via syringe and the resulting *n*-butyltrimethylstannane determined quantitatively by GLPC; the calculated concentration of Me₃SnNa was 0.59 M, indicating no significant reaction with DCPH.

(c) Reaction of DCPH with 2-Bromooctane. To 3 mmol of DCPH under argon was added 0.4 mmol of 2-bromooctane in 1 mL of THF at ice–water temperature. After 15 min 1.4 mL of 0.60 M (0.8 mmol) (trimethylstannyl)sodium was added, and the yields of trimethyl-2-octylstannane and C₈ hydrocarbons were determined. In a number of experiments, the combined yields of stannane and C₈ were the same within ±2% as those obtained in the absence of DCPH.

(d) Reaction of Dicyclohexylphosphine with 2-Bromooctane in the Presence of (Trimethylstannyl)sodium. (Trimethylstannyl)sodium (0.021 mmol) was added under argon to a solution of 0.140 mmol of 2-bromo-octane and 1.70 mmol of dicyclohexylphosphine at 0 °C. After 4 h the mixture was analyzed by GLC and found to contain 0.019 mmol of octane.

In a similar experiment (trimethylstannyl)sodium (0.063 mmol) was added to 0.0160 g (0.125 mmol) of nonane (internal standard), 0.0272 g (0.141 mmol) of 2-bromooctane, and 0.337 g (1.70 mmol) of dicyclohexylphosphine in 1.5 mL of dry THF under argon. After 4 h at 0 °C the mixture was analyzed by GLC and found to contain 0.060 mmol of octane.

(e) (Trimethylstannyl)sodium as Initiator in the Reaction of 2-Bromooctane with Trimethylstannane. Reaction of Trimethylstannane with 2-Bromooctane. Trimethylstannane (0.20 g; 1.21 mmol) was added to 0.0313 g (0.244 mmol) of nonane (internal standard) and 0.0913 g (0.473 mmol) of 2-bromooctane in 3.0 mL of dry THF under argon. The vial was cooled to 0 °C for 40 min. GLC analysis indicated reaction of

0.043 mmol of bromide and the formation of 0.042 mmol of octane.

Reaction of Trimethylstannane with 2-Bromooctane in the Presence of (Trimethylstannyl)sodium. To a solution of 0.50 mmol of 2-bromooctane and 1.20 mmol of trimethylstannane at 0 °C was added under argon 0.05 mmol of (trimethylstannyl)sodium in THF. After 40 min the mixture was analyzed by GLC and found to contain 0.34 mmol of octane and less than 1% trimethyl-2-octylstannane; 0.35 mmol of 2-bromooctane had reacted.

A similar experiment to the above in which 100% excess (1.0 mmol) of (trimethylstannyl)sodium was added to a solution of 2-bromooctane (0.50 mmol) and trimethylstannane (1.0 M) resulted in the immediate consumption of 2-bromooctane and the formation of 94% octane and 2.5% trimethyl-2-octylstannane.

(Trimethylstannyl)alkalies in Mixed Solvents. Preparations in 80% benzene/20% THF have been described previously.[17b] Solutions in 80% ethyl ether/20% THF were prepared by adding 5.0 g (15 mmol) of (Me₃Sn)₂ and 40 mmol of the metal to 20 mL of a 50/50 (v/v) mixture of ether/THF in a flame-dried flask in an argon atmosphere. The mixture was stirred vigorously for 6–8 h at 0 °C and diluted with 30 mL of ether. The resultant slurry was centrifuged. The supernatant of Me₃SnLi was clear with a slight brownish cast; those from Me₃SnNa and Me₃SnK were deeper in color. Reactions of aliquants with 1-bromobutane followed by GLPC determination of the 1-butyltrimethylstannane formed indicated yields of 70–85%.

Absolute Stereochemistry of (+)-1,8a-Dihydro-3,8-dimethylazulene, a Labile Biosynthetic Intermediate for 1,4-Dimethylazulene. Determination by Theoretical Calculation of CD Spectra and Verification by Synthesis of Model Compounds

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Contribution from the Chemical Research Institute of Nonaqueous Solutions, Tohoku University, 2-1-1 Katahira, Sendai 980, Japan, the Institute for Molecular Science, Okazaki National Research Institutes, Myodaiji, Okazaki 444, Japan, the Department of Chemistry, Columbia University, New York, New York 10027, and the Suntory Institute for Bioorganic Research, Shimamoto-cho, Mishima-gun, Osaka 618, Japan. Received April 23, 1984

Abstract: The absolute stereochemistry of (+)-1,8a-dihydro-3,8-dimethylazulene (**1**), a labile trinorsesquiterpenoid biosynthetic intermediate for 1,4-dimethylazulene (**2**), isolated from the liverwort *Calypogeia granulata* Inoue, was determined to be 8a*S* by theoretical calculation of CD spectra; the labile biosynthetic intermediate **1** with a unique 1,8a-dihydroazulene skeleton shows very intense optical rotation, [α]_D +1165°, and CD Cotton effects, λ_ext 314.0 nm, Δε +19.7 and λ_ext 235.2 nm, Δε −47.4, suggesting a strongly distorted conjugated tetraene system. On the basis of the π-electron framework approximation, the CD curve of (8a*R*)-1,8a-dihydroazulene (**5**) was calculated by the SCF–CI–dipole velocity MO method. The resultant calculated CD Cotton effects, λ_ext 313 nm, Δε −13.9 and λ_ext 219 nm, Δε +46.2, were opposite in sign to those of the natural product **1**. Accordingly, the absolute stereochemistry of the labile biosynthetic intermediate (+)-**1** was theoretically determined to be 8a*S*. The conclusion was experimentally proved by the synthesis of model compounds (1*S*,8a*S*)-(+)-1,8a-dihydro-1-methoxy-8a-methylazulene (**7**) and (1*S*,8a*S*)-(+)-1,8a-dihydro-1-methoxy-6,8a-dimethylazulene (**8**) as follows. Compounds **7** and **8** were synthesized starting from optically pure Wieland–Miescher ketone (*S*)-(+)-(**9**), [α]_D +98.5°, via reactions of 15 steps, respectively. The product **7**, bp 35–45 °C (0.067 kPa) and [α]_D +393.3°, shows CD Cotton effects, λ_ext 321.0 nm, Δε +5.7 and λ_ext 221.3 nm, Δε −24.5, which are similar, in both sign and shape, to those of the natural product **1**. Similarly, compound **8**, bp 60–70 °C (0.029 kPa) and [α]_D +323.8°, exhibits CD Cotton effects, λ_ext 318.6 nm, Δε +4.3 and λ_ext 220.7 nm, Δε −18.1. Therefore, by comparison of the CD spectrum of **1** with those of the model compounds, it was experimentally proved that the natural dextrorotatory 1,8a-dihydro-3,8-dimethylazulene (**1**) had 8a*S* absolute configuration.

Recently much attention has been focused on the chemistry of trinorsesquiterpenes with a 1,4-dimethylazulene skeleton, iso-

lated from the sources of marine soft corals or liverworts.[2–7] One of us first isolated chiroptically active 1,8a-dihydro-3,8-di-
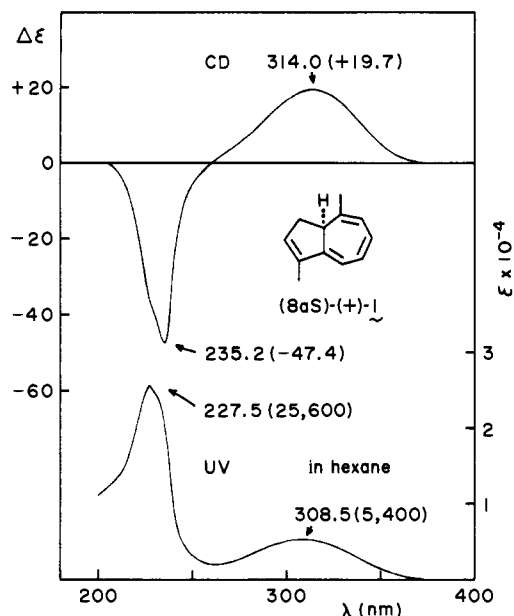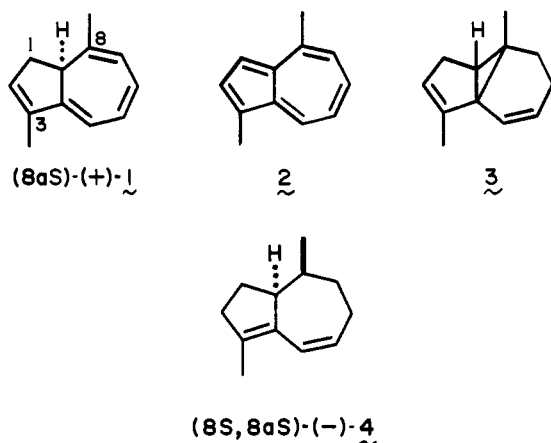
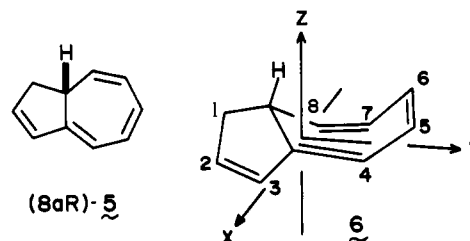**Figure 1.** CD and UV spectra of naturally occurring (8aS)-(+)-1,8a-dihydro-3,8-dimethylazulene (1) in hexane.

methylazulene (1) from the cell culture of the liverwort *Calypogeia granulata* Inoue, as a labile trinorsesquiterpenoid biosynthetic intermediate for 1,4-dimethylazulene (2).[2] The absolute stere-

ochemistry of the labile intermediate is quite interesting from the standpoint of biosynthesis of trinorsesquiterpenes with a 1,4-dimethylazulene skeleton. In fact, trinoranastreptene[3] (3; or inflatene,[6] or clavukerin B[7]), a probable biosynthetic precursor of 1, was isolated from the same liverwort[3] and also from marine soft corals.[6,7] Furthermore, Kitagawa and co-workers recently clarified the absolute structure of clavukerin A (4), a trinorsesquiterpene isolated from a marine soft coral, to be (8S,8aS)-(-)-3,8-dimethyl-1,2,6,7,8,8a-hexahydroazulene.[4] Since the π-electron system of compound 1 consists of a distorted conjugated polyene chromophore, the problem of the absolute configuration is also interesting from the theoretical viewpoint. However, the absolute configuration of 1 has remained undetermined because of its extreme instability and limited amounts of the sample available. In the following, we report the absolute

(1) (a) Tohoku University. (b) Okazaki National Research Institutes. (c) Columbia University. (d) Suntory Institute for Bioorganic Research.

(2) Takeda, R.; Katoh, K. *J. Am. Chem. Soc.* **1983**, *105*, 4056.

(3) Takeda, R.; Katoh, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1265.

(4) Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 2160.

(5) Bowden, B. F.; Coll, J. C.; Tapiolas, D. M. *Aust. J. Chem.* **1983**, *36*, 211.

(6) Izac, R. R.; Fenical, W.; Wright, J. M. *Tetrahedron Lett.* **1984**, *25*, 1325.

(7) Kobayashi, M.; Son, B. W.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 1667.

stereochemistry of the intermediate 1 as determined by the theoretical calculation of CD spectra. In addition, we also describe the experimental verification of the absolute configuration of 1 by the synthesis of model compounds.

The labile intermediate 1 with a unique 1,8a-dihydroazulene skeleton shows the very intense chiroptical activity, $[\alpha]_D$ +1165°, and intense CD Cotton effects[8] as shown in Figure 1, suggesting a strongly distorted conjugated tetraene system. Therefore, it is reasonable to consider that the chiroptical activity of 1 is mainly due to the distortion of the π-electron chromophore. In order to theoretically determine the absolute configuration of 1, we performed the calculation of the CD curve of 1,8a-dihydroazulene (5) on the basis of the π-electron framework approximation, using the SCF–CI–dipole velocity MO method. The absolute con-

figuration of 5 was arbitrarily chosen to be 8aR for the calculation. The molecule has a very rigid skeleton, in which the triene part of a seven-membered ring is almost symmetrical, when reflected through the *yz* plane, as shown in 6. Therefore, it is also reasonable to consider that conjugation of the triene part with the additional double bond in a five-membered ring generates the chiroptical activity.

Methods of Calculation

Molecular Structure. The Cartesian coordinate system for the molecular structure of (8aR)-5 was adopted as shown in 6. The molecule 5 has the following stereochemical features; the 1,8a-dihydroazulene ring skeleton is conformationally very rigid. The triene part (carbon atoms 3a–4–5–6–7–8) of the seven-membered ring is almost symmetrical, when reflected through the *yz* plane. The additional double bond (2–3) in the five-membered ring is coplanar to the double bond (3a–4). On the basis of these characteristics, the coordinates of atoms were calculated by using standard bond lengths and angles: —C—C=, 1.510 Å; —C= C—, 1.370 Å; =C—C=, 1.460 Å. The dihedral angles θ in the groups 3a–4–5–6 and 5–6–7–8 were estimated to be about 40°, respectively.

Numerical Calculation of CD and UV Spectra. The rotational strength R_{ba} of CD spectra and the dipole strength D_{ba} of UV spectra were calculated by employing the following equations of the dipole velocity method[9,10]

$$R_{ba} = 2(\psi_a|\nabla|\psi_b)(\psi_a|r \times \nabla|\psi_b)\beta_M{}^2/(\pi\sigma_{ba}) \qquad (1)$$

$$D_{ba} = 2(\psi_a|\nabla|\psi_b)^2\beta_M{}^2/(\pi\sigma_{ba})^2 \qquad (2)$$

where ∇ is the del operator, r is a distance vector, β_M is the Bohr magneton, and σ_{ba} is the excitation wavenumber of the transition a → b. The z-axis component of the electric and magnetic transition moments are formulated respectively, as[9,10]

$$(\psi_a|\nabla|\psi_b)_z = \sum_{bonds} (C_{ra}C_{sb} - C_{sa}C_{rb})\langle\nabla_{rs}\rangle \cos Z_{rs} \qquad (3)$$

$$(\psi_a|r \times \nabla|\psi_b)_z =$$
$$\sum_{bonds} (C_{ra}C_{sb} - C_{sa}C_{rb})\langle\nabla_{rs}\rangle(X_{rs} \cos Y_{rs} - Y_{rs} \cos X_{rs}) \qquad (4)$$

$$\cos Z_{rs} = (Z_r - Z_s)/R_{rs} \qquad (5)$$

$$X_{rs} = (X_r + X_s)/2 \qquad (6)$$

(8) Reinvestigation of the CD spectrum gave smaller Δε values than those reported in ref 2.

(9) Kemp, C. M.; Mason, S. F. *Tetrahedron* **1966**, *22*, 629.

(10) Harada, N.; Nakanishi, K. "Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry"; University Science Books: Mill Valley, CA, 1983; p 406.
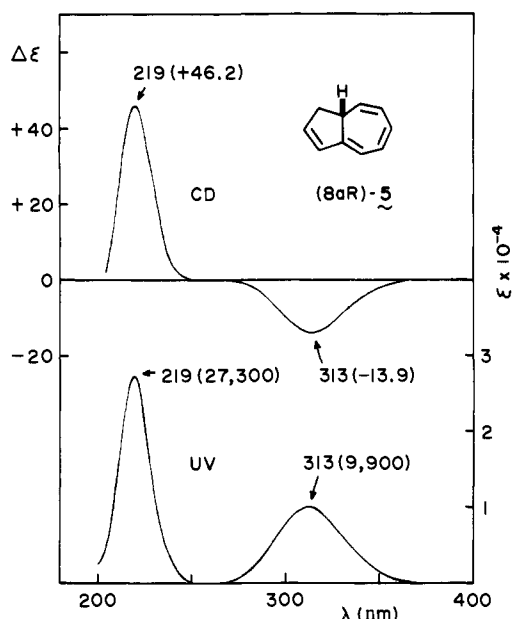
Figure 2. CD and UV curves of (8aR)-1,8a-dihydroazulene (5) calculated by the SCF-Cl-DV MO method.

where C_{ra} is the coefficient of atomic orbital r in the wave function ψ_a, $\langle\nabla_{rs}\rangle$ is the expectation value of a dipole velocity vector ∇_{rs} which is directed along the bond rs in the direction r → s, X_r, Y_r, and Z_r are the x, y, and z coordinates of an atom r, respectively, and R_{rs} is the interatomic distance between atoms r and s. In a similar way, the x and y components of the electric and magnetic transition moments were calculated.

In the π-electron SCF–CI MO calculation, configuration interactions between all singly excited states were included. The component CD and UV bands were approximated by the Gaussian distribution

$$\Delta\epsilon(\sigma) = \sum\Delta\epsilon_k \exp[-((\sigma - \sigma_k)/\Delta\sigma)^2] \qquad (7)$$

$$\epsilon(\sigma) = \sum\epsilon_k \exp[-((\sigma - \sigma_k)/\Delta\sigma)^2] \qquad (8)$$

where $2\Delta\sigma$ is the $1/e$ width of bands. The $\Delta\sigma$ value of 2500 cm^{-1} was adopted as a standard value.

In the MO calculation, the following standard values of atomic orbital parameters were employed: $W(C) = -11.42$ eV, (rr|rr) $= 10.84$ eV, $\beta(C-C, 1.388$ Å) $= -2.39$ eV, $\langle\nabla\rangle(C-C, 1.388$ Å) $= 4.701 \times 10^7$ cm^{-1}. The electric repulsion integral (rr|ss) was estimated by the Nishimoto–Mataga equation. The resonance integral and del value were calculated by employing the following equations, respectively

$$\beta = [S/S(C-C, 1.388 \text{ Å})]\beta(C-C, 1.388 \text{ Å}) \cos \theta \qquad (9)$$

$$\langle\nabla\rangle =$$
$$[\langle\nabla\rangle(\text{empir}, 1.388 \text{ Å})/\langle\nabla\rangle(\text{theor}, 1.388 \text{ Å})]\langle\nabla\rangle(\text{theor}) \cos \theta \qquad (10)$$

where θ is the dihedral angle. The values of overlap integral S and $\langle\nabla\rangle$(theor) were calculated based on the Slater orbitals.

Numerical calculations were carried out on the HITAC M-200H computer at the Computer Center of Institute for Molecular Science.

Results and Discussion

Theoretical Determination of Absolute Stereochemistry by Calculation of CD Spectra. The CD and UV curves theoretically calculated are illustrated in Figure 2. The UV spectrum curve exhibits two allowed π → π* absorption bands: λ_{max} 313 nm (ϵ 9900) and 219 nm (ϵ 27 300). The calculated values agree closely with the observed UV data of compound 1: λ_{max} 308.5 nm (ϵ 5400) and 227.5 nm (ϵ 25 600). The analysis of the calculation results clarified that the two absorption bands at 313 and 219 nm consist

of a single π → π* transition, respectively, and also revealed that, to a first approximation, the transition at 313 nm is polarized along the x axis, while the transition at 219 nm is along the y axis. Therefore, the absorption band at 219 nm is stronger than the band at 313 nm, because the π-electron region along the y axis is longer than that along the x axis. The values of the dipole strength calculated are $D = 12.6 \times 10^{-36}$ and 24.4×10^{-36} cgs units for the 313- and 219-nm transitions, respectively.

In the case of the CD curve calculated, the two transitions yielded negative and positive CD Cotton effects at longer and shorter wavelengths, respectively (Figure 2): λ_{ext} 313 nm ($\Delta\epsilon$ −13.9) and 219 nm ($\Delta\epsilon$ +46.2). These calculated values are in a good agreement with the observed data of compound 1, except for the sign of $\Delta\epsilon$ values (Figure 1): λ_{ext} 314.0 nm ($\Delta\epsilon$ +19.7) and 235.2 nm ($\Delta\epsilon$ −47.4). The observed CD curve of 1 shows a pattern characteristic of the 1,8a-dihydroazulene chromophore, as follows; the CD Cotton effect at longer wavelengths is weaker than that at shorter wavelengths, and the two Cotton effects are opposite in sign to each other. It is evident that the present CD spectral pattern characteristic of the 1,8a-dihydroazulene system was well reproduced by the calculation, when Figures 1 and 2 are compared with each other. The rotational strengths were calculated to be $R = -44.3 \times 10^{-40}$ and $+103.3 \times 10^{-40}$ cgs units for the 313- and 219-nm transitions, respectively.

The observed CD curve of compound 1 is almost a mirror image of the curve calculated for the model compound (8aR)-5, although the $\Delta\epsilon$ values are a little different from each other. Accordingly, the absolute stereochemistry of the labile biosynthetic intermediate (+)-1 was theoretically determined to be 8aS, as shown in structure 1. This conclusion was experimentally proved by the synthesis of model compounds, as described in the following. The present results imply that trinoranastreptene 3 has the same absolute configuration at the bridgehead position. It should be noted that naturally occurring compounds 1 and clavukerin A (4), partially hydrogenated azulene derivatives, have the same absolute configuration at the 8a position, regardless of the different sources.

Experimental Verification by Synthesis of Model Compounds. In order to verify the absolute configuration theoretically determined above, we performed synthesis of chiral model compounds, (1S,8aS)-(+)-1,8a-dihydro-1-methoxy-8a-methylazulene (7) and (1S,8aS)-(+)-1,8a-dihydro-1-methoxy-6,8a-dimethylazulene (8), starting from the optically active Wieland–Miescher ketone (S)-(+)-(9). These compounds were chosen as models for the
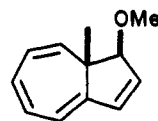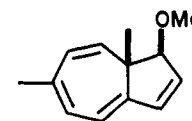
(1S,8aS)-(+)-7   (1S,8aS)-(+)-8
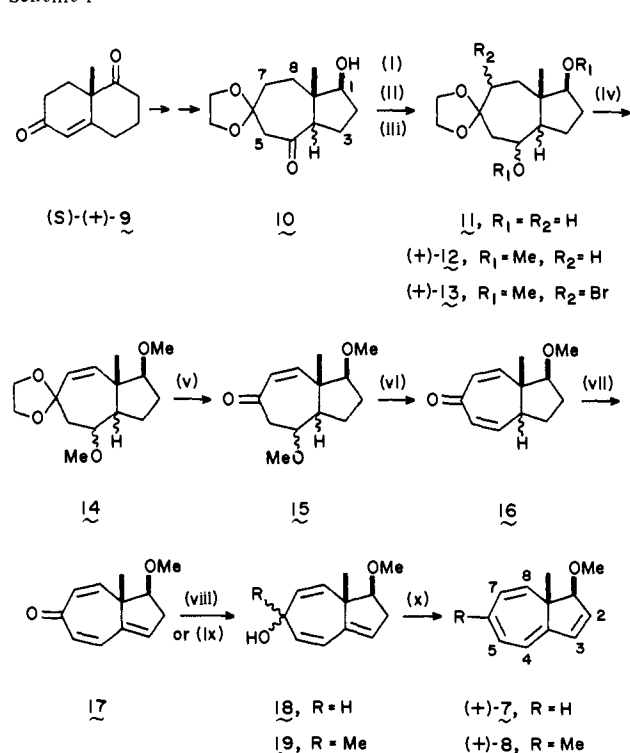
reason of the following advantages; they resist the oxidation to azulene, because the angular position 8a is blocked by a methyl group. In addition, the methoxy group makes the compounds less volatile, and hence the compounds can be easily handled.

According to the procedure reported by Heathcock et al.,[11] the optically pure Wieland–Miescher ketone[12] (S)-(+)-9, $[\alpha]_D$ +98.5° (c 1.0, benzene) was converted to compound 10 with a perhydroazulene nucleus (Scheme I). A mixture of trans and cis epimers of 10 was reduced to glycol 11 and derived to the dimethoxy compound 12; by recrystallization from ether, a single stereoisomer (+)-12 was obtained as a major product, $[\alpha]_D$ +60.8° (c 1.0021, CHCl$_3$). The stereochemistry of positions 3a and 4 in the major isomer was not investigated further, because the chirality of these positions vanishes in the final compounds 7 and 8. Bromination of (+)-12 with PyHBrBr$_2$ occurred at the C-7 position, exclusively; the position of the bromine atom in (+)-13 was determined on the basis of the ^{1}H NMR spectrum, in which

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(12) Gutzwiller, J.; Buchschacher, P.; Furst, A. *Synthesis* **1977**, 167.

Scheme 1[a]

(S)-(+)-9   10

11, R₁ = R₂ = H

(+)-12, R₁ = Me, R₂ = H

(+)-13, R₁ = Me, R₂ = Br

14   15   16

17   18, R = H   (+)-7, R = H

19, R = Me   (+)-8, R = Me

[a] Reagents: (i) LiAlH₄; (ii) NaH/Me₂SO, CH₃I; (iii) PyHBrBr₂; (iv) t-BuOK/Me₂SO; (v) HClO₄/ether; (vi) p-TsOH/benzene; (vii) DDQ/p-TsOH/benzene; (viii) LiAlH₄; (ix) CH₃Li; (x) I₂/benzene.

the C-7 hydrogen appeared as a doublet of a doublet. Dehydrobromination of 13 with t-BuOK gave the olefin 14. Successive deketalization and elimination of methanol afforded the cross dienone 16. Dehydrogenation of 16 with DDQ proceeded only when a catalytic amount of p-TsOH was employed; the trienone 17 was obtained in 50% yield.

Reduction of 17 with LiAlH₄ gave a mixture of two stereoisomeric alcohols 18, which were extremely unstable. Therefore, the alcohols 18 were immediately used for the next reaction. For the purpose of dehydration of 18, various reaction conditions were examined, and the condition employing iodine was finally found to afford the desired compound 7. When heated with a catalytic amount of iodine in benzene, the alcohols 18 were dehydrated, giving (1S,8aS)-(+)-7 in a good yield. Although the product 7 was relatively unstable, it could be distilled in vacuo to give a faintly yellow liquid: bp 35–45 °C (0.067 kPa); [α]_D +393.3° (c 0.11798, hexane). Methylation of the carbonyl group of 17 with methyllithium and subsequent dehydration with iodine in refluxing benzene gave (1S,8aS)-(+)-8: bp 60–70 °C (0.029 kPa); [α]_D +323.8° (c 0.20723, hexane). Since both of the dihydroazulenes 7 and 8 were unstable in neat, they were stored in a freezer as diluted hexane solutions. The structure of (+)-8 was secured by the 360-MHz ¹H NMR spectra, including two-dimensional spectra of shift correlation and difference NOE spectra; all hydrogens were fully assigned as described in the Experimental Section.

The CD and UV spectra of (1S,8aS)-(+)-7 are shown in Figure 3; the UV spectrum exhibits a π → π* band of medium intensity at 324.3 nm (ε6000) and an intense band at 223.2 nm (ε 23 700), which are characteristic of the 1,8a-dihydroazulene chromophore. In the region of these transitions, the CD spectrum shows a weak positive Cotton effect, λ_ext 321.0 nm (Δε +5.7), and an intense negative Cotton effect, λ_ext 221.3 nm (Δε −24.5). The other model compound (1S,8aS)-(+)-8 also shows similar CD and UV spectra, as shown in Figure 4. The CD curves of (1S,8aS)-(+)-7 and 8 are quite similar, in both sign and shape of Cotton effects, to that of dihydroazulene (+)-1. Therefore, it was experimentally proved that the natural dextrorotatory 1,8a-dihydro-3,8-dimethylazulene (1) had 8aS absolute configuration. The present
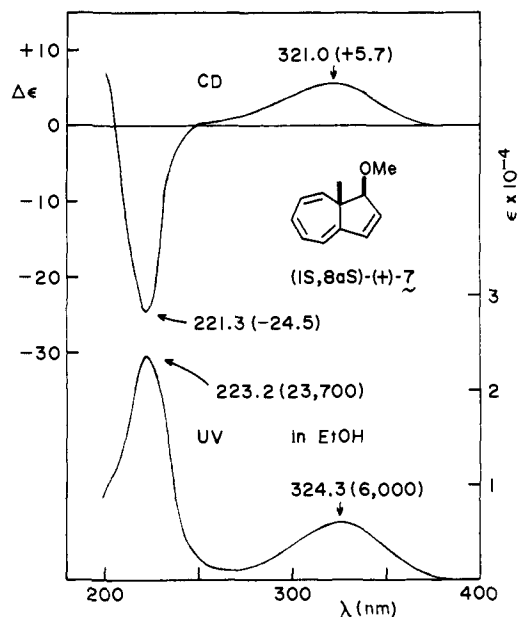

Figure 3. CD and UV spectra of (1S,8aS)-(+)-1,8a-dihydro-1-methoxy-8a-methylazulene (7) in ethanol.

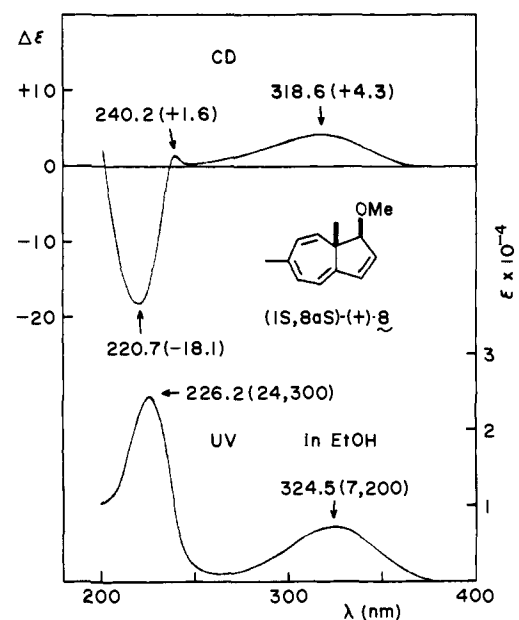**Figure 4.** CD and UV spectra of (1S,8aS)-(+)-1,8a-dihydro-1-methoxy-6,8a-dimethylazulene (8) in ethanol.

results thus verify the theoretical determination of the absolute configuration of (+)-1 discussed above.

There are differences in the Δε values between the natural and model compounds; the gap may be due to an extra chirality caused by the methoxy group and/or to the difference in substitution pattern of methyl groups. In fact, the methyl group at the C-6 position in compound 8 diminishes the Δε value, compared with the Δε value of compound 7. Furthermore, it seems likely that the replacement of a hydrogen in the angular position 8a by a methyl group changes the molecular geometry to some extent and hence affects the CD activity.

Concluding Remarks. The present studies clarified the absolute stereochemistry of (+)-1,8a-dihydro-3,8-dimethylazulene, a labile biosynthetic intermediate for 1,4-dimethylazulene, isolated from the liverwort *Calypogeia granulata* Inoue, by theoretical calculation of CD spectra and by synthesis of model compounds. The methodology employed here would be useful for the determination of absolute configuration and conformation of other distorted conjugated polyene systems.

1,8a-Dihydro-3,8-dimethylazulene

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Experimental Section

General Procedures. Melting points were taken on a Yamato capillary melting point apparatus and are uncorrected. IR spectra were obtained as solutions in CHCl₃ by using a Jasco A-3 or a Hitachi EPI-G2 spectrophotometer. ¹H NMR spectra were recorded on a Jeol PMX60 (60 MHz), a Jeol JNMPS-100 (100 MHz), or a Nicolet Model 293 (360 MHz) spectrometer, employing tetramethylsilane as an internal standard. Optical rotations [α]_D were determined on a Jasco DIP-4S spectropolarimeter. UV and CD spectra were obtained on a Jasco UVDEC-505 spectrophotometer and a Jasco J-400X spectropolarimeter, respectively. MS spectra were recorded on a Jeol JMS-DX300 spectrometer.

The following CD data are those of the extrema and zero line intersections.

Preparation of Optically Active (1S,3aξ,8aS)-2,3,3a,7,8,8a-Hexahydro-1-hydroxy-8a-methyl-4,6(1H,5H)-azulenedione 6-Ethylene Acetal (10). Following the procedure of Heathcock[11] for the synthesis of racemic ketone **10**, optically active compound (1S,3aξ,8aS)-**10**, was prepared starting from (8aS)-(+)-3,4,8,8a-tetrahydro-8a-methyl-1,6-(2H,7H)-naphthalenedione (**9**): mp 50.5–51.0 °C, [α]_D +98.5° (c 1.0, benzene) [lit.[12] mp 50–51 °C, [α]_D +100° (c 1.1, benzene)]. The followings are the data of optically active key compounds for the synthesis of compound **10**.

(4aS,5S)-(+)-5-(Acetyloxy)-4,4a,5,6,7,8-hexahydro-4a-methyl-2-(3H)-naphthalenone: mp 63 °C; ¹H NMR (100 MHz, CDCl₃) δ 1.24 (3 H, s, CH₃), 2.03 (3 H, s, COCH₃), 4.57 (1 H, dd, J = 10, 4 Hz, 5-H), 5.71 (1 H, s, 1-H); [α]_D +107.9° (c 1.003, CHCl₃); UV (EtOH) λ_max 234.9 nm (ε 16 200); CD (EtOH) λ_ext 322.2 nm (Δε –0.8), 269.0 (0.0), 236.0 (+7.4); MS, m/e 222 (parent). Anal. Calcd for C₁₃H₁₈O₃: C, 70.25; H, 8.16. Found: C, 70.66; H, 7.96.

(4aS,5S)-(−)-5-(Acetyloxy)-3,4,4a,5,6,7-hexahydro-4a-methyl-2-(1H)-naphthalenone Ethylene Acetal: mp 90–91 °C; ¹H NMR (100 MHz, CDCl₃) δ 1.17 (3 H, s, CH₃), 2.07 (3 H, s, COCH₃), 3.97 (4 H, s, acetal), 4.86 (1 H, dd, J = 9, 6 Hz, 5-H), 5.39 (1 H, m, W₁/₂ = 9 Hz, 8-H); [α]_D –36.6° (c 1.000, CHCl₃); MS, m/e 266 (parent). Anal. Calcd for C₁₅H₂₂O₄: C, 67.64; H, 8.33. Found: C, 67.54; H, 8.49.

(4aR,5S,8R,8aS)-(+)-5-(Acetyloxy)-3,4,4a,5,6,7,8,8a-octahydro-8,8a-dihydroxy-4a-methyl-2(1H)-naphthalenone Ethylene Acetal: mp 98 °C; ¹H NMR (60 MHz, CDCl₃) δ 1.17 (3 H, s, CH₃), 2.07 (3 H, s, COCH₃), 2.83 (1 H, br s, OH), 3.55 (1 H, m, W₁/₂ = 11 Hz, 8-H), 3.95 (4 H, s, acetal), 4.10 (1 H, br s, OH), 4.98 (1 H, m, W₁/₂ = 14 Hz, 5-H); [α]_D +14.5° (c 0.9997, CHCl₃). Anal. Calcd for C₁₅H₂₄O₆: C, 59.98; H, 8.05. Found: C, 60.42; H, 7.65.

(1S,3aξ,8aS)-2,3,3a,7,8,8a-Hexahydro-1-hydroxy-8a-methyl-4,6-(1H,5H)-azulenedione 6-Ethylene Acetal (10): ¹H NMR (100 MHz, CDCl₃) δ 0.70 (3 H, s, CH₃), 2.66 (2 H, s, 5-H), 3.10 (1 H, dd, J = 8, 8 Hz, 3a-H), 3.83 (1 H, dd, J = 10, 10 Hz, 1-H), 3.90 (4 H, br s, acetal).

(1S,3aξ,4ξ,8aS)-2,3,3a,4,5,7,8,8a-Octahydro-1,4-dihydroxy-8a-methyl-6(1H)-azulenone Ethylene Acetal (11). To a suspension of Li-AlH₄ (12.8 g, 0.337 mol) in dry ether (100 mL) and dry THF (20 mL) was added dropwise under nitrogen a solution of the ketone (1S,3aξ,8aS)-**10** (27.0 g, 0.112 mol) in dry ether (320 mL) and dry THF (95 mL). After being stirred at room temperature for 2 h, the reaction mixture was quenched with wet ether and ethyl acetate and then treated with a minimum amount of water to precipitate hydroxides. The organic layer was evaporated to dryness, giving 23.8 g (87%) of the glycol **11** as a syrup: IR (CHCl₃) ν_max 3600, 3460, 2950, 2880, 1115, 1060 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ 0.86 (3 H, s, CH₃), 3.3–4.3 (2 H, m, 1,4-H), 3.94 (4 H, s, acetal).

(1S,3aξ,4ξ,8aS)-(+)-2,3,3a,4,5,7,8,8a-Octahydro-1,4-dimethoxy-8a-methyl-6(1H)-azulenone Ethylene Acetal (12). A mixture of NaH (9.06 g, 0.377 mol) and dry Me₂SO (150 mL) was heated at 65 °C for 1 h. After the mixture was cooled to room temperature, a solution of the glycol **11** (22.8 g, 0.0941 mol) in dry THF (20 mL) and Me₂SO (45 mL) was added dropwise, during which time solid material of the sodium salt was formed. Iodomethane (46.8 mL, 106.8 g, 0.753 mol) was added dropwise under ice-cooling. The reaction mixture was stirred at room temperature overnight, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine and evaporated to dryness, giving 24.75 g (97%) of the dimethyl ether **12** as crystals. The ¹H NMR spectrum indicated that the product was a mixture of stereoisomers. The product was recrystallized from ether, affording 10.731 g of a major stereoisomer as needles. The mother liquor was subjected to chromatography on silica gel (hexane/EtOAc 5:1) giving an additional crop (4.859 g) of the major stereoisomer: total yield 15.591 g (61%); mp 102.2–103.2 °C; IR (CHCl₃) ν_max 2940, 1465, 1362, 1095 cm⁻¹; ¹H NMR (100 MHz, CDCl₃) δ 0.88 (3 H, s, CH₃), 1.1–2.2 (10 H, m), 2.47 (1 H, dd, J = 14.0, 9.2 Hz), 3.27 (3 H, s, OCH₃), 3.32 (3 H, s, OCH₃), 3.0–3.5 (2 H, m, 1,4-H), 3.94 (4 H, s, acetal); [α]_D +60.8° (c 1.0021, CHCl₃).

(1S,3aξ,4ξ,7ξ,8aS)-(+)-7-Bromo-2,3,3a,4,5,7,8,8a-octahydro-1,4-di-

methoxy-8a-methyl-6(1H)-azulenone Ethylene Acetal (13). To a solution of the major stereoisomer of the dimethyl ether (+)-**12** (5.0 g, 18.5 mmol) in dry THF (60 mL) was added, all at once, pyridinium hydrobromide perbromide (6.5 g, 20.3 mmol) at room temperature under nitrogen. Immediately, a white precipitate was formed. The mixture was stirred for 2 min, poured into aqueous NaHCO₃ solution, and extracted with ethyl acetate. The organic layer was washed with aqueous CuSO₄, water, and brine and evaporated to dryness. The crystalline residue was chromatographed on silica gel (hexane/EtOAc 2:1), giving 6.349 g (98%) of the bromide **13**. The analytical sample was obtained by recrystallization from ether: mp 102 °C (dec); IR (CHCl₃) ν_max 2980, 2830, 1176, 1095 cm⁻¹; ¹H NMR (100 MHz, CDCl₃) δ 0.88 (3 H, s, CH₃), 1.2–2.2 (7 H, m), 2.4–2.8 (2 H, m), 3.27 (3 H, s, OCH₃), 3.33 (3 H, s, OCH₃), 3.0–3.5 (2 H, m), 3.8–4.3 (4 H, m, acetal), 4.46 (1 H, dd, J = 12.5, 5.0 Hz, 7-H); [α]_D +49.6° (c 1.003, CHCl₃).

(1S,3aξ,4ξ,8aS)-2,3,3a,4,5,8a-Hexahydro-1,4-dimethoxy-8a-methyl-6(1H)-azulenone Ethylene Acetal (14). To a solution of the bromide (+)-**13** (5.127 g, 14.7 mmol) in dry Me₂SO (140 mL) was added potassium *tert*-butoxide (6.614 g, 58.9 mmol) under nitrogen. The reaction mixture was stirred at room temperature overnight, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with water and brine and evaporated to dryness. The residue was chromatographed on silica gel (hexane/EtOAc 3:1), affording 2.749 g (69.8%) of the olefin **14** as a crystalline solid material: ¹H NMR (60 MHz, CDCl₃) δ 0.97 (3 H, s, CH₃), 3.33 (6 H, s, OCH₃), 3.97 (4 H, br s, acetal), 5.47 (1 H, dd, J = 12.0, 1.9 Hz, 7-H), 5.97 (1 H, d, J = 12.0 Hz, 8-H).

(1S,3aξ,4ξ,8aS)-2,3,3a,4,5,8a-Hexahydro-1,4-dimethoxy-8a-methyl-6(1H)-azulenone (15). To a solution of the acetal **14** (2.749 g, 10.2 mmol) in ether (50 mL) was added, under nitrogen, ether (10 mL) saturated with aqueous 70% HClO₄. The reaction mixture was stirred at room temperature for 2 h, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with aqueous NaHCO₃, water, and brine and evaporated to dryness giving 2.293 g (99.8%) of the enone **15**: ¹H NMR (60 MHz, CDCl₃) δ 1.12 (3 H, s, CH₃), 3.34 (3 H, s, OCH₃), 3.37 (3 H, s, OCH₃), 5.90 (1 H, dd, J = 11.8, 1.6 Hz, 7-H), 6.68 (1 H, d, J = 11.8 Hz, 8-H).

(1S,3aξ,8aS)-2,3,3a,8a-Tetrahydro-1-methoxy-8a-methyl-6(1H)-azulenone (16). A mixture of the dimethyl ether **15** (2.293 g, 10.2 mmol) and 4-methylbenzenesulfonic acid (0.088 g, 0.51 mmol) in benzene (100 mL) was stirred at 30 °C for 4 h, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with aqueous NaHCO₃, water, and brine and evaporated to dryness. The residue was chromatographed on silica gel (hexane/EtOAc 5:1), affording 1.186 g (60.3%) of the dienone **16** as a syrup: IR (CHCl₃) ν_max 2975, 1645, 1605, 1123, 860 cm⁻¹; ¹H NMR (100 MHz, CDCl₃) δ 0.97 (3 H, s, CH₃), 3.38 (3 H, s, OCH₃), 5.96 (1 H, dd, J₇,₈ = 12.2, J₅,₇ = 1.7 Hz, 7-H), 6.04 (1 H, ddd, J₄,₅ = 16.5, J₃ₐ,₅ = 1.7, J₅,₇ = 1.7 Hz, 5-H), 6.32 (1 H, dd, J₄,₅ = 16.5, J₃ₐ,₄ = 2.4 Hz, 4-H), 6.73 (1 H, d, J₇,₈ = 12.2 Hz, 8-H); UV (EtOH) λ_max 238.5 nm (ε 9900); CD (EtOH) λ_ext 370.0 nm (Δε –0.93), 268.0 (–9.25), 224.5 (–3.42).

(1S,8aS)-1,8a-Dihydro-1-methoxy-8a-methyl-6(2H)-azulenone (17). A mixture of the dienone **16** (0.536 g, 2.79 mmol), DDQ (1.047 g, 4.61 mmol), and 4-methylbenzenesulfonic acid (0.074 g, 0.389 mmol) in dry benzene (100 mL) was stirred, under nitrogen, at 45–50 °C for 22 h. After being cooled to room temperature, the reaction mixture was chromatographed on silica gel (hexane/EtOAc 3:1). The crude product obtained was further purified by preparative LC on silica gel (hexane/EtOAc 3:1), affording 0.268 g (50.4%) of the trienone **17** as an oil: IR (CHCl₃) ν_max 2980, 2910, 1642, 1602, 1572, 1125, 1090 cm⁻¹; ¹H NMR (100 MHz, CDCl₃) δ 1.15 (3 H, s, CH₃), 2.27 (1 H, dd, J₂,₂ = 17.2, J₁,₂ = 8.3 Hz, 2-H), 2.77 (1 H, ddd, J₂,₂ = 17.2, J₁,₂ = 7.3, J₂,₃ = 3.8 Hz, 2-H), 3.46 (3 H, s, OCH₃), 3.92 (1 H, dd, J₁,₂ = 8.3, J₁,₂ = 7.3 Hz, 1-H), 6.01 (3 H, br d, 3,5,7-H), 6.48 (1 H, d, J₇,₈ = 13.5 Hz, 8-H), 6.77 (1 H, d, J₄,₅ = 13.5 Hz, 4-H); MS, m/e 190 (parent).

(1S,6ξ,8aS)-1,2,6,8a-Tetrahydro-1-methoxy-8a-methyl-6-azulenol (18). To a suspension of LiAlH₄ (0.040 g, 1.05 mmol) in dry ether (1 mL) was added dropwise a solution of the trienone **17** (0.094 g, 0.494 mmol) in dry ether (4.5 mL) at –60 °C under nitrogen. The reaction mixture was stirred for 1.5 h, quenched with wet ether, and treated with a minimum amount of water to precipitate hydroxides. The organic layer was evaporated, giving 0.078 g (82%) of the alcohol **18**: ¹H NMR (60 MHz, C₆D₆) δ 1.27 and 1.35 (3 H, s each, CH₃), 2.23 (2 H, m, 2-H), 3.13 (3 H, s, OCH₃), 3.70 (1 H, dd, J = 8, 8 Hz, 1-H), 5.0–6.1 (6 H, m). The ¹H NMR spectrum indicated that the product was a mixture of stereoisomers. Since the alcohol **18** was very unstable, the product was immediately used for the next reaction.

(1S,8aS)-(+)-1,8a-Dihydro-1-methoxy-8a-methylazulene (7). To a solution of the alcohol **18** (0.078 g, 0.41 mmol) in dry benzene (28 mL) was added a solution of iodine (0.0032 g, 0.013 mmol) in dry benzene

(1.5 mL). The mixture was vigorously refluxed for 2.5 h in an oil bath heated at 110 °C. After being cooled, the mixture was passed through a short silica gel column (hexane/EtOAc 5:1). The product obtained was further purified by preparative LC on silica gel (hexane/EtOAc 20:1), giving 0.047 g (66%) of the tetraene 7 as a faintly yellow oil. The analytical sample was obtained by distilling in vacuo: bp 35–45 °C (0.067 kPa); ^{1}H NMR (100 MHz, CDCl$_3$) δ 0.81 (3 H, s, CH$_3$), 3.55 (3 H, s, OCH$_3$), 4.43 (1 H, br s, 1-H), 5.78 (1 H, br d, J = 10.0 Hz, 8-H), 5.96–6.40 (6 H, m); $[\alpha]_D$ +393.3° (c 0.11798, hexane); UV (EtOH) λ_{max} 324.3 nm (ϵ 6000), 223.2 (23700); CD (EtOH) λ_{ext} 321.0 nm ($\Delta\epsilon$ +5.7), 249.2 (0.0), 221.3 (−24.5). High resolution mass spectrum calcd for C$_{12}$H$_{14}$O: 174.1044. Found: 174.1044.

(1S,6ξ,8aS)-1,2,6,8a-Tetrahydro-1-methoxy-6,8a-dimethyl-6-azulenol (19). To a solution of the trienone 17 (0.267 g, 1.40 mmol) in dry ether (30 mL) was added dropwise an ethereal solution of CH$_3$Li (2.2 mL, 1.25 M, 2.81 mmol) at −55 °C. The reaction mixture was stirred at −55 °C for 1.5 h, poured into ice–water, and extracted with ether. The organic layer was washed with brine and evaporated, giving 0.290 g (100%) of the alcohol 19: ^{1}H NMR (60 MHz, CDCl$_3$) δ 1.07 and 1.12 (3 H, s each, 8a-CH$_3$), 1.37 and 1.43 (3 H, s each, 6-CH$_3$), 3.41 (3 H, s, OCH$_3$), 3.79 (1 H, dd, J = 8, 8 Hz, 1-H), 5.3–6.2 (5 H, m, 3,4,5,7,8-H).

(1S,8aS)-(+)-1,8a-Dihydro-1-methoxy-6,8a-dimethylazulene (8). To a solution of the alcohol 19 (0.290 g, 1.40 mmol) in dry benzene (40 mL) was added a solution of iodine (0.003 g, 0.012 mmol) in dry benzene (2 mL). The mixture was vigorously refluxed for 1 h in an oil bath heated

at 110 °C. After being cooled to room temperature, the mixture was passed through a short silica gel column (hexane/EtOAc 5:1). The crude product obtained was purified by preparative LC on silica gel (hexane/EtOAc 20:1), affording 0.139 g (52.5%) of the tetraene 8 as a faintly yellow liquid. The analytical sample was obtained by distilling in vacuo: bp 60–70 °C (0.029 kPa); ^{1}H NMR (360 MHz, CDCl$_3$) δ 0.780 (3 H, s, 8a-CH$_3$), 2.013 (3 H, s, 6-CH$_3$), 3.514 (3 H, s, OCH$_3$), 4.356 (1 H, br s, 1-H), 5.746 (1 H, d, $J_{7,8}$ = 10.9 Hz, 8-H), 5.957 (1 H, dd, $J_{2,3}$ = 5.8, $J_{1,2}$ = 2.1 Hz, 2-H), 5.961 (1 H, d, $J_{7,8}$ = 10.9 Hz, 7-H), 5.986 (1 H, d, $J_{4,5}$ = 7.0 Hz, 4-H), 6.143 (1 H, dq, $J_{4,5}$ = 7.0, $J_{5,6\text{-Me}}$ = 1.1 Hz, 5-H), 6.197 (1 H, dd, $J_{2,3}$ = 5.8 Hz, $J_{1,3}$ = 1.9 Hz, 3-H); NOE correlation, +8.93% between 6-CH$_3$ and 7-H, +12.13%, 6-CH$_3$ and 5-H, +8.81%, OCH$_3$ and 1-H, +8.71% ~ 11.29%, 1-H and 8-H; $[\alpha]_D$ +323.8° (c 0.20723, hexane); UV (EtOH) λ_{max} 324.5 nm (ϵ 7200), 226.2 (24300); CD (EtOH) λ_{ext} 318.6 nm ($\Delta\epsilon$ +4.3), 240.2 (+1.6), 237.0 (0.0), 220.7 (−18.1). High resolution mass spectrum calcd for C$_{13}$H$_{16}$O: 188.1201. Found: 188.1200.

Conjugative Interaction in the Orthogonal Enamine, 1-Azabicyclo[3.2.2]non-2-ene

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Abstract: Synthesis of 1-azabicyclo[3.2.2]non-3-ene and establishment of equilibrium with 1-azabicyclo[3.2.2]non-2-ene by catalysis either with potassium *tert*-butyloxide or hydridonitrosotris(triphenylphosphine)ruthenium reveals no free energy difference between the allyl amine and the orthogonal enamine. In unrestricted examples, the enamine is favored by ~4 kcal/mol. Thus, conjugative interaction in enamines requires parallel overlap of the orbitals containing the non-bonded nitrogen pair and the π-olefinic pair of electrons.

Structure and thermochemistry of enamines derive their importance from the extraordinary versatility of the various Stork reactions in synthesis[1] and from their bearing on the theory of conjugation between an olefinic π-bond and the unshared electron pair of nitrogen.[2]

In this work, an orthogonal enamine is prepared, set into equilibrium with an (equally orthogonal) allylamine, and compared in free energy with configurationally unrestricted enamines. Although much structural and thermochemical information already exists in the literature, there is no direct examination of the influence of orthogonality.

An authoritative crystallographic study of enamines has brought to light a spectrum of structures ranging from the nearly coplanar expected from an sp^2 configuration and 2p$_z$ disposition of the lone pair through the pyramidal, in varying degrees, to an eclipsed, nearly tetrahedral associated with sp^3 hybridization about nitrogen.[3]

Scheme I
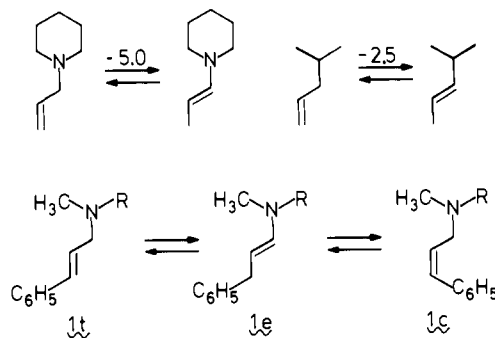
The thermochemistry of the n,π-interaction has been probed by hydrogenation and by equilibration in the allyl–propenyl system (see Scheme I). Comparison of the heats of hydrogenation of *N*-allyl- and *N*-*trans*-propenylpiperidine has revealed a heat of isomerization of -5.0 kcal/mol.[4] Given that the heat of isomerization of 4-methylpentene-1 to *trans*-4-methylpentene-2 is −2.5 kcal/mol, and that of pentene-1 to *trans*-pentene-2 is −2.6

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