Total Syntheses of (±)-Methyl Vinhaticoate and (+)-Methyl Vouacapenate

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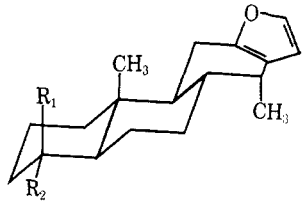
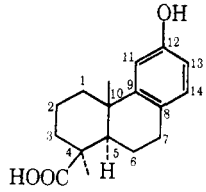
Abstract: Total syntheses of the tetracyclic furanoid diterpenes methyl vinhaticoate (**1**) and methyl vouacapenate (**2**) are described. These syntheses of racemic **1** from the previously described intermediate **4** and of natural (+)-**2** from podocarpic acid (**3**) required solution of two key problems. First, the secondary methyl group at C_{14} had to be introduced with known stereochemistry so that the previously undefined configuration at that center could be determined to be α, as shown in **1** and **2**. Second, a new method for elaboration of the furan moiety had to be developed. Treatment of 2-methoxymethylene ketones **28** and **47** with ethyl diazoacetate in the presence of copper sulfate was found to lead to furoic esters **29** and **48** which could readily be converted to the natural products.

Methyl vinhaticoate (**1**) and methyl vouacapenate (**2**), which are very abundant, easily isolated, South American hardwood constituents, represented particularly intriguing goals for total synthesis among diterpenoid natural products, both because they possess unusual tetracyclic furan structures and because the configurations of their C_{14} secondary methyl groups had not been determined during the structural elucidation of these substances.[1] As disclosed in our preliminary report[2] of the synthesis of racemic **1**, the C_{14} methyl group in methyl vinhaticoate has the α configuration, as shown.



1, $R_1 = CH_3$; $R_2 = COOCH_3$
2, $R_1 = COOCH_3$; $R_2 = CH_3$



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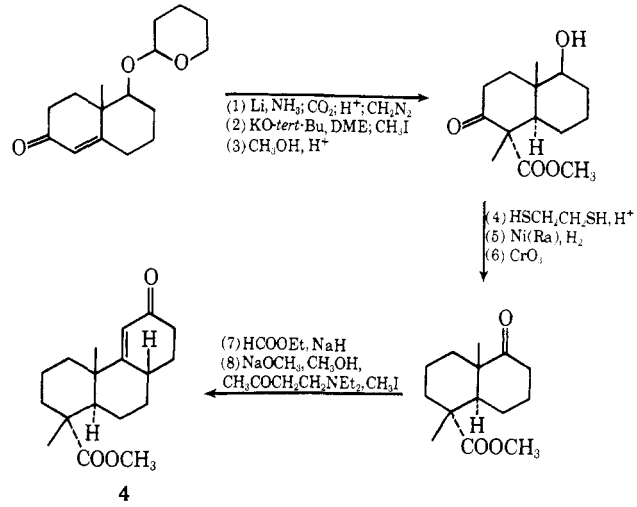
In this paper the details of the completion of the synthesis of racemic **1** are reported, and the synthesis, starting from the readily available podocarpic acid (**3**), of natural (+)-methyl vouacapenate (**2**), which also possesses a C_{14} α-methyl group, is described.[3] Emphasis in the following discussion is on the introduction and determination of the stereochemistry of the C_{14} methyl groups, and on the development of a novel method for construction of the furan ring.

Synthesis of (±)-Methyl Vinhaticoate (1). Our stereoselective synthesis of enone **4** *via* the AB → ABC approach outlined in Scheme I has previously been described.[4] Enone **4** possesses three of the six contiguous asymmetric carbons of structure **1** (C_4, C_5, and C_{10}) firmly fixed in the proper configurations. A fourth center, at C_8, presumably has its hydrogen β as required in **1**, because **4** was prepared using sodium

Scheme I



4

methoxide in refluxing methanol, conditions which should ensure formation of the more stable C_8 epimer.[5]

Lithium in ammonia reduction of **4** was the obvious choice for completion of the *trans-anti-trans*-perhydrophenanthrene system found in **1**, since such reductions are known to afford very predominantly, if not exclusively, trans fusions between six-membered rings.[6] Dropwise addition of 2–3 equiv of lithium in liquid ammonia to **4** afforded up to 42% of a saturated keto-ester assigned structure **5**, but yields in this selective reduction were erratic, presumably owing to the presence of the reducible C_4 carbomethoxyl group. Catalytic hydrogenation of **4** produced a mixture of **5** and an incompletely characterized substance, probably **6**, from which up to 41% of **5** could be separated. The most efficient, albeit circuitous, method for the preparation of **5** consisted in complete reduction to saturated diol **7** with lithium–ammonia–ethanol, followed by oxidation to keto acid **8** with Jones reagent,[7] and esterification with diazomethane. This sequence afforded the desired **5**, with all the asymmetric centers of **1** except C_{14} in the desired configurations, in *ca.* 70% yield from **4**.

(1) (a) F. E. King, T. J. King, and K. G. Neill, *J. Chem. Soc.*, 1055 (1953); F. E. King and T. J. King, *ibid.*, 4158 (1953); (b) F. E. King, D. H. Godson, and T. J. King, *ibid.*, 1117 (1955).

(2) T. A. Spencer, R. M. Villarica, D. L. Storm, T. D. Weaver, R. J. Friary, J. Posler, and P. R. Shafer, *J. Amer. Chem. Soc.*, **89**, 5497 (1967).

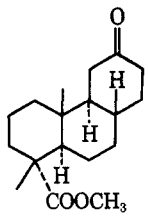
(3) In this paper structures **4–23** and **28–30** refer to racemates, and structures **2**, **3**, **24–27**, and **31–50** refer to (+)-enantiomers. Structure **1** refers to both (+) and (±) material, as indicated.

(4) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

(5) See T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *J. Org. Chem.*, **33**, 719 (1968), for a discussion of C_8 stereochemistry in compounds of this type.

(6) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964); M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

(7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).



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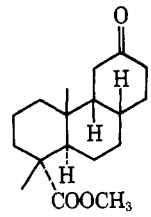

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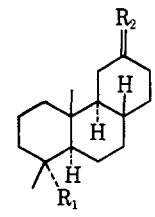
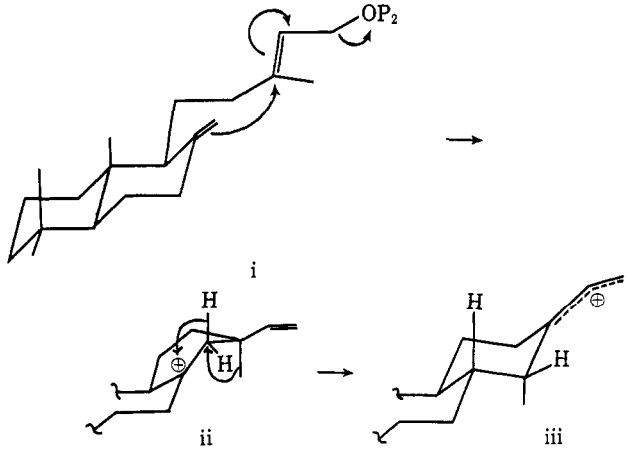


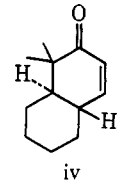
7, $R_1 = CH_2OH$; $R_2 = OH, H$
8, $R_1 = COOH$; $R_2 = O$

By far the simplest path for introduction of the methyl group required at C_{14} appeared to be conjugate addition of an organometallic reagent to enone **9**, which should be readily derivable from **5**. The configuration at C_{14} in the target natural products was not known, but the report of C_{14} α-methylated structures for cassaic acid and related substances,[8] as well as biogenetic considerations,[9] suggested that the secondary methyl group would probably have the α configuration. Since



i ii iii

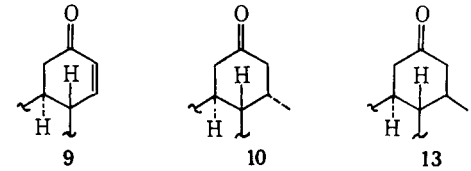
conjugate addition of organometallic reagents tends, in the absence of steric hindrance, to afford axial substitution,[10] this approach was adopted with the expecta-



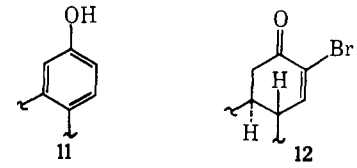
iv

tion of obtaining predominantly **10**.

Conversion of **5** to **9** was accomplished in yields up to 65% by bromination[11] and dehydrobromination with calcium carbonate in dimethylacetamide,[12] but this sequence was capricious, and products of overbromination, phenol **11** and bromoenone **12**, often reduced the yield of **9**. Formation of these undesired by-products could be suppressed by use of less than 1 (0.8) equiv of bromine, which led, after dehydrobromination, to a mixture of just **9** (36%; 82% based on **5** not recovered) and **5** (58%), separable by chromatography.



9 10 13



11 12

Conjugate methylation of **9** was initially[2] carried out with methylmagnesium iodide in the presence of cupric acetate.[10] This procedure afforded some hydroxylic product presumably resulting from addition at the C_{12} carbonyl group, as well as about 40% of desired C_{14}-methylated product. Lithium dimethylcopper[13] proved, as expected, more selective, yielding 80–90% of 1,4-addition product and no appreciable 1,2-addition. Careful tlc and spectral analysis showed the conjugate methylation product to be an approximately 1:1 mixture of two substances, presumably **10** and its β-methyl isomer **13**. The anticipated preponderance of axial alkylation[10] was not observed.

One of the methylation isomers crystallized spontaneously from the crude reaction product, and the investigation of stereochemistry at C_{14} was, understandably, initiated with this solid. It transpired, as recounted below, that nature had smiled on us, for this easily purified intermediate, which proved to **10**, was eventually converted to **1**, and its isomer **13** was never even purified.

The principal method used to determine the C_{14} stereochemistry of the crystalline methylation product involved measurement of the nmr $C_{13}H$–$C_{14}H$ coupling constant of a C_{13} monobromo derivative, as had been done by Marshall in a similar system.[10] In order to conserve material for completion of the synthesis of **1**, these experiments were done on a very small scale, and the bromination products were not fully characterized. The thorough application of this method to the analogous methylation products in the synthesis of **2** is discussed in the second part of this paper.

Bromination in acetic acid of the crystalline methylation isomer afforded a solid product which had an axial bromine substituent (λ_{max}^{EtOH} 310 mμ; $\epsilon \sim 100$),[14] and therefore had structure **14** or **16** (rather than **15** or **17**). The possibility that the substance was the C_{11} derivative **18** could be ruled out because the C_{11} axial bromine would cause a marked deshielding of the C_{10} angular methyl group,[15] which was not observed. The

(8) R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel, and J. M. Sanders, *J. Amer. Chem. Soc.*, **88**, 1766 (1966); *cf.*, D. W. Mathieson, and A. Karim, *J. Chem. Soc. C*, 1705 (1970), for a recent corroborative paper.

(9) Structures with the carbon skeleton of **1** can be most economically envisaged as arising in nature by the sequence i → ii → iii in which the C_{14} α-methyl configuration is a consequence of formation of a C_8 β-hydrogen.

(10) J. A. Marshall and N. H. Andersen [*J. Org. Chem.*, **31**, 667 (1966)] studied conjugate addition of Grignard reagents to enone iv and found that cupric acetate catalyzed addition of methylmagnesium iodide afforded a 5:1 ratio of axial to equatorial alkylation. However, the results discussed in this paper of conjugate addition to enones **9** and **36**, combined with Marshall and Andersen's results with other (larger) Grignard reagents, suggest that caution is advisable in trying to make predictions of stereochemistry in this type of reaction.

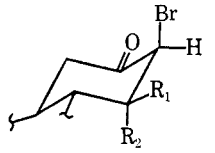
(11) The bromination products (at least two were detected) were not purified and characterized; the total crude reaction product was used routinely in the dehydrobromination.

(12) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

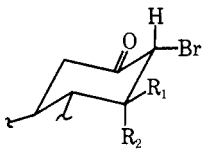
(13) (a) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **33**, 840 (1968); (b) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966).

(14) See A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, p 35, for consideration of uv criteria for stereochemistry of α-bromo ketones.

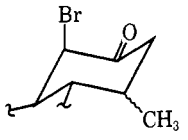
C_{13} hydrogen in this product, which had a chemical shift (δ, $CDCl_3$, 4.04 ppm) confirming that it was equatorial,[16] appeared as a broad singlet.[17] The bromination residues after separation of this solid showed, in addition to the peak at 4.04 ppm, a doublet at 4.42 ppm with J = 5 Hz. There was no indication of a peak with the much larger (*ca.* 10–12 Hz) coupling constant expected[18] from bromo derivative **17**, and we concluded therefore that the residue was a mixture of **14** and **15**, and that the compound brominated was **10** rather than **13**.



14, $R_1 = H$; $R_2 = CH_3$
16, $R_1 = CH_3$; $R_2 = H$



15, $R_1 = H$; $R_2 = CH_3$
17, $R_1 = CH_3$; $R_2 = H$



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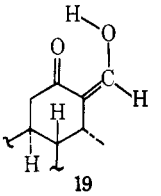
Further evidence suggesting assignment of the α configuration to the C_{14} methyl compound in hand was obtained from the nmr spectrum of the acetoxymethylene ketone **20**,[19] prepared *via* the hydroxymethylene derivative **19**. That the condensation of **10** with ethyl formate occurred, as anticipated, at C_{13} rather than C_{11} could be inferred from the deshielding effect ($\Delta\delta$ = 0.13 ppm) of the hydroxymethylene moiety on the C_{14} methyl doublet. The vinyl proton of **20** appears as a rather broad singlet at 7.85 ppm. If the C_{14} hydrogen were axial (as in **13**) it should appear as a doublet with J = 1.5–2.0 Hz.[20] This prediction was also confirmed during the synthesis of **2**.

Reasonably confident that we had **10**, and hopeful that it was a potential precursor of natural methyl vinhaticoate, we turned to the final synthetic challenge: construction of the furan ring. The classical approach of acid-catalyzed cyclization of a 1,4-dicarbonyl compound was tried first. For the synthesis of the requisite ketoaldehyde **21** we wished to proceed *via* hydroxymethylene derivative **19**, in order to be certain that the prospective $-CH_2CHO$ moiety would be introduced at C_{13}. This aim was achieved by alkylation of the anion of **19** with allyl bromide, which afforded predominantly the O-allyl derivative **22**.[21] Heating **22** at 150° effected rearrangement and decarbonylation to the C_{13}-allyl compound **23**, which upon ozonolysis yielded the desired **21**.

Treatment of this ketoaldehyde under a wide variety of acidic conditions afforded at best only a trace of furan. These results were disappointing, for an analogous sequence had been used successfully by Büchi in his synthesis of the furopelargones.[22] The 0.4 mg (*ca.* 1%) of crude, oily furan which we were able to obtain had tlc mobility and infrared and ultraviolet spectra essentially identical with those of natural methyl vinhaticoate. But because comparison of the C_{14} configuration of the synthetic material with that of the natural product required a larger, purer sample for nmr analysis, and because the yield in this final step was unsatisfying, we turned to investigation of other methods for construction of the heterocyclic D ring.



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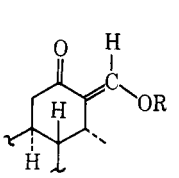
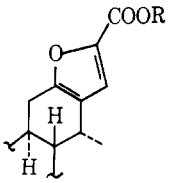
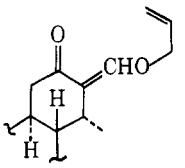


20, R = Ac
28, R = CH_3



29, R = Et
30, R = H



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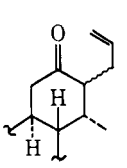

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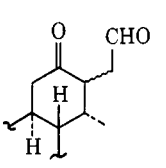

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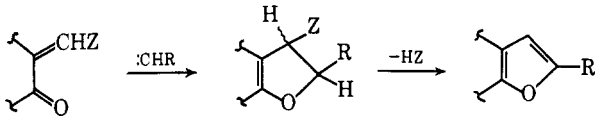
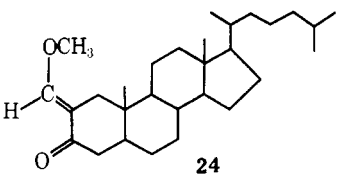
This search for a more efficient way to complete the synthesis of **1** encompassed trial of several known furan

Scheme II





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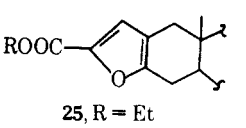
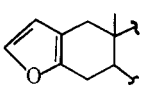


25, R = Et
26, R = H



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(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 22.

(16) Bhacca and Williams (see ref 15, p 74) list 4 α-bromo ketones in which equatorial C*H*Br has δ 4.06, 4.13, 4.17, and 4.28 ppm, and five α-bromo ketones in which axial C*H*Br has δ 4.61, 4.64, 4.80, and 5.03 ppm; *cf.*, however, the δ 4.33 ppm value for **42** (Scheme IV).

(17) This nmr spectrum was determined on a 1-mg sample using a Varian C-1024 time-averaging computer. All lines in spectra so determined were broadened and it is difficult to estimate what $J_{13,14}$ really was. Note, however, that compounds **39** and **41** showed similar broad singlets under more advantagious conditions.

(18) Reference 10 and reference 15, pp 49–54 and 75, provide examples of uses of the dihedral angular dependence of vicinal coupling constants.

(19) (a) Compound **20** and the other derivatives of α-hydroxymethylene ketones described in this paper are assigned the configurations shown on the basis of a comparison of the chemical shifts of their vinyl hydrogens and methoxyl methyl groups (for the α-methoxymethylene compounds) with analogous data for other examples of these classes of compounds, using the correlation which P. Hodge, J. A. Edwards, and J. H. Fried [*Tetrahedron Lett.*, 5175 (1966)] used to make such a distinction; (b) *cf.* D. L. Storm and T. A. Spencer, *ibid.*, 1865 (1967). We thank Dr. J. A. Edwards for private communication of the data on which they based their assignments.

(20) *Cf.* H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965); T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Amer. Chem. Soc.*, **85**, 1699 (1963).

(21) Compounds **22**, **23**, and **21** were not purified and characterized, but were identified on the basis of spectral properties given in the Experimental Section.

(22) G. Büchi and H. Wüest, *J. Amer. Chem. Soc.*, **87**, 1589 (1965). *Cf.*, however, the report by F. Ebel, F. Huber, and A. Brunner [*Helv. Chim. Acta*, **12**, 16 (1929)] of failure to form a furan upon treatment of 2-acetonylcyclohexanone with a variety of acid catalysts. Our findings support the inference that formation of the heterocycle with the α and β positions as part of a cyclohexane ring is relatively difficult.

syntheses[23] in model systems. All of these proved unpromising, and need not be detailed here. In attempting to devise a novel approach we were attracted by the conceptual simplicity of a net 1,4-addition of a methylene equivalent across a conjugated system held in an *s*-cis orientation (as in **20**), to afford a dihydrofuran derivative, which could undergo (spontaneous) elimination to form the aromatic ring, as illustrated in Scheme II.

Exploration of this approach was undertaken on the steroid model system **24**, prepared by methylation of 2-hydroxymethylenecholestan-3-one (or *via* the acetoxymethylene derivative as discussed below). Treatment of **24** with various potential methylene transfer reagents, such as diazomethane,[24] and the Simmons–Smith reagent[25] produced no detectable furan. At this point in our efforts we were encouraged to persevere by learning of the formation of 2,2-difluoro-3-methoxy-2,3-dihydrofurans in the reaction of a 2-methoxymethylene ketone with difluorocarbene.[26] The desired course of reaction was finally attained when methoxymethylene ketone **24** was heated with ethyl diazoacetate at 160° in the presence of a trace of copper sulfate. The principal steroidal product formed was α-furoic ester **25**, which was saponified to the corresponding acid **26** and then decarboxylated to afford the parent furan **27**,[27] providing further evidence for the structure of **25**, as well as model procedures for the completion of the synthesis of **1**.

To this end, the methoxymethylene ketone **28** was prepared from hydroxymethylene derivative **19**. However, this seemingly prosaic transformation was rather frustrating in practice, and yields of the relatively unstable **28** were variable. Direct methylation of **19** with a variety of reagents proved less reliable than synthesis of **28** *via* brief treatment of the previously mentioned acetoxymethylene compound **20** with *p*-toluenesulfonic acid in methanol.[26] This indirect method provided a crude product suitable for use in the next step.

Reaction of **28** with copper-complexed carboethoxycarbene under the same conditions used in the model series afforded furoic ester **29** in about 30% yield.[28] Without purification, this material was selectively hydrolyzed (methanolic sodium hydroxide at 55° for 3 hr) to the furoic acid **30** without appreciably affecting the C_1 carbomethoxyl group. Decarboxylation of **30** at 230° in the presence of copper powder afforded racemic **1**, which after sublimation and recrystallization, had mp 122–123°. Comparison of the distinctive infrared, ultraviolet, nmr, and mass spectral properties of synthetic (±)-**1** with those of natural methyl vinhaticoate[29] established their identity. In particular, both samples displayed the C_{14} methyl doublet at exactly the same chemical shift (δ 0.97 ppm)[30] and gave richly detailed, completely identical mass spectra.[31]

Synthesis of (+)-Methyl Vouacapenate (2). The conversion of podocarpic acid (**3**) into methyl vouacapenate was undertaken not only to establish the complete structure of the natural product, but also to provide amounts of intermediate substances, analogous to those prepared in the synthesis of (±)-**1**, adequate to permit detailed studies of the new furan synthesis and of the conjugate methylation stereochemistry. Although the evidence for assignment of a C_{11} α-methyl group to **10**, and hence to **1**, seemed trustworthy, removal of any nagging doubt about the validity of the small-scale nmr studies described above was deemed important.

The pathway leading from **3** to **2** which we chose is shown in Scheme III. The first part of this synthetic sequence involves preparation of keto ester **31**, which has been reported previously by Bible[32] and by Bell.[33] A modified[34] version of Bible's sequence afforded **31** in 47% overall yield from **3**.

Bromination and dehydrobromination[12] of **31** could be carried out without complication and afforded enone **36** in 60% yield. The reasons for our previous difficulty in preparing **9** in good yield reproducibly by the same method remain obscure. Conjugate methylation of **36** with lithium dimethylcopper afforded 94% of a product which nmr analysis indicated to be a 55:45 mixture of the two saturated keto esters **37** and **38**, respectively. Again, as in the case of enone **9**, there was no pronounced stereoselectivity of alkylation with either lithium dimethylcopper or methyl Grignard reagent in the presence of cupric acetate. In the present experiment, however, it was the C_{11} β-methyl compound **38** which spontaneously crystallized, rather than its isomer **37**, which could be obtained crystalline only after careful chromatography.

Initial assignment of stereochemistry to **37** and **38** was based on comparison of the chemical shifts of their C_{11} methyl doublets (shown in Scheme IV) with those of their analogs **10** and (impure) **13**.[30] With ample supplies of both **37** and **38** in hand, it was readily feasible to obtain convincing evidence that all these assignments were indeed correct. Compounds **37** and **38** each afforded two crystalline monobromo derivatives upon treatment with cupric bromide.[35] Structures **39**–**42** can be assigned to these four bromo ketones on the basis of the nmr data shown in Scheme IV. The values of $J_{13,11}$ for **39**, **40**, and **41** are all per-

(23) *E.g.*, (a) W. Treibs, *Ber.*, **70**, 85 (1937); R. Pallaud and J. Berna, *Ind. Parfum.*, **8**, 154 (1953); (b) W. Broy and R. Mayer, *Z. Chem.*, **3**, 150 (1963); (c) S. Julia and C. Moutonnier, *Bull. Soc. Chim. Fr.*, 979 (1964); (d) H. Minato and T. Nagasaki, *Chem. Ind. (London)*, 899 (1965); *J. Chem. Soc. C*, 377 (1966).

(24) D. Nasipuri and K. K. Biswas [*Tetrahedron Lett.*, 2963 (1966)] reported, during the course of our studies, that the reaction of 2-methoxymethylene ketones with diazomethane affords methyl enol ethers of α-acetyl ketones *via* intermediate pyrazolines. In our hands these reactions did not produce good yields of any single product.

(25) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(26) P. Hodge, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 5175 (1966).

(27) Details of the preparation of compounds **24**–**27**, preliminary reported in ref 19b, will be presented in another publication.

(28) The nmr spectrum of the furanoid product suggested that it might contain a small amount of an isomeric furoic ester [*cf.*, S. T. Murayama and T. A. Spencer, *Tetrahedron Lett.*, 4479 (1969)].

(29) We thank Dr. T. J. King for providing a very generous sample of this natural product.

(30) Comparison of the δ values of all the C_{11} α- and C_{11} β-methyl signals reported in the Experimental Section reveals that a C_{11} β-methyl group invariably appears 0.14–0.21 ppm downfield from its α isomer, and if natural **1** had a C_{11} β-methyl group its resonance should appear at *ca.* 1.15 ppm.

(31) In the preliminary communication of the synthesis of (±)-**1** (ref 2), a peak in the mass spectra of synthetic and natural **1** with *m/e* 344 (mol wt of **1** = 330) was reported. This proved to be a contaminant in the spectrometer for it was not apparent when the mass spectra were redetermined.

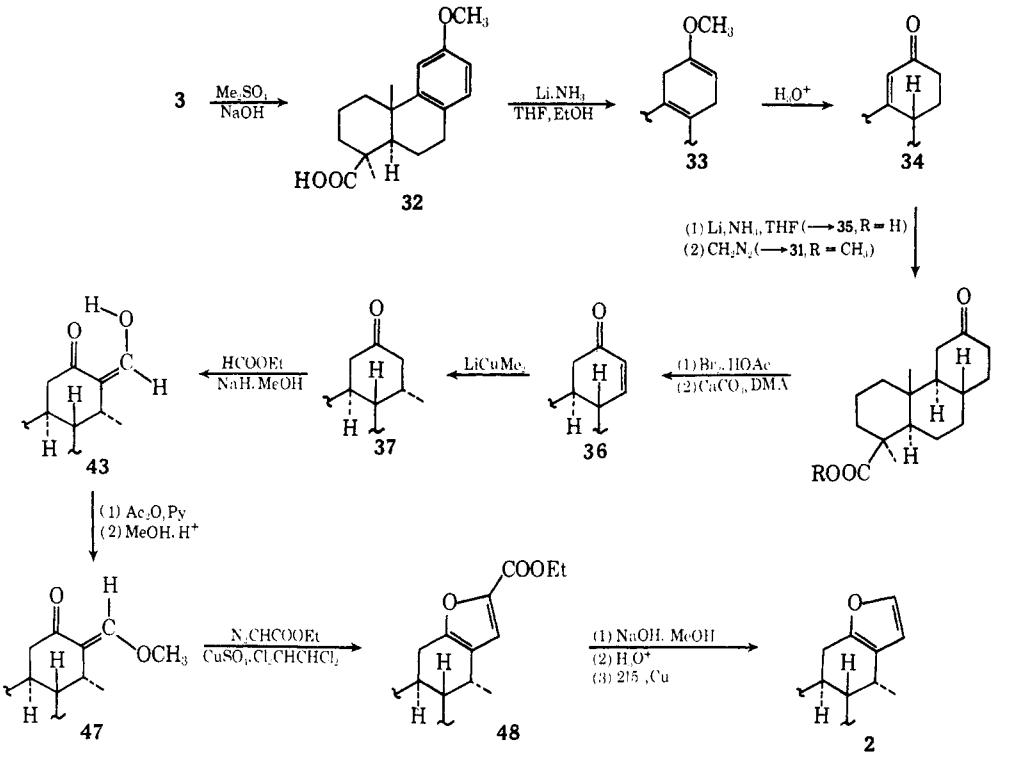
(32) R. H. Bible and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

(33) R. A. Bell and M. B. Gravestock, *Can. J. Chem.*, **47**, 3661 (1969).

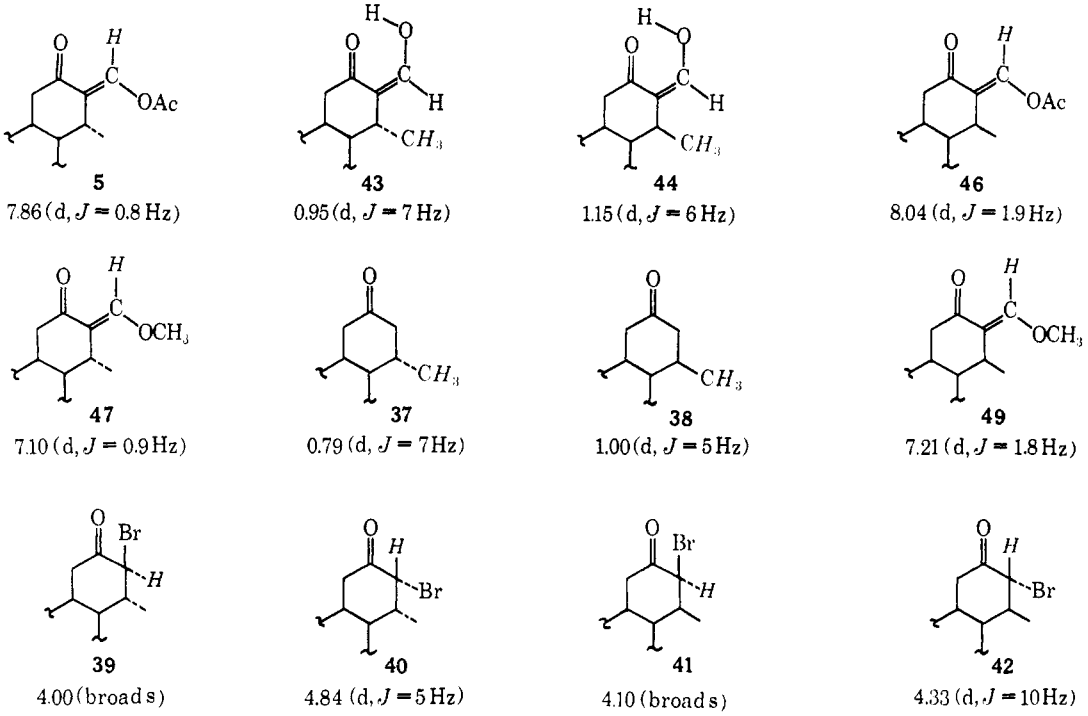
(34) Improved procedures for preparation of **32** and **33** were communicated privately to us by Professor D. J. Goldsmith, to whom we express thanks.

(35) H. C. Brown, M. M. Rogic, and M. W. Rathke, *J. Amer. Chem. Soc.*, **90**, 218 (1968).

Scheme III



Scheme IV[a]



[a] Nmr data are given beneath each structure for the proton(s) in italics.

haps somewhat less than might have been predicted,[18] but the clearly larger value for **42** establishes unequivocally that it possesses trans-diaxial C_{13} and C_{11} hydrogens, and is therefore derived from a C_{11} β-methyl ketone.

The nmr signals for the vinyl protons in acetoxymethylene derivatives **45** and **46**, derived from **43** and **44**, respectively, and shown in Scheme IV, were also consistent with these stereochemical assignments. Compound **46** displayed the doublet at 8.04 ppm with J = 1.9 Hz which would be predicted for a compound with a C_{11} α-hydrogen.[20] The vinyl proton peak in the nmr spectrum of **45** could be resolved into a doublet with J = 0.8 Hz (at 7.86 ppm) on a slow scan, but clearly corresponded more closely to the peak observed earlier for **20** than to that of **43**.

For completion of the synthesis of methyl vouacapenate, 2-methoxymethylene ketone **47** was prepared from **43**, *via* **45**, in the same manner as **28**. Treatment of **47** with excess ethyl diazoacetate in boiling 1,1,2,2-tetrachloroethane containing a trace of cupric sulfate, conditions which had been found to be optimum in the

case of 2-methoxymethylene-1-tetralone,[28] afforded a 40% yield of pure furoic ester **48**. Selective hydrolysis and decarboxylation were performed as described in the synthesis of (±)-**1** to yield (+)-**2**, mp 101–102°, which was identical in all respects with a sample of the natural product.[29] Since podocarpic acid (**3**) has been synthesized in many laboratories, including our own,[5] the total synthesis of methyl vouacapenate may be claimed. The overall yield of **2** from **3** was 1%.

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were taken in an open capillary or on a micro hot stage and are uncorrected. Ultraviolet (uv) spectra were determined in 95% ethanol on a Cary Model 14 spectrophotometer. Infrared (ir) spectra were determined on a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were determined on a Varian HA-60-IL spectrometer in *ca.* 10% w/v solutions in $CDCl_3$ containing tetramethylsilane as an internal reference. Analytical thin-layer chromatography (tlc) was carried out on 0.25-mm thick layers of Merck silica gel G. Preparative tlc (plc) was carried out on 1.25-mm thick layers of Merck silica gel $PF_{254-366}$.

The term "standard work-up" refers to the following general procedure, as applied logically to given preparations. The reaction mixture was partitioned between water and ether. The ether layer was separated. The aqueous layer was extracted with ether, and the ether layers were combined, washed with brine, dried over magnesium sulfate, filtered, and evaporated. The term "brine" refers to saturated aqueous sodium chloride solution.

Keto Ester 5. The precursor of **5**, α,β-unsaturated ketone **4**, was prepared by the sequence outlined in Scheme I, for which experimental details have been reported previously.[4]

(a) Direct Li–NH_3 Reduction of 4 to 5. A solution was prepared of 0.514 g (1.77 mmol) of pulverized **4**, mp 85–90°, in 100 ml of liquid ammonia containing an amount of ether sufficient to give a homogeneous mixture. To this stirred solution was added dropwise over 15 min a solution of 0.31 g (4.4 mg-atom) of lithium wire in 70 ml of liquid ammonia. This lithium-in-ammonia solution had been prepared in a 300-ml round-bottomed flask, specially equipped with a standard-taper stopcock appended to its bottom. This flask was placed on its side in a Dry Ice–acetone bath, and the reagents were introduced and magnetically stirred. When the lithium had dissolved, the flask, equipped with a drying tube at its top neck, was simply fitted to the reaction flask, and addition of the reductant was begun. After the addition of the lithium in ammonia was completed, 1 g of solid ammonium chloride was added, and the ammonia was allowed to evaporate. Standard work-up of the residue yielded 0.47 g of oily solid which was chromatographed on 20 g of acid-washed alumina. With 1:3 ether–hexane, 0.226 g (42%) of crystalline **5** was eluted. Recrystallization from ether–hexane afforded an analytical sample: mp 126–127°; ir (KBr) 5.79 and 5.86 μ; nmr ($CDCl_3$) δ 0.92 (s, 3, H_3C–C⩽, 1.20 (s, 3, $H_3CCCOOCH_3$), and 3.64 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.00; H, 9.59.

(b) Hydrogenation of 4. A mixture of 0.348 g (1.20 mmol) of **4**, mp 85–90°, 0.035 g of 10% palladium-on-carbon, and 10 ml of 95% ethanol was hydrogenated at atmospheric pressure for 1 hr. The mixture was filtered, the catalyst was rinsed with ethanol, and the combined filtrates were evaporated to yield 0.326 g of solid, mp 90–110°. By recrystallization from hexane 0.090 g of **5**, mp 122–124°, could be separated. Chromatography of the residues on 7 g of acid-washed alumina afforded, with 1:12 ether–hexane, 0.113 g, mp 86–107°, which yielded 0.044 g of **5**, mp 123–125°, upon recrystallization, for a total yield of 0.134 g (41%).

(c) By the Sequence 4 → 7 → 8 → 5. A solution of 1.12 g (3.86 mmol) of **4** in 30 ml of absolute ethanol was added over 5 min to 400 ml of liquid ammonia in a flask equipped with a Dry Ice condenser and a magnetic stirrer. Over a 50-min period, 4.2 g (0.617 g-atom) of lithium ribbon was added at a rate sufficient to maintain a blue color. After 20 min of further stirring, the blue color was discharged by addition of ethanol, and then 250 ml of ether was added. The ammonia was evaporated, and the residue was subjected to the standard work-up to afford 1.033 g of yellow oil. Some of this crude diol crystallized to a white solid: mp 162–166°; ir (KBr) 3.05 μ; it was not further purified or characterized.

The 1.03 g of product from the above reduction was dissolved in 50 ml of acetone and treated with 5.0 ml of Jones reagent.[7] The mixture was stirred at room temperature for 40 min, and excess oxidant was destroyed by the addition of isopropyl alcohol, followed by water. The acetone was evaporated and the residue was worked up in the standard manner to afford 1.124 g of a yellow oil which showed spectral properties indicative of a mixture of acid and aldehyde. The crude product was therefore redissolved in 50 ml of acetone and stirred for 4 hr at room temperature with 1 ml of Jones' reagent. Standard work-up afforded a crude product which was partitioned between sodium carbonate solution and ether. Acidification of the sodium carbonate extracts and extraction into ether afforded 0.913 g (85%) of crude keto acid **8**: mp 194–198° dec; ir (KBr) 3.0–4.0, 5.84, and 5.91 μ; this substance was not purified or characterized further.

An ethereal solution of the crude **8** was treated with excess ethereal diazomethane. The mixture was concentrated, extracted with aqueous sodium carbonate solution, dried over magnesium sulfate, and evaporated to afford 0.890 g (79% from **4**) of crude **5**. Recrystallization from ether–hexane afforded 0.691 g (63%) of pure **5**.

Conversion of 5 to 9. **(a)** A solution of 0.105 g (0.362 mmol) of **5** in 5 ml of glacial acetic acid was stirred under nitrogen at room temperature while a solution of 0.060 g (0.375 mol) of bromine in 5 ml of glacial acetic acid was added dropwise over a 20-min period. The solvents were removed under reduced pressure and the residue was dissolved in 10 ml of freshly distilled *N,N*-dimethylacetamide. The resulting solution was stirred and heated under reflux with calcium carbonate (0.8 g) for 30 min, then filtered and diluted with 50 ml of ether. The standard work-up gave 0.095 g of a mixture which was separated by plc using 7:13 ether–hexane. By this procedure there was obtained 0.035 g (34%) of **11** which, after crystallization from methylene chloride–hexane, had mp 186–188°; ir (KBr) 3.1, 5.78, 6.08, and 6.23 μ; nmr ($CDCl_3$) δ 1.20 (s, 3, H_3C–C⩽), 1.27 (s, 3, $H_3CCCOOCH_3$), 3.66 (s, 3, H_3COOC–), and 6.5–7.0 ppm (m, 3, aromatic H's) (see ref 4 for a previous report of less pure **11**).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97, H, 8.39. Found: C, 75.05; H, 8.47.

There was also isolated 0.040 g (30%) of **12** which, after crystallization from hexane, had mp 134–135°; uv max (EtOH) 254 mμ (ϵ 6200); ir (KBr) 5.82, 5.97, and 6.24 μ; nmr ($CDCl_3$) δ 0.94 (s, 3, H_3CC⩾), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), and 7.12 ppm (d, 1, J = 1.8 Hz, HC=CBr).

Anal. Calcd for $C_{19}H_{25}O_3Br$: C, 58.55; H, 6.78. Found: C, 58.60; H, 6.80.

The remainder of the product was indicated by tlc to be largely a mixture of **12** and **9**.

(b) A solution of 0.219 g (1.37 mmol) of bromine in 25 ml of glacial acetic acid was added to a solution of 0.50 g (1.71 mmol) of **5** in 25 ml of glacial acetic acid at room temperature and, immediately after mixing, the solvents were removed under reduced pressure. The residue was dissolved in 20 ml of *N,N*-dimethylacetamide, 2.5 g of calcium carbonate was added, and the resulting mixture was stirred under reflux for 30 min. Standard work-up gave an oily residue (0.495 g) which was heated under reflux in 50 ml of ethanol with 5 g of zinc dust for 20 hr. The solution was filtered and the filtrate was evaporated to give a product (0.485 g) which, after separation by plc using 1:3 ether–hexane, afforded 0.290 g of unreacted **5**, mp 126–127°, and 0.170 g of **9** (34% actual yield; 82% based on amount of **5** consumed) which, after crystallization from methylene chloride–hexane, had mp 116.5–117.5°; uv max (95% EtOH) 228 mμ (ϵ 7800); ir (KBr) 5.83 and 5.98 μ; nmr ($CDCl_3$) δ 0.95 (s, 3, H_3C–C⩽), 1.20 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), 5.90 (d, each peak split further with J = ~2 Hz, 1, J = 10 Hz, HC=CHCO–) and 6.65 ppm (d, each peak split further with J = ~1 Hz, 1, J = 10 Hz, HC=CHCO–).

Anal. Calcd for $C_{13}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.57; H, 8.83.

Conjugate Methylation of 9 to 10 and 13. A solution of lithium dimethylcopper was prepared by adding 1.12 ml of a 1.25 *M* ethereal solution of methyllithium (1.4 mmol) (Alfa Inorganics) to a suspension of 0.135 g (0.69 mmol) of cuprous iodide (Alfa Inorganics) in 10 ml of anhydrous ether at 0° under a static nitrogen atmosphere. After 15 min a solution of 0.100 g (0.345 mmol) of **9** in 10 ml of anhydrous ether was added, resulting in the immediate precipitation of a yellow solid. After 30 min at 0° the reaction mixture was washed with 10% aqueous ammonium chloride solution and then was subjected to the standard work-up. The yellow oily product (0.115 g) was adsorbed from hexane onto 5 g of

alumina (Grade I). Elution with 1:4 ether–hexane gave fractions totalling 0.090 g (86%) which ir and nmr spectra showed to be mixtures of **10** and **13**. The earlier fractions were rich in **10** and later fractions contained mainly **13**. Repeated crystallization of appropriate fractions from hexane afforded pure **10**: mp 119–121°; ir (KBr) 5.84 and 5.87 μ; nmr ($CDCl_3$) δ 0.82 (d, 3, J = 7 Hz, H_3CCH), 0.93 (s, 3, H_3C–C<), 1.19 (s, 3, $H_3CCCOOCH_3$), and 3.65 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.20; H, 9.67.

The 2,4-dinitrophenylhydrazone derived from **10** had mp 203–207°.

Anal. Calcd for $C_{25}H_{34}N_4O_6$: C, 61.71; H, 7.04. Found: C, 61.37; H, 6.84.

A partially purified sample of **13** showed nmr ($CDCl_3$) δ 0.91 (s, 3, H_3C–C<), 0.96 (d, 3, J = 6 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), and 3.62 ppm (s, 3, H_3COOC–).

Bromination of 10. To a solution of 0.0089 g (0.029 mmol) of **10** in 0.5 ml of acetic acid was added dropwise a solution of bromine in acetic acid (1 μl/1 ml) until the bromine color persisted. After a few more drops of the bromine solution were added, the mixture was stirred at room temperature for 1 hr, and then was evaporated *in vacuo*. Addition of ether to the residual brown oil afforded 0.004 g of solid, mp 140–153°. Several recrystallizations from ether afforded 0.0013 g: mp 155–160°; uv max (95% EtOH) 310 mμ (ϵ ~100); ir (KBr) 5.81 μ; nmr ($CDCl_3$) δ 3.67 (s, H_3COOC–), and 4.04 ppm (2-Hz broad s, $HCBr$). An nmr spectrum ($CDCl_3$) of the residual oily material left after the above solid had been separated showed, in addition to the 4.04 ppm peak, resonances at 4.42 (d, J = 5 Hz, $HCBr$) and 4.77 ppm (s, broad, ?).

Hydroxymethylene Derivative 19. A solution of 0.111 g (0.36 mmol) of **10** in 5 ml of freshly distilled ethyl formate was stirred in an ethanol–ice bath while 0.086 g of a 50% dispersion of sodium hydride in oil (1.79 mmol) was added gradually over 30 min. Anhydrous methanol (14.6 μl, 0.36 mmol) was then added, producing a yellow solution. The mixture was stirred for 22 hr at room temperature under nitrogen. The solution was poured onto ice and the resulting basic aqueous mixture was extracted with 50 ml of ether. The ethereal extract was washed twice with 30 ml of 1 M sodium hydroxide solution and the combined alkaline extracts were cooled and acidified with 50% v/v hydrochloric acid. Extraction with ether and the standard work-up gave 0.115 g (95%) of **19** as a yellow oil: ir (film) 5.79, 5.81, and 6.30 μ; nmr ($CDCl_3$) δ 0.90 (s, 3, H_3C–C<), 0.95 (d, 3, J = 7.0 Hz, H_3CCH), 1.20 (s, 3, $H_3CCCOOCH_3$), 3.65 (s, 3, H_3COOC–), and 8.72 ppm (s, 1, H–C(OH)=). Owing to negligent oversight this compound was not characterized further.

Acetoxymethylene Derivative 20. A solution of 0.100 g (0.34 mmol) of **19** in 20 ml of pyridine and 1 ml of acetic anhydride was stirred at room temperature for 36 hr. Dilution with 100 ml of water and extraction with ether afforded 0.105 g (82%) of crude acetate **20**, from which separated 0.075 g (59%) of solid **20**: mp 111–120°; ir (KBr) 5.66, 5.83, 5.95, and 6.25 μ; nmr ($CDCl_3$) δ 0.90 (s, 3, H_3C–C<), 0.94 (d, 3, J = ~6–7 Hz, H_3CCH), 1.18 (s, 3, $H_3CCOOCH_3$), 2.20 (s, 3, H_3CCOO–), 3.65 (s, 3, H_3COOC–), and 7.85 ppm (s (?), 1, H–C(OOCCH$_3$)=). Purification of **20** was not feasible owing to the compound's instability.

Synthesis of a Trace of (±)-1 by the Route 19 → 22 → 23 → 21 → 1. None of the new compounds described in these experiments was completely characterized, nor were any attempts made to determine accurately or improve yields, except in the last conversion (**21** → **1**) where numerous modifications were tried. A mixture of 0.144 g (0.43 mmol) of hydroxymethylene compound **19**, 0.061 g (0.44 mmol) of potassium carbonate, 0.25 ml (2.9 mmol) of freshly distilled allyl bromide, and 3 ml of reagent grade acetone was stirred under nitrogen at room temperature for 12 hr. The mixture was filtered and evaporated in *vacuo* to afford 0.170 g of oil which was determined to be largely **22** by its spectral properties: ir (film) 5.79, 5.91 (w), and 6.24 μ; nmr (CCl_4) δ 3.60 (s, H_3COOC–), and the distinctive complex pattern of an O-allyl group[36] with principal resonances at 4.4, 4.5, 5.0–5.4, and 5.6–6.1 ppm. This entire crude product was heated neat under nitrogen at *ca.* 150° for 12 hr. Periodically, ir spectra were taken in order to follow diminution of the band at 6.24 μ which was indicative of the conversion **22** → **23**. The product (0.165 g) from this pyrolysis was chromatographed on 8 g of acid-washed alumina. Elution with 1:4 ether–hexane afforded 0.033 g of solid **23**: ir (KBr) 5.78 and 5.88 μ; nmr ($CDCl_3$) δ 3.61 (s, H_3COOC–), and the distinctive complex pattern of a $-CH_2CH{=}CH_2$ group[37] with principal resonances from 4.8 to 6.0 ppm. Later fractions from the chromatogram contained substantial additional amounts of **23**. Ozonized oxygen from a Wellsbach generator was passed through a solution of the 0.033 g of **23** in 5 ml of methylene chloride at *ca.* −40° in a Dry Ice–acetone bath for 4 min. Then 0.2 g of zinc dust and 20 drops of acetic acid were added and the reaction was allowed to come to room temperature. The mixture was filtered and evaporated to give 0.030 g of semisolid residue. A mixture of 0.024 g of this crude ketoaldehyde **21**, 0.4 ml of acetic acid, and 0.04 ml of acetic anhydride was heated at reflux under nitrogen for 4 hr. Uv analysis of the reaction as it progressed showed development of a peak (in hexane) at 222 mμ over the first hr ((+)-**1** has a reported[1a] uv max (hexane) of 220 mμ). The reaction mixture was evaporated *in vacuo* and the residue was analyzed by tlc. A spot with the same mobility as natural (+)-**1** was separated and eluted to give 0.4 mg of an oil which had an ir spectrum essentially identical with that of natural (+)-**1**.

Methoxymethylene Compound 28. (a) Direct Methylation of 19. A mixture of a solution of 0.088 g (0.26 mmol) of **19**, prepared as described above, in 1 ml of methanol, a solution formed by the addition of 0.0046 g (0.20 g-atom) of sodium to 0.45 ml of methanol, and 18.5 μl (0.194 mmol) of dimethyl sulfate was allowed to stand at room temperature for 2 days. A quickly conducted standard work-up afforded 0.075 g of oil which was largely the desired methoxymethylene derivative **28**: ir (film) 5.80, 5.95, and 6.27 μ. However, this high yield of methylation product could only occasionally be reproduced by the above or other procedures.

(b) From Acetoxymethylene Compound 20. A mixture of 0.075 g (0.224 mmol) of **20**, prepared as described above, 20 ml of methanol which had been refluxed with magnesium turnings and iodine and carefully distilled, and 0.0001 g of *p*-toluenesulfonic acid was refluxed for 5 min and then was poured onto a column of 5 g of alumina. The column was eluted with ether which was evaporated to afford 0.070 g of material which tlc analysis showed to be almost entirely methoxymethylene compound **28**, and this crude product was used directly in the next step.

Synthetic (±)-Methyl Vinhaticoate (1). The conversions **28** → **29** → **30** → **1** were carried out without complete characterization of intermediate products. A mixture of 0.070 g (0.20 mmol) of **28**, prepared as described above, and 0.003 g of anhydrous cupric sulfate was heated at 160° under nitrogen and vigorously magnetically stirred while 0.23 ml (2.0 mmol) of ethyl diazoacetate was added cautiously from a syringe inserted through a rubber septum on a side neck of the flask. After 3 min the reaction mixture was washed through a column of 5 g of Florisil with 1:1 hexane–chloroform. The eluents were evaporated and the residue was steam distilled for 1 hr to remove ethyl maleate and fumarate by-products. Ether extraction and evaporation afforded a residue of 0.067 g of material not volatile with steam. This product was chromatographed on 10 g of grade III Florisil, using 1:9 ether–hexane, to afford 0.0257 g (32%) of furoic ester **29**, contaminated with a small amount of what spectral properties (nmr ($CDCl_3$) δ 7.23 ppm) suggested was an isomeric furan.[28] Plc using 7:13 ether–hexane failed to remove all of this impurity, but afforded 0.017 g of **29** of good quality as a yellow oil with the following spectral properties: uv max (hexane) 250 (?), 255, 260, 265, 271, 276, and 283 mμ; ir (film) 2.75–2.80, and 6.50 μ; nmr ($CDCl_3$) δ 0.92 (s, 3, H_3C–C<), 1.09 (d, J = 7 Hz, 3, H_3CCH), 1.22 (s, 3, $H_3CCCOOCH_3$), 1.35 (t, J = 7 Hz, 3, H_3CCH_2–), 3.65 (s, 3, H_3COOC–), 4.32 (q, J = 7 Hz, 2, $-H_2CCH_3$), and 6.97 ppm (s, 1, furan β-H).

A mixture of 0.0113 g (0.028 mmol) of this **29**, 0.030 g of sodium hydroxide, and 2.0 ml of methanol was heated at 55° for 3 hr and then allowed to stand at room temperature for 15 hr. The mixture was poured into 20 ml of water and was acidified with 50% v/v hydrochloric acid. The standard work-up afforded 0.0105 g of impure **30** as a yellow oil: ir (film) 3.0–4.0 (broad), 5.8, 5.9, and 6.5 μ; nmr ($CDCl_3$) δ 0.92 (s, 3, H_3C–C<), 1.25 (s, 3, $H_3CCCOOCH_3$), 3.67 (s, 3, H_3COOC–), and 7.07 ppm (s, 1, furan β-H).

A mixture of 0.0100 g (0.027 mmol) of this crude furoic acid **30** and 0.001 g of copper powder was heated to 230° in a sublimation apparatus in a nitrogen atmosphere. A pressure of 0.25 mm was applied and the temperature was maintained at 230° for 45 min,

(36) *Cf.* spectra no. 34 (allyl alcohol) and 134 (allyl ether) in Varian Associates NMR Spectra Catalog, Vol. I, Varian Associates, 1962.

(37) *Cf.* spectrum no. 298 (7,9-dimethyldecene-1) in Varian Associates NMR Spectra Catalog, Vol. 1.

affording 0.005 g of sublimate which tlc indicated to be largely (±)-methyl vinhaticoate (**1**). Plc using 1:9 ether–benzene (affording 0.002 g of tlc-pure (±)-**1**), followed by sublimation (90° (0.05 mm)), and, finally, several recrystallizations from methanol (avoiding heating), yielded pure (±)-**1**: mp 122–123°; ir (KBr) 5.80, 6.63, and 11.10 μ; nmr ($CDCl_3$) δ 0.92 (s, 3, H_3C–C⩽), 0.97 (d, J = 6–7 Hz, 3, H_3CCH), 1.22 (s, 3, $H_3CCCOOCH_3$), 3.66 (s, 3, H_3-COOC–), 6.13 (d, J = 2 Hz, 1, furan β-H), and 7.20 ppm (d, J = 2 Hz, 1, furan α-H); mass spectrum M^+ (m/e) 330.2197 (calcd 330.2195). All spectral properties were identical with those of an authentic sample of (+)-**1**.[29]

Conversion of Podocarpic Acid (3) to Keto Ester 31. Podocarpic acid, used as supplied[38] without purification, was converted to its methyl ether derivative **32**, mp 145–149°, in 65% yield with dimethyl sulfate in 4 *N* sodium hydroxide solution according to a procedure of Goldsmith.[34] Birch reduction of **32** was conducted by a Goldsmith[34] modification of the Bible and Burtner procedure.[32] A solution of 15.0 g (0.052 mol) of **32** in 300 ml of anhydrous tetrahydrofuran was added to 1 l. of liquid ammonia in a 2-l. three-necked round-bottomed flask fitted with a mechanical stirrer and a Dry Ice condenser. Dry, clean lithium wire (16.0 g, 2.3 g-atom) was added over a 15-min period and then absolute alcohol was added until the blue color disappeared. After solid ammonium chloride (118 g) was added, the solution was allowed to warm to room temperature and then was heated gently (water bath) to remove the bulk of the ammonia. The solution was acidified with 80% aqueous acetic acid, diluted with 3.5 l. of water, and extracted with ether (3 × 500 ml) to give 14.62 g of crude **33** as a yellow oil: ir (film) 3.0–4.0 (broad), and 5.95–6.0 (broad) μ. This entire product was dissolved in 400 ml of methanol containing 50 ml of concentrated hydrochloric acid and 30 ml of water, and the mixture was heated at reflux for 20 min. The standard work-up afforded 14.3 g of crude **34** as a yellow oil; ir (film) 3.0–4.0 (broad), 5.9 and 6.0 μ.

A solution of this entire product in 250 ml of anhydrous tetrahydrofuran was added as quickly as practicable to a solution of 5 g (0.72 g-atom) of clean, dry lithium wire in 800 ml of redistilled liquid ammonia in a 2-l. three-necked round-bottomed flask fitted with a mechanical stirrer and a Dry Ice condenser. After 3 min the blue color was dispelled by the addition of solid ammonium chloride. The ammonia was allowed to evaporate at room temperature and the residue was acidified with 50% v/v aqueous hydrochloric acid. The standard work-up gave dried ethereal extracts which were treated with excess ethereal diazomethane at room temperature for 2 hr. The solvents were removed by distillation and the yellow oily product (13.92 g) which showed strong hydroxyl absorption in the infrared was dissolved in 500 ml of acetone and treated with excess Jones reagent[7] at room temperature. After 30 min the excess Jones reagent was destroyed with isopropyl alcohol. The standard work-up gave 13.6 g of oily crystalline product which was adsorbed from 75 ml of 1:9 benzene–hexane onto 250 g of Florisil. Elution with 1:19 ether–hexane gave 3.16 g of a mixture of compounds which showed only the ester band at 5.80 μ in the ir and which may be products of overreduction without any oxygen function in ring C. Elution with 1:9 ether–hexane gave 0.24 g of **methyl *O*-methylpodocarpate,** identical with the product obtained from treatment of **32** with diazomethane. Elution with 1:4 ether–hexane gave 5.67 g of tlc-pure **31** which, after crystallization from hexane, had mp 115–116°; ir (KBr) 5.85 μ (lit.[32] mp 110–113° or 120–121.5°; ir ($CHCl_3$) 5.83 μ). Further elution with 1:4–1:1 ether–hexane gave 2.85 g of impure **31** which, after rechromatography on Florisil, afforded 1.5 g of pure **31**. The total yield of **31** (7.17 g) based on **32** was 47%.

Conversion of 31 to Enone 36. A solution of 4.89 g (0.031 mol) of bromine in 25 ml of glacial acetic acid was added dropwise with stirring to a solution of 9.54 g (0.031 mol) of **31** in 60 ml of glacial acetic acid at room temperature under a nitrogen atmosphere. After 30 min the solvents were removed under high vacuum at room temperature. The yellow-green solid residue was immediately dissolved in 120 ml of freshly distilled *N*,*N*-dimethylacetamide, 15 g of calcium carbonate was added, and the mixture was heated with stirring at reflux for 40 min. The mixture was cooled and filtered, and the standard work-up gave 9.67 g of crude oily product which crystallized on standing overnight. Recrystallization did not provide material of acceptable purity, so the total reaction product was adsorbed from benzene onto 400 g of Florisil. Elution with 1:9 ether–hexane gave 1.69 g of a mixture of unidentified compounds. Elution with 1:4 ether–hexane gave 2.57 g of pure **36** which, after crystallization from hexane, had mp 130–131.5°; uv max (95% EtOH) 228 mμ (ε 10,000); ir (KBr) 5.80 and 5.96 μ; (lit.[32] mp 126.5–129°; uv max (MeOH) 230 mμ (ε 8710); ir 5.79 and 5.95 μ; lit.[33] mp 127–130.5°; uv max (MeOH) 230 (ε 10,500)); nmr ($CDCl_3$) δ 0.72 (s, 3, H_3C–C⩽), 1.17 (s, 3, $H_3CCCOOCH_3$), 3.65 (s, 3 H_3COOC–), 5.90 (d of d, 1, J = 10, 3 Hz, –COC*H*=CH–) and 6.66 ppm (d of d, 1, J = 10, 2 Hz, –COCH=C*H*–); (lit.[33] nmr ($CDCl_3$) 0.715 (s, 3), 1.15 (s, 3), 3.64 (s, 3), 5.85 (q, 1, $J_{13,14}$ = 10 Hz, $J_{14,15}$ = 2.6 Hz) and 6.65 ppm (q, 1, $J_{13,14}$ = 10 Hz, $J_{11,13}$ = 1.6 Hz)). Further elution with 1:4 ether–hexane gave fractions containing impure **36** (5 g) which after rechromatography afforded 3.11 g of additional pure **36** for a total yield of 5.68 g (60%).

Conjugate Methylation of 36 to 37 and 38. An ethereal solution of lithium dimethylcopper was prepared by adding 48 ml of a 1.25 *M* ethereal solution of methyllithium (0.06 mol) to a stirred suspension of 5.72 g (0.03 mol) of purified, dry cuprous iodide in 50 ml of anhydrous ether at 0° under a nitrogen atmosphere. After 30 min, a solution of 3.80 g (0.013 mol) of **36** in 50 ml of anhydrous ether was added, resulting in an immediate yellow precipitate. The mixture was stirred for 30 min at 0°, and then was washed with 10% aqueous ammonium chloride. The standard work-up afforded 3.75 g (94%) of a yellow-white crystalline mass, mp 70–100°, which did not show any hydroxyl absorption in the ir, which gave two nearly equally mobile spots upon careful tlc, and which was found to be a 55:45 mixture of **37** and **38** by nmr integration. Recrystallization of the total reaction product from hexane afforded 1.04 g, mp 148–151°, and further recrystallization gave pure **38**: mp 154–155°; ir (KBr) 5.83 μ (broad); nmr ($CDCl_3$) δ 0.70 (s, 3, H_3CC⩽), 1.00 (d, 3, J = 5 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), and 3.62 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.63; H, 9.67.

Chromatography of the residue on alumina (Grade II), eluting with 3:7 ether–hexane, and multiple-run plc afforded 0.250 g of tlc-pure **37** which, after crystallization from dilute aqueous alcohol, had mp 85.5–86°; ir (KBr) 5.85 μ (broad); nmr ($CDCl_3$) δ 0.72 (s, 3, H_3C–C⩽), 0.79 (d, 3, J = 7 Hz, H_3CCH), 1.18 (s, 3, H_3-$CCCOOCH_3$), and 3.63 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.47, H, 9.78.

Bromination of 37. A mixture of 0.117 g (0.38 mmol) of **37** and 0.171 g (0.76 mmol) of cupric bromide[35] in 10 ml of 1:11 chloroform–ethyl acetate was stirred at room temperature under a vacuum sufficient to produce a slow bubbling of the solvent. After 6.5 hr the precipitated green-white cuprous bromide was removed by filtration and the standard work-up afforded 0.13 g of a yellow oil. This was purified by plc using 3:7 ether–hexane to yield 0.080 g (54%) of **39** which, after crystallization from hexane, had mp 95–97°; uv_{max} (95% EtOH) 302 mμ (ε 123); ir (KBr) 5.82 μ (broad); nmr ($CDCl_3$) δ 0.81 (s, 3, H_3C–C⩽), 0.92 (d, 3, J = 7.5 Hz, H_3CCH), 1.19 (s, 3, $H_3CCCOOCH_3$), 3.62 (s, 3, H_3COOC–), and 4.00 ppm (s, broad, 1, *H*CBr).

Anal. Calcd for $C_{19}H_{29}O_3Br$: C, 59.22; H, 7.59. Found: C, 59.28; H, 7.52.

The plc also gave 0.021 g (14%) of **40** which, after recrystallization from hexane, had mp 160–161°; ir (KBr) 5.83 μ (broad); nmr ($CDCl_3$) δ 0.74 (s, 3, H_3CC⩽), 0.90 (d, 3, J = 8.0 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), and 4.84 ppm (d, 1, J = 5 Hz, *H*CBr).

Anal. Calcd for $C_{19}H_{29}O_3Br$: C, 59.22; H, 7.59. Found: C, 59.44, H, 7.49.

Also recovered from the plc was 0.020 g (17%) of unreacted **37**.

Bromination of 38. Treatment of 0.20 g (0.65 mmol) of **38** with 0.291 g (1.3 mmol) of cupric bromide for 1 hr in the procedure used for bromination of **37** gave, after purification by plc, 0.157 g (63%) of **41** which, after crystallization from hexane, had mp 148–149°; uv max (95% EtOH) 306 mμ (ε 123); ir (KBr) 5.83 μ; nmr ($CDCl_3$) δ 0.73 (s, 3, H_3C–C⩽), 1.05 (d, 3, J = 9 Hz, H_3CCH), 1.17 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), and 4.10 ppm (s broad, 1, $W_{1/2}$ = 5 Hz, *H*CBr).

Anal. Calcd for $C_{19}H_{29}O_3Br$: C, 59.22; H, 7.59. Found: C, 58.97, H, 7.46.

Also obtained from the plc was 0.04 g (16%) of **42** which, after crystallization from ethanol, had mp 162–163°; ir (KBr) 5.80 μ; nmr ($CDCl_3$) δ 0.68 (s, 3, H_3C–C⩽), 1.17 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), and 4.33 ppm (d, 1, J = 10 Hz, *H*CBr).

Anal. Calcd for $C_{19}H_{29}O_3Br$: C, 59.22; H, 7.59. Found: C, 59.30; H, 7.46.

Conversion of 37 to Hydroxymethylene Derivative 43. To a stirred solution of 0.652 g (2.13 mmol) of **37** in 50 ml of freshly

(38) Timber Processing Company Ltd., Auckland, New Zealand.

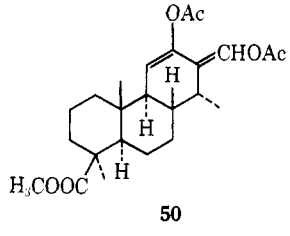
distilled ethyl formate at 0° was added 0.442 g (11 mmol) of a 58% dispersion of sodium hydride in mineral oil. Anhydrous methanol (86 μl, 2.13 mmol) was then added and the mixture was stirred at room temperature under a nitrogen atmosphere for 20 hr. The resulting suspension was poured into a mixture of 100 ml of water and 40 ml of ether and the organic layer was separated and extracted with two 100-ml portions of 2 *N* aqueous sodium hydroxide solution. Acidification of the cold aqueous extracts with 50% v/v aqueous hydrochloric acid and subsequent ether extraction afforded, after removal of the solvent, 0.635 g (89%) of **43**, as a light yellow solid, mp 134–139°. Recrystallization from hexane gave a sample with mp 136–140°; uv max (95% EtOH) 282 mμ (ε 5400); uv max (95% EtOH–NaOH) 314 mμ (ε 16,500); ir (KBr) 5.84 and 6.2–6.4 μ (broad); nmr ($CDCl_3$) δ 0.68 (s, 3, $H_3CC\leqslant$) 0.95 (d, 3, J = 7 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), and 8.75 ppm (s, 1, $HC(OH)$=).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.87; H, 8.95.

Acetoxymethylene Derivative 45. A solution of 0.60 g (1.8 mmol) of **43** in a mixture of 50 ml of pyridine, freshly distilled from potassium hydroxide, and 15 ml of acetic anhydride, freshly distilled from sodium acetate, was stirred at room temperature under a nitrogen atmosphere for 36 hr. Dilution with water (500 ml) and extraction with ether (3 × 100 ml) afforded crude **45** as a yellow oily solid. The last traces of pyridine were removed from the product under high vacuum at room temperature and the semisolid residue of **45** (0.66 g) had ir (film) 5.68, 5.83, 5.91, and 6.18 μ; nmr ($CDCl_3$) δ 0.66 (s, 3, H_3C–C≤), 0.94 (d, 3, J = 7 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 2.20 (s, 3, H_3CCOO–), 3.63 (s, 3, H_3COOC–), and 7.86 ppm (d, 1, J = 0.8 Hz, $HC(OOCCH_3)$=). Purification of **45** was not feasible owing to the compound's instability. The nmr and tlc of the crude product showed that the major impurity was the diacetate **50** (*ca.* 25%), which was isolated after the preparation of **47** (below).

Methoxymethylene Derivative 47. A solution of the 0.660 g of crude **45** from above and 0.015 g of *p*-toluenesulfonic acid in 60 ml of dry methanol was heated at reflux under a nitrogen atmosphere for 5.5 min. The solution was cooled and poured directly onto a column of 30 g of alumina (grade II). Immediate elution with ether gave 0.585 g of a yellow oil which, after purification by plc, afforded 0.37 g (59% based on **43**) of **47** as a clear oil which was *ca.* 90% pure by tlc and nmr analysis. Further purification was not feasible owing to the compound's instability. The **47** obtained showed ir (film) 5.82, 5.97, and 6.25 μ (broad); nmr ($CDCl_3$) δ 0.65 (s, 3, H_3C–C≤), 0.90 (d, 3, J = 7.0 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.62 (s, 3, H_3COOC–), 3.80 (s, 3, $H_3COC(H)$=), and 7.10 ppm (d, 1, J = 0.9 Hz, $HC(OCH_3)$=).

Also isolated from this reaction mixture was 0.180 g of material which was largely one substance and which had the following spectral properties: uv max (EtOH) 247 mμ; ir (KBr) 5.75 and 5.88 μ; nmr ($CDCl_3$) δ 0.67 (s, 3), 0.95 (d, 3, J = 7 Hz), 1.18 (s, 3), 2.16 (s, 3), 2.18 (s, 3), 3.64 (s, 3), 5.43 (s, broad, 1), and 7.12 ppm (s, 1). On the basis of these properties structure **50** is suggested for this substance, which was not investigated further.



50

Conversion of 38 to Hydroxymethylene Derivative 44. Treatment of 0.30 g (0.98 mmol) of **38** with sodium hydride, methanol, and ethyl formate at room temperature for 24 hr as described above for **37** gave 0.24 g (73%) of **44** which, after crystallization from hexane, had mp 102–105°; ir (KBr) 5.80 and 6.1–6.3 μ (broad); nmr ($CDCl_3$) δ 0.67 (s, 3, H_3C–C≤), 1.15 (d, 3, J = 6 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.62 (s, 3, H_3COOC–), and 8.73 ppm (s, 1, $HC(OH)$=).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.94; H, 9.14.

Acetoxymethylene Derivative 46. Treatment of 0.090 g (0.27 mmol) of **44** with pyridine and acetic anhydride for 23 hr as in the case of **43** afforded 0.105 g (99%) of crude **46** as a yellow oil: ir (film) 5.68, 5.85, 5.93, and 6.20 μ; nmr ($CDCl_3$) δ 0.67 (s, 3, H_3C–C≤), 1.12 (d, 3, J = 7 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 2.20 (s, 3, H_3CCOO–), 3.63 (s, 3, H_3COOC–), and 8.04 ppm (d, 1, J = 1.9 Hz, $HC(OAc)$=). Purification of **46** was not feasible owing to the compound's instability; tlc and nmr analysis of the crude product indicated that it was *ca.* 90% pure.

Methoxymethylene Derivative 49. A solution of 0.110 g (0.28 mmol) of **46** in 20 ml of dry methanol was treated with *p*-toluenesulfonic acid as in the case of **45** above. The 0.090 g of solid product was judged to be *ca.* 90% pure **49** by tlc and nmr analysis. Two recrystallizations from ethanol gave **49** with mp 145–146°; ir (KBr) 5.80, 5.95, and 6.25 μ (broad); nmr ($CDCl_3$) δ 0.64 (s, 3, H_3C–C≤), 1.08 (d, 3, J = 7 Hz, H_3CCH), 1.17 (s, 3, $H_3CCCOOCH_3$), 3.62 (s, 3, H_3COOC–), 3.82 (s, 3, $H_3COC(H)$=), and 7.21 ppm (d, 1, J = 1.8 Hz, $HC(OCH_3)$=). Owing to sample instability, a good elemental analysis was not obtained.

Furoic Ester 48. A mixture of 0.35 g (1.0 mmol) of **47** and 0.020 g of white anhydrous cupric sulfate in 10 ml of 1,1,2,2-tetrachloroethane was stirred and refluxed in a nitrogen atmosphere. Ethyl diazoacetate (1.3 ml, 12.3 mmol) was added dropwise over 5 min. The mixture was cooled and was steam distilled for 1.5 hr to remove ethyl maleate and fumarate by-products, and the tetrachloroethane. The residue not volatile with steam was extracted with ether to give 0.55 g of yellow-brown oily product which was adsorbed from 1:9 benzene–hexane onto 30 g of Florisil (grade III). Elution with 1:19 ether–hexane and 1:19 ether–benzene gave 0.16 g (40%) of tlc-pure **48** which, after crystallization from hexane, had mp 121–122°; uv max (hexane) 250 (ε 8600), 255 (ε 11,700), 260 (ε 14,000), 265 (ε 15,000), 270 (ε 14,300), 275 (ε 10,000), and 282 mμ (ε 6800); ir (KBr) 5.85 (broad) and 6.52 μ; nmr ($CDCl_3$) δ 0.72 (s, 3, H_3C–C≤), 0.99 (d, 3, J = 7 Hz, H_3CCH), 1.20 (s, 3, $H_3CCCOOCH_3$), 1.35 (t, 3, J = 7 Hz, H_3CCH_2–), 3.64 (s, 3, H_3COOC–), 4.34 (q, 2, J = 7 Hz, $-CH_2CH_3$), and 6.97 ppm (s, 1, furan β-H).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.50; H, 8.40.

Synthetic (+)-Methyl Vouacapenate (2). A mixture of 0.157 g (0.39 mmol) of **48** and 0.6 g of sodium hydroxide in 30 ml of methanol was refluxed in a nitrogen atmosphere for 3 hr and then was stirred at room temperature for 17 hr. The mixture was diluted with 300 ml of water, and was extracted with two 60-ml portions of ether. The combined ethereal layers were extracted with two 50-ml portions of 2 *N* aqueous sodium hydroxide solution. The combined basic aqueous extracts were cooled in an ice bath, and acidified with 50% v/v aqueous hydrochloric acid. Extraction with three 100-ml portions of ether afforded 0.145 g (99%) of crude furoic acid–ester as a light yellow solid, mp 230–240° dec; ir (KBr) 5.80, 5.95 (broad), and 6.55 μ; nmr ($CDCl_3$) δ 0.69 (s, 3, H_3C–C≤), 0.96 (d, 3, J = 7 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.62 (s, 3, H_3COOC–), 7.10 (s, 1, furan β-H), and 10.67 ppm (s, 1, $HOOC$–).

This 0.145 g of crude product was heated to 215° in a nitrogen atmosphere in the presence of 0.03 g of copper powder for 5 min. Sublimation of the total reaction product at 225° and 0.25 mm gave a yellow oily solid, which, after adsorption onto 20 g of Florisil (grade II) and elution with 1:49 and 1:19 ether–hexane, followed by two crystallizations from methanol, afforded 0.066 g (50%) of **2**: mp 99.5–100.5°; $[\alpha]^{30}D$ + 96° (*c* 5.5, CCl_4); uv max (95% EtOH) 221 mμ (ε 4700) [lit.[1b] mp 103–104°; $[\alpha]D$ +101° (*c* 1.5, CCl_4); uv max (EtOH) 222 mμ (ε 4680)]; ir (KBr) 5.83, 6.08, 6.31 and 6.65 μ; nmr ($CDCl_3$) δ 0.70 (s, 3, H_3C–C≤), 0.96 (d, 3, J = 7 Hz, H_3CCH), 1.18 (s, 3, $H_3CCCOOCH_3$), 3.63 (s, 3, H_3COOC–), 6.13 (d, 1, J = 1.5 Hz, furan β-H), and 7.18 ppm (m, 1, furan α-H). A mixture melting point of **2** and authentic (+)-methyl vouacapenate[29] (mp 103–104°) was 101–102°.

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