The ^{13}C NMR spectra were determined at 25.03 MHz on a modified JEOL JNM-PS-100 FT NMR interfaced with a Nicolet 1085 Fourier-transform computer system. The samples were spun in 10 mm o.d. tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of the solvent as the internal lock signal. Chloroform-*d* or dimethyl sulfoxide-d_6 were used as the solvent and all δ values reported in the tables were in parts per million downfield from Me_4Si: $\delta^{Me_4Si} = \delta^{CDCl_3} + 76.91 = \delta^{Me_2SO\text{-}d_6} + 39.56$. All proton lines were decoupled by a broad band (~2500 Hz) irradiation from an incoherent 99.538-MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000 Hz sweep width spectra. Typical pulse widths were 12.5 μs (45° flip angle), and the delay time between pulses was fixed at 1.0 s. Normally 1012 (twice as many for single frequence off-resonance experiments) data accumulations were obtained on a 100 mg/2 ml of solvent sample. The precision of the chemical shifts is ±0.05 ppm.

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Registry No.—**1a,** 57-27-2; **1b,** 76-57-3; **1c,** 561-27-3; **1d,** 2784-73-8; **2a,** 509-60-4; **2b,** 125-28-0; **3,** 125-29-1; **4,** 115-37-7; **5a,** 41135-98-2; **5b,** 508-54-3; **5c,** 50798-31-7; **5d,** 978-76-7; **6a,** 465-65-6; **6b,** 16590-41-3; **6c,** 57664-96-7; **7a,** 20410-98-4; **7b,** 49625-89-0; **8,** 15358-22-2; **9a,** 14521-96-1; **9b,** 16180-23-7; **9c,** 16180-26-0; **10,** 16196-82-0; **11a,** 14357-78-0; **11b,** 16196-64-8; **11c,** 16671-47-9.

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(15) The letter in parenthesis refers to the signal multiplicity obtained from single frequency off-resonance experiments; s = singlet, d = doublet, t = triplet, and q = quartet.
(16) Johnson and Jankowski have reported the ^{13}C NMR spectrum of co-*deine phosphate* (Spectra 479 in ref 4). However, they were able to make assignments to only 8 of the 18 carbons. Taking into account that their spectrum was of the salt in D_2O, our assignments are in agreement with theirs.
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Alkaloids of *Vinca rosea* L. (*Catharanthus roseus* G. Don). XXXVII. Structure of Vincathicine[1]

S. S. Tafur, J. L. Occolowitz, T. K. Elzey, Jonathan W. Paschal, and Douglas E. Dorman*

Lilly Research Laboratories, Indianapolis, Indiana 46206

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The structure of the dimeric alkaloid vincathicine is deduced from physical and chemical methods. The conversion of leurosine to vincathicine under acidic conditions is described.

Vincathicine (1), a dimeric indole alkaloid showing moderate oncolytic activity in experimental animals, was first isolated by Svoboda and Barnes.[2] On the basis of ultraviolet, infrared, and ^1H nuclear magnetic resonance (NMR) spectroscopies, these authors suggested that vincathicine included an oxindole moiety. Since this initial report, no further work on the structure of vincathicine has been published. The more recent discovery that vincathicine is chemically related to leurosine[3] has rekindled interest in this alkaloid.

Table I. ^{1}H NMR Data for Vinblastine and Vincathicine

	Proton	VLB[a]	Vincathicine[a]
Vindoline portion	2	3.70	3.67
	9	6.63	6.45
	11-OCH_3	3.77	3.76
	12	6.10	6.08
	14	5.27	5.23
	15	5.82	5.79
	16-OH	9.5	9.5
	17	5.46	5.40
	18-CH_3	0.80	0.57[b]
	21	2.64	2.58
	$COOCH_3$	3.77	3.77
	NCH_3	2.70	2.69
	$OCOCH_3$	2.09	2.05
"Indole" portion	9′	~7.1	7.60[c]
	10′		7.33[d]
	11′		7.57[d]
	12′	~7.5	7.66[c]
	18′-CH_3	0.87	0.53[b]
	NH	8.03	
	$COOCH_3$	3.59	3.65

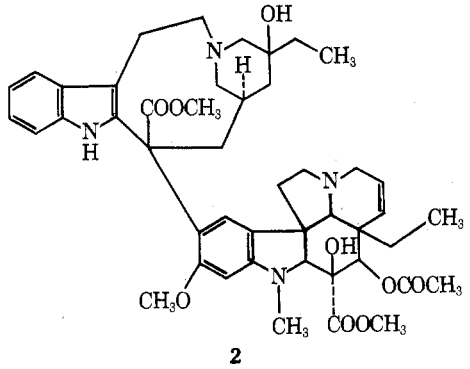
[a] Spectra taken in deuteriochloroform. Chemical shifts are measured in parts per million from internal Me_4Si. [b-d] Resonances so designated cannot be differentiated in assignment.

Vincathicine is isomeric with leurosine (MS: found, 808.4038; calcd for $C_{46}H_{56}N_4O_9$, 808.4047). Peaks which can be attributed to fragmentation of the vindoline moiety of dimeric alkaloids[4] were present in the mass spectrum of vincathicine. These included *m/e* 649 (M − $C_6H_7O_5$), 469 ($C_{26}H_{33}N_2O_6$), 282 ($C_{14}H_{20}NO_5$), and 135 and 122. A peak at *m/e* 353 ($C_{21}H_{25}N_2O_3$) corresponds to the molecular ion less the vindoline radical.

Vincathicine proved to be particularly prone to intermolecular transmethylation in the mass spectrometer. By determining the spectrum from a film at the lowest possible temperature, the transmethylation peak at *m/e* 822 and peaks at *m/e* 765 and 750, nominally M − C_2H_3O and M − $C_2H_2O_2$, respectively, were eliminated.

A relatively intense peak at *m/e* 366 ($C_{22}H_{26}N_2O_3$), which is unshifted in the spectra of 16-acetylvincathicine and 17-deacetylvincathicine and occurs at *m/e* 368 in the spectrum of dihydrovincathicine, must arise from the modified velbanamine moiety plus CH. It is difficult to account for this peak, as the additional carbon atom would have to arise by the unlikely fission of the aromatic ring of the vindoline moiety. We believe that this peak arises from a hitherto unobserved intramolecular transmethylation. In support of this contention is a peak at *m/e* 661 (M − $C_5H_7O_5$), corresponding to loss of the oxygenated ethylene bridge of the vindoline moiety less CH, indicating that the itinerant carbon is transferred from the oxygenated ethylene bridge of vindoline to the modified velbanamine moiety.

In Table I, the chemical shifts of the identifiable ^{1}H resonances of vinblastine (2) and vincathicine are compared.



2

It will be noted that the two spectra correspond well in the vindoline halves of the molecules except for protons at positions 9 and 18. In our experience,[5] chemical shift changes of this sort are frequently attributable to significant changes in the structure and/or conformation of the other half of the molecule. In support of this, the ^{1}H NMR spectra of the modified velbanamine portions of vinblastine and vincathicine are quite different. It is particularly significant that the N proton which usually occurs in the spectra of these alkaloids is missing. This fact argues against the possibility of an oxindole structure.[2]

^{13}C NMR spectra of vincathicine are shown in Figure 1. The lower spectrum was measured under normal conditions and with full proton decoupling. The middle spectrum of Figure 1 was measured using an inversion-recovery pulse sequence designed to identify methyl and nonprotonated carbon resonances. The upper spectrum, measured using the same pulse sequence in conjunction with off-resonance decoupling, distinguishes the resonances of methylene and methine carbons. This procedure[6] allows clear distinction of the resonances of methyl, methylene, methine, and nonprotonated carbons (see Table II).

The ^{13}C spectrum of vincathicine shows 25 resonances whose chemical shifts and multiplicities are consistent with the spectrum of the dihydroindole (10-vindolinyl) portion of vinblastine.[6,7a] This supports the conclusion, drawn from mass spectral and NMR evidence (vide supra), that vincathicine contains a 10-vindolinyl moiety, and "subtraction"[1] of these resonances from the full ^{13}C NMR spectrum of vincathicine should yield the spectrum of the other half of the molecule. Of these 21 resonances, the two due to the carbomethoxyl group are easily assigned. This leaves seven resonances due to sp^2-hybridized carbons, rather than the eight typical of an indole system. Furthermore, one of these resonances occurs in the "carbonyl" region of the spectrum. The chemical shift (187.0 ppm) of this resonance is different than observed for the carbonyl resonance of oxindoles,[7b] thereby supporting the above conclusion that vincathicine does not include an oxindole moiety. The chemical shifts of these seven resonances are, in fact, in good agreement with those of a 3*H*-indolenine system.[8] Also in support of the indolenine structure was the fact that vincathicine was reduced by borohydrides under mild conditions[9] to yield a dihydro derivative containing a new exchangeable proton.

In the remainder of the ^{13}C NMR spectrum of this unknown half of vincathicine, there are 12 resonances, i.e., one more than in the other dimeric alkaloids.[5,6,7a] The spectra of Figure 1 clearly demonstrate three of these resonances to represent nonprotonated carbons (75.8, 63.1, and 57.1 ppm), while one is due to a methyl (7.0 ppm). The chemical shift of this methyl is very similar to those of a series of alkaloids containing an ethyl group attached to a nonprotonated carbon bearing an oxygen atom.[5,6,7a,10] Because the carbomethoxyl chemical shifts appear similar to those of other examples, one may suppose that this group is attached to a quaternary carbon 16′ as usual. The remaining singlet resonance can be attributed to the quaternary carbon of an indolenine system. Of the remaining eight resonances, two were shown to be due to methines and the remainder to methylenes.

The key to the structure of vincathicine is derived from chemical evidence. During their early work with leurosine, Neuss and his co-workers discovered that under a variety of acidic conditions, this alkaloid was converted to two major products, one of which was vincathicine.[2] On the basis of this evidence and the recent proposal[7a,11] of 3 as the structure of leurosine, we may therefore propose that vincathicine has either structure 1 or 4 (Figure 2). Either

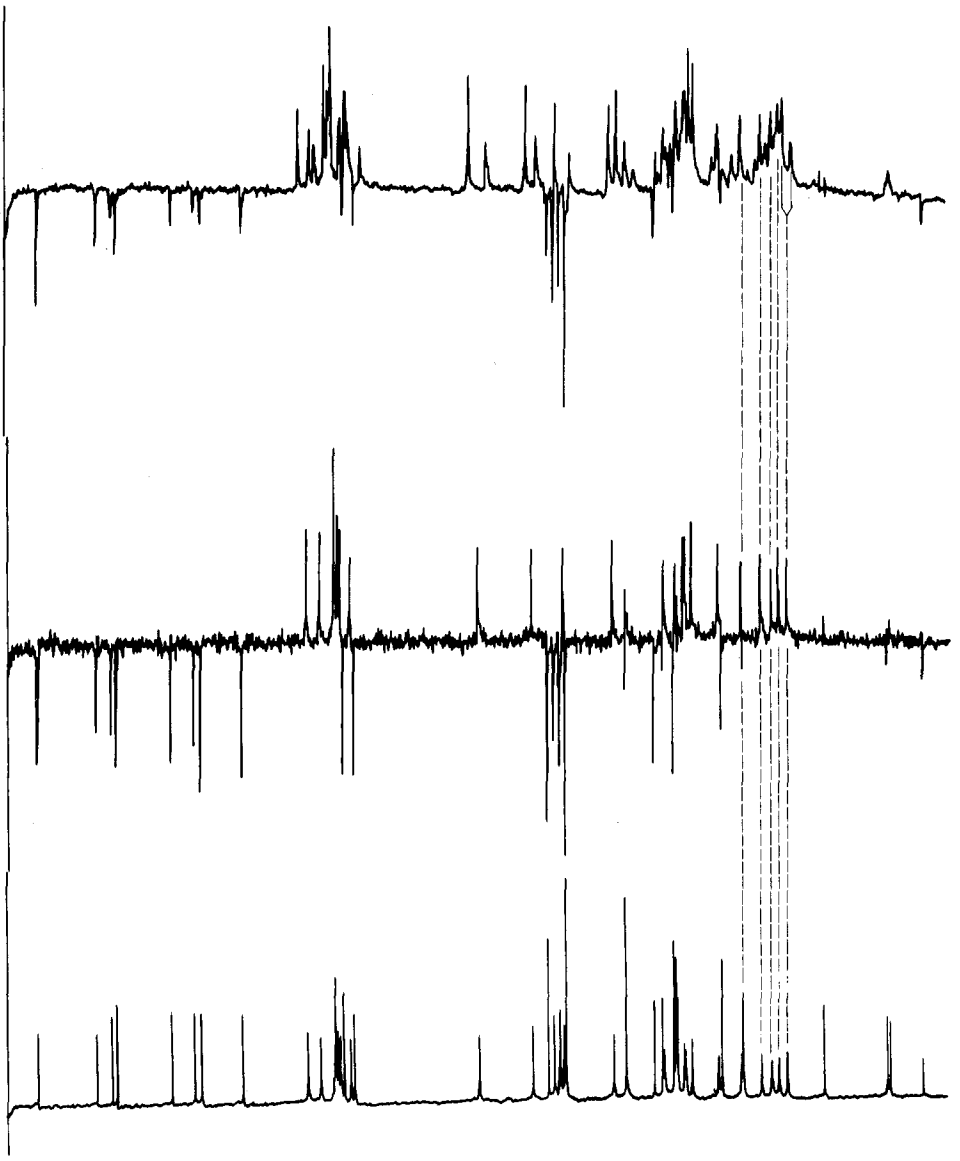


Figure 1. ^{13}C NMR spectra of vincathicine. Lower: spectrum measured using $(-\pi/2-T-\pi/2-)$ pulse sequence with T = 3 s. Middle: spectrum measured using $(-\pi-\tau-\pi/2-T-)$ pulse sequence with τ = 0.35 s and T = 5 s. Upper: spectrum measured as in middle, but with specific decoupling at about δ 7.

structure fits the constraints imposed by the multiplicities of the carbon resonances, and both include the 3*H*-indolenine system. Carbon chemical shifts, however, strongly favor structure **1**. From structure **4**, for example, one would expect that one of the methine resonances would occur in the region of chemical shifts typical of carbinyl carbons (C-15′).[12] A model for this resonance might be the chemical shift of the similarly substituted carbon 15′ vincadioline (75.2 ppm).[6] In fact, the two doublet resonances occur at substantially higher field (28.9 and 49.2 ppm). In contrast, one of the singlet resonances of vincathicine (75.8 ppm) is at lower field than would be expected from structure **4**. From these and other arguments, we therefore favor structure **1** for vincathicine. Also consistent with the tertiary alcohol structure **1** is the fact that acetylation has no effect on the indolenine half of the molecule.

In fact, the assumption of **1** as the correct structure leads to a reasonable, if tentative, assignment of all the carbon resonances of vincathicine (cf. Table II). Thus, the C-15′ resonance of vincathicine is nearly 8 ppm lower field than its position in vinblastine,[6,7a] consistent with its more highly branched character.[13] Carbons 6′ and 20′ are also deshielded relative to vinblastine, a result expected by virtue of the fact that each of these carbons has one more β-carbon[13] in vincathicine. It is surprising that C-14′ is slightly more shielded in vincathicine, since this carbon also is subject to an additional β effect. A study of molecular models suggests that in structure **1**, this carbon is subject to severe steric interactions.[14]

Studies of molecular models also show that in both **1** and **4**, the 18′-methyl protons would be expected to be shielded by the diamagnetic anisotropy of the 3*H*-indolenine system, as, in fact, is observed (Table I). In the case of **1**, however, the models also suggest that one of the 19′-methylene protons would be spatially proximal to H-9′. Such a situation should give rise to a nuclear Overhauser effect (NOE)[15] between these protons. Irradiation of the overlapping methyl triplets near δ 0.5 led to no observable changes in the aromatic region, indicating that the rotameric states available to the ethyl group do not bring the 18′-methyl protons close to H-9′, a conclusion supported by the models. Irradiation at approximately δ 1.8, however, leads both to changes in the appearance of the overlapping methyl triplets and to a small (5%) but reproducible increase in the

Table II. ^{13}C NMR Spectrum of Vincathicine

Dihydroindole portion				"Indole" portion			
Carbon	δ^a	"T_1"^{b}	Ord^c	Carbon	δ^a	"T_1"^{b}	Ord^c
2	83.0	d/t	d	2′	187.0	s	
3	50.6^d	d/t	t	3′	52.6^d	d/t	t
5	50.9^d	d/t	t	5′	55.0^d	d/t	t
6	43.6	d/t	t	6′	32.2^e	d/t	t
7	53.0	s		7′	57.1^f	s	
8	122.8	s		8′	144.2	s	
9	123.6	d/t	d	9′	124.6^g	d/t	d
10	120.6	s		10′	127.7^g	d/t	d
11	159.1	s		11′	124.1^g	d/t	d
12	94.3	d/t	d	12′	121.3^g	d/t	d
13	152.8	s		13′	154.0	s	
14	124.6	d/t	d	14′	28.9	d/t	d
15	130.5	d/t	d	15′	49.2	d/t	d
16	79.6	s		16′	63.1^f	s	
17	76.3	d	d	17′	38.7^e	d/t	t
18	7.6	CH_3		18′	7.0	CH_3	
19	30.6	d/t	t	19′	34.4^e	d/t	t
20	42.8	s		20′	75.8	s	
21	65.7	d/t	d	21′	63.1^d	d/t	t
*$COOCH_3$	170.7	s		*$COOCH_3$	174.8	s	
$COO*CH_3$	52.2	CH_3		$COO*CH_3$	52.6	CH_3	
$N*CH_3$	38.4	CH_3					
CH_3*COO	171.7	s					
$*CH_3COO$	21.1	CH_3					
$AR\text{-}O*CH_3$	55.4	CH_3					

^{a} Chemical shifts in parts per million from internal Me_4Si. ^{b} Subdivision of carbon types by inversion-recovery pulse sequence (see text): "s" represents singlet (nonprotonated carbon), "CH_3" signifies a methyl resonance, and "d/t" means doublet or triplet (i.e., methines or methylenes, respectively). ^{c} Subdivision of resonances on the basis of off-resonance decoupling (ord): "d" indicates doublet and "t" indicates triplet. $^{d-g}$ Resonances so designated cannot be distinguished in assignment.

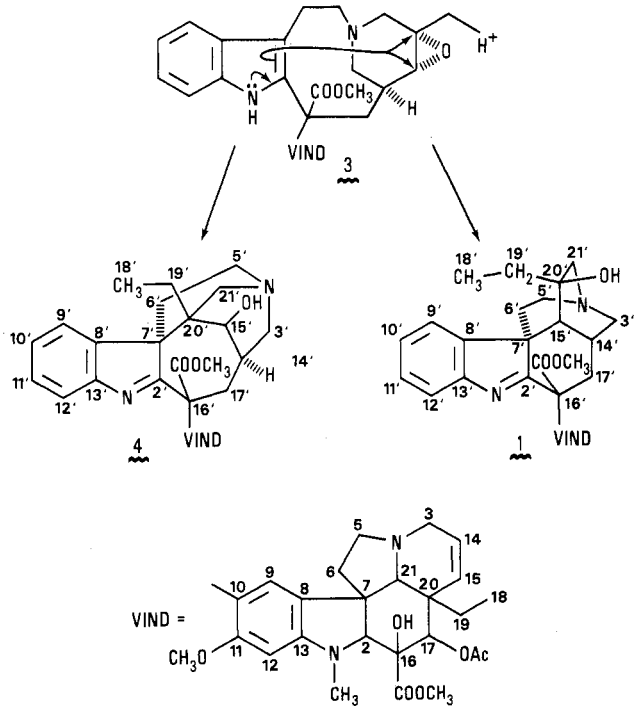


Figure 2. Acid-catalyzed conversion of leurosine (3) to vincathicine (1).

integral of the overlapping H-9′ and H-12′ resonances. These results therefore support the proposal of 1 as the structure of vincathicine.

Experimental Section

Vincathicine was isolated by the method of Svoboda and Barnes.[2] Proton NMR spectra were measured on a Varian HA-100 spectrometer, while ^{13}C NMR spectra were measured on a JEOL PFT-100 spectrometer equipped with a JEOL EC-100 data system. All spectra were measured at ambient temperature (ca. 30 °C) in chloroform solution; concentrations ranged from 0.05 to 0.1 M. The conditions of data accumulation and transformation should lead to line broadening of less than 0.7 Hz. Chemical shifts are considered accurate to ±0.1 ppm. Mass spectra were measured on a Varian MAT Model 731 mass spectrometer using direct introduction of sample.

16-Acetylvincathicine. An excess of acetic anhydride was added to a solution of 35 mg of vincathicine in dry pyridine and was stirred at room temperature overnight. After evaporating to dryness in vacuo, the reaction mixture was shown by TLC on silica gel in ethyl acetate–95% ethanol (3:1) to contain a small amount of unreacted vincathicine and one reaction product. Preparative TLC separation afforded 17.4 mg of a monoacetate of vincathicine (M^+ 850). The ^1H NMR data were consistent with placement of the acetyl at C-16.[5]

Dihydrovincathicine. To a solution of 2 ml of HCl in 48 ml of methanol, 700 mg of sodium cyanoborohydride was added. Two hundred milligrams of vincathicine was added with stirring and refluxed for 60 min. Fifty milliliters of water was added to the reaction solution, and the methanol was removed in vacuo. The solution was made alkaline with ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. TLC on silica gel in ethyl acetate–methanol (1:1) indicated unreacted vincathicine and one reduction product. Preparative TLC yielded 40 mg of dihydrovincathicine (M^+ 810).

In alkaline solution, the C-17 acetyl is readily hydrolyzed. Consequently, attempts to reduce vincathicine with sodium borohydride in alkaline or neutral solution yielded only 17-deacetylvincathicine (M^+ 766).

Registry No.—**1**, 57665-10-8; **2**, 865-21-4.

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Diterpenoid Total Synthesis, an A → B → C Approach. VIII. Introduction of Oxygen at Carbon-11. Total Synthesis of (±)-Carnosic Acid Dimethyl Ether and (±)-Carnosol Dimethyl Ether[1]

Walter L. Meyer,* Richard A. Manning, Erich Schindler, Robert S. Schroeder,[1d] and D. Craig Shew

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701, and Department of Chemistry, Indiana University, Bloomington, Indiana*

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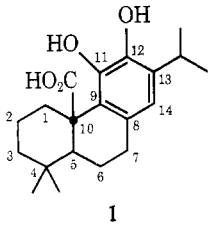
Total syntheses of the title compounds are described. Condensation of 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone (**4**)[2] with ethyl formate followed by DDQ dehydrogenation produces the 8-formyl-Δ^8-7-octalone **6**, which is the key intermediate. Michael addition of *tert*-butyl acetoacetate or *tert*-butyl isovalerylacetate to **6** followed by acid-catalyzed *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration of the resulting adducts affords trans-syn-cis tricyclic enediones **8a** and **8b**, which are dehydrogenated to 7-keto-12-phenols **9a** and **9b**, respectively. Hydrogenolysis of **9b** leads to 12-phenol **10a**, into which an 11-methoxy substituent was introduced by coupling with *p*-nitrobenzenediazonium chloride, O-methylation, sodium dithionite reduction, diazotization, and methanolysis to produce **14**. Ester cleavage (*t*-BuOK–Me_2SO) affords (±)-carnosic acid dimethyl ether. Alternatively, Michael addition of 1-methylsulfinyl-4-methyl-2-pentanone to **6** produces an adduct **22** which was subjected to Pummerer rearrangement, enol etherification, base-catalyzed cyclization, and O-methylation to afford **25b**. Hydrogenolysis gives **14**, while treatment with sodium borohydride followed by sodium hydride gives (±)-carnosol dimethyl ether. On exposure to hydrochloric acid in dimethyl sulfoxide, adduct **22** cyclizes with sulfoxide elimination, giving **9b**. Preparation of **4** by hydrogenation of the corresponding octalone is discussed, and the by-products sometimes encountered are identified as **28, 29, 30, 31, 33,** and **34**. Lactone **32** is described in connection with structure determination of **30**.

One of the advantages of the general A → B → C approach to diterpenoid synthesis which we have described[1a,3] is its potential for direct adaptability to construction of terpenoids containing a functional group rather than methyl at the angular position. Such a system is exemplified by carnosic acid (**1**)[4,5] and its derivatives carnosol (**2**)[6–10] (picrosalvin[7]) and rosmaricine (**3**).[5,11] Although the



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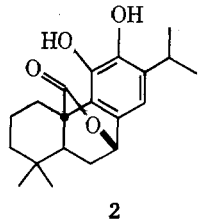

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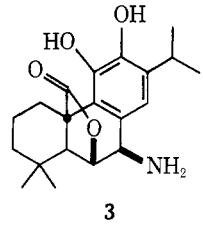

3

latter two of these substances now appear to be artifacts from isolation rather than natural products,[5] the unusual state of oxidation at the angular position in carnosic acid and the interesting niche which has been proposed for it or analogous angular acids in diterpenoid biosynthesis[8] led us to investigate the total synthesis of such substances.

The A/B Ring System. The ideal bicyclic starting point for extension of this general synthetic plan[3] to the carnosic acid system is 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone (**4**),[2] which contains both the appropriate oxidation level at the angular carbon and the necessary configuration of the A/B ring fusion. Preparation of this keto ester by an efficient and stereoselective route has already been reported.[12] Several improvements in the reactions leading to its synthetic progenitor, the corresponding Δ^5-7-octalone,[12] have subsequently been discovered and are recorded in the Experimental Section; they have raised the overall yield of the octalone to 87% from 6-carbethoxy-2,2-dimethylcyclohexanone. Some difficulties were encountered in reproducing the hydrogenation of this octalone to decalone **4**, but, as will be described later in this paper, these problems are largely circumvented by adjusting the solvent for the reduction.

Conversion of decalone **4** to the corresponding 8-formyl-Δ^8-7-octalone (**6**), the principal intermediate for attachment of ring C, followed the usual path[1a,3] (Scheme I). As anticipated,[1a] condensation of the decalone with ethyl formate affords its 8-hydroxymethylene derivative **5a**[13] to the exclusion of the 6-hydroxymethylene isomer. Dehydrogenation of enol **5a** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[1a,14] was found to be considerably improved by acetic acid catalysis, and under carefully controlled conditions this reaction leads to formyl enone **6** in 92% yield.

With the angular carboxyl in place and the skeletal configuration under control at this early stage of the synthesis, the major structural feature requiring attention in extension of the general synthetic scheme[3] to carnosic acid and its derivatives is the 11-hydroxyl group which is present in those natural products. Two fundamental approaches have been examined for obtaining such 11,12-dioxygenated systems rather than the 12-hydroxy compounds which were the objectives of initial work.[1a,3,15] In the first, an 11 oxygen is introduced into an 11-unsubstituted intermediate after ring C has been constructed. In the second, the C-ring elaboration scheme is varied so as to obtain an 11 functional group as an integral part of the ring extension sequence.

Carnosic Acid through 11-Unsubstituted Intermediates. As a model for the initial C-ring construction sequence, aldehyde **6** was treated with the sodium enolate of *tert*-butyl acetoacetate in benzene[3] or dimethyl sulfoxide