benzonitrile (**2j**) in the GLC yields of 88% for NaCl, ca. 100% for NaBr, 88% for NaI, and 73% for Et_4NOTs.

Electrochemical Formation of Isoxazolines 4a and 4f. Into an undivided cell equipped with two platinum electrodes (2 cm × 2 cm) and a magnetic stirring bar was placed a solution of methanol (30 mL) containing aldoxime **1a** or **1f** (6 mmol), styrene (60 mmol), and sodium iodide (3 mmol). Electrochemical reaction was carried out under the condition of constant current (0.025 A/cm^2) at room temperature. After the electricity of 5–6 F/mol was passed, the usual workup gave isoxazolines **4a** and **4f**[16] in the yields of 56% and 34%, respectively.

3-Hexyl-5-phenyl-2-isoxazoline (4a): ^{1}H NMR (CCl_4) δ 0.85 (br t, 3 H, J = 5 Hz), 1.05–1.60 (m, 8 H), 2.23 (br t, 2 H, J = 7 Hz), 2.63 (dd, 1 H, J = 16 and 8 Hz), 3.20 (dd, 1 H, J = 16 and 10 Hz), 5.27 (dd, 1 H, J = 10 and 8 Hz), 7.11 (s, 5 H); IR (neat) 3065, 3040, 2960, 2930, 1625, 1609, 1500, 1460, 875, 760, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.73; H, 9.33; N, 6.29.

3,5-Diphenyl-2-isoxazoline (4f): ^{1}H NMR ($CDCl_3$) δ 3.18 (dd, 1 H, J = 16 and 9 Hz), 3.69 (dd, 1 H, J = 16 and 11 Hz), 5.58 (dd, 1 H, J = 11 and 9 Hz), 7.11–7.67 (m, 5 H), 7.25 (s, 5 H); IR (KBr) 3075, 3050, 2800, 1603, 1576, 1503, 1459, 1371, 1360, 935, 905, 870, 759, 701, 695 cm^{-1}; mp (from CCl_4) 71–73 °C (lit.[16] 76 °C). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.66; H, 5.79; N, 6.12.

Acknowledgment. One of us (Y.M.) thanks the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for Scientific Research on Priority Area 1 (62607001 and 63607001).

Registry No. **1a**, 629-31-2; **1b**, 13372-74-2; **1c**, 4715-11-1; **1d**, 59647-78-8; **1e**, 1197-50-8; **1f**, 100-52-7; **1g**, 104-88-1; **1h**, 104-87-0; **1i**, 123-11-5; **1j**, 487-68-3; **2a**, 629-08-3; **2b**, 1975-78-6; **2c**, 766-05-2; **2d**, 1823-91-2; **2e**, 645-59-0; **2f**, 100-47-0; **2g**, 623-03-0; **2h**, 104-85-8; **2i**, 874-90-8; **2j**, 2571-52-0; **3j**, 2904-57-6; **4a**, 119656-89-2; **4f**, 4894-23-9; NaCl, 7647-14-5; NaBr, 7647-15-6; NaI, 7681-82-5; Et_4NOTs, 733-44-8; $LiClO_4$, 7791-03-9; methanol, 67-56-1.

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An Enantioselective Synthesis of D-(−)-2-Amino-5-phosphonopentanoic Acid

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As a part of our program aimed at the synthesis of novel antagonists selective for the *N*-methyl-D-aspartic acid (NMDA) excitatory amino acid receptor subtype,[1] we had need for quantities of the NMDA selective antagonist D-(−)-2-amino-5-phosphonopentanoic acid (**1**, D-(−)-AP5, Chart I).[2] Watkins reported the synthesis and pharmacological characterization of a series of ω-phosphono-α-amino acids and showed that the compound known as AP5 was the most potent of the series as an antagonist of NMDA-mediated neurotransmission.[2] Watkins also demonstrated that the antagonist activity of AP5 resided in the D-(−) isomer.[2] We recently reported an efficient large-scale synthesis of D,L-AP5[3] and would like to report here our results aimed at the first enantioselective synthesis of D-(−)-AP5.

(1) For a recent review of NMDA receptor function, see: *Trends Neurosci.* **1987**, *10*, 263–302.
(2) Evans, R. H.; Francis, A. A.; Jones, A. W.; Smith, D. A. S.; Watkins, J. C. *Br. J. Pharmacol.* **1982**, *75*, 65.
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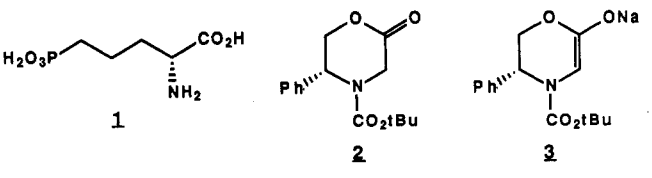
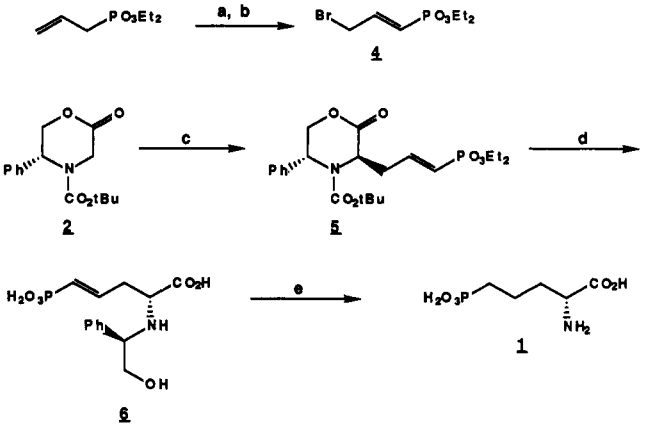
Chart I



Scheme I[a]



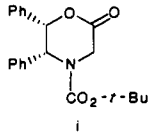
[a] (a) Br_2, CH_2Cl, 0 °C; (b) DBU, ether, 0 °C to room temperature; (c) i. $NaN(SiMe_3)_2$, THF, DME, −78 °C; ii. 4, THF, DME, −78 °C; (d) i. Me_3SiBr, CH_2Cl_2, room temperature; ii. 6 N HCl, room temperature; (e) H_2, 5% Pd/C, 55 °C, 60 psi.

The preparation of D- and L-AP5 by Watkins was achieved by resolution of the racemic mixture via the L-lysine salt.[2] This procedure was plagued by the inability to completely resolve the two enantiomers. We felt that the use of a chiral glycine synthon[4] would provide a more efficient means for preparation of the desired D-amino acid.

Dellaria[5] has recently reported on the preparation and use of the oxazinone **2** (Chart I) as a chiral glycine enolate synthon for the synthesis of amino acids via alkylation of the corresponding sodium enolate **3** (Chart I). We felt this method would be quite suitable to the preparation of D-(−)-AP5. The phenyl group of **2** is constrained to exist in a pseudoaxial conformation due to $A_{1,3}$ strain from the *tert*-butoxycarbonyl (BOC) protecting group on the nitrogen, therefore blocking the α-face of **3** and ensuring that alkylation occurs predominantly from the β-face of **3**. If we start with oxazinone **2** derived from D-phenylglycinol (as shown above) we will obtain the desired D isomer of AP5. Because alkylations with this enolate typically require more reactive alkylating agents, our synthesis of **1** necessitated the preparation of a suitably active reagent, e.g. the phosphono allylic bromide **4** (see Scheme I).

The synthesis of **1** was straightforward (see Scheme I). Treatment of diethyl allylphosphonate with bromine afforded the corresponding dibromide. This dibromide was not isolated but simply treated with DBU to provide the

(4) (a) Schollkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293 and references cited therein. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 2501 and references cited therein.
(5) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079. During the course of this work we also became aware of a structurally similar glycine enolate synthon i, that has also been used in alkylations. Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075.



i

cis and trans allylic and vinylic[6] bromides. The trans allylic isomer **4** can be isolated in 46% yield after preparative HPLC contaminated with only a small amount of the cis vinyl bromide. Observation of a 16.8-Hz coupling constant for the olefinic hydrogens confirmed the trans stereochemistry of **4** (see Experimental Section). The oxazinone **2** was metalated with sodium bis(trimethylsilyl)amide in THF/DME followed by addition of **4** (see Scheme I) to smoothly afford **5** in 60% yield after chromatography and recrystallization. HPLC analysis of the product showed >98% one diasteriomer.[7]

Dellaria demonstrated that it was necessary to open the oxazinone ring prior to hydrogenolysis of the chiral auxiliary, because approach of hydrogen to both faces of the ring is hindered by the phenyl and alkyl substituents.[5] We also needed to remove the BOC-protecting group as well as hydrolyze the phosphono esters. If we first removed the BOC group with trifluoroacetic acid in dichloromethane followed by dealkylative hydrolysis of the phosphono ester with bromotrimethylsilane and ring opening with aqueous hydrochloric acid, we found that about 30% epimerization had occurred. Epimerization was easy to detect because diasteriomeric products were readily distinguished in the ^{1}H NMR[8] spectrum. Successful ring opening and deprotection was achieved by treating **5** with bromotrimethylsilane to effect dealkylative hydrolysis of the diethyl phosphonate moiety followed by stirring overnight with 6 N aqueous HCl to provide the protected amino acid **6** (75%, as the hydrochloride salt). ^{1}H NMR analysis at this point showed that no epimerization had taken place. The desired amino acid **1** was revealed by hydrogenation of **6** to afford D-(−)-AP5 in 40% recrystallized yield from **5**. Compound **1** was homogeneous by ^{1}H NMR and elemental analyses and had a rotation[9] of $[\alpha]_D = -21.0°$ (c = 1, 6 N HCl).

It was difficult to compare the rotation of our synthetic material with that of the resolved material of Watkins[2] because these authors did not publish the concentrations that they used to determine their optical rotations (they reported a value of $[\alpha]_D = -18.4°$ [6 N HCl]). However, the signs of rotation were identical for Watkins and our material, so D-phenylglycinol did produce the correct stereochemistry for D-(−)-AP5. We are confident that both intermediates **5** and **6** were stereochemically homogeneous by ^{1}H NMR and/or HPLC analysis,[7] and Dellaria has already shown that no racemization occurs during hydrogenolysis of the chiral auxiliary, so the amino acid **1** derived from this synthesis should be of very high optical purity.

Experimental Section

All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium/benzophenone ketyl prior to use. All other solvents and reagents were used as obtained. ^{1}H and ^{13}C NMR spectra were obtained on a GE QE-300 spectrometer at 300.15 and 75.48 MHz, respectively, with tetramethylsilane as an internal standard. Coupling constants reported for ^{13}C NMR refer to ^{13}C–^{31}P couplings.

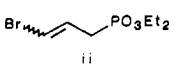
Diethyl ((*E*)-3-Bromoprop-1-en-1-yl)phosphonate (4). To a 0 °C solution of 35.75 g (0.20 mol) of diethyl allylphosphonate in 355 mL of dichloromethane was added dropwise 10.5 mL (32.7 g, 0.20 mol) of bromine over 20 min. After 1.5 h more at 0 °C, the mixture was concentrated in vacuo. The resulting oil was dissolved in 720 mL of ether and cooled to 0 °C, and then 31.0 mL (31.6 g, 0.21 mol) of DBU was added dropwise over 20 min. After addition, the mixture was warmed to room temperature and stirred an additional 2 h. To the mixture was added 300 mL of 1 N aqueous HCl, the organic layer was separated, and the aqueous layer was extracted twice with 100 mL each of ether. The combined organic extracts were washed with 300 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by preparative HPLC to afford 23.8 g (46%) of **4** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.79 (ddt, J = 20.5, 16.8, 6.7 Hz, 1 H), 5.91 (ddt, J = 18.3, 16.8, 1.2 Hz), 4.06 (quintet, J = 7.0 Hz, 4 H), 3.97 (dd, J = 6.7, 1.2 Hz, 2 H), 1.34 (t, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.5 (d, J = 6.0 Hz), 123.8 (d, J = 162.3 Hz), 62.0 (d, J = 6.0 Hz), 30.4 (d, J = 27.1 Hz), 16.3 (d, J = 6.0 Hz). Anal. Calcd for $C_7H_{14}BrO_3P$: C, 32.71; H, 5.49. Found: C, 32.51; H, 5.27.

(*E*)-3-(3-(Diethylphosphono)prop-2-en-1-yl)-4-(*tert*-butoxycarbonyl)-5-phenyl-2*H*-1,4-oxazin-2-one (5). To a −78 °C solution of 7.4 g (26.7 mmol) of **2** in 40 mL of DME and 15 mL of THF was added 25 mL (1.0 M in THF, 25 mmol) of sodium bis(trimethylsilyl)amide. After 30 min at −78 °C, 6.25 g (24.3 mmol) of **4** in 5 mL of THF was added in one portion via syringe (2 × 2.5 mL rinses with DME) and then stirred at −78 °C for 3.5 h. The mixture was quenched with 50 mL of 10% aqueous sodium bisulfate and extracted three times with 50 mL each of ether, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. The residue was purified by preparative HPLC to afford an oil, which solidified upon trituration with ether. Recrystallization from ether then afforded 6.6 g (60%) of **5**, mp 86–87 °C, $[\alpha]_D = -140.4°$ (c = 1, CH_2Cl_2).[9] HPLC analysis[7] of **5** shows one peak: IR ($CHCl_3$, cm^{-1}) 3000, 1755, 1695; ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 3 H), 7.08 (m, 2 H), 6.80 (ddt, J = 21.3, 17.2, 7.4 Hz, 1 H), 5.85 (dd, J = 19.8, 17.2 Hz, 1 H), 4.85–5.25 (m, 2 H), 4.77 (dd, J = 12.0, 2.9 Hz, 1 H), 4.45 (m, 1 H), 4.11 (quintet, J = 7.0 Hz, 2 H), 4.09 (quintet, J = 7.0 Hz, 2 H), 2.94 (m, 2 H), 1.34 (overlapping t, J = 7.0 Hz, 6 H), 1.10–1.60 (b s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.0, 153.4, 145.9, 139.4, 128.8, 127.7, 125.3, 123.2, 120.7, 81.6, 69.9, 61.8 (d, J = 8.3 Hz), 56.1, 54.4, 38.6, 27.9, 16.2 (d, J = 6.0 Hz). Anal. Calcd for $C_{22}H_{32}NO_7P$: C, 58.27; H, 7.11; N, 3.09. Found: C, 58.51; H, 6.86; N, 3.26.

(*E*)-*N*-(2-Hydroxy-1-phenyleth-1-yl)-5-phosphonopent-4-enoic Acid (6). To a room temperature solution of 5.0 g (10.9 mmol) of **5** in 40 mL of dichloromethane was added 8.7 mL (10 g, 65.6 mmol) of bromotrimethylsilane, and the mixture was left to stand for 4 h at room temperature and then concentrated in vacuo. To the residue was added 200 mL of 6 N aqueous hydrhloric acid, and the mixture was left to stand overnight at room temperature while becoming homogeneous. The resultant aqueous solution was extracted thrice with 50 mL each of ether, and then the aqueous layer was concentrated in vacuo. The residue was chromatographed on 100 mL of HP-20 (4-cm column), eluting with water and collecting 40 25-mL fractions. Fractions 3–30 (ninhydrin positive, UV active) were combined and concentrated in vacuo to afford 2.9 g (75%) of **6** as a hard foam: $[\alpha]_D = -43.9°$ (c = 1, 6 N HCl);[9] IR (KBr, cm^{-1}) 2000–3600, 1750; ^{1}H NMR (D_2O/DCl) δ 6.94 (s, 5 H), 5.93 (ddt, J = 22.1, 17.1, 7.0 Hz, 1 H), 5.48 (dd, J = 20.6, 17.1 Hz, 1 H), 4.01 (dd, J = 7.1, 5.5 Hz, 1 H), 3.64 (dd, J = 7.4, 5.3 Hz, 1 H), 3.58 (dd, J = 12.3, 7.4 Hz, 1 H), 3.49 (dd, J = 12.3, 5.3 Hz, 1 H), 2.25–2.50 (m, 2 H); ^{13}C NMR (D_2O/DCl) δ 169.5, 142.4, 130.6, 130.3, 129.3, 128.6, 123.7 (d, J = 181.2 Hz), 63.4, 61.5, 57.5, 32.9 (d, J = 24.2 Hz). Anal. Calcd for $C_{13}H_{20}NO_6P$: C, 44.65; H, 4.90; N, 4.01; Cl, 10.14. Found: C, 44.75; H, 5.18; N, 3.91; Cl, 10.23.

D-2-Amino-5-phosphonopentanoic Acid (1, D-AP5). A solution of 4.2 g of **6** in 96 mL of water was hydrogenated with 0.7 g of 5% Pd/C at 55 °C and 60 psi overnight. The resultant mixture was filtered through Celite and concentrated in vacuo. The residue was dissolved in 50 mL of water and extracted twice with 25 mL of dichloromethane and once with 25 mL of ether,

(6) While we believe that ^{1}H NMR evidence supports the obtention of vinylic bromides such as ii, we have not isolated and rigorously characterized these compounds.



ii

(7) HPLC with a 25 cm × 4.6 mm Spherisorb S10W 10 μm silica gel HPLC column (serial no. 10215), eluting with ethyl acetate at 1.5 mL/min, t_R for **5** = 7.22 min.

(8) For the diasteriomeric product of **6**, we observed a triplet at 3.92, believed to be one of the protons of the phenethanol substituent on nitrogen. This absorption is absent in pure samples of **6**.

(9) All rotations were determined at 33 °C.

and then the aqueous layer was concentrated in vacuo. The residue was dissolved in 10 mL of water and 50 mL of ethanol, treated with 2 mL of propylene oxide for 30 min at 50 °C (pH <1 to pH ~2-3), and then concentrated in vacuo. The residue was treated with 50 mL of ethanol, the ethanol was decanted, and then the residue was recrystallized from aqueous ethanol to afford 1.07 g (54%) of 1: mp 245-246 °C (foams); $[\alpha]_D$ = -21.0° (c = 1, 6 N HCl);[9] ^{1}H NMR (D_2O) δ 4.01 (t, J = 7.0 Hz, 1 H), 1.90-2.20 (m, 2 H), 1.60-1.90 (m, 4 H). Anal. Calcd for $C_5H_{12}NO_5P$: C, 30.47; H, 6.14; N, 7.11. Found: C, 30.67; H, 6.07; N, 6.90.

Acknowledgment. The author thanks the physical chemistry department for providing analytical and spectral data and D. Zimmerman for helpful discussions.

Determination of a New Sesquiterpene Skeleton through Selective INEPT Spectroscopy[1,2]

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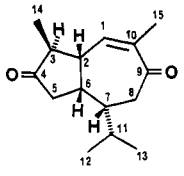
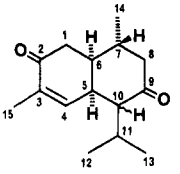
Eupatorium adenophorum Spreng. (Compositae), Saap maa, is native to the Chiang Mai Province of Thailand, and is claimed to be useful in traditional Thai medicine. Recently, the binominal name for this plant has been changed to *Ageratina adenophora* (Spreng.) R. King and H. Robinson.[4] According to *A Geographical Atlas of World Weeds*, the *Ageratina adenophora* (Spreng.) R. King and H. Robinson is synonymous with *Eupatorium adenophorum* Spreng.[5] Previous phytochemical study on this plant reported the isolation[6] of a cadinane-type sesquiterpene 9-oxoageraphorone (**2**), which was also obtained together with its epimer **3** from *Eupatorium trapezoideum* Kunth,[7] subsequently renamed as *Ageratina trapezoidea* (Kunth) R. King and H. Robinson.



1



2 10-H α
3 10-H β

We report here on the isolation and structure elucidation of eupatorenone (**1**), the first representative of a new bicyclic sesquiterpene skeleton,[8] which was obtained by chromatographic separation of the petroleum ether soluble part of the ethanolic extract of the whole plant of *Eupatorium adenophorum*. Mass spectrometric analysis of eupatorenone (**1**), mp 66-67 °C, $[\alpha]_D$ +72.2° (MeOH, c 1.3), indicated a molecular ion at m/z 234, corresponding to an elemental composition $C_{15}H_{22}O_2$. Intense absorptions in the UV (MeOH) spectrum at λ_{max} 242 nm (log ε 3.86) and in the IR (KBr) spectrum at ν_{max} 1725, 1710, and 1605 cm^{-1} suggested the presence of both saturated and α,β-unsaturated ketonic groups. The ^{1}H NMR spectrum of eupatorenone, obtained in $CDCl_3$ (Table I), indicated the presence of an olefinic hydrogen (δ 6.35, d, J = 1.5 Hz), both allylic (δ 1.73, d, J = 1.5 Hz) and aliphatic (δ 1.02, d, J = 6.4 Hz) methyl groups, and an isopropyl group (δ 0.88, d, J = 6.1 Hz; 1.08, d, J = 6.1 Hz; 2.00, m). Two geminally coupled methylene groups (δ 2.08, 2.20, J_{gem} = 8.8 Hz; and δ 2.54, 2.81, J_{gem} = 16.6 Hz) were also observed in the molecule.

From the structural elements found, two types of bicyclic sesquiterpene structures could be proposed for eupatorenone; either a condensed cyclopentanone-cycloheptenone structure (**1**) or a cadinene skeleton comprised of a cyclohexanone and a cyclohexenone unit. Two isomeric sesquiterpenes with the latter skeleton, cadinanes **2** and **3**, have already been isolated from *Eupatorium trapezoidum* Kunth (syn. *Adenophora trapezoidea* (Kunth) R. King and H. Robinson), and their structures have been established by a combination of spectroscopic and chemical correlation studies, together with X-ray analysis of a derivative.[8] The IR and ^{1}H and ^{13}C NMR spectral data of eupatorenone differ in numerous ways from the corresponding reported values for cadinanes **2** and **3**. The highest wavenumber for carbonyl absorption in the IR spectrum of **2** and **3** is 1700-1705 cm^{-1} versus 1725 cm^{-1} for eupatorenone. The ^{1}H NMR spectrum in $CDCl_3$ of **3** exhibits three overlapping methyl groups at δ 0.90 and a fourth methyl group at δ 1.60, whereas the corresponding values of eupatorenone are δ 0.88, 1.02, 1.08, and 1.73. In the ^{13}C NMR spectrum of **2**, two doublets and two triplets were reported at δ 45.2, 50.3 and δ 23.3, 33.3, respectively. The ^{13}C NMR spectrum of eupatorenone, however, shows two doublets at δ 28.1 and 39.24 and two triplets at δ 41.04 and 45.80. The reported α_D values for cadinanes **2** and **3** are +156° and +72.2°, respectively, whereas the α_D value of eupatorenone is +72.2°.

On the basis of the above listed spectroscopic differences, we perceived that eupatorenone could not be characterized by a cadinane structure such as as **2** or **3**, where structure elucidation had been performed by reliable chemical derivatization and X-ray crystallography.[7] Therefore, from the structural elements present and the coupling pattern of the homonuclear COSY spectrum (measured either in $CDCl_3$ or in pyridine-d_5), an unsaturated azulene skeleton was suggested for eupatorenone. The presence of a five-membered ring ketone explains the higher wavenumber carbonyl absorption of eupatorenone than that of cadinanes **2** and **3**. Optimum resolution of the ^{1}H NMR signals was achieved in pyridine-d_5 and in $CDCl_3$, with C_6D_6 yielding minimal signal dispersion (Table I). The ^{1}H-^{1}H COSY spectrum indicated a long-range coupling between the allylic methyl protons (δ 1.73) and the vinyl hydrogen 1-H (δ 6.35), which itself was coupled to the anellated methine, 2-H (δ 3.22). From the relatively small (>4 Hz) coupling between 2-H and 6-H (δ 2.28) a cis junction between the five- and seven-membered rings was indicated. An additional small coupling (>1 Hz), observed

(1) Traditional Medicinal Plants of Thailand. 14.
(2) Part 13. See: Meksuriyan, D.; Cordell, G. A. *J. Sci. Soc. Thailand* **1988**, *14*, 3.
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(8) For recent comprehensive reviews on natural sesquiterpenes, see: Roberts, J. S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105. Fraga, B. M. *Nat. Prod. Rep.* **1985**, *2*, 147; **1986**, *3*, 273.

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