyl-2-oxobicyclo[3.1.0]hexane as a clear oil, bp 74–78 ° (0.5 mm), homogeneous by TLC and spectroscopic criteria: IR (CCl_4) 1735 (br), 1440, 1315; NMR (CCl_4) δ 1.08 (3 H, s), 1.10 (3 H, s), 1.50–2.50 (5 H, m), 3.57 (3 H, s). Anal. Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0943.

2-(Carbomethoxy)-3-isopropenylcyclopentanone (5). A solution of **4** (2.5 g, 13.7 mmol) and hexane (10 mL) was added dropwise over 30 min into a hot column (length = 40 cm, inside diameter = 2.5 cm, column volume = 300 mL) packed with glass helices heated to 350 °C. A nitrogen flow (500 mL/min) was maintained through the column. The column exit was equipped with two U-traps containing glass beads and maintained at −78 °C. Upon completion of the addition, the column was washed with hexane and cooled. After a final washing with ether, the combined washings from the traps and column were dried over anhydrous sodium sulfate and concentrated in vacuo. The residual oil was dissolved in ether and extracted with cold (13 °C, critical temperature) 4 N aqueous potassium hydroxide (3 × 100 mL). The cold aqueous portions were *immediately* acidified with cold (0 °C) 6 N aqueous hydrochloric acid to pH 5. The acidified aqueous portion was exhaustively back-extracted with ether (6 × 175 mL). The combined organic portions were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 1.95 g (79%) of 2-(carbomethoxy)-3-isopropenylcyclopentanone as a clear oil, homogeneous by TLC and spectroscopic criteria: IR (CCl_4) 1770, 1740, 1670, 1440, 896; NMR (100 MHz, CCl_4) δ 1.68 and 1.76 (3 H, 2 broad singlets), 2.05–2.60 (4 H, m), 3.12 (1 H, d, J = 4.0 Hz), 3.22–3.75 (1 H, m), 3.69 (3 H, s), 4.66 and 4.71 (1 H, 2 broad singlets). Anal. Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0943.

2-(Carbomethoxy)-3-isopropenyl-2-methylcyclopentanone (6a). A solution of **5** (2.05 g, 11.2 mmol) in anhydrous acetone (20 mL) containing anhydrous potassium carbonate (3.45 g, 25.0 mmol) was heated to reflux. Methyl iodide (3.1 mL, 7.05 g, 50 mmol) was added to the refluxing slurry in three portions at 1-h intervals. After the last addition, the slurry was refluxed for an additional 2 h, cooled, and added to ether (150 mL) and water (50 mL) and the phases were separated. The organic portion was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by Kugelrohr distillation to give 1.86 g (85%) of 2-(carbomethoxy)-3-isopropenyl-2-methylcyclopentanone as a clear almost colorless oil, bp 80–88 °C (0.9 mm), homogeneous by TLC and spectroscopic criteria: IR (CCl_4) 2980, 2960, 1750, 1720, 1645, 1435, 1380, 1150, 1085, 896; NMR (100 MHz, CCl_4) δ 1.36 (3 H, s), 1.80 (3 H, s), 1.60–2.80 (5 H, m), 3.60 (3 H, s), 4.88 (2 H, bd, J = 7 Hz). Anal. Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1100.

3-Isopropenyl-2-methylcyclopentanone (7a). A solution of **6a** (1.05 g, 5.37 mmol), tetramethylammonium acetate (2.66 g, 20.0 mmol), and anhydrous hexamethylphosphorictriamide (5 mL) was heated to 100 °C and maintained there for 12 h. The reaction mixture was cooled and exhaustively extracted with ether. The combined organic portions were washed with water, saturated aqueous sodium carbonate, and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and then concentrated by distillation through a 10-cm Vigreux column. The residual oil was distilled at reduced pressure to yield 0.53 g (72%) of 3-isopropenyl-2-methylcyclopentanone[14] as a clear colorless oil, bp 75–77 °C (7.5 mm), homogeneous by TLC, VPC, and spectroscopic criteria. Its spectral properties agree with the published values.

2-(Carbomethoxy)-2-(4′-iodobutyl)-3-isopropenylcyclopentanone (6b). To a slurry of **5** (0.745 g, 4.10 mmol), anhydrous potassium carbonate (1.04 g, 7.5 mmol), and anhydrous acetone (5 mL) stirring at room temperature was added 1,4-diiodobutane (4.32 g, 14.0 mmol) via syringe. The resulting reaction mixture was refluxed for 18 h and then stirred at room temperature for 1 h. The reaction mixture was added to ether and water and the phases were separated. The aqueous portion was exhaustively extracted with ether. The combined organic portions were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The excess alkylating agent was relatively nonpolar and could be separated by column chromatography (column length = 60 cm, inside diameter = 2.5 cm, 100 g silica gel) by eluting with hexane. Continued elution with 10% ether/hexane gave 0.85 g (57%) of 2-(carbomethoxy)-2-(4′-iodobutyl)-3-isopropenylcyclopentanone as a clear oil: IR (CCl_4) 1760, 1745, 1650, 895; NMR (100 MHz, CCl_4) δ 1.78 (3 H, bs), 1.6–2.95 (5 H, m), 3.18 (2 H, t, J = 7 Hz), 3.55 (3 H, s), 4.78 (1, H, bs), 4.88 (1 H, bs). Anal. Calcd for $C_{14}H_{21}O_3I$: 364.0535. Found: 364.0535.

Methyl 5-(Carbomethoxy)-4-isopropenyl-8-oxononoate (8). A solution of sodium methoxide was freshly prepared by adding sodium metal (50 mg, 2.2 mg-atom) to anhydrous methanol (3 mL) and stirring at room temperature for 5 min. To the resulting solution was added a solution of **5** (243 mg, 1.33 mmol) and anhydrous benzene (8 mL). After stirring for 10 min, methyl vinyl ketone (0.25 mL, 210 mg, 3.00 mmol) was added via syringe to the reaction mixture. Stirring at room temperature was continued for 10 h. The solution was added to ether and saturated aqueous ammonium chloride. The phases were separated and the aqueous portion extracted with benzene. The combined organic portions were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC to give 267 mg (71%) of methyl-5-(carbomethoxy)-4-isopropenyl-8-oxononoate as a clear viscous oil, R_f 0.4 (4 elutions), homogeneous by TLC and spectroscopic criteria: IR (CCl_4) 2940, 1745, 1440, 1160, 895; NMR (100 MHz, CCl_4) δ 1.62 (3 H, bs), 2.03 (3 H, s), 1.10–2.45 (10 H, m), 3.52, 3.55, 3.57, 3.62 (6 H, 4 singlets), 4.74 (2 H, bt, J = 9.5 Hz). Anal. Calcd for $C_{15}H_{24}O_5$: 284.1624. Found: 284.1623.

2-(Carbomethoxy)-3-isopropenyl-2-(3′-oxobutyl)cyclopentanone (9). To a slurry of **5** (385 mg, 2.12 mmol), anhydrous potassium carbonate (413 mg, 3.0 mmol), and benzene (12 mL) stirring at room temperature was added via syringe methyl vinyl ketone (0.25 mL, 210 mg, 3.0 mmol). After stirring for 3 h a second aliquot of methyl vinyl ketone (0.25 mL, 210 mg, 3.0 mmol) was added and stirring continued for 4 h. The solution was added to benzene and water and the layers were separated. The aqueous portion was extracted with benzene and the combined organic portions were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (10% 2-propanol in hexane) to give 428 mg (80%) of pure 2-(carbomethoxy)-3-isopropenyl-2-(3′-oxobutyl)cyclopentanone as a clear oil, R_f 0.47 (3 elutions), homogeneous by TLC and spectroscopic criteria: 3080, 2940, 1760, 1740, 1725, 1645, 1440, 1360, 1220, 1170, 859; NMR (100 MHz, CCl_4) δ 1.73 (3 H, s), 2.01 (3 H, s), 1.60–2.9 (9, H, m), 3.56 (3 H, s), 4.76 (1 H, bs), 4.85 (1 H, bs). Anal. Calcd for $C_{14}H_{20}O_4$: 252.1362. Found: 252.1363.

5,6,7,8-Tetrahydro-8β-(carbomethoxy)-1β-isopropenyl-5-oxo-$\Delta^{4(9)}$-indane (10). A solution of **9** (143 mg, 0.57 mmol) and anhydrous benzene (4 mL) containing aluminum *tert*-butoxide (265 mg, 1.1 mmol) was refluxed for 72 h. The reaction mixture was cooled to approximately 0 °C (ice bath) and neutralized by the addition of cold (0 °C) 3 N aqueous hydrochloric acid to pH 5. The phases were separated and the aqueous portion exhaustively extracted with ether. The combined organic portions were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by Kugelrohr distillation to give 50 mg (38%) of 5,6,7,8-tetrahydro-8β-(carbomethoxy)-1β-isopropenyl-5-oxo-$\Delta^{4(9)}$-indane as an opaque oil, bp 140–150 °C (0.7 mm), homogeneous by TLC and spectroscopic criteria: IR (CCl_4) 2980, 1730, 1680, 1650, 1170, 910; NMR (CCl_4) δ 1.76 (3 H, s), 1.5–3.1 (9 H, m), 3.65 (3 H, s), 4.84 (2 H, bd, J = 8 Hz), 5.72 (1 H, unresolved t, J = 1.5 Hz). Anal. Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1256.

Acknowledgment. We wish to thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We also thank BASF for a generous gift of 6-methyl-5-hepten-2-one.

Registry No.—**1**, 53067-23-5; **3**, 62344-23-4; **4**, 68151-47-3; **5**, 68151-48-4; **6a**, 68151-49-5; **6b**, 68151-50-8; **7a**, 24903-98-8; **8** isomer 1, 68151-51-9; **8** isomer 2, 68151-54-2; **9**, 68151-52-0; **10**, 68151-53-1; 6-methyl-5-hepten-2-one, 110-93-0; 1,4-diiodobutane, 628-21-7; methyl vinyl ketone, 78-94-4.

References and Notes

(1) For reviews see: (a) Mitra, A. "The Synthesis of Prostaglandins"; Wiley-Interscience: New York, 1977; (b) Bindra, J. S.; Bindra, R. "Prostaglandin

Synthesis"; Academic Press: New York, 1977; (c) Bentley, P. H. *Chem. Soc. Rev.* **1973,** *2,* 29.
(2) (a) Posner, G. H.; Sterling, J. L.; Whitten, C. E.; Lentz, C. M.; Burnelle, D. J. *J. Am. Chem. Soc.* **1975,** *97,* 107; (b) Stork, G.; Singh, J. *ibid.* **1974,** *96,* 6181; (c) Stork, G.; d'Angelo, J. *ibid.* **1974,** *96,* 7114; Boeckman, Jr., R. K. *ibid.* **1974,** *96,* 6179.
(3) (a) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976,** 3857; (b) Taber, D. F. *J. Am. Chem. Soc.* **1977,** *99,* 3513; (c) Kondo, K.; Unemoto, T.; Takahatake, Y.; Tunemoto, D. *Tetrahedron Lett.* **1977,** 113; (d) Kondo, K.; Araki, N.; Tunemoto, D. *ibid.* **1977,** 109; (e) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978,** *100,* 348.
(4) Marx, J. N.; Cox, J. H.; Norman, L. R. *J. Org. Chem.* **1972,** *37,* 4489.
(5) For an alternative see Yates, P.; Jorgenson, M. J.; Singh, P. *J. Am. Chem. Soc.* **1969,** *91,* 4739.
(6) (a) Green, N.; Schechter, M. S.; LaForge, F. B. *J. Am. Chem. Soc.* **1949,** *71,* 3165; (b) Leyedecker, F. *Tetrahedron,* **1976,** *32,* 349.
(7) Regitz, M.; Hocker, J.; Leidhegener, A. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V.
(8) Cf. Stork, G.; Ficini, J. *J. Am. Chem. Chem. Soc.* **1961,** *83,* 4678; Julia, J.; Linstrumelle, G. *Bull. Chim. Soc. Fr.* **1966,** 3490.
(9) McGreer, D. E.; Chiu, N. W. K. *Can. J. Chem.* **1968,** *46,* 2217.
(10) Barco, A.; Benetti, S.; Pollini, G. P. *Synthesis* **1973,** 316.
(11) (a) W. S. Johnson, private communication; (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976,** *98,* 630; **1978,** *100,* 3435.
(12) For a related reaction see Dauben, W. G.; McFarland, J. W.; Rogan, J. B. *J. Org. Chem.* **1961,** *26,* 297.
(13) Cf. Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974,** *52,* 2157; *J. Am. Chem. Soc.* **1974,** *96,* 1082.
(14) Mayer, C. F.; Crandall, J. K. *J. Org. Chem.* **1970,** *35,* 2688.

Simple Method for the Reductive Dehalogenation of 9α-Bromo Steroids

Howard Parnes* and John Pease

Contribution No. 508, the Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

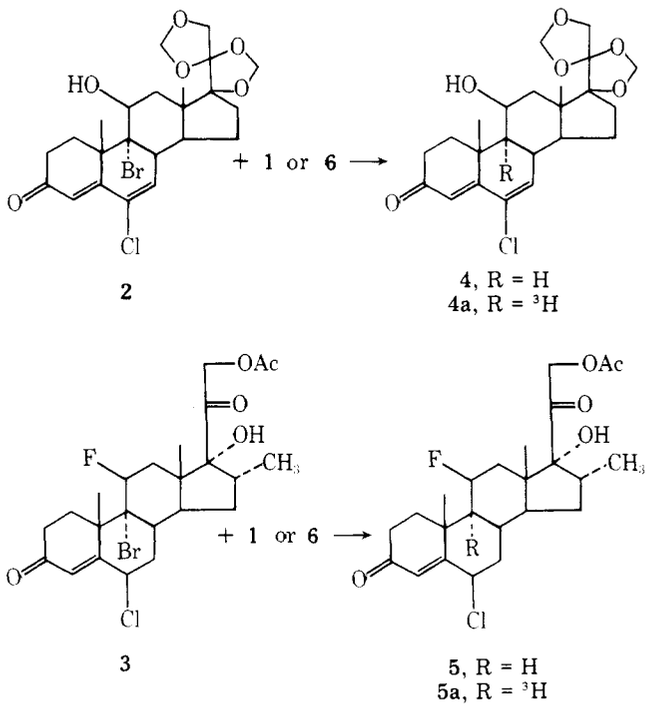
Received April 24, 1978

The 11β-hydroxy group is an important structural feature which contributes to the high biological activity of corticosteroids. It is reasonable to suppose, therefore, that other substituents at C-11 might lead to new, highly active compounds. A convenient route to such compounds would be by reductive dehalogenation of an 11β-substituted 9α-bromo steroid. This type of precursor is readily available from various $\Delta^{9(11)}$ steroids.[1-3] A survey of the literature shows, however, that only one reagent, chromous acetate in the presence of butanethiol (or other hydrogen atom transfer agent),[4] has been found to effect the desired reduction. Other reducing agents are either unreactive or cause elimination to the $\Delta^{9(11)}$ compound. The $Cr^{II}(OAc)_2$/BuSH procedure, however, is cumbersome and operationally difficult to implement. We wish, therefore, to describe a new and efficient method for the reductive dehalogenation of 9α-bromo steroids using *n*-Bu_3SnH (**1**).

The use of *n*-Bu_3SnH as a selective reducing agent toward halogen is well known and has been reviewed by Kuivila,[5,6] yet there have been no attempts to reduce 9α-bromo steroids[9] with this reagent. We felt that **1** would effect the desired debromination for two reasons. First of all, as in the case of $Cr^{II}(OAc)_2$/*n*-BuSH, reductions involving **1** are believed to proceed by a free-radical process. Furthermore, bromohydrins and certain vicinal dihalides undergo reduction rather than elimination,[7] which is the case with other reducing agents.

The bromohydrin **2** and the 9α-bromo-11β-fluoro steroid **3** were chosen as model compounds and our process is outlined in Scheme I. In each case the 9α-bromo steroid was stirred in THF solution either at room temperature or at reflux with a small excess of *n*-Bu_3SnH (in some cases a trace of azobis(isobutyrylnitrile) was added to initiate the reaction). The reaction mixture was examined by TLC until no further change in composition was observed. Aqueous workup followed by chromatographic purification or crystallization afforded the reduced products **4** and **5** in yields of 63 and 64%, respectively. There was no trace of the $\Delta^{9(11)}$ elimination product.

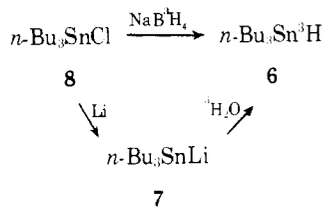
Scheme I



2 4, R = H; 4a, R = ^3H

3 5, R = H; 5a, R = ^3H

Scheme II



7

The NMR and mass spectra of the products were consistent with their proposed structures. The NMR spectra of **4** and **5** were easily distinguishable from their respective starting materials **2** and **3** by a clear upfield shift in the 19-CH_3 resonance [30 Hz for **4** and 17 Hz for **5**] of the former.

The method described above was extended to the synthesis of 9α-tritiated steroids with the preparation of *n*-Bu_3Sn^3H (**6**). Neither **6** nor 9α-^3H steroids have been previously reported.

Two methods were used to prepare **6** (Scheme II). In method a, *n*-Bu_3SnLi[8] (**7**) was quenched with freshly prepared ^3H_2O. In method b, **6** was generated by reduction of *n*-Bu_3SnCl (**8**) with NaB^3H_4. In each case **6** was reacted, without isolation, with either **2** or **3** (Scheme I). The 9α-tritiated products, **4a** and **5a,** respectively, were isolated from the reaction mixture by extraction and purified by TLC. Both labeled products were identified by comparing their radiochromatography scans against the authentic standards, **4** and **5**, which were prepared as described above. Method b is clearly preferred over method a for the generation of **6**. It is operationally much simpler to carry out, results in cleaner reaction mixtures, and affords higher yields.

We are currently investigating the scope of the selective debromination reaction described here toward the preparation of other 11β-substituted steroids. In addition, our preparation of *n*-Bu_3Sn^3H now offers the possibility of synthesizing a variety of specifically labeled compounds, many of which would be quite difficult to prepare by other methods.

0022-3263/79/1944-0151$01.00/0