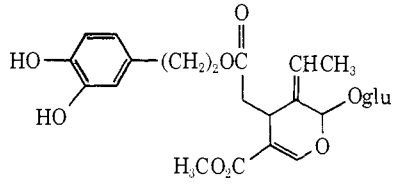
Communications to the Editor

Structure and Stereochemistry of Elenolic Acid

Sir:

Of particular interest because of its potent, broad range antiviral activity, the oleuropein (**1**)[1] related natural product[2] elenolic acid (**2**) was assigned structure **3a** (in equilibrium with the open-chain enol aldehyde



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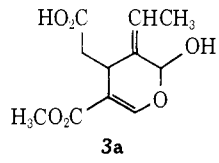
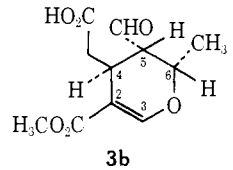
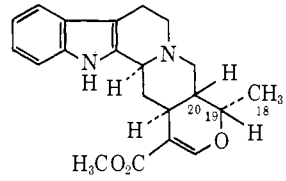


3a

and dialdehyde counterparts) by Panizzi, *et al.*[1] On the basis of new spectral data and the stereorational[3] conversion of **2** to (−)-ajmalicine (**4**), we suggest that elenolic acid possesses the structure and absolute configuration depicted in **3b**. This proposal is supported



3b



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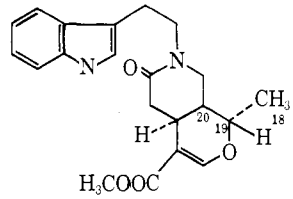
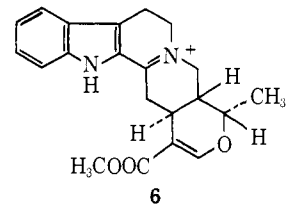
by the total synthesis of *dl*-elenolic acid methyl ester reported in the accompanying communication.[4]

The nmr spectrum of elenolic acid (Table I) exhibited signals for one aldehyde proton, one methyl and one proton attached to the same carbinol carbon, one carboxy proton, one carbomethoxyl methyl, one proton on a highly conjugated double bond, one α-aldehyde proton, and an ABX system. As revealed by spin decoupling experiments, the X proton interacts with the α-aldehyde hydrogen, which in turn is coupled to the hydrogen in the methylcarbinol unit.

Certain features anticipated for structure **3a**, namely, peaks for an isolated hemiacetal moiety and a nonconjugated ethylidene unit, are not present in the nmr spectrum. Obviously during the hydrolytic conversion of **1** to elenolic acid, the acylic hydroxy aldehyde system corresponding to hemiacetal **3a** undergoes conjugate addition of the α-hydroxymethylene ester unit to the α,β-unsaturated aldehyde moiety, forming **3b**.

Conversion of elenolic acid to (−)-ajmalicine was initiated by condensing the methyl ester of the former with tryptamine in benzene, followed by *in situ* $NaBH_4$ reduction of the intermediate imine and cyclization of the resulting δ-amino ester to lactam **5**: mp 172–174°





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(60% overall yield);[5] mol wt (mass spectrum) 368; nmr (100 MHz) 97 Hz (d, C_6CH_3), 371 (s, OCH_3), 423 (m, C_6H), 786 (s, vinyl H), 700–740 and 759–767 (m, indole CH), 846 (s, indole N–H).

Bischler–Napieralski cyclization of **5** ($POCl_3$ in refluxing benzene) provided the expected quaternary salt **6**, which was immediately reduced with $NaBH_4$ to (−)-ajmalicine (25% from **5**).[6] Identity of the partial synthesis was established by ir, nmr, mass spectral, optical rotational ($[\alpha]^{MeOH}$ D −44°), and melting point/mixture melting point (260–261°/256–258°) comparison with the natural product ($[\alpha]^{MeOH}$ D −39°; mp 257°).

The following observations demonstrate that no epimerization occurred during the overall conversion of elenolic acid to ajmalicine and that therefore the stereochemistry of the former corresponds to that in the E ring of the latter. Comparison of 6-CH_3–6-H nmr splittings in **3b** (7 Hz), the Ca^{2+} salt of **2** (7 Hz), and the methyl ester of **3b** (7 Hz) does not reveal any difference in relative stereochemistry among the members of the trio, as anticipated. Similarly, decoupling of 19-CH_3 and 19-H in **4** and 6-CH_3 and 6-H in **5** reveals that no change in the relative configurations of the corresponding chiral centers has occurred during conversion of **5** ($J_{5,6}$ = 4.0 Hz) to **4** ($J_{19,20}$ = 3.25 Hz), as expected. However, a similar decoupling experiment on methyl elenolate gave $J_{5,6}$ = 8.5 Hz, a value which does not permit a C-5–C-6 assignment but only reflects conforma-

Table I. Nmr Spectrum of Elenolic Acid[a]

Line position, ppm	Pattern	Coupling, Hz	Assignment
1.58	Doublet	$J_{1.58,4.28}$ = 7	$CH_3C(O)H$
4.28	Doublet of quartets	$J_{4.28,2.72}$ = 2.5	$CHC(O)HCH_3$
2.72	Multiplet	$J_{2.72,4.28}$ = 2.5 $J_{2.72,3.04}$ = 2.5 $J_{2.72,9.70}$ = 2	$C(O)HCH(CH)CHO$
3.40	Doublet of doublets	$J_{3.40,2.72}$ = 2.5	$>CHCH_2CO_2$
2.95 2.37		$J_{2.95,2.37}$ = 16.5 $J_{2.95,3.40}$ = 3.0 $J_{2.37,3.40}$ = 11.0	$>CHCH_2CO_2$
3.75	Singlet		CO_2CH_3
7.70	Doublet	$J_{7.70,3.40}$ = 1	Conjugated C=CHO
9.70	Doublet	$J_{9.70,2.73}$ = 2	CHCHO
9.92	Broad		CO_2H exchangeable

[a] Nmr spectrum recorded on a Varian A-60 spectrometer. It was run in $CDCl_3$ solution with internal TMS as standard.

(1) L. Panizzi, M. L. Scarpati, and G. Oriente, *Gazz. Chim. Ital.*, **90**, 1449 (1960).

(2) (a) H. E. Renis, *Antimicrob. Agents Chemother, 1969*, 167 (1970); (b) M. G. Soret, *ibid.*, 160 (1970); (c) G. A. Elliot and E. N. DeYoung, *ibid.*, 173 (1970).

(3) E. E. van Tamelen, M. Shamma, and P. Aldrich, *J. Amer. Chem. Soc.*, 78, 4628 (1956).

(4) R. C. Kelly and I. Schletter, *ibid.*, **95**, 7156 (1973).

(5) For a close precedent, see R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 2, 1 (1958).

(6) For related cyclization–reduction sequences in a similar system see ref 3 and 5.

tional flexibility in this case. Proton exchange at C-5 leading to epimerization or any other change resulting from proton loss at this center during the conversion of methyl elenolate to lactam **5** was ruled out by the use of C-5 deuterium-labeled ester, prepared by the subjection of calcium elenolate to the action of excess D_2O for 24 hr and conversion to the free acid by DCl, followed by treatment with diazomethane. Repetition with this material of the steps involving formation of lactam **5** from unlabeled ester provided deuterium-labeled **5**, mol wt (mass spectrum) 369, in which the multiplet (doublet of quartets) due to C-6 H in unlabeled **5** is cleanly decoupled to a single quartet.[7]

In a parallel observation, radioactive lactam **5** was isolated after C-5 tritium-labeled **3b** was carried through the sequence already described for preparation of unlabeled **5**.

Acknowledgment. The Stanford authors appreciate financial support from the National Science Foundation (GP 23019). The XL-100 nmr spectrometer was provided by National Science Foundation Grant No. GP 28142.

(7) A referee has suggested that the possibility of isoinversion might invalidate the condensation experiment with deuterium-labeled **3b**. However, in their paper[8] describing isoinversion, Cram, *et al.*, state "the limiting k_e/k_α value of zero has never been attained." In accord with the above statement we believe that had inversion occurred some deuterium loss should have been seen.

(8) W. T. Ford, E. W. Graham, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 4661 (1967).

(9) National Science Foundation Fellow, 1970–1972.

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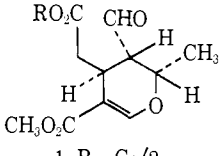
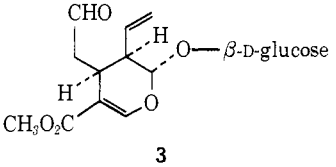
Total Synthesis of *dl*-Methyl Elenolate

Sir:

Elenolic acid derivatives, particularly the calcium salt (**1**) and methyl ester (**2**),[1] have generated considerable interest because of their potent broad range antiviral activity.[2] These compounds are structurally quite similar to *seco*-loganin (**3**), a precursor in indole alkaloid



1, R = Ca/2
2, R = CH_3



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biosynthesis.[3] These considerations and the difficult accessibility of these compounds from olive press juices[4] led to the initiation of a program aimed at their total synthesis. This communication reports a total synthesis of *dl*-methyl elenolate and a formal total synthesis of *dl*-calcium elenolate.

Addition of a tetrahydrofuran solution of cyclopentadienylsodium to a twofold excess of methyl bromoacetate at −10° resulted in the formation of methyl 1,3-cyclopentadienyl-5-acetate[5] [nmr ($CDCl_3$) δ 2.38 (d, 1, J = 8.5 Hz), 3.67 (s, 3, OCH_3), 6.42 (s, 4, =CH)] which when treated with a two- to threefold excess of citraconic anhydride at −10° afforded **4** (see Chart I) in 50% overall yield after crystallization from ether [mp 105–108°;[6] nmr ($CDCl_3$) δ 1.66 (s, 3, CH_3), 2.41 (A_2B, 2, CH_2CO_2), 2.6 (A_2B, 1, $CHCH_2CO_2$), 3.65 (s, 3, OCH_3), 6.30 (AA′XX′, 2, =CH)]. Hydrolysis of **4** in hot water gave an 80% yield of crystalline **5**[7] on cooling [mp 151–152°;[6] nmr (D_2O) δ 1.53 (s, 3, CH_3), 2.35 (A_2B, 2, CH_2CO_2), 3.62 (s, 3, OCH_3), 6.1 (m, 2, =CH)]. Oxidation of **5** with potassium chlorate and osmium tetroxide[8] gave **6** in 35% yield [mp 122–126°;[6,9] nmr (Me_2SO-d_6) δ 1.44 (s, 3, CH_3), 1.97–2.40 (m, 4), 2.77–3.00 (m, 2), 3.60 (s, 3, OCH_3), 3.70–3.90 (m, 1, OCH), 4.33–4.55 (m, 1, OCH)]. Treatment of **6** with acetone, 2,2-dimethoxypropane, and a trace of acid resulted in a quantitative conversion to **7** [mp 154–155°;[6] nmr (Me_2SO-d_6) δ 1.20, 1.43, 1.50 (3 s, 9, CH_3), 2.75–2.98 (m, 2), 3.61 (s, 3, OCH_3)].

Electrolytic decarboxylation[10] of **7** gave up to a 50% yield of **8** (oil) after silica gel chromatography: nmr ($CDCl_3$) δ 1.35, 1.53 (2 s, 6, CH_3), 1.72 (d, J = 2 Hz, 3, $=CCH_3$), 3.65 (s, 3, OCH_3). Oxidation of **8** with potassium permanganate–potassium periodate afforded **9** in 45% yield: mp 91–93°[6]; ir (mull) 1745, 1730, 1710 cm^{-1}; nmr ($CDCl_3$) δ 1.33, 1.57 (2 s, 6, CH_3), 2.29 (s, 3, $COCH_3$), 2.5–3.2 (m, 5), 3.67 (s, 3, OCH_3), 4.47–4.72 (m, 1, OCH), 4.75–4.99 (m, 1, OCH). Treatment of **9** with diazomethane gave a quantitative yield of the dimethyl ester **10** (oil): nmr ($CDCl_3$) δ 1.33, 1.57 (2 s, 6, CCH_3), 2.28 (s, 3, $COCH_3$), 3.66 (s, 3, OCH_3). Reduction of **10** with excess sodium borohydride at 0° in methanol gave an essentially quantitative yield of an oily mixture of the diastereomeric alcohols **11**, which when treated with mesyl chloride in

(1) For further information regarding the newly proposed structure for elenolic acid see the accompanying paper: F. A. MacKellar, R. C. Kelly, E. E. van Tamelen, and C. Dorschel, *J. Amer. Chem. Soc.*, **95**, 7155 (1973).

(2) (a) H. E. Renis, *Antimicrob. Agents Chemother., 1969*, 167 (1970); (b) M. G. Soret, *ibid.*, 160 (1970); (c) G. A. Elliot and E. N. DeYoung, *ibid.*, 173 (1970).

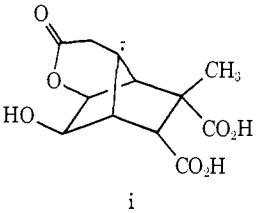
(3) (a) A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc. C*, 1187 (1969), and references therein; (b) R. Guarnaccia and C. J. Coscia, *J. Amer. Chem. Soc.*, **93**, 6320 (1971).

(4) J. H. Ford, F. A. MacKellar, P. A. Meulman, R. J. Wnuk, and G. C. Prescott, *Org. Prep. Proced.*, **4**, 97 (1972).

(5) This product rapidly rearranges to methyl 1,3-cyclopentadienyl-1-acetate at 25° ($t_{1/2} \simeq 1$ hr at 25°).

(6) Satisfactory elemental analyses were obtained.

(7) (a) The assignment of the relative stereochemistry at the 7 position as shown in **4** and **5** is based on the resistance of **4** to epoxidation and the formation of i and ii when **5** is oxidized with potassium chlorate



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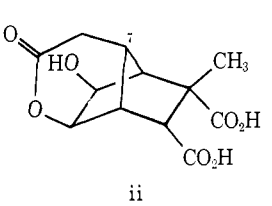

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and osmium tetroxide in basic medium.[7b] (b) For a similar stereochemical outcome in the preparation of a 7-substituted norbornene see E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(8) N. A. Milas and E. M. Terry, *J. Amer. Chem. Soc.*, **47**, 1412 (1925).

(9) The melting point of **6** varied greatly depending on the crystallization solvent and the degree of solvation.

(10) (a) P. Radlick, R. Klem, S. Spurlock, J. J. Sims, E. E. van Tamelen, and T. Whitesides, *Tetrahedron Lett.*, 5117 (1968); (b) H. H. Westberg and H. J. Dauben, Jr., *ibid.*, 5123 (1968).