Stereoselective Total Synthesis of (±)-Eremoligenol, (±)-Eremophilene, (±)-Valerianol, and (±)-Valencene[1]

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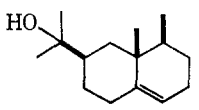
Synthetic access to the two stereoisomeric classes of bicyclic eremophilone-type sesquiterpenes has been gained through the lithium–ammonia reduction of the methoxymethyl enol ether of ethyl 8β,8aβ-dimethyl-1-oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (**5**). This reaction affords directly the less stable axial ester (**11**), ethyl 8β,8aβ-dimethyl-1,2,3,4,6,7,8,8a-octahydro-2β-naphthoate, which was converted into (±)-eremoligenol and (±)-eremophilene. (±)-Valerianol and (±)-valencene were obtained from the epimeric equatorial ester (**12**).

In recent years the number of naturally occurring sesquiterpenoids having the nonisoprenoid decalin nucleus of eremophilone has grown from a few rare examples to a major group of natural products.[3] Among the bicarbocyclic members of this group, there exist two major subclasses which are distinguished by the relative stereochemistry between the C-7 substituent and the *cis* vicinal methyl groups. The biogenetically simplest members with a *cis* relationship between each of the three nuclear substituents are eremoligenol **1**[4] and eremophilene **2**.[5] In the *trans* series the structures **3** and **4** correspond to the natural sesquiterpenes valerianol **3**[6,7] and valencene **4**.[8]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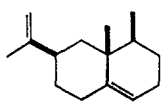
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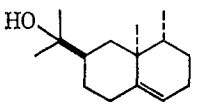
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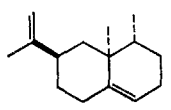
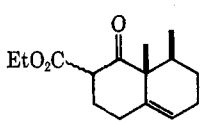

(+)-4

In a previous investigation[9] we have described a synthesis of the bicyclic β-keto esters, **5** and **6**. The former substance, having the annular methyl groups in a *cis* orientation, appeared to offer a simple synthetic entry into either or both of these two stereoisomeric classes of sesquiterpenes. The principal obstacle to this approach was the conversion of the relatively hindered ketone group in the β-keto ester **5** to a methylene group. In this paper we describe a new and direct method for effecting this reductive transformation which has enabled the stereoselective total synthesis of the four sesquiterpenoids **1**–**4** in racemic form.[10,11]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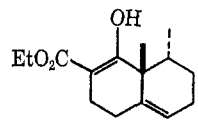
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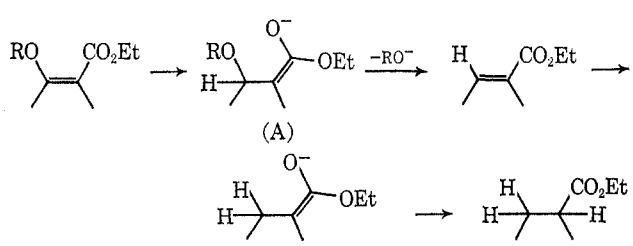
Although there are a number of different chemical procedures available for the reduction of a ketone carbonyl to a methylene group, the proximity of the ester function in a β-keto ester can present serious complications. The harsh alkaline conditions of the Wolff–Kishner reduction would very likely lead to either (or both) hydrolysis of the ester group[12] and decarboxylation or "acid" cleavage products.[13] The Clemmensen method[14] was not suitable to present case for fear of acid-catalyzed rearrangement or double-bond migration. Although the hydrogenolysis of the dithio ethylene ketal has been used successfully for the reduction of β-keto esters,[15] this approach is not feasible with **5** because the sterically hindered environment of the ketone precludes ketal formation.[9a,c]

With the knowledge that α,β-unsaturated acids may be reduced to saturated acids by means of metal–ammonia solutions,[16] we considered that an enol derivative of a β-keto ester might undergo a double reduction to a saturated ester under these conditions. That is, the enolate anion intermediate (A) in such a reduction should eliminate the enol oxygen to form the α,β-unsaturated ester. The latter would be subject to a second reduction leading to the saturated ester upon quenching of the reaction with a proton donor.


(A)

(1) Taken in part from Ph.D. Thesis of J. E. Shaw.

(2) National Science Foundation Trainee, 1965–1969.

(3) For recent reviews see A. R. Pinder, *Perfum. Essent. Oil Rec.*, **59**, 280, 645 (1968).

(4) H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc., C*, 1545 (1966).

(5) J. Krěpinský, O. Motl, L. Dolejš, L. Novotný, V. Herout, and R. B. Bates, *Tetrahedron Lett.*, 3315 (1968); J. Hochmannová and V. Herout, *Collect. Czech. Chem. Commun.*, **29**, 2369 (1964); E. Piers and R. J. Keziere, *Tetrahedron Lett.*, 583 (1968).

(6) G. Jommi, J. Krěpinský, V. Herout, and F. Sörm, *Collect. Czech. Chem. Commun.*, **34**, 593 (1969).

(7) Also referred to as kusunol: H. Hikino, N. Suzuki, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 832 (1968).

(8) (a) G. L. K. Hunter and W. B. Brogden, *J. Food Sci.*, **30**, (1965); (b) W. D. MacLeod, Jr., *Tetrahedron Lett.*, 4779 (1965).

(9) (a) R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47 (1968); (b) *ibid.*, 515 (1968); (c) *J. Amer. Chem. Soc.*, accepted for publication.

(10) A part of this research has appeared as a preliminary communication: R. M. Coates and J. E. Shaw, *Tetrahedron Lett.*, 5405 (1968).

(11) The recently announced synthesis of nootkatone [M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Commun.*, 1152 (1968)], constitutes a total synthesis of (±)-valencene since natural nootkatone has been converted into valencene.[8b] See also J. A. Marshall and R. A. Ruden, *Tetrahedron Lett.*, 1239 (1970).

(12) *Cf.* D. Todd, *Org. React.*, **4**, 378 (1948).

(13) The "acid" cleavage of β-diketones under Wolff–Kishner conditions has been reported: H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 290, 1061 (1952); **86**, 693 (1953); H. Stetter and E. Klauke, *ibid.*, **86**, 513 (1953).

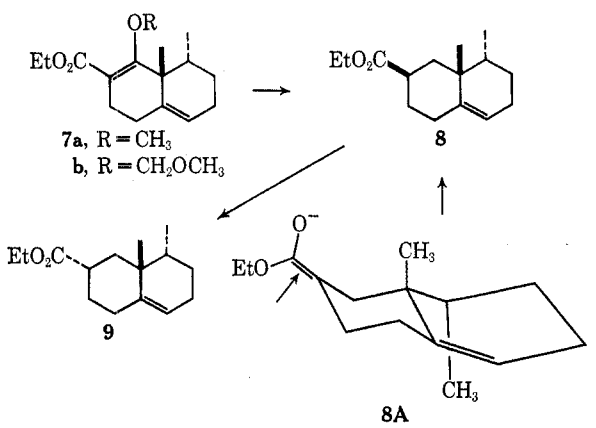
(14) A. Afonso, *J. Amer. Chem. Soc.*, **90**, 7375 (1968).

(15) (a) G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962); (b) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); (c) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3095 (1968).

(16) G. E. Arth, G. J. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Sarett, *J. Amer. Chem. Soc.*, **76**, 1715 (1954); F. Sondheimer, W. McCrae, and W. G. Salmond, *ibid.*, **91**, 1228 (1969).

The conversion of 3-ethoxy-2-cyclohexenone to cyclohexanone with lithium in liquid ammonia[17] provides recent precedent for this sequence of reactions with an enol ether of a β diketone.[18] The Birch reduction of trimethylgallic acid to 3,5-dimethoxy-1,4-dihydrobenzoic acid must also involve elimination of alkoxide.[19]

The reaction was first tested with the methyl enol ether **7a**, previously prepared from **6** by treatment with diazomethane.[9b,c] Addition of **7** in ether solution to a 50% excess (*i.e.*, 6 equiv) of lithium in liquid ammonia afforded the octalin ester **8** in 67% yield after quenching with ammonium chloride. That the carbethoxy group of **8** is *cis* (axial) to the quaternary methyl group was established by sodium ethoxide catalyzed equilibration to a more stable isomer **9** (equatorial). This conclusion is confirmed by the difference in the chemical shift for the angular methyl group in the nmr spectra of **8** (τ 9.01) and **9** (τ 8.87). The downfield shift is consistent with literature data for similar pairs of axial and equatorial esters.[15b,20] The formation of the less stable axial isomer **8** is presumably the result of a kinetically controlled protonation of the ester enolate anion (**8A**) from the less hindered equatorial direction.[21]

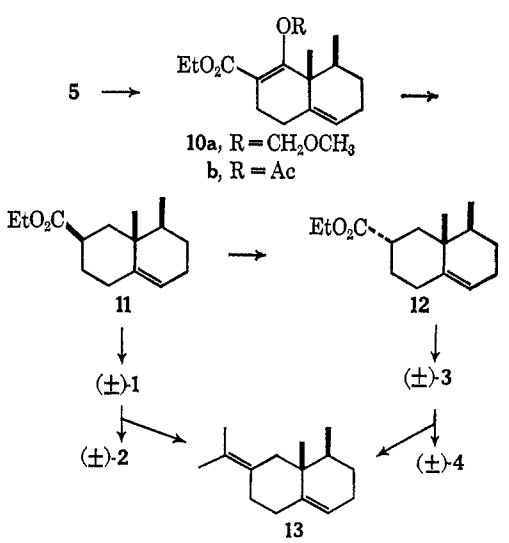


The application of this reduction method to the β-keto ester **5** having the natural *cis* stereochemistry required first conversion to an enol ether derivative. Since methylation with diazomethane proved to be impractically slow, we turn to alkylation of the enolate anion. Although alkylation in dipolar aprotic solvents has been found to give increased proportions of O-alkylation from the ambident enolate anion of β-keto esters,[22] even under optimum conditions the usual alkylating reagents afford considerable quantities of C-alkylation as well. However, Simonsen and Storey have reported that the sodium salt of ethyl acetoacetate reacts with chloromethyl methyl ether to yield only the O-alkylated product.[23] We decided, therefore, to examine the alkylation of the enolate anion of **5** with chloromethyl methyl ether. Hexamethylphosphoramide was selected as solvent since this medium has been found to give high percentages of O-alkylation.[22c-f]

The sodium salt of β-keto ester **5** was formed by initial reaction with sodium hydride in hexamethylphosphoramide at room temperature. Addition of chloromethyl methyl ether gave rise to the methoxymethyl enol ether **10a** (ν_{max} 1710 and 1605 cm^{-1}) to the complete exclusion of the C-alkylated isomer. The nmr chemical shift for the methylene protons of the methoxymethyl group (AB system centered at τ 5.18; $\Delta\nu_{AB}$ = 30 Hz, J_{AB} = 6.0 Hz) is consistent only with the O-alkylated product.

The crude enol ether **10a** was submitted to reduction with lithium in liquid ammonia and the octalin ester **11** was obtained in 60% overall yield. Once again the less stable isomer was formed preferentially since equilibration produced the epimeric ester **12**. The nmr signal for the angular methyl group in **11** (τ 9.18) is shifted upfield with respect to **12** (τ 9.05). The methoxymethyl enol ether of β-keto ester **6** was also prepared by reaction of the sodium salt with chloromethyl methyl ether in hexamethylphosphoramide. Reduction of the crude enol ether (**7b**) with excess lithium in liquid ammonia gave ester **8** in 61% overall yield from **6**.

Since acylation of β-keto esters affords mainly O-acyl derivatives,[24] we also prepared the enol acetate derivative (**10b**) of β-keto ester **6**. Treatment of the sodium enolate with acetyl chloride in 1,2-dimethoxyethane produced exclusive O-acetylation to give **10b** in good yield. The infrared spectrum of **10b** shows absorption bands at 1770, 1715, and 1630 cm^{-1} representing the enol acetate carbonyl, the conjugated ester carbonyl, and the conjugated double bond, respectively. Reduction of unpurified **10b** with lithium in liquid ammonia provided ester **11** in 34% overall yield from **5**, a yield inferior to that obtained from reduction of the methoxymethyl enol ether **10a**.



Treatment of ester **11** with excessm ethyllithium in ether gave (±)-eremoligenol (**1**) in 81% yield. The

(17) D. S. Watt, J. M. McKenna, and T. A. Spencer, *J. Org. Chem.*, **32**, 2674 (1967).

(18) See also, M. Vandewalle and F. Compernolle, *Bull. Soc. Chim. Belg.*, **76**, 43 (1967).

(19) W. J. Gensler, C. D. Gatsonis, and Q. A. Ahmed, *J. Org. Chem.*, **33**, 2968 (1968), and references cited therein.

(20) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *ibid.*, **30**, 713 (1965).

(21) For a case of similar stereoselectivity, see W. G. Dauben and R. M. Coates, *J. Amer. Chem. Soc.*, **86**, 2490 (1964).

(22) (a) G. Brieger and W. M. Pelletier, *Tetrahedron Lett.*, 3555 (1965); (b) S. J. Rhoads and R. W. Hasbrouck, *Tetrahedron*, **22**, 3557 1966); (c) (c) A. L. Kurz, I. P. Beletskaya, A. Macías, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968); (d) W. J. Le Noble and J. E. Puerta, *ibid.*, 1097 (1966); (e) A. L. Kurtz, I. P. Beletskaya, A. Macías, and S. S. Yafit, *J. Org. Chem. USSR*, **4**, 1327 (1968); (f) W. J. Le Noble and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1969).

(23) J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 2106 (1909).

(24) J. P. Ferris, B. G. Wright, and C. C. Crawford, *J. Org. Chem.*, **30**, 2367 (1965).

infrared and nmr spectra of the synthetic eremoligenol are identical with those of naturally occurring (−)-eremoligenol.[4,25] The nmr spectrum of (±)-eremoligenol in chloroform-*d* shows the two methyl groups adjacent to the hydroxyl group as a six-proton singlet at τ 8.87. In pyridine these two methyl groups are shifted downfield to τ 8.71. The effect of pyridine on the chemical shifts of protons adjacent to hydroxyl groups has been studied previously.[26]

Dehydration of the synthetic eremoligenol with thionyl chloride in pyridine[4] gave (±)-eremophilene (**2**) and its double bond isomer **13** in a 2:1 ratio. The infrared and nmr (100 MHz) spectra of the synthetic eremophilene are identical with those of an authentic sample, (−)-eremophilene.[5,27] The glpc retention times of the synthetic and authentic eremophilene were also identical on two different columns. The nmr and infrared spectral data obtained for the double-bond isomer **13** are in agreement with those reported for **13** derived from naturally occurring (+)-valerianol (**3**).[6]

The reaction of ester **12** with excess methyllithium in ether furnished (±)-valerianol (**3**) in 84% yield. The infrared and nmr spectra of the synthetic valerianol are identical with those of an authentic sample of (+)-valerianol.[6,7,28] The glpc retention times of the synthetic and authentic valerianol were also identical on two different columns. Although the nmr spectrum of (±)-valerianol is very similar to that of (±)-eremoligenol, the infrared spectra of these two isomers are easily distinguished.

Dehydration of the synthetic valerianol with thionyl chloride in pyridine[6,7] gave (±)-valencene (**4**) along with the double-bond isomer **13** in a 3:1 ratio. The infrared spectrum of synthetic valencene is identical with that of naturally occurring (+)-valencene.[6,8a,29] The chemical shifts in the nmr spectrum of synthetic valencene are the same as those reported for (+)-valencene except for the secondary methyl group which is a doublet centered at τ 9.10. This doublet has been previously reported at τ 9.05.[6] The refractive index of the synthetic valencene is the same as that reported for (+)-valencene.[6,8a] The infrared and nmr spectra of (±)-valencene are distinctly different from the corresponding spectra of (±)-eremophilene.

The syntheses of (±)-eremoligenol (**1**), (±)-eremophilene (**2**), (±)-valerianol (**3**), and (±)-valencene (**4**) provide a rigorous proof of the structure and stereochemistry of these sesquiterpenes. The total syntheses of valerianol and valencene also constitute the total syntheses of other eremophilane sesquiterpenes since (+)-valerianol has been previously converted to nootkatone and α-vetivone,[6,7] and (+)-valencene has also been converted to nootkatone.[8]

(25) Copies of the infrared (film) and nmr ($CDCl_3$ and pyridine) spectra of (−)-eremoligenol were furnished by Dr. H. Ishii (Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan), to whom we are most grateful.

(26) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

(27) This sample of (−)-eremophilene was generously donated by Professor V. Herout (Czechoslovak Academy of Science, Institute of Organic Chemistry and Biochemistry, Flemingovo Nam. 2, Prague, Czechoslovakia).

(28) We wish to thank Professor G. Jommi (Institute of Organic Chemistry, University of Milano, Milano, Italy) and Dr. H. Hikino (Pharmaceutical Institute, Tohoku School of Medicine, Kitu-4-bancho, Sendai, Japan) for samples of (+)-valerianol.

(29) An infrared spectrum of (+)-valencene was kindly provided by Professor V. Herout.

The transformation of **5** and **6** to esters **11** and **8**, respectively, indicates that the lithium–ammonia reduction of methoxymethyl enol ethers can serve as an effective method for selective removal of the ketone group in a β-keto ester. In addition, the generation of the less stable, axial stereoisomer permits the synthesis of either ester epimer. The scope of this two-step sequence has been examined with a series of simple β-keto esters; the results of this investigation will be presented in a separate paper.[30]

Experimental Section[31]

Methoxymethyl Enol Ether (10a) of Ethyl 8β,8aβ-Dimethyl-1-oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (5).—To a stirred mixture of 885 mg (22.0 mmol) of a 60% dispersion of sodium hydride in mineral oil and 80 ml of dry hexamethylphosphoramide at 5° under nitrogen was added a solution of 5.00 g (20.0 mmol) of β-keto ester **5**[9] in 20 ml of hexamethylphosphoramide. The mixture was stirred for 1.0 hr at room temperature. The solution was then cooled to 5°, and 1.93 g (24.0 mmol) of chloromethyl methyl ether was added. After stirring for 2.0 hr at room temperature, the solution was cooled to 0° and poured into 50 ml of ice-cold saturated sodium bicarbonate solution. The sodium bicarbonate solution was diluted with 50 ml of water and was then extracted with two 100-ml portions of petroleum ether (bp 30–60°). The petroleum ether solution was washed four times with 40–50-ml portions of water, dried with sodium sulfate, and evaporated under reduced pressure to give a yellow oil. Evaporation under reduced pressure gave 5.70 g of a yellow oil which was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column A, 183°, 200 ml/min) of the crude oil revealed a single peak. An analytical sample of enol ether **10a** was obtained by preparative glpc (column B, 190°): ir 1710 (C=O) and 1605 (conjugated double bond) cm^{-1}; nmr τ 4.63 (m, 1 H), 5.18 (AB, d, $\Delta\nu_{AB}$ = 30 Hz, J_{AB} = 6.0 Hz, $-OCH_2O-$), 5.91 (quartet, 2 H, J = 7.0 Hz), 6.53 (s, 3 H), 8.74 (t, 3 H, J = 7.0 Hz), and 8.82 (s, 3 H). The secondary methyl group is hidden by the absorption at τ 8.74 and 8.82.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.51; H, 8.81.

Ethyl 8β,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2β-naphthoate (11) from Reduction of the Methoxymethyl Enol Ether 10a.—A solution of 5.70 g of the crude enol ether **10a** in 105 ml of ether was rapidly added to a magnetically stirred, dark blue solution of 750 mg (0.108 g-atom) of lithium in 330 ml of anhydrous ammonia under argon. Powdered Dry Ice was used to cool the reaction flask while the addition was made. After stirring for 12 min at the liquid ammonia boiling point (−33°), the reaction flask was again cooled with powdered Dry Ice for 10 min, and then 30 g of ammonium chloride was added essentially all at once to quench. The blue color of the solution actually faded 2 min befor quenching. After 250 ml of ether was added, the Dry Ice–isopropyl alcohol condenser was replaced with a sodium hydroxide drying tube. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The mixture was then filtered, and the inorganic salts were crushed and washed

(30) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2601 (1970).

(31) All melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 137 or Model 521 spectrometer in carbon tetrachloride solution unless otherwise specified and were calibrated with the polystyrene band at 1603 cm^{-1}. Proton magnetic resonance spectra were determined with a Varian Associates Model A-60A or A-56-60 spectrometer using tetramethylsilane as an internal standard. A Varian Associates Model HA-100 spectrometer was used where indicated. All nmr spectra were determined in carbon tetrachloride solution unless otherwise specified. Mass spectra were determined on an Atlas CH4 mass spectrometer. Microanalyses were determined in the University of Illinois microanalytical laboratory. Gas chromatography (glpc) was performed on a Wilkens Aerograph A-90-P instrument employing helium as the carrier gas. The following columns were used: a 5 ft × 0.25 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column A), a 6 ft × 3/8 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column B), a 5 ft × 0.25 in. column of 3% SE-30 on 60–80 mesh Chromosorb W (column C), a 6 ft × 0.25 in. column of 15% Carbowax 20M on 60–80 mesh Chromosorb W (column D), a 6 ft × 3/8 in. column of 15% Carbowax 20M on 60–80 mesh Chromosorb W (column E), and a 5 ft × 0.25 in. column of 15% FFAP on 60–80 mesh Chromosorb W (column F).

three times with ether. The ether solution was then evaporated under reduced pressure to give 4.65 g of a slightly yellow oil. Glpc analysis (column B, 165°, 200 ml/min) of this oil revealed that there was essentially only one volatile component. Chromatography of the crude product on 80 g of Woelm neutral alumina (activity II) and elution with 0–10% ether in petroleum ether (bp 30–60°) gave 2.85 g (60% from β-keto ester **5**) of ester **11** as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 165°): $n^{25}D$ 1.4905; ir 1729 (C=O), 1460, 1375, 1200, 1176, 1100, 1063, and 1045 cm^{-1}; nmr τ 4.73 (m, 1 H), 5.90 (quartet, 2 H, J = 7.0 Hz), 8.74 (t, 3 H, J = 7.0 Hz), 9.12 (d, 3 H, J = 6.0 Hz), and 9.18 (s, 3 H).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.22; H, 10.18.

Ethyl 8β,8aβ-Dimethyl-1-acetoxy-3,4,6,7,8a-hexahydro-2-naphthoate (10b).—To a stirred mixture of 354 mg (8.83 mmol) of a 60% dispersion of sodium hydride in mineral oil and 27 ml of 1,2-dimethoxyethane at 0° under nitrogen was added dropwise over a period of 20 min a solution of 2.00 g (8.00 mmol) of β-keto ester **5** in 5 ml of 1,2-dimethoxyethane. After stirring an additional 20 min at room temperature, 754 mg (9.60 mmol) of acetyl chloride was added, and the solution was then stirred at room temperature for 30 min. The solution was then cooled and poured into 50 ml of an ice-cold saturated sodium bicarbonate solution. The petroleum ether (bp 30–60°) extract was washed with water until neutral, dried with sodium sulfate, and evaporated to give 2.38 g of enol acetate **10b** which was used without any further purification. An analytical sample was obtained by preparative glpc (column B, 188°): ir 1770 (C=O), 1715 (C=O), and 1629 (conjugated double bond) cm^{-1}; nmr τ 4.58 (m, 1 H), 5.94 (quartet, 2 H, J = 7.0 Hz), 7.89 (s, 3 H), 8.78 (t, 3 H, J = 7.0 Hz), 8.88 (s, 3 H), and 8.89 (d, 3 H, J = ~6 Hz).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.63; H, 8.32.

Ester 11 from Reduction of the Enol Acetate 10b.—To a stirred solution of 300 mg (0.0432 g-atom) of lithium in 132 ml of anhydrous ammonia under argon was added a solution of 2.38 g of the crude enol acetate **10b** in 42 ml of ether. After stirring for 35 min, the solution was cooled for 10 min in powdered Dry Ice, and then 12 g of ammonium chloride was added, and the Dry Ice–isopropyl alcohol condenser was replaced with a sodium hydroxide drying tube. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The mixture was then filtered, and the inorganic salts were washed with more ether. The ether solution was then evaporated to give 1.80 g of a yellow oil which was chromatographed on 55 g of Woelm neutral alumina (activity II). Elution with 0–10% ether in petroleum ether (bp 30–60°) gave 640 mg (34% from β-keto ester **5**) of ester **11** as a colorless oil which had infrared and nmr spectra identical with those previously reported.

(±)-Eremoligenol (1).—Methyllithium was prepared by adding 3.62 g (25.5 mmol) of methyl iodide to 0.354 g (0.0510 g-atom) of small lithium pieces in 21 ml of anhydrous ether under argon at such a rate that there was only very mild refluxing of the ether. After the addition was completed, the solution was stirred an additional 0.5 hr. To the stirred methyl lithium solution under argon was slowly added a solution of 600 mg (2.54 mmol) of ester **11** in 3 ml of ether. After stirring for 2.5 hr at room temperature, the solution was cooled in ice water and poured into an ice-cold solution of 3 g of ammonium chloride in 45 ml of water. The petroleum ether (bp 30–60°) extract was washed with water until neutral, dried with sodium sulfate, and evaporated to give 570 mg of a slightly yellow oil which was then chromatographed on 15 g of Woelm neutral alumina (activity III). Elution with 25% ether in petroleum ether (bp 30–60°) gave 457 mg (81%) of (±)-eremoligenol (**1**) as a colorless viscous oil. Alternatively, the alcohol could be purified by preparative glpc (column A, 157°). The infrared (film) and nmr ($CDCl_3$ or pyridine) spectra of the synthetic eremoligenol were identical with the corresponding spectra of authentic (−)-eremoligenol.[4,25]

(±)-Eremophilene (2).—To a solution of 300 mg (1.35 mmol) of (±)-eremoligenol (**1**) in 1.8 ml of pyridine at 0° was added 300 mg (2.5 mmol) of thionyl chloride.[4] After stirring for 15 min at 0°, the solution was poured into ice-cold water. The ether extract was washed with 10% concentrated hydrochloric acid, saturated sodium bicarbonate, and water, dried with sodium sulfate, and evaporated to give 270 mg of a yellow oil. Glpc analysis (column A, 136°, 200 ml/min) of the oil revealed that it was a 2:1 mixture of two compounds. Preparative glpc (column B, 128°) of the major component which had the shorter retention time gave 78 mg (28%) of (±)-eremophilene (**2**) as a colorless oil. The synthetic eremophilene was identified by comparison of its infrared and 100-MHz nmr spectra with those of an authentic sample of (−)-eremophilene.[5,27] Glpc retention times (column A, 118°, 200 ml/min, and column F, 118°, 125 ml/min) of the synthetic and authentic samples were also identical. Preparative glpc of the minor component gave 38 mg (14%) of the double bond isomer **13** as a colorless oil which gave infrared and nmr spectral data in agreement with those reported for **13**.[6]

Ethyl 8β,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2α-naphthoate (12).—To a solution of sodium ethoxide prepared from 1.90 g (0.082 g-atom) of sodium and 100 ml of absolute ethanol was added a solution of 1.40 g (6.00 mmol) of ester **11** in 10 ml of absolute ethanol. After refluxing for 45 min under nitrogen, the solution was cooled and poured into ice cold water, and the basic aqueous solution was washed with water, dried with sodium sulfate, and evaporated to give 1.26 g of a yellow oil. The crude oil was chromatographed on 40 g of Woelm neutral alumina (activity II). Elution with 0–10% ether in petroleum ether (bp 30–60°) gave 988 mg (71%) of ester **12** as a colorless oil: ir 1731 (C=O), 1457, 1375, 1307, 1177, 1163, and 1034 cm^{-1}; nmr τ 4.72 (m, 1 H), 5.96 (quartet, 2 H, J = 7.0 Hz), 8.78 (t, 3 H, J = 7.0 Hz), 9.05 (s, 3 H), and 9.09 (d, 3 H, J = ~6 Hz). The nmr spectrum indicated that no ester **11** was present in the product. An analytical sample was obtained by preparative glpc (column B, 155°).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.27; H, 10.07.

(±)-Valerianol (3).—Methyllithium was prepared by adding 3.62 g (25.5 mmol) of methyl iodide to 0.354 g (0.0510 g-atom) of small lithium pieces in 21 ml of anhydrous ether under argon at such a rate that there was only very mild refluxing of the ether. After the addition was completed, the solution was stirred an additional 0.5 hr. To the stirred methyllithium solution under argon was slowly added a solution of 600 mg (2.54 mmol) of ester **12** in 3 ml of ether. After stirring for 2.5 hr at room temperature, the solution was cooled in ice water and poured into an ice-cold solution of 3 g of ammonium chloride in 45 ml of water. The petroleum ether (bp 30–60°) extract was washed with water until neutral, dried with sodium sulfate, and evaporated to give 595 mg of a slightly yellow oil which was chromatographed on 15 g of Woelm neutral alumina (activity III). Elution with 25% ether in petroleum ether (bp 30–60°) gave 472 mg (84%) of (±)-valerianol (**3**) as a colorless viscous oil. Alternatively, the alcohol could be purified by preparative glpc (column B, 156°). The synthetic valerianol was identified by comparison of its infrared (film) and nmr ($CDCl_3$) spectra with those of an authentic sample of (+)-valerianol provided by Dr. G. Jommi.[6,28] In the nmr spectrum of the synthetic valerianol the absorption at τ 8.65 is due to the hydroxyl proton since it disappears upon addition of D_2O. The infrared spectrum of the synthetic valerianol also appeared to be identical with that of a sample of (+)-valerianol provided by Dr. H. Hikino;[7,28] however, there were some minor impurities in this authentic sample. The glpc retention times (column A, 148°, 150 ml/min, and column D, 164°, 125 ml/min) of the synthetic and two authentic samples were also identical.

(±)-Valencene (4).—To a solution of 300 mg (1.35 mmol) of (±)-valerianol in 1.8 ml of pyridine was added 300 mg (2.5 mmol) of thionyl chloride. After stirring for 12 min at 0°, the solution was poured into 12 ml of ice water. The petroleum ether (bp 30–60°) extract was washed with 10% concentrated hydrochloric acid, saturated sodium bicarbonate, and water, dried with sodium sulfate, and evaporated to give 278 mg of a yellow oil. Glpc analysis (column A, 152°, 100 ml/min) of the oil revealed that it was a 3:1 mixture of two compounds. Preparative glpc (column A, 152°) of the major component which had the shorter retention time gave 121 mg (44%) of (±)-valencene (**4**) as a colorless oil; $n^{20}D$ 1.5070 (lit.[7,9] $n^{20}D$ 1.5073, 1.5075). The infrared spectrum of the synthetic valencene appeared to be identical with the infrared spectrum of (+)-valencene published by Hunter and Brogden[8a] and a spectrum of (+)-valencene.[6,29] The chemical shifts of the nmr ($CDCl_3$) spectrum of the synthetic valencene are the same as those reported for valencene derived from (+)-valerianol except for the secondary methyl group which is a doublet centered at τ 9.10. This doublet has been previously reported at τ 9.05.[6] Preparative glpc of the minor component gave 37 mg (14%) of the double-bond isomer **13** as a colorless oil which gave infrared and nmr spectral data in agreement with reported values.[6]

Methoxymethyl Enol Ether (7b) of Ethyl 8α,8aβ-Dimethyl-1-

oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (6).—The procedure was identical with that described for the methoxymethyl enol ether **10a**. Reaction of 5.00 g (20.0 mmol) of β-keto ester **6**[3] gave 5.60 g of the crude methoxymethyl enol ether as a yellow oil. This material was used in the lithium–ammonia reduction step without further purification. Glpc analysis (column A, 178°, 200 ml/min) of the crude product revealed a single peak. The infrared spectrum of the crude enol ether showed bands at 1710 (C=O) and 1610 (conjugated double bond) cm^{-1}.

Ethyl 8α,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2β-naphthoate (8) by Reduction of Methoxymethyl Enol Ether 7b.—The procedure was idential with that described for the reduction of the methoxymethyl enol ether **10a**. Reduction of 5.60 g of the crude methoxymethyl enol ether **7b** with 750 mg (0.108 g-atom) of lithium gave 4.76 g of a yellow oil which showed a single peak on glpc analysis (column A, 163°, 200 ml/min). Chromatography of the crude product on 80 g of Woelm neutral alumina (activity II) and elution with 10% ether in petroleum ether (bp 30–60°) gave 2.86 g (61% from β-keto ester **6**) of ester **8** as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 168°): $n^{25}D$ 1.4907; ir 1729 (C=O), 1193, and 1041 cm^{-1}; nmr τ 4.68 (m, 1 H), 5.88 (quartet, 2 H, J = 7.0 Hz), 8.73 (t, 3 H, J = 7.0 Hz), 9.01 (s, 3 H), and 9.07 (d, 3 H, J = ~7 Hz).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.09; H, 10.07.

Ester 8 by Reduction of the Methyl Enol Ether 7a.—The procedure was similar to that used in the reduction of methoxymethyl enol ether **10a**. A solution of 350 mg (1.33 mmol) of the methyl enol ether **7a**[3] was added with stirring to a dark blue solution of 50 mg (0.0072 g-atom) of lithium in 22 ml of anhydrous ammonia under argon. The solution was stirred for 1.0 hr at the liquid ammonia boiling point and was then cooled in powdered Dry Ice before quenching with 2.0 g of ammonium chloride. After addition of 25 ml of ether, evaporation of the ammonia, filtration, and evaporation of the ether, 312 mg of a slightly yellow oil was obtained. Glpc analysis (column A, 166°, 200 ml/min) revealed that there was essentially only one peak. Purification of the oil by preparative glpc (column B, 167°) gave 210 mg (67%) of ester **8** which was found to be identical with that obtained above.

Ethyl 8α,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2α-naphthoate (9).—To a solution of sodium ethoxide prepared from 280 mg (0.012 g-atom) of sodium and 17 ml of absolute ethanol was added a solution of 200 mg (0.85 mmol) of ester **8** in 3 ml of ethanol. After refluxing for 1.25 hr under nitrogen, the solution was cooled and poured into ice-cold water, and the resulting basic aqueous solution was extracted with petroleum ether (bp 30–60°). The petroleum ether extract was washed with water, dried with sodium sulfate, and evaporated to give 202 mg of a yellow oil. Preparative glpc (column B, 162°) of the oil gave 65 mg (33%) of ester **9** as a colorless oil: ir 1730 cm^{-1} nmr τ 4.70 (m, 1 H), 5.96 (quartet, 2 H, J = 7.0 Hz), 8.79 (t, 3 H, J = 7.0 Hz), 8.88 (s, 3 H), and 9.07 (d, 3 H, J = 6.5 Hz). The glpc and nmr data showed that no ester **8** remained after equilibration.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.02; H, 10.27.

Registry No.—(±)-Eremoligenol, 22343-25-5; (±)-eremophilene, 22343-24-4; (±)-valerianol, 24741-63-7; (±)-valencene, 24741-64-8; **7b**, 24799-48-2; **8**, 24744-07-8; **9**, 24744-08-9; **10a**, 24744-09-0; **10b**, 24744-10-3; **11**, 22343-27-7; **12**, 24744-12-5.

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Reduction of β-Keto Ester Methoxymethyl Enol Ethers to Saturated Esters with Lithium in Liquid Ammonia[1]

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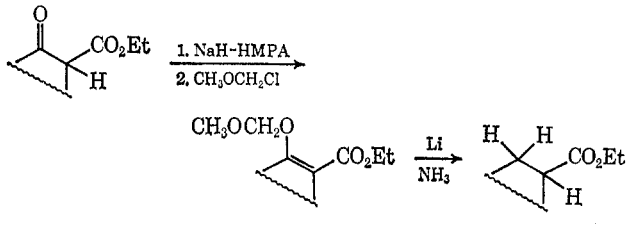
Methoxymethylation of a series of β-keto esters in hexamethylphosphoramide gave, with one exception, high proportions (96–100%) of O-alkylation. The reduction of the enol ethers with lithium in liquid ammonia furnished the corresponding saturated esters in variable overall yields (23–61%). This new method for reducing the ketone group of a β-keto ester is apparently most efficient with relatively hindered compounds.

We have recently described a new synthetic procedure for the reduction of a β-keto ester to a saturated ester.[3] The method consists of first conversion to the methoxymethyl enol ether by alkylation of the sodium salt of the β-keto ester with chloromethyl methyl ether in hexamethylphosphoramide. The enol ether without purification is then subjected to reaction with lithium in liquid ammonia which effects a "double" reduction to the saturated ester.



In order to explore the generality of this method, we have applied the two-step sequence to a series of cyclic and acyclic β-keto esters. The results of this investigation are summarized in Table I.

In all cases except ethyl 2-*n*-butylacetoacetate (**15**), the reaction of the sodium enolate with chloromethyl methyl ether produced essentially exclusive O-alkylation. When less polar aprotic solvents were used instead of hexamethylphosphoramide, the amount of O-alkylated product decreased. In hexamethylphosphoramide the relative percentages of O- and C-alkylation for 2-carbethoxycyclohexanone (**5**) were 97 and 3%, respectively, but in 1,2-dimethoxyethane the corresponding values were 75 and 25%. In dimethyl sulfoxide there was 90% O-alkylation and 10% C-alkylation. The effect of the alkylating agent in promoting O-alkylation can be seen by comparison with results reported by other workers.[4] Alkylation of the sodium enolate of ethyl acetoacetate (**11**) in hexa-

(1) Taken in part from Ph.D. Thesis of J. E. S., University of Illinois, Urbana, 1969.

(2) National Science Foundation Trainee, 1965–1969.

(3) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597 (1970); see also *Tetrahedron Lett.*, 5405 (1968).

(4) A. L. Kurz, I. P. Beletskaya, A. Macías, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968).