Table I
Reaction of Alkyl Halides with the Dilithium Salt of Monoethyl Malonate
$RX + LiCH(COOLi)COOEt \rightarrow RCH_2COOEt$

RX		RCH_2COOEt		Yield, %[a]
Methallyl chloride	563-47-3	$CH_2{=}C(CH_3)CH_2CH_2COOEt$	4911-54-0	71
Allyl bromide	106-95-6	$CH_2{=}CHCH_2CH_2COOEt$	1968-40-7	80
Benzyl chloride	100-44-7	$PhCH_2CH_2COOEt$	2021-28-5	75
Ethyl chloroacetate	105-39-5	Diethyl succinate	123-25-1	98
Chloroacetone	78-95-5	$CH_3COCH_2CH_2COOEt$	539-88-8	25
Ethyl iodide	75-03-6	$CH_3CH_2CH_2COOEt$	105-54-4	60
n-Butyl bromide	109-65-9	$CH_3(CH_2)_4COOEt$	123-66-0	80
n-Decyl bromide	112-29-8	$CH_3(CH_2)_{10}COOEt$	106-33-2	60
2-Bromopropane	79-26-3	$(CH_3)_2CHCH_2COOEt$	108-64-5	50
2-Bromobutane	78-76-2	$CH_3CH_2CH(CH_3)CH_2COOEt$	5870-68-8	22

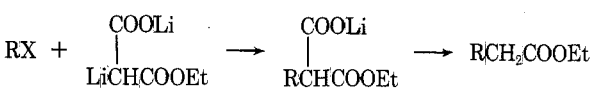
[a] Yields given represent distilled product.

mally a three-step alkylation, saponification, decarboxylation sequence is used,[1] a recently introduced variation, in which decarbalkoxylation can be effected in a single step, seems to give better overall yields.[2]

Ideally, one could simplify the procedure still further by alkylating directly with lithio ethyl acetate, but this does not seem to be feasible. Lithio ethyl acetate can be readily prepared at −78° and caused to undergo aldol addition to simple carbonyl compounds.[3] In reaction with alkyl halides, however, it reacts poorly, giving the product in 20–30% yields.[4] Lithio *tert*-butyl acetate seems to alkylate well,[4] but the use of *tert*-butyl esters can introduce unwanted complications in synthesis.

A further possibility is the alkylation of an acid dianion according to Creger's method,[5,6] but again this does not seem to be feasible. Although the dianions of substituted acetic acids alkylate well, especially when the solvent modification of Pfeffer and Silbert is used,[7,8] the parent dilithioacetate reacts poorly. Even were this reaction to go well, a separate esterification step would be required.

We reasoned that these difficulties could be resolved, and the malonic ester synthesis simplified considerably, if one were to alkylate with the dianion of monoethyl malonate. On simple warming of the reaction, the intermediate alkylated monoethyl malonate should decarboxylate, giving the desired product directly. The starting material is readily available by partial saponification of diethyl malonate.[9]



The expected reaction does in fact proceed as planned, giving the ester products in fair to excellent yields. Some of our results are given in Table I.

As can be seen from Table I activated halides (R = allylic, benzylic) alkylate in excellent yields. Primary halides also give good results, but, as expected, secondary halides react less well.

In summary, we feel that this new method is clearly superior to the classical malonic ester synthesis both in yield and in ease of operation, and we expect that it will find use in synthesis.

Experimental Section

General Reaction Procedure. Isopropylcyclohexylamine (4.15 g, 29.4 mmol) was dissolved in 10 ml of dry tetrahydrofuran (THF) under a nitrogen atmosphere, and the temperature of the solution was lowered to −78° by means of a Dry Ice bath. *n*-Butyllithium (14.3 ml of 2.06 *M* solution in hexane, 29.4 mmol) was then added via syringe. Monoethyl malonate (1.94 g, 14.7 mmol) in 10 ml of THF was added, and the reaction was allowed to warm to ice temperature to form the dianion. After 15 min of stirring, 4.0 ml of dry hexamethylphosphoramide was added, followed by addition of the alkyl halide (14.7 mmol) in 5 ml of dry THF. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hr to effect alkylation. After this time the reaction mixture was refluxed (68°) overnight to effect decarboxylation.

After cooling, the reaction mixture was poured into water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid, with saturated sodium bicarbonate, and with brine, then dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. The residue was distilled to yield the product.

Product identification was made through a combination of spectroscopic methods (ir, NMR, mass spectra) and through comparison of the product boiling points with literature values.

Acknowledgment. We thank the National Institutes of Health for their support of this work through Grant CA11277.

Registry No.—Monoethyl malonate, 1071-46-1.

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Complete Stereochemistry of Tenulin. Carbon-13 Nuclear Magnetic Resonance Spectra of Tenulin Derivatives

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Determination of the gross structure of the sesquiterpene lactone tenulin (1)[1] was an early example of the successful use of ^1H NMR spectrometry in natural products chemistry. Subsequently, the relative and absolute configuration of tenulin at C-1, C-5, C-7, and C-10 was deduced by

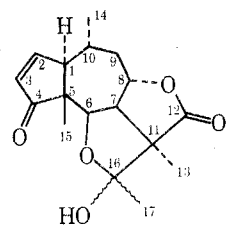
Table I
^{13}C NMR Spectra of Tenulin and Derivatives

	1a	1b	2a	2b	3	4	5	6	7	8
C-1	54.3	54.7	48.3	48.6	150.1	48.4	52.7	47.3	173.2	47.8
C-2	162.6	162.3	24.7	24.2	122.7	24.4	161.1	24.3	138.4	23.0
C-3	130.4	130.0	34.6	34.5	39.7	34.4	130.3	35.1	207.0	35.8
C-4	212.7	212.3	221.6	221.2	217.6	220.3	210.6	219.8	37.2	209.7
C-5	56.3	55.3	54.5	53.4	53.5	53.4[a]	54.5	54.3	44.0	64.0
C-6	77.4	74.0	78.4	74.8	78.6	49.1	66.0	67.5	66.0	201.6
C-7	63.3	63.8	61.7	62.0	60.2	59.6	55.1	53.6	58.4	61.8
C-8	76.5	76.0	76.1	75.6	75.5	75.3	75.8	75.9	75.8	76.5
C-9	42.9	42.5	42.4	42.0	41.3	41.8	44.7	44.9	38.1	44.9
C-10	28.4	28.0	30.8	30.3	291.8	30.3	27.2	29.5	31.3	29.2
C-11	58.8	58.8	58.5	58.3	56.5	54.4[a]	37.0	37.0	41.2	36.8
C-12	176.4	176.42	175.6	177.6	175.4	75.4	177.4	177.6	178.0	177.2
C-13	18.3[a]	19.0[a]	18.0[a]	18.5[a]	21.2[a]	21.3[a]	20.6[a]	20.6[a]	20.6	20.1
C-14	19.6[a]	20.4[a]	13.7	13.8	16.2	13.7	19.7	14.8	8.12[a]	14.8
C-15	19.9[a]	20.4[a]	19.8[a]	19.6[a]	19.2[a]	19.7[a]	13.9	13.8	12.0[a]	18.7
C-16	108.4	105.2	107.6	104.4	161.4	162.0	169.2	169.2		
C-17	24.7	27.3	24.6	26.8	83.7	82.7	20.0[a]	19.8[a]		

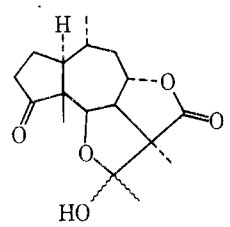
[a] Assignments may be interchanged.

analysis of the complex interrelationships between isotenulin (4) and its congeners,[2] their ORD curves,[2,3] and an X-ray analysis of 2-bromoisotenulin.[4,5] Although the stereochemistry of tenulin at C-11 and C-16 has not been specified previously, fusion of the γ-lactone and five-membered hemiketal rings is only possible if the C-11 methyl group is α (11*R*). Consequently, the only remaining point of uncertainty in the structure of tenulin was the configuration at C-16.

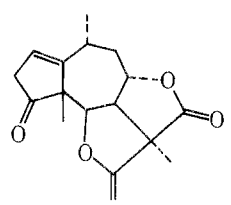
In the course of collecting ^{13}C NMR spectra of various sesquiterpene lactones, we noticed that spectra of chromatographically pure tenulin (1) and dihydrotenulin (2) consistently exhibited two sets of signals (Table I) whereas samples of pyrotenulin (3) and anhydrodihydrotenulin (4), formed by dehydration of 1 and 2, respectively, and other transformation products such as isotenulin (5), dihydroisotenulin (6), and deacetylneotenulin (7)[6] were spectroscopically homogeneous. The observation that chemical shift differences between members of the two sets were greatest for C-16 and for carbon atoms in close proximity to C-16 such as C-8, C-11, and C-12 (for assignments see below) permitted the deduction that tenulin as isolated from the plant consists of a mixture of C-16 epimers.[7]



1a, C-17 Me α
b, C-17 Me β



2a, C-17 Me α
b, C-17 Me β



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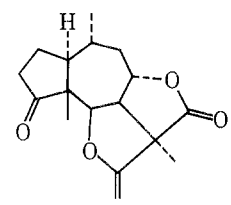

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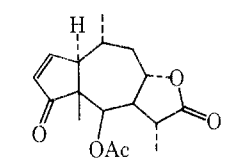

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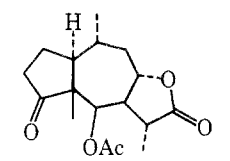

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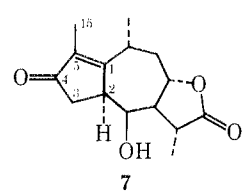

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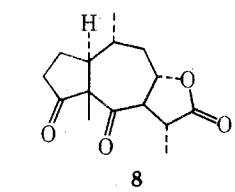

8

Further evidence for this rather anticlimactic finale to nearly 40 years of research on tenulin was provided by examining the ^{1}H NMR spectra of 1 and 2 at higher fields. At 90 and particularly at 270 MHz two sets of signals in the approximate ratio 4:1 characteristic of H-6, H-13, and H-17 in the two separate isomers were reasonably well resolved, whereas other signals not obscured by the methylene and methinyl envelope (H-14, H-8, and H-15 of 1 and 2 as well as H-1, H-2, and H-3 of 1) remained superimposed and quite sharp.[8] Since the H-6 doublet of the two minor isomers appears at lower field (4.57 vs. 4.45 ppm in 1), we infer that it represents H-6 of epimers **1b** and **2b** in which H-6 is cis to the hydroxyl group attached to C-16.

Assignments to most signals in the ^{13}C NMR spectra of 1 and 2 are fairly obvious on the basis of multiplicities, chemical shift data in the literature, and comparison with signals in the spectra of compounds **3–8**. Thus a triplet near 42 ppm, one of three representing the methylene carbons of **2**, is assigned to C-9 by comparison with **1** and **3–8**, leaving the 24.5-ppm triplet to C-2 and the 33.7-ppm triplet to the more deshielded C-3. The identity of a methinyl doublet near 76 ppm, fairly constant throughout the series, as that of C-8 was established by single-frequency off-resonance decoupling; although superposition of signals in the ^{1}H NMR spectra of 1 and 2 prevented direct identification of the slightly more deshielded (in **1–3**) methinyl doublet of C-6, comparison with the spectra of **5**, where single-frequency off-resonance decoupling of C-6, now at somewhat higher fields, was possible, and **8**, where C-6 is a carbonyl carbon, left no ambiguity.[9] The most shielded methinyl is clearly that of C-10, thus permitting assignment of C-7, which should be more affected by the changes at C-11, by default. The doublet of C-1 can be recognized by its upfield

shift on hydrogenation of 1 to 2 and 5 to 6 and by its conversion to a singlet—far downfield—in the spectrum of 3.

The chemical shifts of the various carbonyl carbons may be deduced from known parameters of cyclopentenones, cyclopentanones, cycloheptanones, substituted esters (or lactones), and acetates.[10] The upfield shift in the cyclopentanone carbonyl frequency of 8 relative to 6 is notable. Among the remaining nonprotonated carbon atoms, C-16 of 1 and 2 is unique; recognition is eased by its downfield shift in 3–6 and disappearance in 7 and 8. Differentiation between C-5 and C-11 of 1 and 2 is based on comparison with the spectra of 5, 6, and 8 where the upfield shift of one of the signals, that of C-11, and the relative constancy of the second, that of C-5, which moves downfield on oxidation of the neighboring carbon atom, leaves no ambiguity.

Among the methyl signals, assignment of the quartet at lowest field to C-17 is based on single-frequency off-resonance decoupling in 1 and its conversion to a triplet near 86 ppm, characteristic of vinyl ethers, in the spectra of 3 and 4. Differentiation between the remaining methyl signals is difficult because of the superposition of methyl frequencies in the proton NMR spectra. Inspection of Table I reveals a significant upfield shift of one of the methyl signals upon hydrogenation (compare 1 with 2 and 5 with 6) and an upfield shift of a second methyl signal upon opening the hemiacetal ring (compare 1 with 4 and 2 with 6). We assume that the signals affected are those of C-14 and C-15, because (a) the chemical shift of C-13 should not be affected significantly by hydrogenation, (b) conversion of 1 to 2 or 2 to 4 produces a small downfield shift of one of the methyl signals which must be that of C-13, and (c) 5–8 all exhibit at least one relatively invariant signal in the 19–20-ppm region which again must be attributed to C-13. Comparison of 3 and 4 with 2, and 6 and 8 with 5, suggests that the signal which moves upfield on hydrogenation is that of C-14, the shift probably being associated with the introduction of a hydrogen atom peri to C-14. The signal which is shifted upfield on opening of the hemiacetal ring (and downfield on conversion of 6 to 8) is therefore that of C-15, although the reasons for the upfield shift are not clear as opening of the hemiacetal ring would appear to result in removal of a gauche interaction.

Experimental Section

Spectra were recorded on a Bruker HFX-270 instrument in $CDCl_3$ (1–4, 6) and Me_2SO-d_6 (5) solution, using Fourier transform techniques.

Registry No.—**1a,** 55721-12-5; **1b,** 55780-22-8; **2a,** 55660-88-3; **2b,** 55700-79-3; **3,** 55660-89-4; **4,** 55660-90-7; **5,** 10092-04-3; **6,** 55700-80-6; **7,** 54933-23-2; **8,** 55660-91-8.

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(6) The stereochemistry shown in the formula is based on a recent X-ray analysis (private communication from Dr. P. J. Cox, University of Glasgow).
(7) Anhydrodihydrotenulin (4) can be prepared from 2 in >80% yield.[1] Consequently the unlikely (because of the H-6 and H-8 proton shifts) possibility that 1 and 2 are 4:1 mixtures of C-8 epimers (the existence of a C-6 epimer of 1 is not possible) and that purification of 3, 4, and 5 has resulted in fractionation of the more abundant isomer product can be dismissed.
(8) Reexamination of 60-MHz traces recorded 15 years ago revealed a weak doublet (H-6 of minor isomer) partially obscured by the H-6 doublet of the major isomer and two shoulders on the sharp singlets of H-13 and H-17.
(9) The downfield shift of C-9 and the upfield shifts of C-1, C-4, C-5, C-6, and C-7 on going from 1 to 5 (and 2 to 6) are due partially to changes in electron density at C-6 and partially to changes in conformation of ring B and subsequent alterations of spatial relationships on opening the hemiacetal ring.
(10) The conversion of C-6 from sp^3 to sp^2 must be responsible for the surprisingly large upfield shift of C-4 in going from 6 to 8.

Reaction of (+)-1,3-Dimethylallene with Lead Tetraacetate

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Although there has been a great deal of interest in the reaction of lead tetraacetate (LTA) with alkenes,[1] there have been few examples utilizing this reaction with allenes. An earlier study by Laforge and Acree[2] reported that the major product of the reaction of acyclic allenes with LTA was a diacetate. More specifically, the reaction of 1,3-dimethylallene with LTA in acetic acid was also assumed to afford a diacetate. In a more recent disclosure, we have shown that the electrophilic addition of LTA to (−)-1,2-cyclononadiene in acetic acid solvent afforded (+)-3-acetoxycyclononyne by a suprafacial addition.[3] This was a particularly interesting result since the dominant pathway in the oxymercuration[3] and the oxythallation[4] of 1,2-cyclononadiene has been shown to be antarafacial addition to an alkene–metal π complex. The above results of Laforge and Acree[2] with acyclic allenes and our own results[3] with a cyclic allene, which afforded an alkyne as the major product, prompted us to examine the orientation and the stereochemistry of the addition of LTA to (+)-1,3-dimethylallene (1). We now report that the electrophilic addition of LTA to 1 also proceeds principally by a suprafacial pathway affording (*S*)-(+)-4-acetoxy-2-pentyne as the major product.

Results and Discussion

When 1,3-dimethylallene (1) was treated with LTA in acetic acid solvent, gas chromatographic analysis (GLC) showed that the major product of the reaction was 4-acetoxy-2-pentyne (7). When the reaction was carried out with optically active (*S*)-(+)-1,[5] $[\alpha]_D$ +22.4°, the product 7 had $[\alpha]_D$ +6.6° (Scheme I). The absolute configuration of 7 was established as *S* by saponification of 7 followed by catalytic hydrogenation of 4-hydroxy-2-pentyne to (*S*)-(+)-2-pentanol (8), $[\alpha]_D$ +1.4°. The stereochemistry of 7 was also established by direct hydrogenation of 7 to (+)-2-acetoxypentane (9). The absolute configuration of 9 was established by conversion of (*S*)-(+)-2-pentanol, $[\alpha]_D$ +12.2°, of known configuration to (*S*)-(+)-9, $[\alpha]_D$ +13.8°, by the action of acetyl chloride (Scheme II).

The relative stereospecificity of the addition of LTA to 1 was determined in the following manner. The rotation of optically pure (+)-2-pentanol is 18.8°.[7] Therefore, the optical purity of 2-pentanol having $[\alpha]_D$ +1.4° is approximately 7.4%. The optical purity of the allene 1, $[\alpha]_D$ +22.4°, from which 8 was derived may also be estimated to be about 13% based upon a calculated rotation for optically pure (*R*)-(−)-1 of −174° (EtOH).[6b] Thus, we may conclude that the stereospecificity of LTA addition to 1 is at least 57%. The specificity could conceivably be higher since our data cannot exclude some racemization of the allene or the acetoxypentyne under the reaction conditions.

In the reaction of 1 with LTA, there are two possible