The Total Synthesis of (±)-Isonootkatone. Stereochemical Studies of the Robinson Annelation Reaction with 3-Penten-2-one

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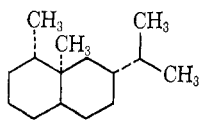
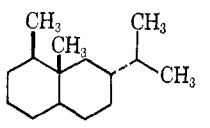
The total synthesis of (±)-isonootkatone (α-vetivone) is described. The key step involves annelation of 4-isopropylidene-2-carbomethoxycyclohexanone with *trans*-3-penten-2-one to give the bicyclic enone with cis-related CH_3 and CO_2CH_3 substituents. A study on the stereochemistry of this reaction using 2-carbomethoxycyclohexanone as the keto ester component showed that the cis isomer was favored in *tert*-butyl and *tert*-amyl alcohol at low temperature. Completion of the isonootkatone synthesis involved reduction (to CH_3) of the CO_2CH_3 grouping in the ketal derivative of the aforementioned annelation product and, finally, ketal hydrolysis. The reduction was effected most efficiently *via* the sequence $CO_2CH_3 \rightarrow CH_2OH \rightarrow CHO \rightarrow CH_3$.

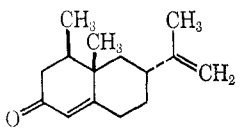
One of the more interesting aspects of the eremophilane–valencane sesquiterpenes from a synthetic point of view is the cis-related vicinal methyl substituents on the hydronaphthalene framework. Over the past decade a number of efforts, some successful, have been made to devise general solutions to this problem.[1] Our initial interest in this area arose from the finding that α-vetivone, long regarded as a hydroazulene, was in fact a double bond isomer of nootkatone.[2]



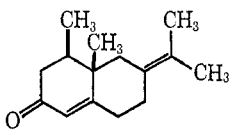
eremophilane



valencane

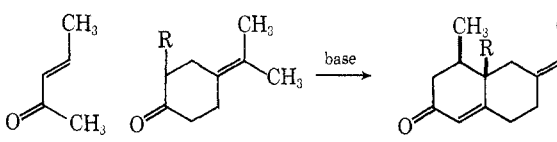


nootkatone

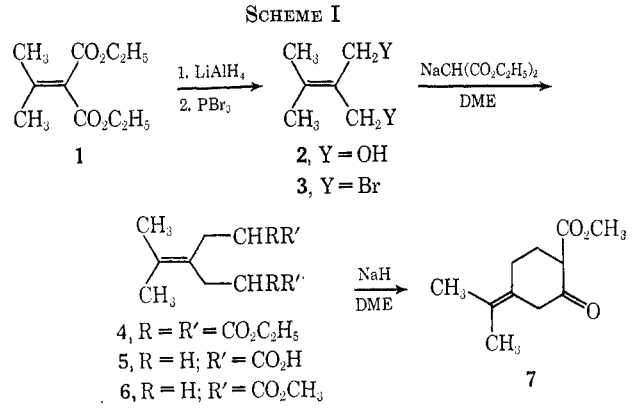


isonootkatone (α-vetivone)

In considering potential synthetic routes to isonootkatone, we were intrigued by the possibility of a direct approach involving simultaneous introduction of the vicinal methyl groupings, or their equivalents, and the conjugated ketone functionality *via* basic condensation of 3-penten-2-one with a 4-isopropylidenecyclohexanone. An *a priori* analysis of the probable stereochemical outcome of such a condensation reaction suggested that the desired cis isomer might predominate if the cyclohexanone moiety possessed an activating group such as carbomethoxyl at the 2 position.[3] This requirement detracted only slightly from the directness of our proposed scheme since such a grouping could presumably be readily converted to the desired angular methyl substituent. Accordingly, we undertook a synthesis of the requisite cyclohexanone **7** (Scheme I).



SCHEME I



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(1) (a) D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 4337 (1960); (b) R. F. Church, R. E. Ireland, and D. R. Shridhar, *J. Org. Chem.*, **27**, 707 (1962); (c) J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); (d) R. M. Coates and J. E. Shaw, *ibid.*, 47 (1968); (e) R. M. Coates and J. E. Shaw, *ibid.*, 515 (1968); (f) C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968); (g) E. Piers and R. J. Keziere, *ibid.*, 583 (1968); (h) R. M. Coates and J. E. Shaw, *ibid.*, 5405 (1968); (i) S. Murayama, D. Chan, and M. Brown, *ibid.*, 3715 (1968); (j) H. Roebke, "Addition of Organocopper Reagents to Conjugated Ketones," Ph.D. Thesis, Northwestern University, 1968; (k) E. Piers, R. W. Britton, and W. Dewaal, *Can. J. Chem.*, **47**, 4307 (1969); (l) M. Pesaro, G. Bozatto, and P. Schudel, *Chem. Commun.*, 1152 (1968); (m) H. C. Odom and A. R. Pinder, *ibid.*, 26 (1969). The approach used by this group is similar to that used in our synthesis of isonootkatone (ref 1c) except for the use of a 2-methylcyclohexanone rather than a 2-carbomethoxyl derivative in the stereochemically critical condensation with *trans*-2-penten-3-one. However, recent developments indicate that this step of the Odom–Pinder synthesis is markedly influenced by certain unknown experimental factors which drastically change the stereochemical outcome. The synthesis has therefore been retracted pending clarification of these factors: H. C. Odom, A. K. Torrence, and A. R. Pinder, "Synthetic Studies in the Eremophilane Sesquiterpene Group," presented at the Symposium on Synthesis and Substitutes for the Food Industry, American Chemical Society, Division of Agricultural and Food Chemistry, 158th National Meeting of the American Chemical Society, Sept 8–12, 1969, New York, N. Y., Abstract 48.

(2) J. A. Marshall and N. H. Andersen, *Tetrahedron Lett.*, 1011, (1967); K. Endo and P. de Mayo, *Chem. Commun.*, 89, (1967).

Diethyl isopropylidenemalonate (**1**)[4] upon reduction with lithium aluminum hydride afforded the corresponding diol **2**. This reaction also gave a considerable amount of 2-isopropyl-2-propen-1-ol, the product of 1,4-hydride addition to malonate **1** followed by reduction–elimination of the resulting enolate.[5] Various attempts to diminish this side reaction were to no avail. Nonetheless, since the desired diol **2** could be readily separated from the allylic alcohol by-product, and in view of the ready availability of the malonic ester **1**, alternative routes to diol **2** were not explored.

(3) For a preliminary report, see J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *ibid.*, 753 (1967).

(4) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **60**, 2644 (1938).

(5) For a mechanistic analysis of this reaction, see J. A. Marshall, N. H. Andersen, and A. R. Hochstetler, *J. Org. Chem.*, **32**, 113 (1967).

TABLE I

CONVERSION OF 2-CARBOMETHOXYCYCLOHEXANONE (8) TO METHYL *cis*- AND *trans*-4-METHYL-1(9)-OCTAL-2-ONE-10-CARBOXYLATE (9a AND 9b)

Entry	Base[a]	Base/keto ester ratio	Solvent	Temp, °C	Yield, %	cis (9a)/ trans (9b)[b]
1	KO-*tert*-Am	0.064	*tert*-AmOH	−15	65	3.08
2	KO-*tert*-Bu	0.068	*tert*-BuOH	0	77	2.32
3	KO-*tert*-Bu	0.116	*tert*-BuOH	0	55	2.2
4	KO-*tert*-Bu	0.043	*tert*-BuOH	30	68	1.45
5	KO-*tert*-Bu	0.180	*tert*-BuOH	27	69	1.39
6	KO-*tert*-Bu	0.298	*tert*-BuOH	30	78	1.25
7	LiO-*tert*-Bu	0.197	*tert*-BuOH	25	62	0.84
8	KOMe	0.113	MeOH	0	39	1.12
9	NaOMe	0.113	MeOH	−15	62	1.07
10	NaOMe	0.109	MeOH	−10	72	0.93
11	NaOMe	0.133	MeOH	40	58	0.98
12	NaOMe	0.180	DMSO	29	72	0.61
13	NaOMe	0.200	THF	22	75	0.75
14	NaH	0.091[c]	THF	0	63	1.07
15	NaH	0.050	Et_2O	0	38	0.52
16	LiH	0.200	Et_2O	30	50	1.00

[a] Conversion to the enone products was effected with 2 *M* NaOMe. [b] Analysis of the enol ether derivatives. [c] 4-Chloro-2-pentanone was employed in this experiment and an additional equivalent of base was initially present to effect dehydrochlorination.

Treatment of diol **2** with phosphorous tribromide afforded the dibromide **3**. Alkylation of this dibromide with diethyl sodiomalonate in DME followed by hydrolysis, decarboxylation, and esterification produced the diester **6**. This substance readily cyclized upon treatment with sodium hydride in DME to give the keto ester **7** in 60% overall yield based on diol **2**.

Before proceeding further with our projected isonootkatone synthesis, we decided to examine the stereochemistry of the proposed condensation step using 2-carbomethoxycyclohexanone (**8**) as the keto ester component. The choice of this keto ester was based upon its availability and the expectation that the reaction products could be readily converted to compounds of known stereochemistry.

The results of this study are summarized in Table I. The conditions described therein led mainly to the diketo ester Michael adducts. Cyclization of these adducts was effected with methanolic sodium methoxide and the product analysis was carried out on the enones **9a** and **9b**. Since the ratios of these cyclized products varied markedly with the Michael reaction conditions, and were reproducible for a given set of conditions, the possibility of stereochemical equilibration *via* reverse Michael condensation in the cyclization step appears unlikely. After considerable searching for a direct method of analyzing enones **9a** and **9b**, we discovered that the enol ether derivatives **11a** and **11b** could be prepared in nearly quantitative yield and were readily separated by vapor phase chromatography. The stereochemistry of these enones was ultimately ascertained through their conversions to the methyl octalones **20a** and **20b** of known structure. We defer discussion of this correlation to a later point in this paper.

The data shown in Table I indicate the range of isomer ratios obtainable through changes in conditions for the Michael addition of keto ester **8** to *trans*-3-penten-2-one. We could not examine all the conceivable variables and the postulates which follow therefore must be considered tentative. However, they do suggest directions for further study and are set forth in this context.

In methanol, temperature changes appeared to exert little influence on product stereochemistry. Increasing the reaction temperature from −15 to 40° decreased the isomer ratio from 52:48 to 50:50 (entries 9–11). Although this change is in the direction of lower specificity, it is well within the range of experimental error, and we do not regard the variation as significant. Attempts to extend the range of the temperature study were thwarted by the low solubility of the keto ester and its enolate below −20°.

In *tert*-butyl alcohol the percentage of cis isomer **9a** increased from 58–59% to 70–75% upon lowering the reaction temperature from 30 to 0° (entries 2–6). Thus, low temperature appears to enhance the selectivity of the reaction in this solvent. Unfortunately, lower reaction temperatures could not be examined owing to solidification of the *tert*-butyl alcohol. The product formed in *tert*-amyl alcohol at −15° contained over 75% of the cis isomer **9a**. This change could be attributed to the lower reaction temperature, although the greater bulk of *tert*-amyl alcohol relative to *tert*-butyl alcohol may also be a contributing factor (see below).

The basicity of the reaction medium determines the relative concentration of keto ester anion and may also influence the reaction by altering the ionic strength (a salt effect). Studies on this point were made using potassium *tert*-butoxide in *tert*-butyl alcohol (entries 2 *vs.* 3 and 4 *vs.* 6). In each case, lower concentrations of base led to increased proportions of the cis isomer **9a**. In entry 14, 4-chloro-2-pentanone was used as a 3-penten-2-one equivalent. Here, an equimolar amount of sodium hydride, in addition to the catalytic amount required for the Michael addition, was added to effect dehydrochlorination during the reaction.

Inasmuch as all the bases employed are capable of converting keto ester **8** into its conjugate base, we reasoned that the basic anion should have little influence on the course of the reaction. The cation on the other hand, can affect the enolate in two ways: (1) it can change the steric bulk of the transition state by its size and degree of solvation; (2) it can alter the reactivity of the enolate by the degree of covalency or ionic char-

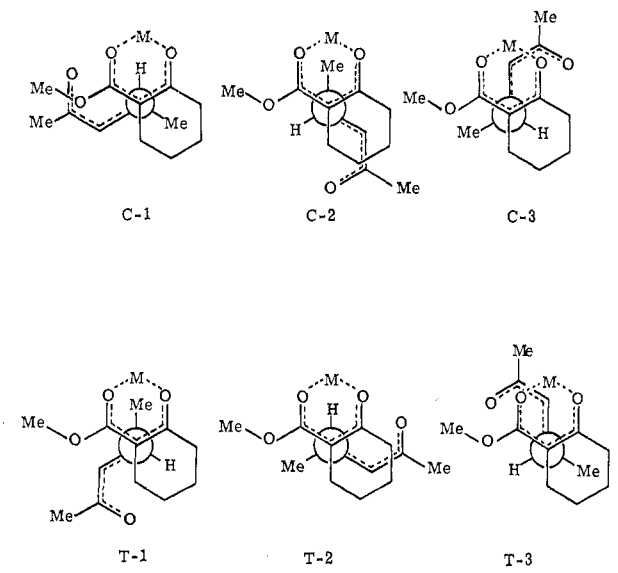
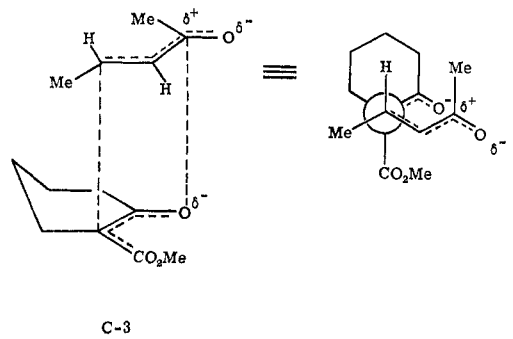


Figure 1.—Transition states for the Michael addition of 2-carbomethoxycyclohexanone to *trans*-3-penten-2-one.

acter associated with the cation–enolate pair. Potassium and sodium enolates gave essentially identical results (entry 8 *vs.* 9) whereas lithium enolates tended to give lower proportions of the cis isomer **9a** (entry 6 *vs.* 7). The magnitude of the variation between lithium and potassium enolates was not great enough to encourage exhaustive searches in that direction. Attempts to utilize magnesium enolates were unsuccessful, possibly owing to the apparent insolubility of these enolates and the requisite alkoxide bases.

Table I clearly shows that the reaction solvent exerts a marked influence upon product stereochemistry. This effect may arise from polar interactions in the transition state and from dissociative interactions with the cation–enolate ion pair. It could also simply stem from steric factors through solvated ions and polar portions of the reacting molecules. In methanol little stereoselectivity was observed, whereas in bulkier alcohol solvents increased amounts of the cis product **9a** were formed. Aprotic solvents generally favored the trans isomer **9b** regardless of solvent polarity.

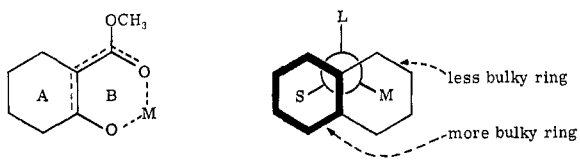
In proposing a mechanism to account for these observations, we considered explanations based upon both electronic and steric factors. Our original hypothesis assumed that the preferred transition state would be one in which steric interactions between the enone and enolate were minimized, and in which there existed a stabilizing electronic interaction between the enolate anion and the electropositive carbon of the enone carbonyl.[3] Such a transition state would resemble C-3 shown below and would lead to octalone **9a**. This simple hypothesis had to be modified since it provided no role for the metal cation or the solvent and could not adequately account for observed variations in the ratio of cis to trans isomers (Table I).



Before going further into the question of stereochemistry, we must consider the conformations available to the reactant molecules. Noack and Jones[6] have shown by infrared and Raman measurements that both the s-cis and s-trans conformations of trans-3-penten-2-one are appreciably populated. We assume that the carbomethoxy portion of keto ester **8** adopts an antiperiplanar conformation analogous to that of methyl acetate.[7,8]

Our proposal assumes that Michael addition of keto ester **8** anion to *trans*-3-penten-2-one involves perpendicular approach to the U form of the keto ester enolate.[9,10] Newman projection formulas which show the various staggered group arrangements along the axis of the developing C–C bond are diagrammed in Figure 1. Conformations C-1 through C-3 would lead to the cis isomer **9a**, whereas the trans isomer **9b** could arise *via* the conformers T-1 through T-3. The s-cis and s-trans conformations of the pentenone appear to have similar steric and electronic requirements, and therefore only the former are shown.

In light of the foregoing considerations our findings seem best explained on steric grounds. The chelated anion of β-keto ester **8** may be regarded as a bicyclo[4.4.0]decane substituted with heteroatoms (I). In this system, the most favored steric arrangement in the Michael addition transition state is illustrated below (II).



II

S = H, M = CH_3,

L = CH_3COCH

The actual steric interactions between rings A and B and the incoming vinyl ketone undoubtedly depend on the nature of cation M^+ and upon the solvent. For potassium and sodium enolates in alcohol, the metal–enolate bond should be highly solvated and thus dissociated. When the alcohol is bulky, as is the case with *tert*-butyl and *tert*-amyl alcohol, the solvated ring B (see above) offers greater steric hinderance than ring A. The lower energy transition state then resembles C-1, and the principal product is the cis isomer **9a**.

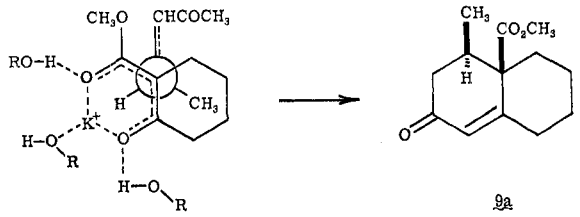
(6) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(7) J. K. Wilmburst, *J. Mol. Spectrsc.*, **1**, 201 (1957); T. Mizazawa, *Bull. Chem. Soc. Jap.*, **34**, 691 (1961).

(8) W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

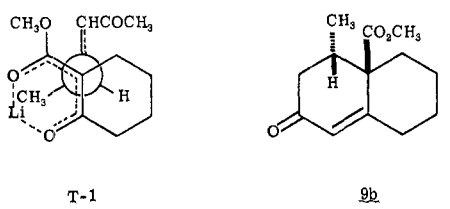
(9) *Cf.* A. Brandstrom, *Ark. Kemi*, **6**, 155 (1953); S. J. Rhoads and A. W. Decora, *Tetrahedron*, **19**, 1645 (1963); S. J. Rhoads and R. W. Hasbrouch, *ibid.*, **22**, 3557 (1966); S. J. Rhoads and R. W. Holder, *ibid.*, **25**, 5443 (1969); H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, **87**, 1857 (1965).

(10) *Cf.* E. Wenkert, A. Afonso, J. B. Bredenbert, C. Kaneka, and A. Tahara, *ibid.*, **86**, 2038 (1964); T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); M. E. Kuehne and J. A. Nelson, *ibid.*, **35**, 616 (1970).



C-1 9a

In aprotic solvents, and with lithium enolates, the metal–oxygen bond has considerable covalent character, and there are fewer tightly bound solvent molecules. Under these conditions, ring A (see above) is the more sterically demanding ring, and the favored transition state T-1 leads to the trans isomer **9b**.



T-1 9b

Having discovered conditions for obtaining the desired stereochemical results in the model studies, we could now test the applicability of this discovery to our proposed isonootkatone synthesis. We were gratified to find that the annelation of keto ester **7** with 3-penten-2-one in *tert*-amyl alcohol–potassium *tert*-amylate followed by treatment with methanolic sodium methoxide to effect aldol cyclization proceeded smoothly and gave the desired keto ester **10a** as a crystalline readily purifiable substance.

In our initial studies on the further conversion of keto ester **7** to isonootkatone, we effected reduction of the methanesulfonate derivative of ketal alcohol **17a** with lithium in ammonia.[3] This reaction led mainly to recovered alcohol *via* S–O cleavage; the desired hydrogenolysis product **19a** (C–O cleavage) was formed in low yield. Our attempts to improve the ratio of C–O to S–O cleavage in this reaction showed little promise and we therefore sought other means for the $CO_2CH_3 \rightarrow CH_3$ conversion.

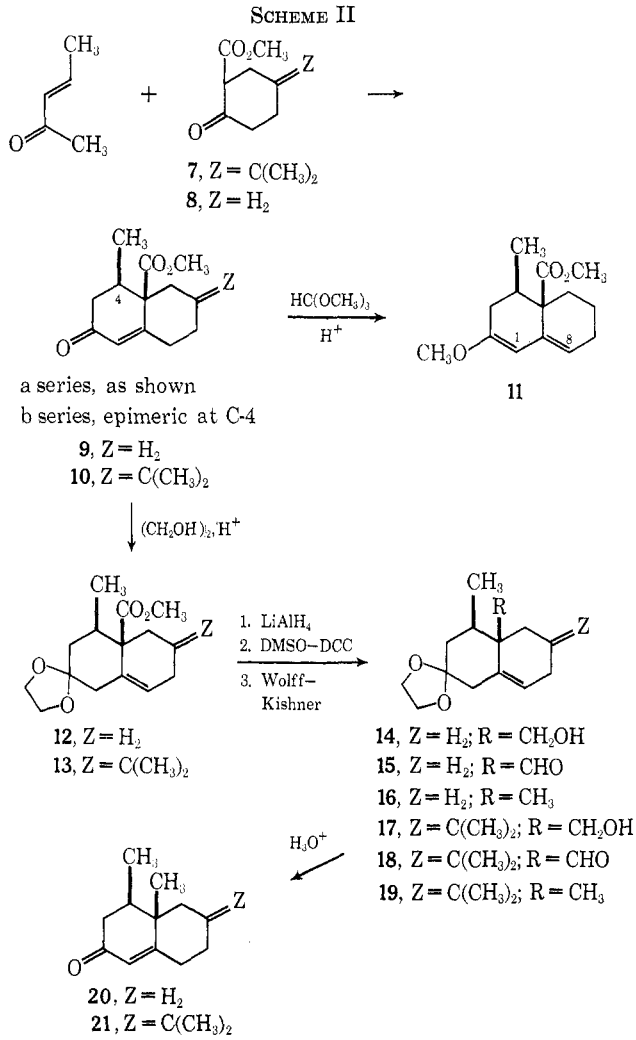
After an unfruitful survey[11] of methods based upon the sequence $CO_2CH_3 \rightarrow CH_2OH \rightarrow CH_2X \rightarrow CH_3$, we examined the alternative sequence $CO_2CH_3 \rightarrow CH_2OH \rightarrow CHO \rightarrow CH_3$. This route proved highly satisfactory when the alcohol oxidation step was effected with Moffatt's dimethyl sulfoxide–dicyclohexylcarbodiimide reagent (Scheme II).[12] Other oxidation methods gave poor results apparently owing to competing oxidation involving the double bond of ketal alcohol **14**. Reduction of the aldehyde **15** *via* a modified Wolff–Kishner procedure afforded the desired methyl compound in high yield.

Application of this sequence to mixtures of the keto esters **9a** and **9b**, secured through annelation of keto ester **8**, led to the corresponding mixtures of ketones **20a** and **20b**. The identity of these two isomers was con-

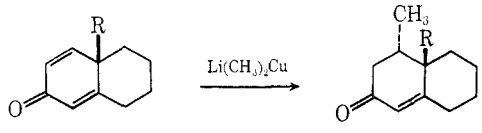
(11) T. M. Warne, Jr., "The Total Synthesis of (±)-Isonootkatone," Ph.D. Thesis, Northwestern University, June 1970, pp 67–72.

(12) K. E. Pitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

SCHEME II



firmed as follows. Addition of lithium dimethylcopper[13] to dienone **22** afforded a 91:5 mixture of enones **20a** and **20b**. Mechanistic considerations[14] and analogy[1e,15] support the assignment of structure **20b** as the major conjugate addition product. The identity of enones **20a** and **20b** was further substantiated through spectral comparison with authentic samples.[16] An enriched specimen of the trans CH_3/CO_2CH_3 enone **9b** was obtained through conjugate addition of lithium dimethylcopper to the dienone ester **23**. The above-mentioned considerations also apply to this conjugate methylation reaction and support the indicated stereochemistry for the major product.



22, R = CH_3 **20b**, R = CH_3
23, R = CO_2CH_3 **9b**, R = CO_2CH_3

(13) H. O. House, W. L. Respess, and G. M. Witesides, *J. Org. Chem.*, **31**, 3128 (1966).

(14) J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966).

(15) R. Weichert, U. Kerb, and K. K. Kieslish, *Chem. Ber.*, **96**, 2765 (1963); W. J. Wechter, *J. Org. Chem.*, **29**, 163 (1964); H. Mori, *Chem. Pharm. Bull.*, **10**, 386 (1962); W. J. Wechter, G. Slomp, F. A. MacKellar, R. Weichert, and U. Kerb, *Tetrahedron*, **21**, 1625 (1965).

(16) (a) R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47 (1968). (b) R. L. Hale and L. H. Zalkow, *ibid.*, 1249 (1968). (c) Private communication with J. J. Sims. We are indebted to Professor Sims for providing an infrared spectrum of the trans-fused decalone related to enone **20a**.

With a reliable method in hand for the $CO_2CH_3 \rightarrow CH_3$ conversion the completion of our isonootkatone synthesis posed no problems. Keto ester **10a** was converted to the ketal derivative **13a** and this material was subjected to the aforementioned sequence to give the ketal **19a**. Acidic hydrolysis then afforded racemic isonootkatone (**21a**) identified through spectral and chromatographic comparison with the natural material isolated from vetiver oil.

Experimental Section[17]

2-Isopropylidene-1,3-propanediol (2).—To a stirred mixture of 89 g (2.35 mol) of lithium aluminum hydride in 3.8 l. of ether[17a] was added 385.2 g (1.93 mol) of diethyl isopropylidene malonate[4] at a rate to maintain reflux. The mixture was stirred for 100 hr, and treated in turn with 89 ml of water, 89 ml of 15% aqueous NaOH, and 267 ml of water.[18] Stirring was continued until the salts had coagulated, solid sodium sulfate was added, and the mixture was filtered and concentrated under reduced pressure to give the crude alcohol mixture.

The inorganic salt cake was stirred overnight with 3 l. of refluxing ethyl acetate to give, after filtration and concentration under reduced pressure, 40.4 g of the acetate of diol **2**. Saponification with aqueous methanolic KOH afforded 21 g of crude diol **2** which was combined with the above described alcohol mixture. Distillation afforded two major fractions: (1) **2-isopropenyl-2-propen-1-ol** [60.5 g (31%); bp 34–52° (10 mm); $n^{28}D$ 1.432; $\delta_{TMS}^{CCl_4}$ 4.97, 4.80 (doublets, $J \sim 1.5$ Hz, C=CH_2), 4.02 (-CH_2O-), and 1.05 ppm (doublet, $J = 7$ Hz, isopropyl CH_3)]; (2) diol **2** [64.5 g (29%); bp 74–78° (0.1 mm); $n^{25}D$ 1.483; $\delta_{TMS}^{CCl_4}$ 4.45 (OH), 4.12 (-CH_2O-), and 1.85 ppm (CH_3)].

The benzylidene derivative was prepared by treatment of diol **2** with benzaldehyde in refluxing benzene containing a small amount of *p*-toluenesulfonic acid. The analytical sample, mp 55.5–56°, was secured by recrystallization from hexane.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.7; H, 7.8.

2-Isopropylidene-1,3-dibromopropane (3).—Following the procedure of Hwa and Sims,[19] 5.78 g (50 mmol) of diol **2** was added with efficient stirring over 90 min to 4.00 ml (42 mmol) of phosphorous tribromide containing a drop of 48% HBr and maintained at 0°.[17a] The mixture was stirred an additional 1 hr, whereupon the product separated as a dark oil. After standing overnight the upper product layer was removed by pipet and isolated *via* ether extraction at low temperature[17b] affording 9.86 g (82%) of dibromide **3**: bp 50° (0.01 mm); mp *ca.* 10°; $\delta_{TMS}^{CCl_4}$ 4.12 (CH_2-Br) and 1.85 ppm (CH_3).

This highly lachrymatory substance deteriorated rapidly, even when stored at −20° and it was therefore used immediately after distillation.

Diethyl 2,6-Di(ethoxycarbonyl)-4-isopropylideneheptanedioate (4).—A solution of 176 g (1.1 mol) of diethyl malonate in 350 ml of DME was added slowly to a suspension of NaH (1.0 mol, secured from 48.0 g of 50% mineral oil dispersion through hexane washing) in 300 ml of DME.[17a] A solution of 14.48 g (0.060 mol) of dibromide **3** was added over a 2–3 hr period and the mixture was stirred for an additional 20 hr. Ethereal acetic acid was added to neutralize the excess sodiomalonate and the product was isolated with ether[17b] and distilled, affording 22.84 g (95%) of the tetraester **4**, bp 180° (0.007 mm). The analytical sample was secured by two additional short-path distillations.

Anal. Calcd for $C_{20}H_{32}O_8$: C, 59.98; H, 8.06. Found: C, 60.2; H, 8.1.

4-Isopropylideneheptanedioic Acid (5).—A solution of 15.05 g (37.5 mmol) of tetraester **4** and 10.0 g of KOH in 200 ml of ethylene glycol was heated at reflux for 12 hr.[17a] The cooled mixture was poured into water and extracted with ether to remove neutral by-products. The aqueous solution was acidified with concentrated HCl and the product was isolated with ether[17b] affording 6.89 g (97%) of solid diacid **5**. Recrystallization from ethyl acetate–hexane afforded needles, mp 96°. The analytical sample, mp 99°, was obtained *via* sublimation [95° (0.01 mm)].

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.1; H, 8.1.

Dimethyl 4-Isopropylideneheptanedioate (6).—According to the esterification procedure of Clinton and Laskowski,[20] 7.28 g (37.4 mmol) of diacid **5** in 160 ml of 1,2-dichloroethane, 18 ml of methanol, and 0.3 ml of concentrated sulfuric acid was stirred at reflux for 3 hr.[17a] The product was isolated with 1,2-dichloroethane[17b] and distilled affording 7.23 g (87%) of diester **6**, bp 85–95° (0.01 mm).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.1; H, 8.9.

Methyl 4-Isopropylidene-2-oxocyclohexanecarboxylate (7).—A solution of 16.30 g (67.0 mmol) of diester **6** in 50 ml of DME was added to a suspension of NaH (230 mmol secured from 9.68 g of 51% mineral oil dispersion through hexane washing) in 1.15 l. of DME.[17a] The mixture was stirred at reflux for 6.5 hr, allowed to cool, and acidified with ethereal acetic acid. The product was isolated with ether[17b] and distilled, affording 11.75 g (90%) of keto ester **7**, bp 103–105° (0.50 mm).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.3; H, 8.2.

Annelation of Keto Ester 8 with *trans*-3-Penten-2-one.—The following procedure is representative of the reactions described in Table I. To a solution of 4.71 g (30 mmol) of keto ester **8** in 14 ml of 1.4 *M* KO-*tert*-Am (1.9 mmol) in *tert*-AmOH at −10 to −15° was added 3.20 g (38 mmol) of *trans*-3-penten-2-one over 8.5 hr.[17a] The solution was maintained at 0° for 15 hr and the product was isolated with ether[17b] affording 5.94 g of crude Michael adduct. This material was cyclized by treatment with 15 ml of 2 *M* NaOMe in MeOH at room temperature for 22 hr.[17a] Isolation with ether[17b] and distillation afforded 4.30 g (65%) of keto ester mixture **9a** and **9b**: bp 128–132° (0.01 mm); $\delta_{TMS}^{CCl_4}$ 5.76 (vinyl H), 3.70 (CO_2CH_3), 0.95 (axial CH_3 doublet, $J = 6.3$ Hz), and 0.91 ppm (equatorial CH_3 doublet, $J = 5.9$ Hz).

Recrystallization of the above sample from pentane afforded material, mp 75–76°, whose spectral properties coincided with those of the cis isomer **9a**. Vpc analysis of the enol ether derivative of this material showed it to be an 88:12 mixture of the epimers **11b** and **11a**.

Methyl 4*t*-Methyl-1(9)-octal-2-one-10*r*-carboxylate (9b).—Lithium dimethylcopper was prepared according to House, *et al.*,[13] from 4.67 ml of 1.6 *M* ethereal MeLi and 0.743 g (3.90 mmol) of CuI in 10 ml of ether at 0°.[17a] To this stirred solution was added 0.400 g (1.90 mmol) of dienone **22** in 25 ml of ether.[17a] After one hr at 0° the mixture was poured into aqueous ammonium chloride–ammonium hydroxide and the product was isolated with ether[17b] affording 0.414 g of enone **9b**, bp 121° (0.01 mm), mp 70.5–72°, after recrystallization from pentane. The spectral data for this compound coincided with that of the trans component **9b** of the annelation product. Vpc analysis of the enol ether derivative of this material showed it to be an 87:13 mixture of the epimers **11b** and **11a**.

Conversion of Keto Esters 9 to the Enol Ethers 11.—A solution of 200 mg (0.90 mmol) of a keto ester **9** mixture and 70 mg of *p*-toluenesulfonic acid monohydrate in 5.0 ml of trimethyl orthoformate was stirred at room temperature for 1.5–2 hr.[17a] The initially colorless solution became green and a precipitate could be observed after 1 or 2 min. The reaction was quenched with aqueous sodium bicarbonate and the product was isolated[17b] and distilled affording 205 mg (97%): bp 100–110° (0.01 mm); $\delta_{TMS}^{CCl_4}$ 5.43 (H-8 triplet of **11a**, $J \sim 4$ Hz), 5.29 (H-8 triplet of **11b**, $J \sim 4$ Hz), 5.15 (H-1), 3.50 and 3.57 (CH_3O), 0.99 (CH_3 doublet of **11a**, $J = 5.5$ Hz), and 0.83 ppm (CH_3 doublet of **11b**, $J = 6.4$ Hz). The two epimers were cleanly separated *via* gas chromatography on both Carbowax 20M and FFAP columns.

Conversion of Keto Ester 9 to Enone 20.—A mixture of 300 mg (1.35 mmol) of keto esters **9a** and **9b** (Table I, entry 10), 10 ml of ethylene glycol, and 52 mg of *p*-toluenesulfonic acid in 25 ml of benzene was stirred at reflux with azeotropic water removal *via* a Dean–Stark trap for 23 hr.[17a] The cooled mixture

(17) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(18) *Cf.* L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

(19) J. C. Hwa and H. Sims, *Org. Syn.*, **41**, 49 (1961).

(20) R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

was poured into aqueous sodium bicarbonate and the product was isolated with ether[17b] affording 329 mg (92%) of ketal **12**.

A solution of this ketal in 25 ml of ether was heated with 76 mg (2.0 mmol) of lithium aluminum hydride at reflux for 5 hr. Water, 15% NaOH, and sodium sulfate were added (see above)[18] and the mixture was filtered to give, after removal of solvent under reduced pressure, 270 mg (92%) of the hydroxy ketal **14**.

A 490-mg (2.05 mmol) sample of alcohol **14** comparable to that described above was stirred overnight with a solution of 1.27 g (6.15 mmol) of dicyclohexylcarbodiimide, 0.08 ml of trifluoroacetic acid, 0.16 ml of pyridine, and 4.0 ml of dimethyl sulfoxide[12] in 4.0 ml of benzene.[17a] The mixture was poured into 25 ml of EtOAc and 540 mg of oxalic acid in 5 ml of MeOH was added. After 0.5 hr the product was isolated with EtOAc[17b] and distilled affording 439 mg (90%) of aldehyde **15**: bp 105° (0.02 mm); λ_{max}^{film} 3.69 and 5.80 μm (CHO).

A 220-mg (0.93 mmol) sample of the above aldehyde in solution with 2.5 ml of 64% aqueous hydrazine and 6 ml of ethylene glycol was heated at 110° for 1 hr[17a] A 1-g portion of KOH was added and the temperature was increased to 200° for 2 hr. The solution as allowed to cool and the product was isolated with hexane.[17b]

A 475-mg sample of material comparable in quality to that described above was heated at reflux with a solution of 45 ml of methanol and 15 ml of 10% aqueous HCl for 5 hr.[17a] The product was isolated with methylene chloride[17b] and distilled affording 312 mg (82%) of enone **20**, bp 80–95° (0.01 mm). Analysis by vpc indicated a 50:41 mixture of **20a** and **20b**. The identity of these isomers was confirmed by peak enhancement with authentic samples.[16]

The above sequence was carried out on a sample of the keto ester 9 secured *via* addition of lithium dimethylcopper to dienone ester **23**, affording a 78:18 mixture (vpc analysis) of enones **20b** and **20a**.

4*t*,10*r*-Dimethyl-1(9)-octal-2-one (20b).—Lithium dimethylcopper was prepared from 3.6 ml of 1.6 *M* ethereal MeLi and 0.571 g (3.0 mmol) of CuI in 20 ml of ether at 0°.[13] A solution of 0.244 g (1.5 mmol) of dienone **22** in 8 ml of ether was added,[17a] and the mixture was stirred for 1 hr and poured into aqueous ammonium chloride–ammonium hydroxide. The product was isolated with ether[17b] and distilled, affording 0.247 g (92%) of enone **20** (a 91:5 mixture of **20b** and **20a** according to vpc analysis), bp 85–95° (0.10 mm).

Methyl 4*c*-Methyl-6-isopropylidene-1(9)-octal-2-one-10*r*-carboxylate (10a).—The Michael–aldol sequence was carried out on 7.26 g (37.0 mmol) of keto ester **7** according to the procedure described above affording 6.47 g (67%) of solid keto ester **10**. Recrystallization from hexane afforded 2.45 g of white needles: mp 70–71°; λ_{max}^{KBr} 5.75, 5.95, and 6.13 μm; $\delta_{TMS}^{CCl_4}$ 5.83 (H-1), 3.67 (CH_3O), 1.68 (vinyl CH_3), and 1.02 ppm (CH_3 doublet, J = 6 Hz). The analytical sample was obtained by sublimation at 55–60° (0.01 mm).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46. Found: C, 73.5; H, 8.5.

Methyl 2,2-Ethylenedioxy-4*c*-methyl-6-isopropylidene-10*r*-carboxylate (13a).—A 0.726-g (2.77 mmol) sample of keto ester **10a** was stirred at reflux with 24 mg of *p*-toluenesulfonic acid and 5 ml of ethylene glycol in 32 ml of benzene with water removal *via* a Dean–Stark trap.[17a] The product was isolated with ether[17b] and distilled affording 0.813 g (96%) of ketal **13a**: bp 120–125° (0.02 mm); $\delta_{TMS}^{CDCl_3}$ 5.58 (H-8), 3.92 ($-OCH_2CH_2O-$), 3.60 (CH_3O), 1.72, 1.60 (vinyl CH_3s), and 1.00 ppm (CH_3 doublet, $J \sim 5$ Hz).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.6; H, 8.6.

2,2-Ethylenedioxy-4*c*-methyl-6-isopropylidene-1(9)-octalin-10*r*-carboxaldehyde (18a).—Ketal ester **13a** (0.93 g, 3.26 mmol) was reduced with lithium aluminum hydride according to the procedure described above for ester **12** affording the alcohol **17a**. This material was oxidized using 6.4 ml of DMSO, 0.254 ml of pyridine, 0.127 ml of trifluoroacetic acid, and 2.035 g (9.9 mmol) of DCC in 6.40 ml of benzene as described above to give the aldehyde **18a** (0.89 g, 98%): bp 119–125° (0.01 mm); λ_{max}^{film} 3.67 and 5.80 μm; $\delta_{TMS}^{CDCl_3}$ 9.48 (aldehyde H), 5.68 (H-1), 3.90 ($-OCH_2-CH_2O-$), 1.71 1.64 (vinyl CH_3s), and 1.05 ppm (CH_3 doublet, J = 5 Hz).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.7; H, 8.7.

(±)-Isonootkatone (21a).—The reduction procedure described above for ketal aldehyde **15** was employed using 0.520 g (1.88 mmol) of aldehyde **18a** affording 0.399 g (81%) of ketal **19a**: bp 108–113° (0.01 mm); $\delta_{TMS}^{CDCl_3}$ 5.30 (H-1), 3.92 ($-OCH_2CH_2O-$), 1.70 (vinyl CH_3), 0.93 (CH_3 doublet, J = 5.5 Hz), and 0.84 ppm (CH_3).

The above sample of ketal **19** in 12 ml of acetone, 1 ml of water, and 0.25 ml of concentrated HCl was stirred at reflux for 0.5 hr.[17a] Solid sodium bicarbonate was added and the product was isolated with pentane[17b] and distilled affording 0.316 g (95%) of impure isonootkatone (**21a**), bp 110° (0.015 mm). This material was purified *via* chromatography on silica gel and distillation [85–95° (0.01 mm)]. The material thereby obtained (166 mg) solidified. The spectral properties of this substance matched those of natural isonootkatone.[2]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.5; H, 10.1.

Methyl 1(9),3-Hexal-2-one-10-carboxylate (23).—A solution of 3.28 g (15.7 mmol) of methyl 1(9)-octal-2-one-10-carboxylate and 3.97 g (17.5 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in 130 ml of benzene and 6.8 ml of acetic acid was stirred at reflux for 40 hr.[17a] The mixture was filtered and the filtrate was washed with 10% aqueous NaOH, saturated aqueous sodium bicarbonate, and dried to give, after removal of solvent under reduced pressure, 2.66 g (82%) of yellow solid. Recrystallization from hexane afforded 1.98 g of dienone ester **23**: mp 115–117°; λ_{max}^{KBr} 5.78, 6.01, 6.12, and 6.22 μm; $\delta_{TMS}^{CCl_4}$ 6.68 (H-4 doublet, J = 10 Hz), 6.18 (H-3, 4 lines, $J_{3,4}$ = 10 Hz, $J_{3,1}$ = 1.5 Hz), 6.11 (H-1 doublet, J = 1.5 Hz), and 3.72 ppm (CH_3O). The analytical sample, mp 118.5–119°, was obtained by sublimation [65° (0.01 mm)].

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.9; H, 6.8.

Registry No.—**2**, 2035-85-0; **2** benzylidene derivative, 26419-14-7; **3**, 26430-96-6; **4**, 26430-97-7; **5**, 26430-98-8; **6**, 16981-92-3; **7**, 26431-00-5; **9a**, 26431-01-6; **9b**, 26419-15-8; **10a**, 26431-02-7; **11a**, 26431-03-8; **11b**, 26431-04-9; **13a**, 26431-05-0; **15a**, 26431-06-1; **15b**, 26431-14-1; **18a**, 26431-07-2; **19a**, 26431-08-3; **20a**, 26431-09-4; **20b**, 26431-10-7; **21a**, 16981-90-1; **23**, 26431-12-9; 2-isopropenyl-2-propen-1-ol, 26431-13-0.

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