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SESQUITERPENOIDS—III[1]

TOTAL SYNTHESIS OF EUDESMANE SESQUITERPENOIDS

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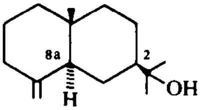
Abstract—(±)-β-Eudesmol (**1**) has been synthesized in a highly stereoselective, 10-stage route from the octalone **2**. Several of the synthetic intermediates are potentially useful compounds for the synthesis of other eudesmane sesquiterpenoids.

β-EUDESMOL (**1**) is one of the most wide-spread sesquiterpene alcohols,[*] and has played a key role in the correlation of terpenoid and steroid configurations.[2] Two syntheses of β-eudesmol, one of the racemate[3] and the other of the dextrorotary antipode,[4] have recently been reported.

As a part of our own investigations of synthetic methods for the elaboration of terpenoids, we have examined several possible routes to eudesmane sesquiterpenoids. We now wish to report a highly stereoselective total synthesis of (±)-β-eudesmol, which complements the routes previously disclosed,[3,4] and which proceeds through intermediates which may be useful for the synthesis of other eudesmanes.

The major problem in the synthesis of eudesmanes is stereochemistry, since several good methods are already available for the construction of the requisite decalin framework. Since β-eudesmol is a *trans*-decalin,[2,5] and has the isopropanol moiety in the equatorial position,[2] it must surely be the more stable of the four possible isomerides. The obvious solution to the stereochemical problem is to conduct the synthesis so that it proceeds through intermediates in which carbons 2 and 8a are epimerizable.[†] In this manner, any synthetic non-stereospecificity may be corrected by causing equilibration to occur.



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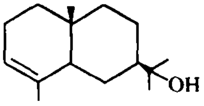
[*] A search of Chemical Abstracts indices through June, 1965, reveals that this compound, usually admixed with the α- and γ-isomers (i and ii) has been isolated from more than thirty sources.



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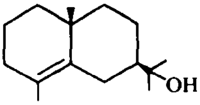
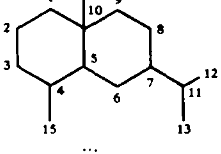


ii

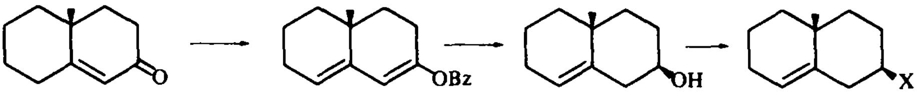
[†] Throughout this paper, compounds will be numbered as derivatives of naphthalene, in keeping with current Chemical Abstracts practice. The traditional numbering system for eudesmane sesquiterpenoids is given in Fig. iii.



iii

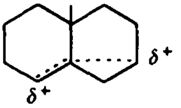
The starting point for our synthesis was the octalone 2, which has previously been converted, *via* the enol benzoate 3, into the unsaturated alcohol 4.[6] We have devised an improved procedure which allows 4 to be obtained in 60% overall yield for the two steps, in contrast to the 25% reported.[6]

Alcohol 4 is transformed into the bromide 5 with phosphorous tribromide or into the chloride 6 with phosphorous pentachloride.



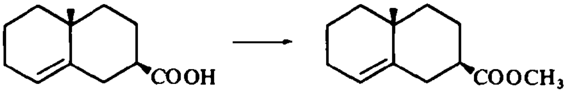
2 3 4 5: X = Br
6: X = Cl

That both 5 and 6 have their halogen atoms in the equatorial position is attested by the respective NMR spectra. The resonances due to the C-2 methine protons appear at δ 4·15 and δ 4·30, respectively, as approximate pentuplets with apparent coupling constants of 8 c/s. Thus, the transformations of 4 into 5 and 6 occur with net retention of configuration, probably due to intervention of the homoallylic cation iv.* Shoppee[8] and Winstein[9] have postulated that the analogous cyclocholesteryl cation accounts for the net retention of configuration observed in replacement reactions of 3β-cholesteryl derivatives.



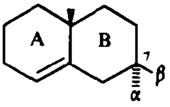
iv

Carbonation of the Grignard reagent derived from 5 or 6 leads to the unsaturated acid 7. Acid 7 yields a methyl ester (8) on treatment with ethereal diazomethane or methanolic sulfuric acid.



7 8

The stereochemistry of 7 and 8 was revealed when it was found that ester 8 may be recovered unchanged after prolonged treatment with methanolic sodium methoxide. An inspection of models shows that there are only two stable conformations for 10-methyl-$\Delta^{1,9}$-octalin (vii), differing in the geometry of ring A. This ring may



vii

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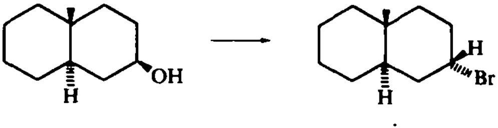
* This result is in marked contrast to the analogous reaction of decalol v with phosphorous tribromide, in which inverted bromide vi is the sole product.[7]

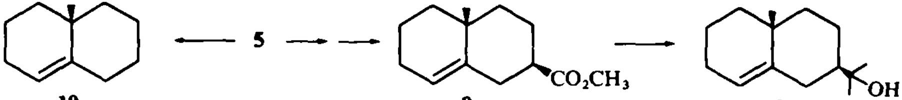


v vi

adopt either a half-chair or a half-boat form.* However, both stable conformations of compound vii must have the angular Me group axial with respect to ring B, and if this ring is to have the greatly favored chair configuration, the β-bond at C-7 must be equatorial. Conformations of vii with the angular Me group equatorial to ring B are too highly strained to be considered. Since the more stable C-7 epimer of **8** must be that in which the carbomethoxyl is *cis* to the angular Me group, and since the compound is stable under epimerizing conditions, ester **8** and acid **7** must possess the stereostructures depicted.

The stereospecificity observed in carbonation of the Grignard reagents derived from **5** and **6** has ample precedent in the observation that carbonation of cholesterylmagnesium chloride gives only one acid,[11] shown to be the equatorial acid,[12] and by the observation that 4-phenylcyclohexylmagnesium chloride reacts with carbon dioxide to afford only *trans*-4-phenylcyclohexanecarboxylic acid.[13]

The unsaturated ester **8** was further transformed into (±)-nor-γ-eudesmol (**9**)† by treatment with methylmagnesium iodide. Attempts to produce **9** directly from the Grignard reagent derived from chloride **5** met with only limited success. The major product obtained from the reaction of this Grignard reagent with acetone was the octalin **10**, resulting from enolization of the acetone. However, we were able to isolate alcohol **9** in a semi-pure state in approximately 15% yield.



10
+
9

8

9

Hydroboration of the unsaturated alcohol **9** yields a mixture of the crystalline diols **11** and **12** in a ratio of 2:1. Compounds **11** and **12** may be separated by fractional crystallization, or the mixture may be directly oxidized by the Jones reagent[14] to the corresponding mixture of ketols **13** and **14**. After treatment of the mixture with methanolic sodium methoxide, the crystalline ketol **14** is obtained in good yield. Since it has previously been shown that the dextrorotary antipode of **14** is stable to base,[5] the stereochemistry of this material must be that shown. Ketol **14** was finally transformed into (±)-β-eudesmol (**1**) by treatment with methylenetriphenylphosphorane in DMSO.[15]

The synthetic β-eudesmol thus produced was identical by IR spectrum, NMR spectrum, and chromatographic mobility with a specimen of (±)-β-eudesmol kindly supplied by Professor J. A. Marshall.[3]

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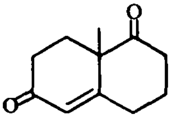
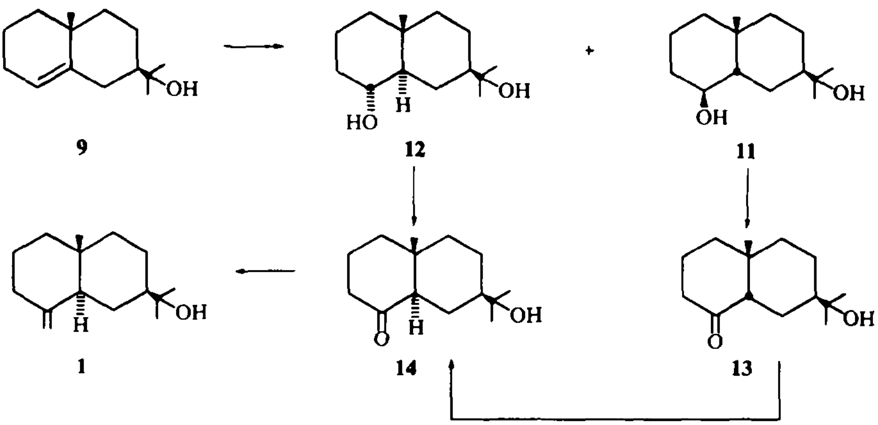
* It becomes readily apparent by a casual manipulation of stereomodels that $\Delta^{1,9}$-octalins (i.e., vii) cannot assume conformations in which the angular substituent bears an equatorial relationship with respect to ring B. However, such a conformation has been considered a possibility in the case of the octalindione viii.[14] To the credit of these authors, this impossible conformation was rejected, albeit on the wrong grounds.

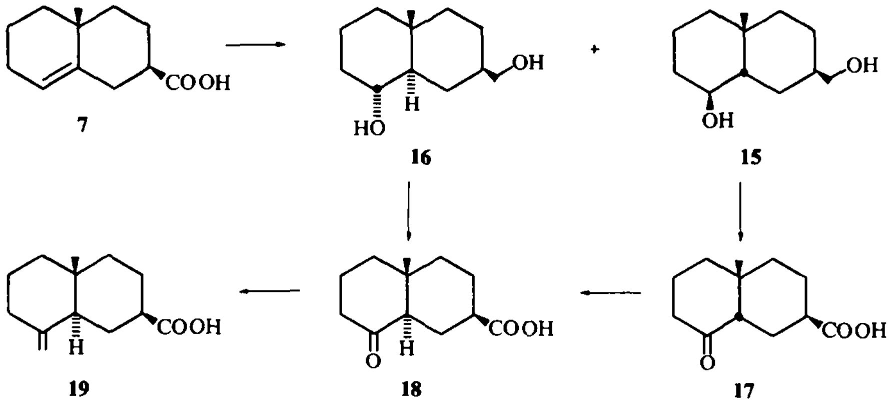


viii

† The optically active counterpart of **9** has been prepared, by a different route, and transformed into (+)-β-eudesmol in essentially the same manner that we shall describe; Ref. 4.



An alternative route to **1** involves the hydroboration of acid **7**, with concomitant reduction of the carboxyl group, to the mixture of diols **15** and **16** in a ratio of 2:1. The mixture is oxidized, again by the Jones reagent, to the mixture of keto acids **17** and **18**. Treatment of this mixture with aqueous base yields the pure acid **18**. Compound **18** is converted by the Wittig procedure into the unsaturated acid **19**, which has previously been converted into (±)-β-eudesmol.[3]



EXPERIMENTAL

M.ps were determined in Pyrex capillaries and are uncorrected. IR spectra were determined in CCl_4 soln on a Perkin–Elmer 137 IR spectrometer. NMR spectra were determined on a Varian A-60 NMR spectrometer. Chemical shifts are quoted in ppm downfield from internal TMS. Combustion analyses were performed by the Microanalytical Laboratory of the University of California, Berkeley, California.

4aβ-*Methyl*-1,2,3,4,4a,5,6,7-*octrahydronaphth*-2β-*ol* (4)

A mixture of 460 g of 2, 850 cc of benzoyl chloride, and 1400 cc of hexane was refluxed for 10 hr in the dark.* At the end of this period, all material boiling below 105° at 13 mm was removed. The residue was poured into 1200 cc 95% EtOH and cooled to −70°. The ppt was collected by filtration and the filtrate was cooled again to obtain a second crop. The total yield of moist enol benzoate 3 was 1050 g.

The crude benzoate 3 was immediately placed in a flask containing 5 l. 95% EtOH. A soln of 290 g $NaBH_4$ in aqueous EtOH (5200 cc 95% EtOH and 960 cc water) was added to the benzoate slurry over a

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* Compound 3 is light sensitive. Best results were obtained when the material was protected from light until after the sodium borohydride reduction was complete (*vide infra*).

period of 3 hr, while maintaining the temp at 0 to 10°. After the mixture had been stirred at room temp overnight, it was heated to boiling and 250 g NaOH was added. The soln was concentrated to 1·5 l. by distillation at atm press, 3 l. water was added, and the 2-phase mixture was allowed to cool. The mixture was extracted with ether (three 1000 cc portions) and the combined extracts were washed with 500 cc sat NaCl aq. After filtration through dry cotton, the ether was evaporated on a steam bath to yield a liquid residue. The residue was distilled to afford 275 g (60%) of **4**, b.p. 80° at 0·7 mm; NMR in CCl_4: δ 1·06 (Me), δ 4·15 (C_2—H) and δ 5·27 (C_8—H). The analytical sample was obtained by preparative VPC (5 ft × 0·25 in SF-96 on Chromosorb at 210°). (Found: C, 79·24; H, 10·72. Calc. for $C_{11}H_{18}O$: C, 79·47; H, 10·91%.)

2β-*Bromo*-4aβ-*methyl*-1,2,3,4,4a,5,6,7-*octahydronaphthalene* (**5**)

A soln of 36·1 g of **4** and 25 cc PBr_3 in 175 cc benzene was refluxed for 2 hr. After cooling to room temp. ice, and then water, was added. The benzene layer was separated, dried over Na_2SO_4, and concentrated to an oil. Distillation of the residue gave 29·7 g (60%) of **5**, b.p. 101° at 0·55 mm; NMR in CCl_4: δ 1·10 (Me), δ 4·15 (C_2—H) and δ 5·38 (C_8—H). A center cut from the above distillation gave analytically pure material. (Found: C, 57·85; H, 7·66; Br, 35·02. Calc. for $C_{11}H_{17}Br$: C, 57·65; H, 7·48; Br, 34·87%.)

2β-*Chloro*-4aβ-*methyl*-1,2,3,4,4a,5,6,7-*octahydronaphthalene* (**6**)

To 100 g of **4** was added, with stirring, 124 g PCl_5. During the addition, done in portions over a period of 90 min, the temp was kept below 10°. After the chloride had been added, the soln was stirred 15 min. The reaction was quenched by adding MeOH, followed by ice. The resulting mixture was poured into water and extracted with ether. The combined ether extracts were washed with sat $NaHCO_3$aq, sat NaCl aq, and dried over Na_2SO_4. After removal of the ether, the brown liquid was distilled to afford 80 g (72%) of **6**, b.p. 55–58° at 70μ; NMR in CCl_4: δ 1·10 (Me) δ 4·30 (C_2—H) and δ 5·36 (C_8—H). A center cut from the above distillation gave analytically pure material.* (Found: C, 71·76; H, 9·42; Cl, 19·02. Calc. for $C_{11}H_{17}Cl$: C, 71·52; H, 9·28; Cl, 19·20%.)

4aβ-*Methyl*-1,2,3,4,4a,5,6,7-*octahydronaphth*-2β-*oic acid* (**7**)

A soln of 99 g of **6** in 100 cc dry THF was added over a period of 90 min to 13·7 g Mg turnings under 100 cc refluxing THF. The soln was refluxed for 15 min after the addition was complete. CO_2 was bubbled through the soln at 0° until heat evolution ceased (approximately 6 hr). After removal of a portion of the THF with a stream of N_2, the residue was poured into cold, dil H_2SO_4. The resulting 2-phase mixture was extracted 5 times with ether, and the resulting ether extracts were thrice extracted with dil NaOH aq. The basic extracts were combined, acidified with dil H_2SO_4, and extracted 5 times with ether. The combined ether layers were dried over $MgSO_4$ and evaporated to yield 81·7 g (78%) of crystalline **7** of sufficient purity for further preparative use. The analytical sample was obtained by recrystallization from hexane, followed by 4 sublimations (80° at 0·1 mm). The pure material has m.p. 86·4–87·0°; NMR in CCl_4: δ 1·10 (Me), δ 5·38 (C_8—H) and δ 12·45 (COOH); IR in CCl_4: ν_{max} 1705 cm^{-1} (C=O). (Found: C, 73·81; H, 9·23. Calc. for $C_{12}H_{18}O_2$: C, 74·19; H, 9·34%.)

Methyl 4aβ-*methyl*-1,2,3,4,4a,5,6,7-*octahydronaphth*-2β-*oate* (**8**)

A soln of 25·0 g of **7** and 6 cc conc H_2SO_4 in 450 cc abs MeOH was refluxed for 18 hr. One-half of the MeOH was then evaporated and the residue poured into water. The resulting mixture was extracted

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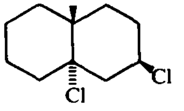
* In one run, beginning with 340 g of alcohol **4**, there was obtained a small amount of high-boiling material, b.p. 100–105° at 0·5 mm, which crystallized on trituration with light pet. ether. One additional crystallization from the same solvent gave 5·6 g of white crystals, m.p. 72–73·5°. We have assigned structure ix to this material, on the basis of its elemental analysis (Found: C, 59·82; H, 8·51; Cl, 31·78. Calc. for $C_{11}H_{18}$[illegible] C, 60·00; H, 8·18; Cl, 31·80%) and its NMR spectrum, which displays a one-proton broad multiplet at δ 5·5 ($W^{\frac{1}{2}}$ = 20 c/s), indicating an axial proton adjacent to chlorine,[16] and a 3-proton singlet at δ 1·1a (Me).[24]



ix

thrice with ether. The combined ether extracts were washed with dil NaOH aq, dried over $MgSO_4$, and evaporated to yield a liquid residue. Distillation at reduced press gave 23·5 g (88%) of **8**, b.p. 69° at 60 μ; NMR in CCl_4: δ 1·07 (Me), δ 3·58 (OMe) and δ 5·34 (C_8—H); IR in CCl_4: 1735 cm^{-1} (C═O). The analytical sample was obtained by preparative VPC (5 ft × 0·25 in SF-96 on Chromosorb at 210°). (Found: C, 74·84; H, 10·09. Calc. for $C_{13}H_{20}O_2$: C, 74·96; H, 9·68%.)

A soln of 1·5 g of **8** and 1·4 g NaOMe in 15 ml anhyd MeOH was refluxed for 140 hr. The reaction mixture was worked up as usual. The recovered methyl ester (homogeneous by VPC) had IR and NMR spectra which were identical with those of the starting ester.

4aβ-*Methyl*-2β-(*2-hydroxy-2-propyl*)1,2,3,4,4a,5,6,7-*octahydronaphthalene* [*nor-γ-Eudesmol*] (**9**)

a. *From compound* **8**. A soln of 3·90 g of **8** in 10 cc dry ether was added to a cold ethereal soln of MeMgI (from 8·1 g MeI and 1·22 g Mg). After stirring for 5 hr at room temp, the reaction mixture was poured into cold NH_4Cl aq. The ether layer was separated and the aqueous phase extracted with ether. The combined ether layers were washed with $NaHSO_3$ aq, water, and dried over $MgSO_4$. Removal of solvent under high vacuum yielded 3·57 g (95·5%) of **9** which slowly crystallized. Compound **9** may be distilled (b.p. 75° at 40 μ) or recrystallized from a small amount of ether at dry ice temp (m.p. 47–50°). NMR in CCl_4: δ 1·02 (Me), δ 1·12 (isopropanol Me's), and δ 5·35 (C_8—H). The analytical sample was obtained by preparative VPC (5 ft × 0·25 in SF-96 on Chromosorb at 140°). (Found: C, 80·64; H, 11·51. Calc. for $C_{14}H_{24}O$: C, 80·71; H, 11·61%.)

b. *From compound* **6**. To 15 cc of a soln of the Grignard reagent derived from 4·8 g (26 mmoles) of **6** and 0·67 g Mg in THF was added a soln of 2·2 cc (30 mmoles) acetone in 10 cc ether at 0° over a period of 15 min. The reaction was allowed to stir at room temp overnight and then worked up in the usual manner to give 5·19 g of an oil. Chromatography on silica gel, using hexane as eluent, gave 2·50 g of non-polar material, which was nearly pure 4a-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene **10**, as evidenced by its NMR and mass spectra. The column was eluted with MeOH to give an oily residue which was rechromatographed on 50 g silica gel. Elution with 1:1 benzene–ether gave 1·92 g of an oil which was approximately 60% **9**. This material was rechromatographed on 50 g silica gel, using 20:1 benzene–ether as eluent, to give 0·74 g of an oil whose NMR spectrum was identical to that of authentic **9**. The material was still slightly impure, since it could not be induced to crystallize.

4aβ-*Methyl*-2β-(*2-hydroxy-2-propyl*)8aβ-*decahydronaphth*-8β-*ol* (**11**) and 4aβ-*methyl*-2β-(*2-hydroxy-2-propyl*)8aα-*decahydronaphth*-8α-*ol* (**12**)

To a soln of 7·87 g of **9** in 100 ml dry ether was added 40 cc of a 0·5 M soln of diborane in THF[18] over a period of 1 hr. After stirring the resulting soln for 2 hr, 13 ml water was added dropwise, followed by a soln of 5 g NaOH in 40 cc MeOH. The soln was warmed to 60° to remove the ether, then the heating was discontinued and 3 cc of 30% H_2O_2 soln was added. After refluxing for 2 hr, the soln was cooled, saturated with NaCl, and extracted with ether (five 100 cc portions). The combined ether extracts were dried over $MgSO_4$ and evaporated to afford 8·60 g (quantitative yield) of a mixture of **11** and **12**. The mixture was shown by NMR analysis to have a composition of 66% **11** and 34% **12** (using the relative areas of the angular Me resonances at δ 1·00 and δ 0·80).

Since epimerization at C_{8a} can be effected at a later stage, the mixture of **11** and **12** could be used for the synthesis of (±)-β-eudesmol. Alternatively, the mixture of diols may be separated by fractional crystallization in the following manner. Crystallization of the mixture from acetone yielded almost pure **11**, which was recrystallized from acetone to give an analytical sample, m.p. 145·6–147·7°. NMR in MeOH: δ 1·00 (angular Me) and δ 1·15 (isopropanol Me's). (Found: C, 74·58; H, 11·77. Calc. for $C_{14}H_{26}O_2$: C, 74·28; H, 11·58%.)

The mother liquor from the above crystallization was evaporated and the residue was crystallized from ether–pentane to give nearly pure **12**. This material was recrystallized twice from water, containing a trace of MeOH, and sublimed at 70° and 20 μ, to give an analytical sample, m.p. 116·5–118·2°, NMR in MeOH: δ 0·80 (angular Me) and δ 1·17 (isopropanol Me's). (Found: C, 74·06; H, 11·38. Calc. for $C_{14}H_{26}O_2$: C, 74·28; H, 11·58%.)

4aβ-*Methyl*-7β-(*2-hydroxy-2-propyl*)3,4,4a,5,6,7,8,8aα-*octahydronaphthalen*-1(2H)-*one* (**14**)

To a soln of 8·00 g of a mixture of **11** and **12** (*vide supra*) in 150 ml acetone was added dropwise 12 ml Jones reagent[14] at 0–10°. The reaction mixture was poured into 500 cc sat NaCl aq, and the resulting mixture was extracted 5 times with ether. The combined ether extracts were dried and evaporated to yield 7·14 g of a viscous oil. The NMR spectrum of the product showed it to consist of a mixture of **13** and **14** in a ratio of 2:1 (the angular Me resonances at δ 1·15 and δ 0·75 were used for the analysis). The above oil was dissolved in 250 cc 95% EtOH containing 7 g NaOH and the resulting soln was refluxed under N_2 for 22 hr. One-half of the EtOH was then evaporated, water was added, and the resulting soln was saturated with NH_4Cl. The mixture was extracted 5 times with ether. The combined ether extracts were washed with $NaHCO_3$aq, sat NaClaq, and then dried over $MgSO_4$. Removal of the ether gave 6·66 g of oily residue which was distilled from an oil-jacketed flask (bath temp 123–144° at 40 μ) to give 6·03 g of colorless ketol. The NMR spectrum of this material showed it to be a mixture of **13** and **14** in a ratio of approximately 9:1.

A portion of the distilled ketol (5.4 g) was mixed with pet. ether (b.p. 30–60°) and cooled to −70°. The resulting mixture was warmed to room temp while scratching with a glass rod, whereupon 2·95 g of crystalline **14** precipitated. The mother liquors from this crystallization were concentrated and reworked in the same manner to afford an additional 0·40 g of **14**. The analytical sample, m.p. 88–89·5°, was obtained by recrystallization from benzene–pet. ether, followed by sublimation at 55° and 40 μ; NMR in $CDCl_3$: δ 0·76 (angular Me) and δ 1·17 (isopropanol Me's); IR in CCl_4: 3600, 3450 and 1720 cm^{-1}. (Found: C, 74·75; H, 10·68. Calc. for $C_{14}H_{24}O_2$: C, 74·95; H, 10·78%.)

4aβ-*Methyl*-7β-(2-*hydroxy*-2-*propyl*)3,4,4a,5,6,7,8,8aβ-*octahydronaphthalen*-1(2H)-*one* (**13**)

To a soln of 510 mg of pure **11** (*vide supra*) in 20 cc acetone containing 2 cc water, was added 0·6 cc Jones reagent.[14] The resulting soln was poured into water and worked up in the usual manner to yield 460 mg of crystalline **13**. The analytical sample, m.p. 55·6–57·3°, was obtained by recrystallization from benzene, followed by sublimation at 60° and 30 μ; NMR in MeOH: δ 1·15 (angular Me and isopropanol Me's, coincident). (Found: C, 74·91; H, 10·73. Calc. for $C_{14}H_{24}O_2$: C, 74·95; H, 10·78%.)

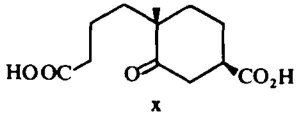
4aβ-*Methyl*-2β-(2-*hydroxy*-2-*propyl*)8-*methylene*-8aα-*decahydronaphthalene* [(±)-β-*Eudesmol*] (**1**)

To 0·275 g NaH was added 6 cc DMSO and the resulting suspension was heated at 75° under N_2 until gas evolution had ceased.[15] The soln was cooled, and a soln of 3·9 g of methyltriphenylphosphonium bromide in 10 cc DMSO was added. After the yellow soln had been stirred for 10 min, a soln of 1·09 g of **14** in 4 cc DMSO was added. The resulting mixture was stirred under N_2 at 55° for 17 hr, then poured into water. The heterogeneous mixture was extracted 3 times with pentane. After drying the combined pentane extracts over $MgSO_4$, the solvent was evaporated to yield a semi-solid mass. A small amount of pentane was added and the remaining solid (triphenylphosphine oxide) was removed by filtration. The filtrate was evaporated to give 1·07 g of oily product. Sublimation of 0·73 g of this oil at 55° and 0·5 mm yielded 0·55 g of **1**, m.p. 58–69°. This solid was heated at 55° in an evacuated tube (0·4 mm) for 100 hr, whereupon waxy needles, m.p. 69–71·4°, were obtained. The m.p. did not change after storage for several months, although the material appeared to have changed crystalline form. The material was identical by IR and NMR spectra and VPC retention time with an authentic sample of (±)-β-eudesmol, kindly supplied by Prof. J. A. Marshall;[3] NMR in CCl_4: δ 0·67 (angular Me), δ 1·13 (isopropanol Me's), δ 4·36 and δ 4·60 (vinyl protons); IR in CCl_4: 3600, 3450, 1670, and 890 cm^{-1}. (Found: C, 80·70, 80·81; H, 11·52, 11·19. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·33%.)

4aβ-*Methyl*-2β-*hydroxymethyl*-8aβ-*decahydronaphth*-8β-*ol* (**15**) and 4aβ-*methyl*-2B-*hydroxymethyl*-8aα-*decahydronaphth*-8α-*ol* (**16**)

To a soln of 10·91 g of **7** in 100 cc ether was added 100 ml of a 0·5 M soln of diborane in THF[18] over a 30 min period. After the soln had been stirred at room temp for 2 hr, the excess hydride was destroyed by the dropwise addition of water. A soln of 8·7 g NaOH in a mixture of 65 cc water and 130 cc MeOH was then added. The 2-phase mixture was warmed to 60°, allowing the ether to distill off. Heating was then discontinued and 1 cc of 30% aqueous H_2O_2 soln was added.[*]

[*] Oxidation at this point with sodium dichromate, after the method of Brown and Garg[19] did not yield the desired keto acids **17** and **18**. The only isolable product from this attempted oxidation was a keto-diacid, m.p. 147·5–149°, which we have assigned structure x. (Found: C, 59·12; H, 7·44. Calc. for $C_{12}H_{18}O_5$: C, 59·50; H, 7·44%).



x

After refluxing this soln for 2 hr, water was added, the soln was saturated with NaCl and extracted 5 times with ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to yield 11·9 g of a semisolid mixture of **15** and **16**. NMR analysis of the mixture disclosed it to consist of 66% **15** and 34% **16** [using the angular Me resonances at δ 1·00 (diol **15**) and δ 0·83 (diol **16**)]. The mixture of diols may be directly oxidized to **17** and **18** (*vide infra*) or separated as follows.

Addition of ether to the mixture, followed by filtration, gave the major diol (**15**) as a crystalline solid. After one recrystallization from ether–pet. ether, followed by sublimation at 95° and 0·2 mm, the analytical sample was obtained, m.p. 144·1–145·7; NMR in C_5H_5N: δ 1·00 (Me), δ 3·60 and δ 3·68 ($C\underline{H}_2OH$); IR in KBr: 3350 cm^{-1} (strong), (Found: C, 72·76; H, 10·98. Calc. for $C_{12}H_{22}O_2$: C, 72·67; H, 11·19%.)

After no more diol **15** could be removed by trituration with ether, the residue was crystallized from benzene to give **16**. Recrystallization from benzene, followed by sublimation, gave analytically pure material, m.p. 120·0–120·4°, with sintering at 98°; NMR in C_5H_5N: δ 0·83 (Me) and δ 3·65 (CH_2OH); IR in KBr: 3350 cm^{-1} (strong). (Found: C, 72·78; H, 11·16. Calc. for $C_{12}H_{22}O_2$: C, 72·67; H, 11·19%.)

4β-*Methyl-7β-carboxy*-3,4,4a,5,6,7,8,8aα-*octahydronaphthalen*-1(2H)-*one* (**18**)

The mixture of **15** and **16**, prepared as above (11·9 g) was dissolved in 120 cc 80% aqueous acetone and oxidized at 0° with 45 cc Jones reagent.[14] The resulting 2-phase mixture was poured into water and saturated with NaCl. This mixture was extracted 5 times with ether. The combined ether layers were extracted with four 75 cc portions of 10% NaOH aq.* Acidification of the resulting basic soln with H_2SO_4, followed by extraction with ether (four 100 cc portions) afforded, after drying over $MgSO_4$ and removal of the ether, 7·9 g of oil whose NMR spectrum indicated that it was predominately the desired **18**. Crystallization from benzene–hexane gave 2·67 g (23%) of **18**. Recrystallization from ether–pet. ether, followed by sublimation at 100° and 25 μ gave the analytical sample, m.p. 124·0–125·8°; NMR in $CDCl_3$: δ 0·82 (Me) and δ 9·80 (COOH); IR in $CHCl_3$: 2400–3500 (O—H) and 1710 cm^{-1} (C═O). (Found: C, 68·37; H, 8·53. Calc. for $C_{12}H_{18}O_3$: C, 68·48; H, 8·64%.)

4aβ-*Methyl-7β-carboxyl*-3,4,4a,5,6,7,8,8aβ-*octahydronaphthalen*-1(2H)-*one* (**17**)

To a soln of 1·00 g of **15** in 25 cc 80% aqueous acetone was added 4 cc Jones reagent.[14] The reaction mixture was poured into water and extracted 4 times with ether. The combined ether extracts were dried and evaporated to yield 0·85 g of white solid which was recrystallized from ether to give analytically pure material, m.p. 133·5–134·9°; NMR in MeOH: δ 1·17 (Me); IR in KBr: 2500–3300 (O—H) and 1700 cm^{-1} (C═O). (Found: C, 68·63; H, 8·62. Calc. for $C_{12}H_{18}O_3$: C, 68·48; H, 8·64%.)

4aβ-*Methyl-8-methylene*-8aα-*decahydronaphth*-2β-*oic acid* (**19**)

To 0·55 g NaH (from 0·92 g of degreased 59·4% NaH emulsion) was added 12 cc dry DMSO[15] under N_2. The resulting suspension was heated at 75° until gas evolution ceased. The soln was cooled and a soln of 7·80 g of methyltriphenylphosphonium bromide in 20 cc DMSO was added. After 10 min, a soln of 2·25 g of **18** in 10 cc DMSO was added. The yellow soln was heated under N_2 at 55° for 17 hr, cooled, and poured into water. The soln was layered with pentane and dil H_2SO_4 was added until pH 3 had been reached. The pentane layer was separated and the aqueous layer was extracted twice with pentane. The combined pentane layers were dried and evaporated to yield 1·49 g of **19**, slightly contaminated with triphenylphosphine oxide. Recrystallization from hexane gave pure **19**, m.p. 117·5–118·5 [lit.[3] 117–117·5°].

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* Simply extracting the mixture of acids in this manner with aqueous base is sufficient to cause epimerization of acid **17** into acid **18**, as judged by NMR examination of the basic soln.

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