ments are shown in Table I.

Unlike saturated ketones or isolated olefins, α,β-unsaturated ketones are regarded as a class of inherently dissymmetric chromophores;[10,11] consequently, no sector rules were applicable for the determination of the absolute configuration of the chiral centers of eupatorenone. The signs of the n–π^* (R band, 320–350 nm) and π–π^* (K band, 220–260 nm) transitions of *trans*-enones, however, have been correlated with the sense of helicity for this dissymmetric type chromophore. Thus, the R band is positive and the K band is negative in the case where the helicity of the chromophore is skewed in a left-handed helix; they are opposite when the chromophore helicity is right-handed.[12,13] Since eupatorenone (1) exhibited a CD spectrum characteristic for the presence of a right-handed helicity of the *trans*-enone chromophore, the absolute configuration of the attached C-2 chirality center was established as *S*. Experimentally, the CD values in methanol were $[\theta]$ +2150 and −840 at 248 and 300 nm, respectively. On this basis, and according to the prior determination of the relative steric positions of 2-H, 6-H, 3-CH_3, and 7-CH_3, the absolute configurations of the stereo centers of 1 are proposed as 2*S*, 3*S*, 6*S*, and 7*R*.

It should be noted that the reported ^{1}H NMR data of one of the cadinanes isolated previously[6] closely resembled those of eupatorenone (1). Unfortunately, no ^{1}H–^{1}H COSY measurements or ^{13}C NMR data are available for this compound, which might establish the relationship between this sesquiterpene and eupatorenone (1) or the possible identity of the two compounds.

Eupatorenone (1) was evaluated for cytotoxicity in the KB and P-388 test systems according to established protocols,[14,15] but was inactive.

Experimental Section

Melting point was determined on a Kofler-type hot-stage apparatus and is uncorrected. Optical rotation was measured with a Perkin-Elmer 241 polarimeter. Ultraviolet spectra were recorded with a Beckman DU-7 spectrophotometer, and infrared spectra were obtained with a Nicolet MX-1 interferometer. Mass spectrum was determined on a Varian MAT 112S double-focusing mass spectrometer at 80 eV. The ^{1}H NMR spectra were obtained with either a Nicolet NMC 360 instrument operating at 360 MHz or a Varian XL-300 instrument operating at 300 MHz. The ^{13}C NMR measurements were recorded with the Nicolet NMC 360 instrument operating at 90.8 MHz. Tetramethylsilane (TMS) was used as the internal standard and chemical shifts are reported as δ values (ppm). Homonuclear COSY spectra and heteronuclear HETCOR spectra were recorded with the Varian XL-300 spectrometer. Standard Varian pulse sequences were used. The selective INEPT experiments were performed on the Nicolet NMC 360 spectrometer. Data sets of 16K covering a spectral width of 10 000 Hz were acquired. Proton pulse widths were calibrated by using a sample of acetic acid in 10% C_6D_6 (^1J = 6.7 Hz) in a 5-mm NMR tube.[16] The radio frequency field strength for the soft proton pulse was on the order of 25 Hz in these experiments. For 1-H and 2-H protons, 6 Hz was used as the ^3J value and 4 Hz was used for the irradiation of the allylic and the isopropyl methyl group protons. Five thousand acquisitions were accumulated in each irradiation.

Plant Material. *Eupatorium adenophorum* Spreng. (*Ageratina adenophora* (Spreng.) R. King and H. Robinson) was collected from Doi Suthep, Chiang Mai Province, Thailand, in May 1987. Authentication was performed by comparison with herbarium specimens at the Botany Section, Technical Division, Department of Agriculture, Ministry of Agriculture and Cooperative, Thailand. A voucher specimen of the plant material was deposited in the Herbarium of the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

Isolation of Eupatorenone (1). The powdered dried plant material (2.3 kg) was extracted with 95% EtOH (20 L), and the combined extracts were evaporated in vacuo. The residue was distributed between H_2O (5 L) and petrol (3 × 2 L), and the organic layer was dried and evaporated to a residue (40 g), which was chromatographed on Si gel column, eluting first with benzene and later with benzene containing increasing amounts of acetone to 2, 4, 5, 10, and 15%, respectively. The fractions were evaporated, examined by TLC, and purified further through prep TLC to yield eupatorenone (1) (120 mg, 0.003%) having the following physical and spectroscopic properties: mp 66–67 °C; $[\alpha]_D$ +72.2° (MeOH, *c* 1.3); UV (MeOH) λ_{max} (log ϵ) 242 (3.86) nm; IR (KBr) ν_{max} 1725, 1710, and 1605 cm^{-1}; ^{1}H NMR, see Table I; ^{13}C NMR, see Table I; mass spectrum, *m/z* (rel intensity) 234 (M^+, 22), 232 (6), 216 (10), 192 (41), 117 (6), 164 (9), 150 (45), 136 (84), 121 (28), 109 (24), 69 (100), 55 (26); CD (MeOH) $[\theta]_{248}$ +2150; $[\theta]_{300}$ −840.

Acknowledgment. The work was supported, in part, by a grant from the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. The authors thank the Research Resources Center of the University of Illinois at Chicago for the provision of NMR and mass spectroscopic facilities, and Dr. J. M. Pezzuto for biological test data.

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Studies on the Extent of Electron Delocalization in β-Nitro Enamines from Dipole Moment Measurements

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Full delocalization of π-electrons in a tertiary enamine system such as described by structure 1 requires the nitrogen lone-pair orbital and the alkene π-system orbitals to be parallel in order to maximize overlap.[1] However,

$$R_2N{-}CH{=}CH_2 \leftrightarrow R_2\overset{+}{N}{=}CH{-}CH_2^-$$
1

most tertiary enamines do not possess such a completely conjugated system. Rather, the enamine is usually distorted from this planar geometry due to some pyramidality of the enamine nitrogen and some torsional twist away from planarity around the carbon–nitrogen bond.[2]

A viable method for determining the extent of π-electron delocalization in a conjugated system is comparing its experimental dipole moment with the dipole moment of a similar compound where mesomerism is excluded or with

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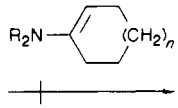
Table I. Dipole Moments and Vertical Ionization Potential Differences for Some Enamines



R_2N	n	dipole moment, D	$IP_2 - IP_1$, eV	ref
pyrrolidino	0	2.16 ± 0.03	2.56	3
pyrrolidino	1	2.24 ± 0.04	2.41	4
morpholino	0	2.19 ± 0.02	2.48	3
hexamethyleneimino	0	2.32 ± 0.03		

a dipole moment calculated from bond moments.

We have experimentally determined the dipole moments of some simple tertiary enamines (see Table I) possessing three different amine moieties. Because of the mesomeric effects shown in structure **1**, the dipole is directed with the positive end toward the nitrogen and the negative end toward the alkene β-carbon atom. Saturated amine *N*-methylpyrrolidine has no possibility of a mesomeric effect. It possesses a dipole moment of 1.10 D[5] with the negative end of the dipole pointing toward the nitrogen and the positive end toward the carbons. Comparison of this value with those of the enamines listed in Table I shows that there is considerable conjugation between the nitrogen lone-pair electrons and the alkene π-electrons in these enamines. The dipole moments of all four of these enamines are almost the same. This near identity in dipole moment magnitude shows that the extent of this conjugation is about the same for each of the enamines.

Another indicator of the relative amount of interaction between an amino group and the double bond in an enamine is the difference between the first and second vertical ionization potentials ($IP_2 - IP_1$) of the enamines (see Table I).[2] This difference is about the same for the pyrrolidino and morpholino enamines listed in the table, again showing a similar extent of conjugative interaction. The difference between IP_2 and IP_1 for dehydroquinuclidine (**2**) (in which resonance interaction between the lone-pair

2

nitrogen electrons and the alkene π-system is impossible because the potential interacting orbitals are orthogonal) is only 0.93 eV. This can be considered a reference standard for $IP_2 - IP_1$ when there is no resonance interaction.[6]

An inducement for a tertiary enamine to possess a fully conjugated system would be the presence of a nitro group in the β-position as seen in structure **3**. This type of conjugative interaction is well known in aromatic systems with a nitro group para to a tertiary amino group.[7,8]

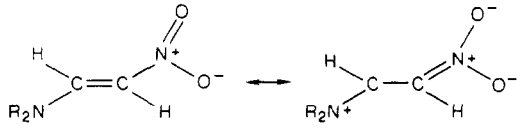


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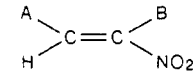
Table II. Dipole Moments of Some β-Nitro Enamines



A	B	dipole moment, D
morpholino	H	5.54 ± 0.02
morpholino	CH_3	5.30 ± 0.02
2,6-dimethylmorpholino	H	5.71 ± 0.05
2,6-dimethylmorpholino	CH_3	5.57 ± 0.03
N-methylanilino	H	6.40 ± 0.03
N-ethylanilino	H	6.48 ± 0.02
N,*N*-dimethylamino	H	6.86 ± 0.02
piperidino	H	7.20 ± 0.02
pyrrolidino	H	7.18 ± 0.02
N,*N*-dicyclohexylamino	H	7.64 ± 0.02

We have found that the presence of a β-nitro group in an enamine greatly increases the dipole moment of these enamines in solution as compared to unsubstituted enamines (see Table II). These experimental dipole moments can be compared with corresponding calculated dipole moments for the β-nitro enamines. With use of bond moments of 3.0 D for C-NO_2[9] and 0.7 D for C-amine for amines such as pyrrolidine or morpholine (with the positive end of the dipole toward the carbon atom),[10] the calculated dipole moment is 2.3 D. The actual experimental dipole moments are much larger than the calculated moments. Therefore, extensive conjugative interaction is taking place in the β-nitro enamines. This is consistent with the NMR lineshape analysis of some 2-nitro enamines reported by Rajappa and Nagarajan.[11]

Furthermore, the magnitude of the dipole moment varies significantly with the different amine moieties in the β-nitro enamines. This is in contrast with the simple enamines listed in Table I whose dipole moments are fairly uniform with varying amine moieties. The β-nitro substituent causes a much greater dipole moment in the pyrrolidino and piperidino β-nitro enamines than in the corresponding morpholino β-nitro enamines in solution. The larger amount of delocalization existing in pyrrolidine and piperidine β-nitro enamines as compared to morpholine β-nitro enamines also has been demonstrated by NMR analysis of these compounds.[11]

It would appear that the pyrrolidine and piperidine enamines are better able to accommodate an electron-withdrawing group at the β-carbon via electron delocalization than are morpholine enamines. This conclusion is consistent with the observation that morpholine enamines are not as reactive toward electrophilic addition reactions in solution as are piperidine or pyrrolidine enamines.[2,12]

Our MNDO calculations for (*E*)-1-(*N*,*N*-dimethylamino)-2-nitroethene show it to be planar with a calculated dipole moment of 7.14 D, in reasonably good agreement with the experimental dipole moment of 6.86 D (see Table II). (The *E* configuration is assumed to be present in solution since MNDO-calculated heats of formation show it to be more stable than the *Z* configuration by 3.6 kcal/mol; 30.241 kcal/mol for the *E* isomer and 33.848 kcal/mol for the *Z* isomer, respectively). Wiberg and coworkers have shown from ab initio molecular orbital calculations that molecules such as amides[14] or primary en-

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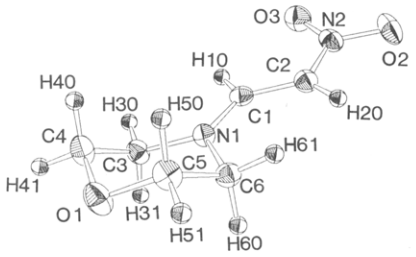

Figure 1.

amines[15] do not have extensive election delocalization between the nitrogen atom and carbon–oxygen or carbon–carbon double bond, respectively. This was demonstrated by the lack of significant change in C=O or C=C bond lengths in these compounds that have the possibility of π-electron interaction with the nitrogen atom as compared with simple, isolated C=O or C=C bonds.

MNDO calculations have shown that the simple tertiary enamine (*N*,*N*-dimethylamino)ethene has a C=C bond distance of 1.34 Å, which is identical with that of an isolated double bond, and that it possesses a C–N bond distance of 1.44 Å, which is somewhat shorter than the normal C–N distance of 1.47 Å found in saturated amines. These results correspond well with those of Wiberg. However, MNDO calculations for (*E*)-1-(*N*,*N*-dimethylamino)-2-nitroethene show a substantial lengthening of the C=C bond of 0.03 Å (going from 1.34 Å to 1.37 Å), and a substantial shortening of the C–N bond of 0.08 Å (going from 1.47 Å to 1.39 Å). Similar changes in bond distances can be seen in the experimental X-ray crystallographic study of a β-nitro enamine described below.

The MNDO-calculated difference between the first and second ionization potentials ($IP_2 - IP_1$) of this β-nitro enamine is from 2 to 3 times the size of this ionization potential difference for the simple enamine. So these theoretical calculations show extensive π-electron delocalization in this β-nitro enamine.

An X-ray crystallographic study of 1-(*N*-morpholino)-2-nitroethene shows the nitro enamine system to be almost completely planar in the solid state. An ORTEP drawing of this is shown in Figure 1. It should be noted that the configuration around the C(1)–C(2) double bond is *E*. The absolute value of the C(2)–C(1)–N(1)–C(6) dihedral angle is 0.2°, and that of the N(1)–C(1)–C(2)–N(2) dihedral angle is 2.3°. The N(1)–C(1) bond distance is unusually short at 1.323 Å, and the C(1)–C(2) bond distance is abnormally long at 1.368 Å. All of this data indicates that there is extensive electron delocalization between the amine, alkene, and nitro groups in the solid state for this nitro enamine.

Experimental Section

The general method used to determine dipole moments was that of Guggenheim.[16] Dielectric constants were measured with a Wissenschaftlich-Technische Werkstatten Model DM-01 dipolmeter fitted with a DFL-1 sample holding cell. Measurments were made in benzene solution at 25.0–0.1 °C with a range of 0.00050 to 0.00350 weight fraction of the solute. Refractive indices of the solutions were measured with an Abbe refractometer, which was maintained at 25 °C. Infrared spectra were obtained with a Beckman IR 4230 infrared spectrophotometer. NMR spectra were obtained using a Varian XLA 400-MHz spectrometer.

Table III. Summary of Crystal Structure Data

formula: $C_6H_{10}N_2O_3$
formula weight: 158.16
Z: 158.16
crystal size, (mm): 0.48 × 0.40 × 0.35
crystal system: monoclinic
space group: $P2_1/C$
unit cell parameters: a = 6.794 (1) Å, b = 9.426 (1) Å, c = 11.775 (1) Å, β = 101.32 (1)°
density, calculated: 1.42 g/cm^3
total data measured to θ_{max} of 50°: 1485
unique data: 1391
data with $I > 3\sigma(I)$: 1122

X-ray data collection and structure determination crystallographic data are summarized in Table III. Diffraction experiments were performed on an Enraf-Nonius CAD4 diffractometer at −120 °C with graphite-monochromated Mo Kα radiation (λ = 0.71063 Å). Lattice parameters were determined by the least-squares techniques applied to setting angles of 25 reflections. The intensities of four standard reflections were measured every 3 h of X-ray exposure showing no significant changes.

All calculations were carried out on a VAX 11/730 computer using the TEXAN crystallographic software.[17] The structure was solved by direct methods (MITHRIL).[18] Full-matrix least-squares refinement with anisotropic temperature factors for all nonhydrogen atoms yielded the final R of 0.033 (R_W = 0.047). All hydrogen atoms were located on difference Fourier maps and refined with isotropic temperature factors. The goodness-of-fit was 1.57. The final difference map was featureless with the highest peak of 0.25 e/Å^3.

The analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Synthesis of β-Nitro Enamines. The following β-nitro enamines were synthesized by using the technique of Faulques, Rene, and Royer:[19]

1-(*N*,*N*-Dimethylamino)-2-nitroethene: mp 108 °C (lit.[20] mp 105 °C).

1-(*N*-Morpholino)-2-nitroethene: mp 141–142 °C (lit.[21] mp 140–141 °C); ν_{max}^{Nujol} 1622 cm^{-1}.

1-(*N*-Pyrrolidino)-2-nitroethene: mp 82–84 °C (lit.[22] mp 77–78 °C).

1-(*N*-Methylanilino)-2-nitroethene: mp 93–94 °C (lit.[23] mp 91–92 °C); ν_{max}^{Nujol} 1624 cm^{-1}; ^{1}H NMR (benzene-d_6) δ 6.38 (d, J = 11.0 Hz, 1 H), 7.50 (d, J = 11.0 Hz, 1 H).

1-(2,6-Dimethylmorpholino)-2-nitroethene: mp 151–152 °C. Anal. Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58. Found: C, 51.57; H, 7.75.

1-(*N*-Hexamethyleneimino)-2-nitroethene: mp 54–55 °C. Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29. Found: C, 56.55; H, 8.43.

1-(*N*-Ethylanilino)-2-nitroethene: mp 65–67 °C; ν_{max}^{Nujol} 1625 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29. Found: C, 61.56; H, 6.26.

1-(*N*,*N*-Dicyclohexylamino)-2-nitroethene: mp 173–174 °C; ^{1}H NMR (benzne-d_6) δ 6.81 (d, J = 11.2 Hz, 1 H), 8.20 (d, J = 11.2, 1 H). Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59. Found: C, 66.62; H, 9.57.

1-(*N*-Morpholino)-2-nitropropene: mp 96–98 °C.

1-(2,6-Dimethylmorpholino)-2-nitropropene: mp 122–123 °C. Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98; H, 8.06. Found: C, 54.03; H, 8.15.

1-(*N*-Piperidino)-2-nitroethene was produced by the method of Hurd and Serwood,[21] mp 95–96 °C (lit.[21] mp 95 °C); ν_{max}^{Nujol} 1620 cm^{-1}.

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Registry No. (*E*)-1-(*N*,*N*-Dimethylamino)-2-nitroethene, 73430-27-0; (*Z*)-1-(*N*,*N*-dimethylamino)-2-nitroethene, 87446-70-6; (*N*,*N*-dimethylamino)ethene, 5763-87-1; 1-(*N*-pyrrolidino)cyclopentene, 7148-07-4; 1-(*N*-pyrrolidino)cyclohexane, 1125-99-1; 1-(*N*-morpholino)cyclopentane, 936-52-7; 1-(*N*-hexamethyleneimino)cyclopentane, 7374-91-6; 1-(*N*-morpholino)-2-nitroethene, 101419-83-4; 1-(*N*-morpholino)-2-nitropropene, 102631-85-6; 1-(2,6-dimethylmorpholino)-2-nitroethene, 119656-36-9; 1-(2,6-dimethylmorpholino)-2-nitropropene, 119656-37-0; 1-(*N*-methylanilino)-2-nitroethane, 61404-93-1; 1-(*N*-ethylanilino)-2-nitroethene, 99068-20-9.

Supplementary Material Available: Complete crystallographic data for 1-(*N*-morpholino)-2-nitroethene (positional parameters, bond lengths, bond angles, and dihedral angles) (5 pages). Ordering information is given on any current masthead page.

Observations on the Reactions of Chiral Pyruvates. Synthesis of (-)- and (+)-Citramalic Acid

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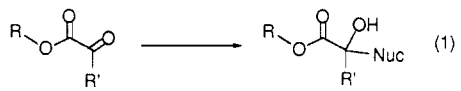
In 1983 we reported on the reduction, nucleophilic addition, and ene reactions (eq 1) of α-keto esters derived from 8-phenylmenthol (**1**)[1] (Figure 1). Unfortunately, the report of an ene reaction between the pyruvate ester and 1-hexene in the presence of $SnCl_4$ was in error as in fact the main products from that reaction appear to be those resulting from aldol reaction–condensation of the pyruvate with itself. Use of other Lewis acids ($EtAlCl_2$, $AlCl_3$, BF_3)



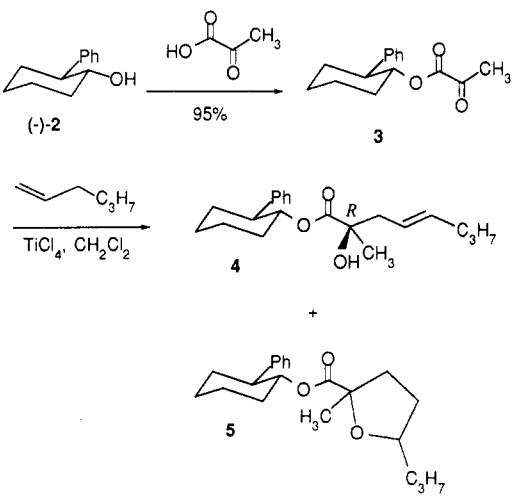
(1)

did not result in significant ene reaction. Apparently, the rate of proton loss from the complex of the pyruvate and the Lewis acid is faster than the addition of the alkene, and the addition of this enol derivative to the complex is faster yet.

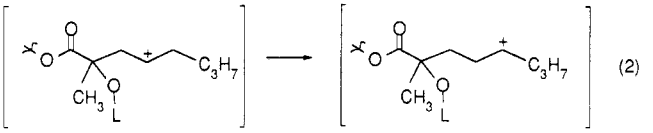
On the other hand, we have found that the corresponding keto esters derived from *trans*-2-phenylcyclohexanol (**2**)[2] undergo ene reactions with good to excellent levels of stereochemical control.[3] Thus, reaction of the pyruvate ester of *trans*-2-phenylcyclohexanol (**3**) with 1-hexene in the presence of $TiCl_4$ afforded adduct **4** with acceptable chemical yield and level of stereochemical control (Scheme I). Interestingly, and in contrast to reaction with the corresponding glyoxylate esters,[4] 2 equiv of the Lewis acid are required—use of only 1 equiv resulted

Figure 1.

Scheme I



in no reaction. Significant amounts of a cyclic product (**5**) were also formed.[5] Optimum conditions for stereochemical control (extended time at low temperature) were also those that afforded the poorest ratio of **4** to **5** (Table I). Presumably, an initially formed cation intermediate suffers 1,2-hydrogen shift to form a regioisomeric cation that is captured internally by oxygen (eq 2) in competition with proton loss to form the adduct **4**. On the other hand, the



(2)

reaction between the pyruvate ester **3** (derived from (–)-**2**) and 3-(trimethylsilyl)-1-propene in the presence of tin tetrachloride at −78 °C afforded the adduct as a single diastereomer (de greater than 99⁺%) (Scheme II). As in the reaction with 1-hexene, a small quantity (<5%) of a cyclic byproduct (**7**), presumably resulting from 1,2-shift of the silyl group in an intermediate cation, was also obtained.[5]

Conversion of adduct **6** to citramalic acid[6] illustrates the potential of this method for stereochemical control and, as well, provided an avenue by which the *absolute* sense of stereochemical direction could be readily determined. Thus, oxidation of the alkene linkage in **6** with potassium permanganate/sodium periodate[13] afforded the ester–acid

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(3) In contrast to the high level of stereochemical control observed in the reaction with alkenes, reaction of **3** with allyl magnesium bromide afforded both diastereomers of **6** with little selectivity (1.3:1).

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(5) Neither the proton nor the carbon NMR spectra are of significant use in assigning the relative stereochemistry within the tetrahydrofuranyl rings of byproducts **5** and **7** as one of the centers in this five-membered ring is quaternary.

(6) Enantiomerically pure citramalic acid is available as a microbial metabolite[7] and has been synthesized previously with good to excellent control of absolute stereochemistry. A number of syntheses of this acid have been reported,[8-13] where Eliel's synthesis[11] of both enantiomers of dimethyl 2-acetyl citramalate in 96% ee represents the highest level of control in setting absolute stereochemistry and Wynberg's[10] potentially the most practical because of its application of catalytic asymmetric induction.

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