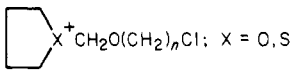
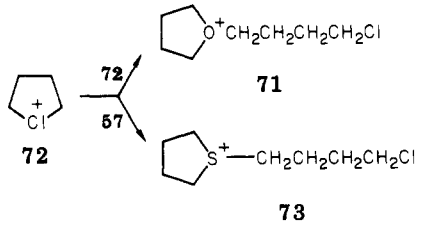
Table V. NMR Parameters of [(Chloroalkyoxy)methyl]tetramethylene Onium Ions in SO_2 Solution at −40 °C



n	$^+XCH_2O$	OCH_2	CH_2Cl	CH_2	CH_2CH_2	$^+XCH_2$	CH_2CH_2
				For X = O			
1	5.97 (s)	5.87 (s)				5.07 (m)	2.63 (m)
2	5.92 (s)	4.46 (t)	4.02 (t)			4.97 (m)	2.60 (m)
3	5.82 (s)	4.25 (t)	3.83 (t)	2.23 (m)		4.83 (m)	2.50 (m)
4	6.00 (s)	4.33 (t)	3.87 (t)		2.05 (m)	5.02 (m)	2.70 (m)
				For X = S			
1	5.33 (s)	5.80 (s)				3.74 (m)	2.52 (m)
2	5.37 (s)	4.23 (t)	4.00 (t)			3.73 (m)	2.60 (m)
3	5.17 (s)	4.07 (t)	3.77 (t)	2.15 (m)		3.50 (m)	2.40 (m)
4	5.33 (s)	4.10 (t)	3.65 (t)		1.98 (m)	3.82 (m)	2.57 (m)

Scheme VI



through which their neutral precursors can act as biological alkylating agents. Work is continuing with regard to alkylation of other substrates, including nucleic acid bases.

Experimental Section

Materials. All halo ethers were obtained from the corresponding alcohols according to previously described methods.[32]

Preparation of Carboxonium Ions. To SbF_5 (or $SbCl_5$) dissolved in about a twofold amount of SO_2 at dry ice/acetone temperature (ca. −78 °C) was slowly added, with vigorous stirring, a similarly cooled slurry or solution of the corresponding halo ethers in SO_2. When the temperature was raised to about −40 °C, dehydrohalogenation takes place, giving an approximately 10% solution of the corresponding carboxonium ion. The same procedure was employed in the case of obtaining the ions via protolysis with FSO_3H–SbF_5. ^1H and ^{13}C NMR spectra were obtained on Varian A56/60, XL-100, and FT-80 NMR spectrometers, respectively, equipped with multinuclei, broad-band, variable-temperature probes. Chemical shifts were referenced to an external (capillary) Me_4Si signal.

Alkylation with (Haloalkyl)carboxonium Ions. To the solution of the oxonium ions in SO_2 at dry ice/acetone temperature (ca. −78 °C) was slowly added a cooled slurry or solution of the corresponding substrate (THF or thiophene). The resulting alkylated products were analyzed by ^1H and ^{13}C NMR spectroscopy.

Preparation of Protonated Fluoromethyl Alcohol 9. Parafomaldehyde (0.1 g) was added to a rapidly stirred solution of FSO_3H–SbF_5 (1:1 mol, 10.0 g) in SO_2 (5 mL) at −78 °C. The resulting stock solution of protonated fomaldehyde 6 was used in the subsequent expeeriments.

An aliquot of the stock solution of protonated formaldehyde was transferred to an NMR tube and then cooled to −78 °C. With rapid stirring anhydrous HF, precooled to −78 °C, was added to this solution. The resulting solution of 9 was then analyzed by ^1H, ^{19}F, and ^{13}C NMR spectroscopy.

Preparation of Protonated Chloromethyl Alcohols 5. An aliquot of the stock solution of 6 was transferred to an NMR tube and cooled to −78 °C. Anhydrous HCl was slowly bubbled into this solution for 1 min. The resulting solution of 5 was then analyzed by ^1H and ^{13}C NMR spectroscopy.

Acknowledgment. Support of our work by the National Institute of Health is gratefully acknowledged.

Registry No. 5, 56003-53-3; **6**, 18682-95-6; **9**, 33010-92-3; **11**, 56003-54-4; **13**, 56003-55-5; **14**, 41879-84-9; **15**, 51624-52-3; **17**, 56003-56-6; **18** (n = 1), 71681-46-4; **20**, 1462-33-5; **21**, 75863-57-9; **24**, 1462-35-7; **26**, 75863-58-0; **27**, 75863-59-1; **31**, 3970-18-1; **32**, 54314-83-9; **33**, 75863-60-4; **34**, 75863-61-5; **41a**, 3970-17-0; **41b**, 53970-36-8; **42**, 75863-62-6; **43**, 51918-70-8; **44**, 75863-63-7; **52**, 75863-64-8; **58**, 75863-65-9; **59**, 75863-66-0; **60**, 75863-67-1; **61**, 75863-68-2; **62**, 75863-69-3; **63**, 75863-70-6; **64**, 75863-71-7; **65**, 75863-72-8; $ClCH_2O$-CH_2CH_2I, 56003-59-9; $ClCH_2O^+(H)CH_2CH_2CH_2CH_2Cl$, 56003-57-7.

(32) D. A. Beal, Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH, 1973, and references given therein.

Synthesis and Configurational Assignment of Geiparvarin: A Novel Antitumor Agent

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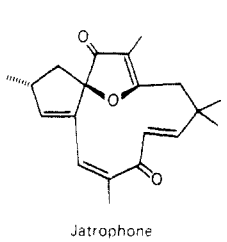
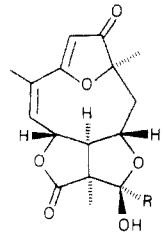
Received July 14, 1980

This report presents the first total synthesis of geiparvarin as well as assignment of configuration of the previously undefined trisubstituted olefin. A central aspect of this synthetic adventure leading to this novel antitumor agent which possesses the 3(2*H*)-furanone ring system was the development of a viable general approach for the elaboration of 5-alkenyl-3(2*H*)-furanones. Configurational assignments were based on NMR correlations, NOE experiments, and completion of a single-crystal X-ray structure on synthetic geiparvarin.

During the past several years considerable effort in our laboratory has been directed toward the synthesis of jatrophone (**1**)[2] and the eremantholides (**2**),[3] naturally occurring antitumor agents which incorporate the 3(2*H*)-

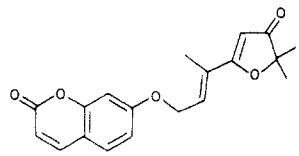

Jatrophone
(1)

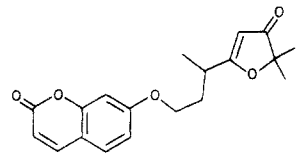

Eremantholides

(2a): R = *i*-Pr
(2b): R = *sec*-Bu
(2c): R = CMe=CH$_2$

furanone ring system as a key skeletal element. Our work in this area has not only led to a general study[4] of the synthesis and chemistry of the 3(2*H*)-furanone system but also has prompted interest in other natural products possessing this heterocyclic ring.

Of particular interest here was geiparvarin (**3**), which was isolated by Lahey and MacLeod from the leaves of *Geijera parviflora* Lindl. (Rutaceae), a shrub indigenous to Queensland and New South Wales.[5] These workers deduced the carbon skeleton from proton NMR and degradation studies but were unable to assign the configuration of the trisubstituted olefinic bond. In addition, they converted geiparvarin to its dihydro derivative (**4**) by selective hydrogenation. Shortly after the initial report on geiparvarin, Dreyer and Lee isolated the dihydro derivative from extracts of the same fruit.[6]

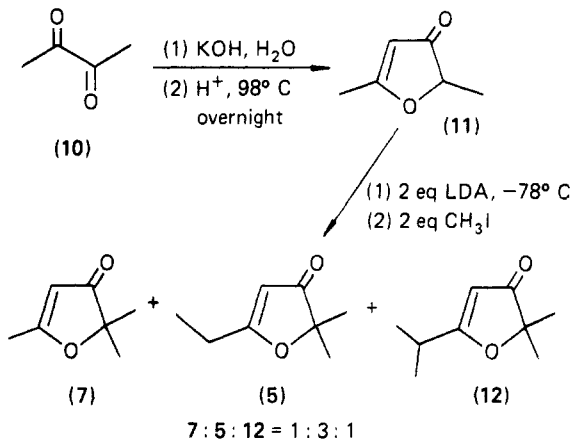

Geiparvarin
(3)


Dihydorgeiparvarin
(4)

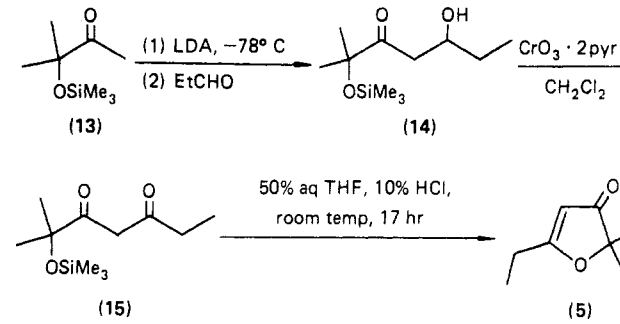
Both geiparvarin and dihydrogeiparvarin exhibit significant biological activity in vitro against human carcinoma of the nasopharynx.[7] In addition, geiparvarin displays activity in the NCI P-388 screen for antitumor agents.[8]

In this, a full account of our work in this area, we record not only the details of the first synthesis of geiparvarin as well as assignment of the configuration of the previously undefined olefinic linkage but also the development of a viable, general route to 5-alkenyl-3(2*H*)-furanones.[9]

Scheme I

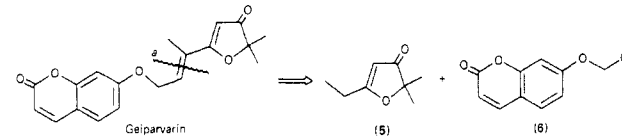


Scheme II



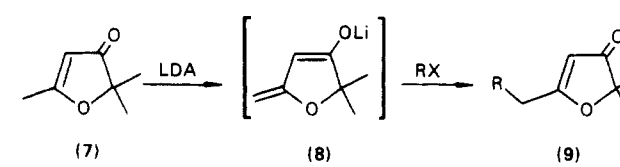
Results and Discussion

(i) Strategy for the Synthesis of Geiparvarin and Its Configurational Isomer. At the outset the undefined stereochemistry of geiparvarin demanded that our synthetic strategy not only allow for elaboration of geiparvarin but also for its configurational isomer. With this constraint in mind, an antithetic analysis involving bond disconnection a, yielding the architecturally simple fragments, 3-(2*H*)-furanone **5** and coumarin **6**, appeared ideal. That is,



aldol condensation at the γ-carbon of furanone **5** followed by dehydration would provide a direct approach to geiparvarin and/or its configurational isomer.

Such an antithetic analysis was not without precedent. Indeed, we recently demonstrated that lithium dienolates derived from 3(2*H*)-furanones disubstituted at the α′-carbon undergo exclusive γ-alkylation in excellent yield (**7** → **9**).[10] The corresponding aldol condensation, however,



had not been examined. Since the success of our strategy for geiparvarin was singularly dependent upon a viable γ-aldol-dehydration dehydration reaction sequence, we initiated our study by examining the low-temperature aldol

(1) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Awardee, 1980–1985.

(2) (a) S. M. Kupchan, C. W. Sigel, M. J. Matz, J. A. Saenz Renauld, R. C. Haltiwanger, and R. F. Bryan, *J. Am. Chem. Soc.*, **92**, 4476 (1970); (b) S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, and R. F. Bryan, *ibid.*, **98**, 2295 (1976); **Note added in proof**: Since acceptance of this manuscript, we have successfully completed the first stereocontrolled total synthesis of both (±)-jatrophone (1) and that of its epimer, (±)-epijatrophone; see A. B. Smith, III, and P. J. Jerris, *J. Am. Chem. Soc.*, **103**, 194 (1981), for the synthetic strategy.

(3) (a) R. F. Raffauf, P.-K. C. Huang, S. B. Levery, T. F. Brennen, and P. W. LeQuesne, *J. Am. Chem. Soc.*, **97**, 6884 (1975); (b) P. W. LeQuesne, S. B. Levery, M. D. Menacherey, T. F. Brennen, and R. F. Raffany, *J. Chem. Soc., Perkin Trans 1*, 1573 (1978).

(4) A. B. Smith, III, P. A. Levenberg, P. J. Jerris, and R. M. Scarborough, Jr., *J. Am. Chem. Soc.*, in press. Also see A. B. Smith, III, and P. J. Jerris, *Synth. Commun.*, **8**, 421 (1978).

(5) (a) F. N. Lahey and J. K. MacLeod, *Aust. J. Chem.*, **20**, 1943 (1967); (b) R. M. Carman, F. N. Lahey, and J. K. MacLeod, *ibid.*, **20**, 1957 (1967).

(6) D. L. Dreyer and A. Lee, *Phytochemistry*, 11, 763 (1972).

(7) K. Padmawinata, *Acta Pharm.*, **4**, 1 (1973); *Chem. Abstr.* **79**, 75897n (1973).

(8) Geiparvarin (NSC 142227) displayed activity against P-388 lymphocytic leukemia (T/c = 130 at 400 mg/kg and 123 at 600 mg/kg) and in the KB screen (ED_{50} 3 mg/mL). It proved inactive in the B-16 melanoma, L-1210 Leukemia, and Lewis lung carcinoma screens.

(9) For a preliminary account of this work see A. B. Smith, III, and P. J. Jerris, *Tetrahedron Lett.*, 711 (1980).

(10) A. B. Smith, III, and R. M. Scarborough, Jr., *Tetrahedron Lett.*, 4193 (1978).

condensation of the lithium dienolate derived from furanone **5** with a number of model aldehydes.

For completion of the proposed model study as well as the synthesis of geiparvarin an efficient large-scale synthesis of 2,2-dimethyl-5-ethyl-3(2*H*)-furanone (**5**) was required. A most logical precursor in this regard appeared to be 2,5-dimethyl-3(2*H*)-furanone (**11**), conveniently available in bulk quantity via the self-condensation of biacetyl (**10**, Scheme I),[11] since it seemed reasonable to anticipate that dimethylation would lead directly to **5**. As expected, treatment of furanone **11** with 2 equiv each of base and methyl iodide provided the desired furanone. Unfortunately, upon scale up, the product mixture proved to contain both the mono- and trialkylated derivatives (**7** and **12**, respectively). Although these could be separated by employing medium-pressure liquid chromatography, the process was deemed impractical for large-scale preparation of **5**.

Fortunately we were at that time investigating the acid-induced cyclization of α'-hydroxy β-diketones as a new and highly efficient route to the 3(2*H*)-furanone ring system.[4] By use of this approach, the lithium enolate of silyloxy ketone **13** underwent condensation with propionaldehyde to afford aldol **14** in good yield (76%, Scheme II). Subsequent oxidation with Collins reagent[12] followed by acid treatment effected deprotection and in situ cyclization–dehydration to **5**. This route provided a most efficient synthesis which is amenable to large-scale reaction, since all intermediates could be purified by simple distillation.

(ii) Synthesis of Model 5-Alkenyl-3(2*H*)-furanones. With ample quantities of furanone **5** in hand we set out to investigate the feasibility of the γ-aldol condensation–dehydration strategy as a general method for elaborating 5-alkenyl-3(2*H*)-furanones. We are pleased to report in this regard that condensation of the lithium dienolate of furanone **5** at −78 °C with benzaldehyde, propionaldehyde, and acetaldehyde followed by quenching at −78 °C after 20 min affords good yields of diastereomeric alcohols resulting from γ attack. Our results are illustrated in Table I. Even the allylic alcohol **19** can be prepared in modest yield by condensation with *trans*-cinnamaldehyde.

The diastereomeric alcohols were easily characterized by IR as well as high-field ^{1}H NMR (360 MHz). That the aldol reaction conditions did not isomerize the 3′,4′-trans olefinic bond in **19** was evident from the large coupling constant (J = 16.6 Hz) observed for the 3′,4′ protons.

Interestingly, in the case of benzaldehyde when the reaction was allowed to warm to room temperature before quenching, a 3:2 mixture respectively of α- and γ-alkylated furanones resulted. The α-aldol derivative **20** was tentatively identified from its NMR (60 MHz) spectrum: δ 1.05 (t, J = 7 Hz, 3 H), 1.30 (s, 6 H), 2.40 (q, J = 7 Hz, 2 H), 3.50 (br s, 1 H), 5.45 (br s, 1 H), 7.10–7.40 (m, 5 H). Furthermore, the IR spectrum indicated the presence of a hydroxyl group (3300–3600 cm^{-1}) as well as an intact 3(2*H*)-furanone ring system (1700, 1600 cm^{-1}).[13] This

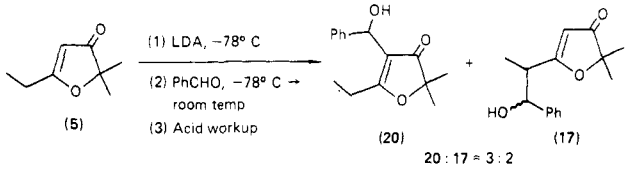
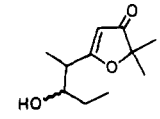
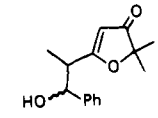
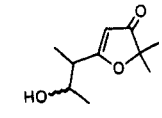
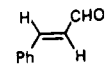
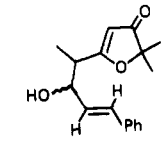


Table I. Aldol Condensations with 2,2-Dimethyl-5-ethyl-3(2*H*)-furanone

aldehyde	aldol product	compd	yield, %
EtCHO		16	69
PhCHO		17	76
MeCHO		18	54
		19	38

information in conjunction with the elemental composition data obtained by high-resolution mass spectrometry [i.e., m/e 246.1267; calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256] allowed assignment of structure **20**.

This product is envisioned to arise via initial kinetic condensation at the γ position followed by a retro-aldol condensation with subsequent attack at the α-carbon. Interestingly, aliphatic aldehydes reacted under similar conditions (i.e., room-temperature quench) afforded only a poor yield of γ-alkylation and no α-alkylation products. Presumably aldehydes possessing acidic α-hydrogens undergo self-condensation–polymerization at temperatures above −78 °C.

In view of the numerous methods available to effect dehydration, it seemed reasonable to expect that elimination of water from furanone alcohols **16–19** would be straightforward. However, due to the apparent instability of the 5-alkenyl-3(2*H*)-furanone system, the desired dehydrations proved to be far more difficult than anticipated.

Initially we examined dehydration protocols involving equilibrating conditions such as (1) *p*-toluenesulfonic acid in benzene heated at reflux, (2) *p*-toluenesulfonic acid in the presence of anhydrous cupric sulfate, (3) thermolytic decomposition of a sulfamate ester derived from the Burgess reagent,[14] and (4) acid-catalyzed decomposition of the mesylate.[15] In each case one isomer, later shown to be the thermodynamically more stable *E* isomer, predominated (>95%). Only trace amounts of the corresponding *Z* isomers could be detected by thin-layer chromatography. Such conditions, while stereoselective for the *E* isomer, were obviously inappropriate, since rigorous configurational assignments necessitated the isolation and characterization of both isomers. Furthermore, in each case cited above, the yields were at best modest (ca. 20–40%), presumably reflecting the instability of the 5-alkenyl-3(2*H*)-furanone system to acidic media.

Fortunately, these difficulties were easily overcome upon deployment of the mild dehydration procedure recently introduced by Alexandre and Rouessac.[16] Toward this end, treatment of the hydroxy furanones with dicyclohexyl carbodiimide in the presence of anhydrous cuprous chloride afforded good yields of both the *E* and *Z* isomers (see

(11) C. Venturello and R. D'Aloisio, *Synthesis*, 754 (1977).
(12) J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972).
(13) P. Bosshard and C. H. Eugster, *Adv. Heterocycl. Chem.* **7**, 377 (1966).
(14) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Org. Chem.*, **38**, 26 (1973).
(15) G. Stork and G. A. Kraus, *J. Am. Chem. Soc.*, **98**, 2351 (1976).
(16) G. Alexandre and F. Rouessac, *Bull. Soc. Chim. Fr.*, 1837 (1973).

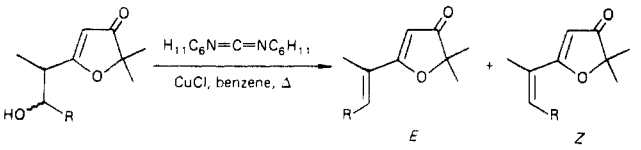
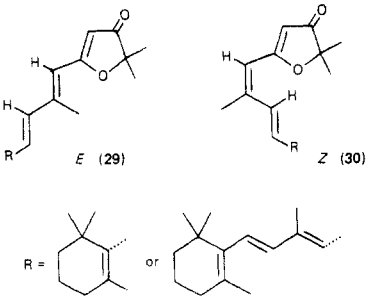


Table II). The progress of this reaction was unusually convenient to monitor in that dicyclohexylurea precipitated from solution when the dehydration was complete. In each case the isomers were separated cleanly by preparative thin-layer silica gel chromatography. The ratios of *Z* and *E* isomers were found to vary depending on the specific system (see Table II).

Concerning the mechanism of the above dehydration protocol, no statements can be made at this time since no attempts were made to separate and characterize the aldol mixtures to determine if one diastereomer yielded exclusively one olefinic product.

(iii) Assignment of Configuration to the Trisubstituted Olefin. With a viable two-step approach to 5-alkenyl-3(2*H*)-furanones assured, we turned our attention toward devising a reliable method for the assignment of the configuration of the trisubstituted olefinic linkages. Particularly noteworthy in this regard was the recent report by Ito on the preparation and stereochemical assignment of the related retinoidal 3(2*H*)-furanones **29** and **30**.[17] More specifically, Ito suggested that the geometry



about the 1′,2′-olefinic bond can be correlated with the observation that the C-2′ methyl absorptions in the *E* isomer appear downfield relative to those in the *Z* isomer, the latter resulting from a deshielding effect of the furanone oxygen. Similarly, the C-3′ protons in the *Z* isomer were predicted to be deshielded by the furanone oxygen.

By employment of this empirical correlation, the configurations of 5-alkenyl-3(2*H*)-furanones **21**–**28**, listed in Table II, were tentatively assigned. The relevant chemical shift data for the C-2′, C-3′, and C-4′ protons are listed in Table III.

An explanation regarding the assignment of the doublet at δ 6.86 in **27** to C-4′ is in order. Conceivably this signal could be due either to the C-2′ or to the C-4′ proton. Two observations led us to make the latter assignment. First, the large coupling constant (J = 15 Hz) is indicative of a trans relationship about an olefinic bond. It is noteworthy that the C-2′,3′ coupling in furanone **28** is slightly smaller (J = 11 Hz). Second, the differences in chemical shifts observed for the C-2′ proton in each isomeric pair ranges from Δδ = 0.67 to 0.75 ppm. Assignment of the signal at δ 6.86 to the C-2′ proton is inconsistent with this trend, since this proton in the *Z* isomer **28** resonates at δ 6.49 (Δδ = 0.37 ppm). Hence, while not rigorously established, the doublet at δ 6.86 in furanone **27** can tentatively be assigned to the C-4′ proton.

(17) M. Ito, M. Ohno, E. Takano, Y. Oda, and K. Tsukida, *Heterocycles*, **12**, 505 (1979).

Table II. Synthesis of 5-Alkenyl-3(2*H*)-furanones

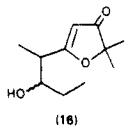
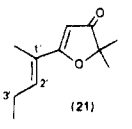
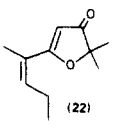
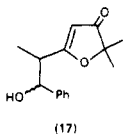
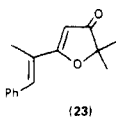
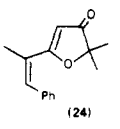
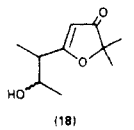
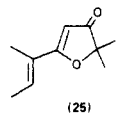
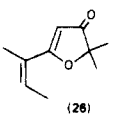
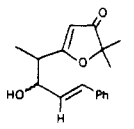
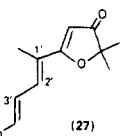
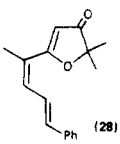
alcohol	dehydration	products	*E*/*Z* ratio	yield, %
 (16)	 (21)	 (22)	1:2	73
 (17)	 (23)	 (24)	1:2	60
 (18)	 (25)	 (26)	1:1	64
 (19)	 (27)	 (28)	3:2	55

Table III. ^{1}H NMR (360 MHz) Data of 5-Alkenyl-3(2*H*)-furanones

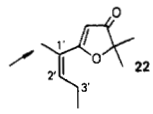
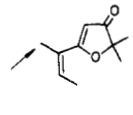
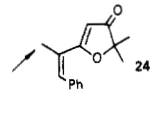
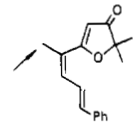
	chemical shift,[c] δ		
compd	C-2′ proton	C-3′ proton	C-4′ proton
21	6.59 (t, J = 7)	2.19–2.31 (m)	
22	5.84 (t, J = 7)	2.28–2.40 (m)	
23	7.74 (br s)		
24	7.06 (br s)		
25	6.72 (q, J = 7)	1.86 (d, J = 7)	
26	6.05 (q, J = 7)	*a*	
27	*b*	*b*	6.86 (d, J = 15)
28	6.49 (d, J = 11)	7.62 (dd, J = 11 and 15)	6.66 (d, J = 15)

[a] Proton resonance observed between δ 1.94 and 2.00 overlapping with a singlet. [b] Proton resonance observed between δ 7.33 and δ 7.42 overlapping with the aromatic absorption. [c] Shifts of $CDCl_3$ solutions from Me_4Si. Coupling constants are given in hertz.

Significantly, only the (*E*)-trans and (*Z*)-trans polyconjugated furanones **27** and **28** were isolated. That is, there was no indication that the dehydration conditions effected the isomerization of the 3′,4′-olefinic bond. That the (*E*)-trans isomer **27** is the thermodynamically more stable of the two was demonstrated by the observation that a $CDCl_3$ NMR sample of pure *Z* isomer isomerized to the corresponding *E* isomer over a period of a few days.

The above tentative stereochemical assignments were confirmed by nuclear Overhauser experiments (NOE) performed on carefully degassed samples. The results of that study are depicted in Table IV. In particular, saturation of the designated vinyl C-1′ methyl absorption in each of the *Z* isomers resulted in 10–30% enhancement of the vinyl C-2′ proton signal, indicating a close spatial

Table IV. Nuclear Overhauser Experiments[a]

compd	% enhancement	compd	% enhancement
 22	10	 26	17
 24	14	 28	30

[a] Enhancement observed in the integrated intensity of C-2′.

Table V. Characteristic IR Data of 5-Alkenyl-3(2*H*)-furanones

compd	ν_{max}, cm^{-1}
21	1680, 1635, 1560
22	1680, 1630, 1550
23	1675, 1620, 1545
24	1675, 1625, 1560
25	1685, 1640, 1555
26	1680, 1630, 1550
27	1670, 1580, 1530
28	1680, 1600, 1530

[a] All spectra were recorded in $CHCl_3$, except those of 27 and 28, which were taken in CCl_4.

orientation.[18] Significantly, no enhancements were observed upon similar irradiations in the corresponding *E* isomers.

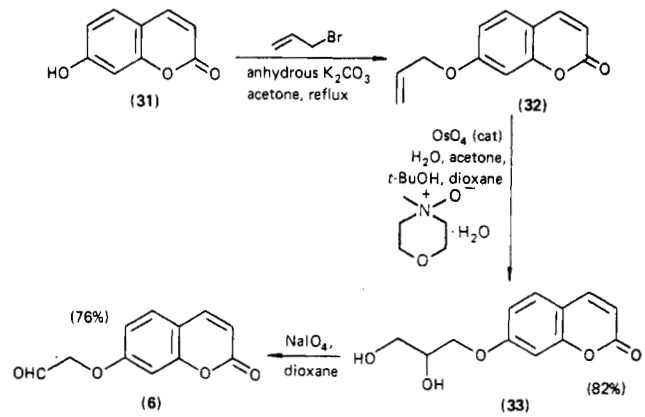
The 5-alkenyl-3(2*H*)-furanones also displayed characteristic IR absorptions (Table V). While simple 3(2*H*)-furanones display two strong absorptions[13] at 1710 and 1610 cm^{-1}, conjugated 3(2*H*)-furanones are characterized by three intense bands, a carbonyl absorption in the 1670–1680-cm^{-1} region and a pair of bands in the 1530–1630-cm^{-1} region for the olefinic C–H bending modes.[17]

Finally, it is interesting to note that in each case the *E* isomers were obtained as crystalline solids with sharp melting points, while the *Z* isomers were isolated as oils.

(iv) Synthesis and Configurational Assignment of Geiparvarin. Having developed both a viable route to 5-alkenyl-3(2*H*)-furanones as well as a basis for assigning the stereochemistry, we focused our attention at last on the synthesis of geiparvarin (**3**). A reasonable precursor to the required coumarin aldehyde (**6**) appeared to be 7-hydroxycoumarin (umbelliferone, **31**), which is commercially available at reasonable cost. Indeed, 7-(2-oxoethoxy)coumarin (**6**) had previously been prepared from umbelliferone via ozonolysis of the intermediate 7-(allyloxy)coumarin (**32**).[19] However, the yield reported for this sequence was only 37%; we therefore sought a more efficient preparation.

An equally feasible route appeared to be hydroxylation of the allyloxy derivative **32** followed by reductive cleavage of the resulting diol. Toward this end 7-hydroxycoumarin (**31**) was alkylated with allyl bromide by employing anhydrous potassium carbonate in acetone at reflux (Scheme III).[20] Initially a one-pot hydroxylation–oxidation procedure was attempted. Although this approach avoided isolation of the intermediate diol, the yield of the coumarin aldehyde **6** was extremely poor. Fortunately the elegant hydroxylation procedure of Kelly et al.[21] provided the solution. In particular, (allyloxy)coumarin **32** was catalytically hydroxylated with osmium tetraoxide and *N*-methylmorpholine *N*-oxide to diol **33**; then in a second step diol **33** was subjected to cleavage with sodium periodate in aqueous dioxane to afford 7-(2-oxoethoxy)coumarin (**6**). The overall yield from 7-hydroxycoumarin (three steps) was 54%.

Scheme III



With access to aldehyde **6** assured, the remainder of the geiparvarin synthesis proved to be straightforward. Condensation of the lithium dienolate of furanone **5** with the coumarin aldehyde afforded a 53% yield of a diastereomeric mixture of alcohols **34** (Scheme IV), isolated by preparative thin-layer (silica gel) chromatography. As expected acid-catalyzed dehydration of the alcohol mixture afforded the *E* and *Z* isomers of geiparvarin (**3** and **35**) albeit in only 22% yield; the ratio was 9:1, respectively. Alternatively, reaction with dicyclohexylcarbodiimide and cuprous chloride provided a 1:1 isomeric mixture of geiparvarin and its configurational isomer. Both isomers recrystallized from methanol as white flakes with sharp, yet distinctly different, melting points (*E* isomer, mp 157–158 °C; *Z* isomer, mp 149–150 °C).

Initial stereochemical assignments were based on the chemical shift correlations which had been employed to advantage in the case of the other 5-alkenyl-3(2*H*)-furanones (see Table III). Specifically, the C-2′ proton in the *E* isomer (**3**) appeared at δ 6.64 (t, J = 5.4 Hz) while the same proton was shifted upfield ($\Delta\delta$ = 0.56 ppm) to δ 6.08 (t, J = 4.3 Hz) in the *Z* isomer (**35**). Conversely, the C-3′ methylene protons in the *Z* isomer [δ 5.02 (d, J = 4.3 Hz)] were deshielded relative to those in the *E* isomer [δ 4.82 (d, J = 5.4 Hz)].

In support of these configurational assignments, saturation of the C-1′ methyl absorption of the *Z* isomer induced a 33% nuclear Overhauser enhancement of the C-2′ proton signal. No change in the integrated intensity of this proton was observed upon similar irradiation in the *E* isomer. It was the *E* isomer which corresponded with respect to melting point and NMR data to natural geiparvarin as reported by Lahey and MacLeod.[5]

To verify rigorously the *E* geometry of geiparvarin and, in turn, to place the above empirical NMR correlations on

(18) For an example in which a NOE was used to assign the spectra of citral a and citral b, see M. Ohtsuru, M. Teraoka, K. Tori, and K. Takeda, *J. Chem. Soc. B*, 1033 (1967).
(19) R. C. Esse and B. E. Christensen, *J. Org. Chem.*, **25**, 1565 (1960).
(20) For a representative procedure used to prepare 7-(allyloxy)-8-methylcoumarin, see K. D. Kaufman, *J. Org. Chem.*, **26**, 117 (1961).
(21) V. VanRheenan, R. C. Kelly, and D.-Y. Cha, *Tetrahedron Lett.*, 1973 (1976).

Scheme IV

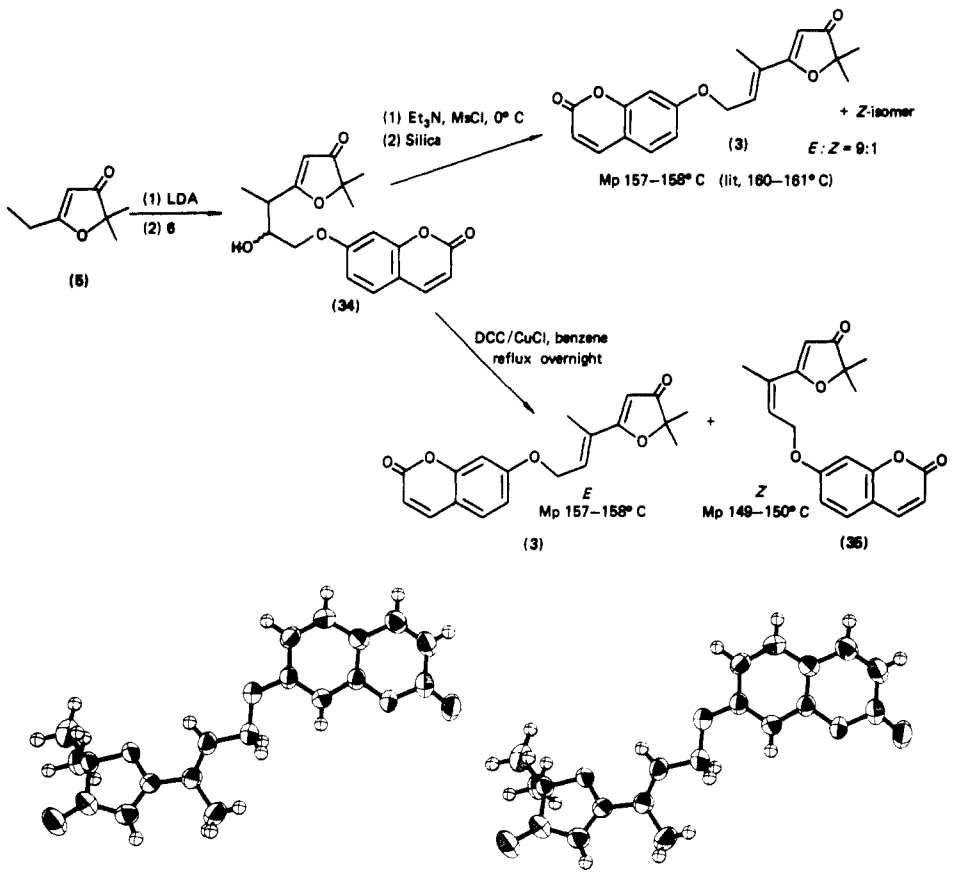


Figure 1. ORTEP stereoplot with 50% probability thermal ellipsoids for nonhydrogen atoms.

a firm basis, we completed a single-crystal X-ray analysis of synthetic geiparvarin.[22] The crystal class was found to be monoclinic in the space group $P2_1/c$ with a = 8.305 Å, b = 11.077 Å, c = 18.287 Å, and β = 98.79°. The ORTEP plot, shown in Figure 1, not only confirms both the structure and the olefinic configuration of geiparvarin but also establishes the validity of the NMR correlations.

Experimental Section

Materials and Equipment. All solvents used were reagent grade. Dimethylformamide was distilled from calcium hydride, methylene chloride was distilled from phosphorous pentoxide, and tetrahydrofuran was distilled from sodium and benzophenone. Benzene was dried over sodium ribbon prior to use. 3-Hydroxy-3-methyl-2-butanone, 7-hydroxycoumarin, and *N,N'*-dicyclohexylcarbodiimide were obtained from Aldrich. The chromium trioxide used in the Collins oxidation[12] was purchased from Fisher. Prepared silica gel plates (250 μm) with a fluorescent indicator (E. M. Merck) were used for analytical thin-layer chromatography (TLC). Preparative separations were performed on precoated 1000-μm silica gel GF (Analtech) plates. Silica gel 60 with a particle size of 0.04–0.063 mm (supplied by E. M. Merck) was used for flash column chromatography. All melting points were obtained on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 337 spectrophotometer while proton NMR spectra were obtained on either a Varian Model A-60 or a Bruker WH-360 (360 MHz) spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00). Samples were degassed for nuclear Overhauser experiments (NOE) by careful freezing at -196 °C (liquid nitrogen), evacuation at 10^{-3} torr, and then slow warming to room temperature. After this freeze–thaw technique was repeated three times in succession, the samples were then sealed at 10^{-3} torr. NOE studies were obtained for deuteriochloroform solutions on a Bruker WH-360 (360 MHz) spectrometer.

Microanalyses were determined by either the Rockefeller Microanalytical Laboratories under the direction of Mr. T. S. Bella or by Galbraith Laboratories, Inc.

High-resolution mass spectra were obtained from the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi Perkin-Elmer RMH-2 high-resolution, double-focusing, electron-impact spectrometer connected to a Kratos DS-50-S data system.

The single-crystal X-ray analysis of geiparvarin was obtained on a Enraf-Nonius CAD-4 automatic diffractometer equipped with an incident-beam crystal monochromator.[22]

3-Methyl-3-[(trimethylsilyl)oxy]-2-butanone (13). To a solution of 20 g (0.196 mol) of 3-hydroxy-3-methyl-2-butanone in 330 mL of freshly distilled dimethylformamide (CaH_2) was added 27 mL (0.195 mol) of triethylamine. After the mixture was stirred 5 min, 25.5 mL (0.2 mol) of chlorotrimethylsilane was added dropwise. The resultant mixture was stirred at ambient temperature overnight (18 h). The reaction mixture was then poured into 600 mL of 1:1 ether–pentane, washed with water, saturated sodium bicarbonate, and brine, and dried over magnesium sulfate. Removal of the solvent in vacuo and subsequent distillation [bp 63–70 °C (30 mmHg)] yielded 26.5 g (76%) pure silyl ether **10**: IR (CCl_4) 2970 (s), 1710 (s), 1475 (s), 1255 (s), 1045 (s, br), 885 (s), 840 (s, br), cm^{-1}; NMR (60 MHz, CCl_4) δ .13 (s, 9 H), 1.24 (s, 6 H), 2.08 (s, 3 H) [lit.[23] partial NMR (CCl_4) δ 0.15 (s, 9 H), 1.25 (s, 6 H); bp 150 °C (760 mmHg)].

5-Hydroxy-2-methyl-2-[(trimethylsilyl)oxy]-3-heptanone (14). To a solution of 150 mL of tetrahydrofuran and 22.6 mL (0.16 moles) of diisopropylamine cooled to −15 °C under nitrogen was added 64.2 mL (0.16 mol) of *n*-butyllithium (2.5 M). The resultant mixture was stirred at −15 °C for 30 min and then cooled

(22) B. H. Toder, D. Boschelli, and A. B. Smith, III, *J. Cryst. Mol. Struct.*, **9**, 189 (1979).

(23) D. J. Costa, N. E. Boutin, and J. G. Riess, *Tetrahedron*, **30**, 3793 (1974).

to −78 °C. A solution consisting of 25.6 g (0.15 mol) of 3-methyl-3-[(trimethylsilyl)oxy]-2-butanone (13) in 20 mL of tetrahydrofuran was then added dropwise. After 45 min, 13.7 mL (0.19 mol) of propionaldehyde was added dropwise with stirring. After 1.5 h the reaction was quenched at −78 °C by being poured into a mixture of saturated ammonium chloride–ether. The organic phase was washed with brine and dried over magnesium sulfate. Removal of the solvent in vacuo followed by distillation [bp 82–92 °C (2 mmHg)] afforded 23.2 g (68%) of 5-hydroxy-2-methyl-2-[(trimethylsilyl)oxy]-3-heptanone (14): colorless oil; IR (CCl_4) 3500–3600 (s, br), 2960 (s), 1710 (s), 1476 (s), 1260 (s), 1040 (s, br), 840 (s, br) cm^{-1}; NMR (60 MHz, CCl_4) δ 0.11 (s, 9 H), 0.82–1.57 (overlapping s, t, m, 11 H), 2.56–2.70 (m, 3 H), 3.52–4.02 (br s, 1 H).

Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41; Si, 12.09. Found: C, 56.58; H, 10.33; Si, 12.32.

2-Methyl-2-[(trimethylsilyl)oxy]-3,5-heptanedione (15). Collins reagent was prepared by the addition of 21.7 g (6.0 equiv) of chromium trioxide (dried under vacuum over P_2O_5 at 100 °C) and 35 mL (12 equiv) of dry pyridine (distilled from CaH_2) to 350 mL of methylene chloride (distilled from P_2O_5), and the resultant mixture was stirred at room temperature for 30 min. To the freshly prepared Collins reagent was added 8.1 g (35 mmol) of 5-hydroxy-2-methyl-2-[(trimethylsilyl)oxy]-3-heptanone (14) in 50 mL of methylene chloride, and the mixture was stirred for 3 h. The workup consisted of addition to methylene chloride which, in turn, was washed with 5% NaOH, 10% HCl, and saturation sodium bicarbonate and finally dried over magnesium sulfate. After filtration of the mixture, the solvent was evaporated in vacuo, and a 1:1 mixture of ether–pentane was added to precipitate the remaining chromium salts. Distillation [bp 50–67 °C (0.8 mmHg)] afforded 3.3 g (41%) of pure 2-methyl-2-[(trimethylsilyl)oxy]-3,5-heptanedione (15): clear liquid; IR (CCl_4) 3400–3600 (br), 2900–3000 (s, br), 1750 (m), 1700 (s), 1590–1620 (s, br), 835 (s, br) cm^{-1}; NMR (60 MHz, CCl_4) δ 0.92 (s, 9 H), 1.02–1.33 (overlapping s, t, 9 H), 2.12–2.57 (m, 2 H), 5.85 (s, 1 H) (enolic hydroxyl is apparently too broad to be observed).

Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63; Si, 12.19. Found: C, 57.51; H, 9.84; Si, 12.02.

2,2-Dimethyl-5-ethyl-3(2*H*)-furanone (5). A mixture of 5.2 g (22.6 mmol) of diketone 15, 120 mL of 50% aqueous tetrahydrofuran, and 300 mL of 10% HCl was stirred at ambient temperature overnight. The solution was then poured into a mixture of saturated brine–ether, the aqueous phase was extracted with ether, and the combined organic layers were dried over magnesium sulfate. Removal of the solvent in vacuo and distillation [bp 82–86 °C (30 mmHg)] yielded 1.3 g (41%) of 2,2-dimethyl-5-ethyl-3(2*H*)-furanone (5): colorless oil; IR (CCl_4) 2980 (s), 1710 (s), 1600 (s), 1183 (s), 1161 (w), 922 (s) cm^{-1}; NMR (60 MHz, CCl_4) δ 1.1–1.4 (overlapping s, t, 9 H), 2.27–2.47 (q, J = 7 Hz, 2 H), 5.23 (s, 1 H) [lit.[24] NMR δ 1.22 (t, 3 H), 1.28 (s, 6 H), 2.47 (q, 2 H), 5.26 (s, 1 H)].

General Procedure for γ-Aldol Condensations. 2,2-Dimethyl-5-(1-methyl-2-hydroxybutyl)-3(2*H*)-furanone (16). To a flask which had been flame dried under a stream of nitrogen were added 0.29 mL (2.1 mmol) of diisopropylamine and 10 mL of tetrahydrofuran. After the mixture was cooled to −15 °C, 0.84 mL (2.1 mmol; 2.5 M solution) of *n*-butyllithium was added and the mixture stirred 5 min. The temperature was then lowered to −78 °C, and a solution of 265 mg (1.9 mmol) of 2,2-dimethyl-5-ethyl-3(2*H*)-furanone (5) in 4.0 mL of tetrahydrofuran was added slowly. After 30 min a solution of 149 mg (2.57 mmol) of propionaldehyde in 3.0 mL of THF was added dropwise and the mixture stirred 20 min. The reaction was quenched at −78 °C by being poured into ether–ammonium chloride and dried over magnesium sulfate. Preparative thin-layer chromatography [1000-μm silica gel plate, elution with 20% ether–methylene chloride (v/v)] yielded 257 mg (69%) of a diastereomeric mixture of alcohols which was washed with hexane to remove colored impurities and gave a white crystalline solid: mp 74–75 °C; IR (CCl_4) 3300–3600 (s, br), 2850–3000 (s), 1680 (s), 1580 (s), 1450 (m), 1375 (m), 1360 (sh), 1180 (s), 935 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ .99 (t, J = 7.2 Hz, 3 H), 1.28, 1.30 (2 d, J = 7.2 Hz, 3 H), 1.39–1.82 (m and s, 9 H), 2.68–2.83 (m, 1 H), 3.68, 3.77 (2 br s, 1 H), 5.43 (br s, 1 H); mass spectrum, m/e 198.1256 (M^+, calcd for $C_{11}H_{18}O_3$ 198.1254).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.56. Found: C, 66.45; H, 9.57.

2,2-Dimethyl-5-(1-methyl-2-hydroxypropyl)-3(2*H*)-furanone (18). By use of the general procedure, condensation of 5 with acetaldehyde afforded, after preparative thin layer chromatography [1000-μm silica gel plate, elution with 20% ether–methylene chloride (v/v)], 77 mg (54%) of a diastereomeric mixture of alcohols (18: IR (CCl_4) 3300–3600 (s, br), 2850–3000 (m), 1700 (s), 1595 (s), 1475 (w), 1395 (w), 1380 (sh), 1180 (s), 930 (m), 905 (w) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.20–1.28 (2 overlapping d, J = 7 Hz, 6 H), 1.38 (s, 6 H), 1.88–1.96 (2 br s, 1 H), 2.65–2.74 (m, 1 H), 3.96–4.05 (br s, 1 H), 5.40–5.43 (2 s, 1 H); mass spectrum, m/e 184.1122 (M^+, calcd for $C_{10}H_{16}O_3$ 184.1100).

2,2-Dimethyl-5-(1-methyl-2-hydroxy-2-phenylethyl)-3-(2*H*)-furanone (17). By use of the above general procedure, aldol condensation of 5 with benzaldehyde afforded, after preparative thin-layer chromatography [1000-μm silica gel plate, elution with 20% ether–methylene chloride (v/v)], 84 mg (76%) of a diastereomeric mixture of alcohols, which recrystallized from hexane–benzene as white flakes: mp 143–144 °C); IR ($CHCl_3$) 3300–3600 (m, br), 2900–3000 (m), 1685 (s), 1590 (s), 1450 (w), 1375 (w), 1360 (w), 1180 (s), 930 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.10 (d, J = 7.2 Hz, 3 H), 1.26–1.42 (m, 2 s, 7 H), 2.80 (br s, 1 H), 3.04–3.18 (m, 1 H), 4.92, 4.96 (2 s, 1 H), 7.48–7.60 (m, 5 H).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.21; H, 7.52.

2,2-Dimethyl-5-(1-methyl-2-hydroxy-4-phenyl-3-butenyl)-3(2*H*)-furanone (19). By use of the above general procedure, aldol condensation of 5 with *trans*-cinnamaldehyde afforded, after purification by preparative thin-layer chromatography (1000-μm silica gel plate, elution with 20% ether–methylene chloride (v/v)], 78 mg (38%) of a diastereomeric mixture of alcohols as a pale yellow solid: mp 78.5–80.5 °C; IR ($CHCl_3$) 3300–3600 (s, br), 2850–3000 (s), 1660–1700 (s, br), 1580 (s), 1450 (m), 1375 (s), 1200–1300 (s, br), 1185 (s), 1075–1125 (s, br), 1015–1050 (s, br), 970 (s) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.29–1.44 (overlapping singlets and doublets, 9 H), 2.38 (br s, 1 H), 2.93–3.04 (m, 1 H), 4.56–4.66 (m, 1 H), 5.59, 6.62 (2 s, 1 H), 6.35 (dd, J = 16.6, 7.28 Hz, 1 H), 6.78, 6.83 (2 d, J = 16.6 Hz, 1 H), 7.40–7.60 (m, 5 H).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.83; H, 7.46.

Purification of Cuprous Chloride.[25] Cuprous chloride used in the dehydration reactions was freed from copper(II) impurities by the following procedure. To a hot solution of 30 g of cupric sulfate pentahydrate and 9 g of sodium chloride in 100 mL of water was added 7 g of sodium bisulfite and 4.5 g of sodium hydroxide, the latter dissolved in 50 mL of water. After being stirred 10 min, the solution was cooled to allow precipitation of cuprous chloride. The supernatant was decanted, and the cuprous chloride was washed quickly with water and finally dried at 1 mmHg for 17 h.

2,2-Dimethyl-5-(1-methyl-1-butenyl)-3(2*H*)-furanone (21, 22). To a solution of 257 mg (1.3 mmol) of 2,2-dimethyl-5-(1-methyl-2-hydroxybutyl)-3(2*H*)-furanone (16) in 10 mL of benzene were added 274 mg (1.3 mmol) of dicyclohexylcarbodiimide and 139 mg (1.4 mmol) of purified cuprous chloride. After being refluxed 2 h, the mixture was cooled and filtered through a pad of magnesium sulfate. Removal of the solvent in vacuo followed by preparative thin-layer chromatography [1000-μm silica gel plate, elution with 10% ether–methylene chloride (v/v)] yielded 141 mg (73% based on recovered alcohol) of a 1:2 mixture of *E* and *Z* isomers, respectively.

For the *E* isomer (21): mp 51.5–53 °C; R_f 0.37; IR ($CHCl_3$) 2900–3000 (m), 1680 (s), 1635 (s), 1560 (s), 1460 (w), 1380 (m), 1330 (w), 1183 (s) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.09 (t, J = 7 Hz, 3 H), 1.39 (s, 6 H), 1.89 (d, J = 1.2 Hz, 3 H), 2.19–2.31 (m, 2 H), 5.48 (s, 1 H), 6.59 (t, J = 7 Hz, 1 H); mass spectrum, m/e 180.1152 (M^+, calcd for $C_{11}H_{16}O_2$ 180.1151).

(24) R. M. Carlson, R. W. Jones, and A. S. Hatcher, *Tetrahedron Lett.*, 1741 (1975).

(25) R. Adams, J. R. Johnson, and C. F. Wilcox, Jr., "Laboratory Experiments in Organic Chemistry", 6th ed., Collier-MacMillan Limited, London, 1970, p 323.

The *Z* isomer (**22**, R_f 0.40) was isolated as a colorless oil with the following spectral data: IR ($CHCl_3$) 2900–3000 (m), 1680 (s), 1630 (m), 1550 (s), 1460 (w), 1380 (m), 1185 (s), 1095 (m), 945 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 0.97 (t, J = Hz, 3 H), 1.33 (s, 6 H), 1.88 (d, J = 1.1 Hz, 3 H), 2.28–2.40 (m, 2 H), 5.39 (s, 1 H), 5.84 (t, J = 7 Hz, 1 H); mass spectrum, m/e 180.1157 (M^+, calcd for $C_{11}H_{16}O_2$, 180.1151).

2,2-Dimethyl-5-(1-methyl-2-phenylethenyl)-3(2*H*)-furanone (23, 24). To a solution of 138 mg (0.56 mmol) of 2,2-dimethyl-5-(1-methyl-2-hydroxy-2-phenylethyl)-3(2*H*)-furanone (**18**) in 10 mL of benzene were added 160 mg (0.77 mmol) of dicyclohexylcarbodiimide and 86 mg (0.81 mmol) of purified cuprous chloride. The mixture was refluxed 7 h, cooled, and filtered through a pad of magnesium sulfate. Removal of the benzene in vacuo followed by preparative thin-layer chromatography [1000-μm silica gel plate, elution with 10% ether–methylene chloride (v/v)] afforded 22 mg of fluffy white crystalline solid (R_f 0.47, mp 96–97 °C) which as been assigned the *E* configuration and 51 mg of an oil (R_f 0.52) which has been assigned the *Z* configuration (60% yield based on recovered alcohol).

The E isomer (**23**) had the following spectral data: IR ($CHCl_3$) 2930–3000 (m), 1675 (s), 1620 (m), 1545 (s), 1375 (w), 1335 (sh), 1180 (s) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.52 (s, 6 H), 2.24 (d, J = 0.6 Hz, 3 H) 5.87 (s, 1 H), 7.52–7.66 (m, 5 H), 7.74 (br s, 1 H).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.85; H, 7.10.

The *Z* isomer (**24**) had the following spectral data: IR ($CHCl_3$) 2930–3000 (m), 1675 (s), 1625 (m), 1560 (s, br), 1440 (w), 1375 (m), 1360 (w), 1325 (w), 1180 (s) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.36 (s, 6 H), 2.19 (d, J = 1.45 Hz, 3 H), 5.46 (s, 1 H), 7.06 (br s, 1 H), 7.38–7.50 (m, 5 H); mass spectrum, m/e 228.1154 (M^+ calcd for $C_{15}H_{16}O_2$ 228.1151).

2,2-Dimethyl-5-(1-methylpropenyl)-3(2*H*)-furanone (25, 26). To a solution of 173 mg (1.12 mmol) of 2,2-dimethyl-5-(1-methyl-2-hydroxypropyl)-3(2*H*)-furanone (**17**) in 10 mL of benzene was added 292 mg (1.4 mmol) of dicyclohexylcarbodiimide and 124 mg (1.26 mmol) of purified cuprous chloride. After being refluxed 3.5 h, the mixture was cooled and filtered through a pad of magnesium sulfate. Removal of the benzene in vacuo followed by preparative thin-layer chromatography [1000-μm silica gel plate, elution with 10% ether-methylene chloride (v/v)] afforded 91 mg (63% based on recovered alcohol) of a 1:1 mixture of *E* and *Z* isomers which were separated by repeated elutions.

The *E* isomer (**25**) was isolated as a colorless solid: mp 41.5–43 °C; R_f 0.31; IR ($CHCl_3$) 2850–3000 (s), 1685 (s), 1640 (s), 1555 (s), 1460 (w), 1380 (m), 1370 (w), 1185 (s), 1095 (m), 945 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.40 (s, 6 H), 1.86 (d, J = 7 Hz, 3 H), 1.89 (br s, 3 H), 5.48 (s, 1 H), 6.72 (q, J = 7 Hz, 1 H); mass spectrum, m/e 166.1005 (M^+, calcd for $C_{16}H_{14}O_2$ 166.0994).

The *Z* isomer (**26**) was obtained as a colorless oil: R_f 0.36; IR ($CHCl_3$) 2860–3000 (s), 1680 (s), 1630 (s), 1550 (s), 1450 (m), 1375 (m), 1360 (m), 1325 (m), 1885 (s), 1080 (m), 970 (m), 945 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.41 (s, 6 H), 1.94–2.00 (overlapping s and d, 6 H), 5.49 (s, 1 H), 6.05 (q, J = 7 Hz, 1 H); mass spectrum, m/e 166.1000 (M^+, calcd for $C_{10}H_{14}O_2$ 166.0994).

2,2-Dimethyl-5-(1-methyl-4-phenylbutadienyl)-3(2*H*)-furanone (27, 28). To a solution of 55 mg (0.2 mmol) of 2,2-dimethyl-5-(1-methyl-2-hydroxy-4-phenyl-3-butenyl)-3(2*H*)-furanone (**19**) in 10 mL of benzene was added 54.2 mg (0.26 mmol) of dicyclohexylcarbodiimide and 18 mg (0.18 mmol) of purified cuprous chloride. After being refluxed 3.5 h, the mixture was cooled and filtered through a pad of magnesium sulfate. Removal of the solvent in vacuo followed by preparative thin-layer chromatography [1000-μm silica gel plate, elution with 10% ether–methylene chloride (v/v)] yielded a 3:2 mixture of (*E*)-trans/(*Z*)-trans isomers, respectively (55% based on recovered alcohol).

The (*E*)-trans isomer (**27**), R_f 0.39) was isolated as bright yellow crystals: 15.5 mg; mp 77.5–80 °C; IR (CCl_4) 2830–3030 (m), 1670 (s), 1580 (s), 1530 (s), 1430 (w), 1460 (m), 1187 (s), 1110 (m), 975 (m), 960 (m), 690 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.42 (s, 6 H), 2.08 (br s, 3 H), 5.58 (s, 1 H), 6.86 (d, J = 15 Hz, 1 H, 7.33–7.42 (m, 7 H); mass spectrum, m/e 254.1273 (M^+, calcd for $C_{17}H_{18}O_2$ 254.1307).

The (*Z*)-trans isomer (**28**) was isolated as a sticky yellow solid: 10.4 mg; R_f 0.41; IR (CCl_4) 2850–3000 (m), 1680 (s), 1600 (m), 1530 (m), 1450 (w), 1320–1375 (w, br) 1179 (s), 970 (m), 925 (m), 910 (m), 685 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.48 (s, 6 H), 2.07 (br s, 3 H), 5.54 (s, 1 H), 6.49 (d, J = 11 Hz, 1 H), 6.66 (d, J = 15 Hz, 1 H), 7.18–7.40 (m, 5 H), 7.62 (dd, J = 15 and 11 Hz, 1 H); mass spectrum, m/e 254.1300 (M^+, calcd for $C_{17}H_{18}O_2$ 254.1307).

7-(Allyloxy)coumarin (32). To a slurry of 23.5 g (0.17 mol) of anhydrous potassium carbonate in 500 mL of acetone were added 6 g (0.37 mol) of 7-hydroxycoumarin (**31**) and 16.8 mL (0.2 mol) of allyl bromide. The resulting mixture was refluxed for 16 h. After the mixture was cooled the acetone was removed in vacuo, and 500 mL of 5% aqueous NH_4OH was added to precipitate 6.4 g (86%) of 7-(allyloxy)coumarin (**32**): mp 80–80.5 °C; IR ($CHCl_3$) 2850–3100 (w), 1725 (s, br), 1620 (s), 1410 (w), 1375 (w), 1125 (s, br), 835 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 4.67 (d, J = 7 Hz, 2 H), 5.40 (d, J = 7 Hz, 1 H), 5.51 (d, J = 14 Hz, 1 H), 6.02–6.18 (m, 1 H), 6.30 (d, J = 10 Hz, 1 H), 6.86–6.91 (s, d, J = 10 Hz, 2 H), 7.42 (d, J = 10 Hz, 1 H), 7.69 (d, J = 10 Hz, 1 H).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 70.97; H, 4.94.

7-[(1,2-Dihydroxypropyl)oxy]coumarin (33). To a solution consisting of 12 mg (.047 mol) of osmium tetraoxide 0.74 g (4.86 mmol) of *N*-methylmorpholine N-oxide hydrate, 7.5 mL of water, 3 mL of acetone, and 1.2 mL of *tert*-butyl alcohol was added dropwise 1 g (4.35 mmol) of 7-(allyloxy)coumarin (**32**) in 18 mL 25% aqueous dioxane (v/v). After being stirred overnight at room temperature under a nitrogen atmosphere, the mixture was treated for 45 min with 630 mg of Celite and 70 mg of sodium bisulfite. After filtration, the pH of the filtrate was adjusted to 7 with 3 M H_2SO_4, and the acetone was then removed in vacuo. The pH of the solution was then further lowered to 2, and the mixture was poured into ethyl acetate and washed with water. The aqueous washings were extracted with ethyl acetate, and the combined organic layers were washed with brine. After the mixture was dried over magnesium sulfate the solvent removed in vacuo, 954 mg (82%) of diol **33** was isolated and recrystallized from ethyl acetate: mp 122–124 °C; IR (Nujol) 3200–3350 (s, br), 1685 (s, br), 1610 (s, br), 1495 (s, br), 1420 (s), 1240 (m), 845 (m) cm^{-1}; NMR (360 MHz, $(CD_3)_2SO$) δ 3.40–3.48 (m, 2 H), 3.76–3.84 (m, 1 H), 3.92–4.02 (dd, J_{AB} = 10.8 Hz, J_{AX} = 3.6 Hz, 1 H), 4.06–4.14 (dd, J_{BA} = 10.8 Hz, J_{BX} = 7.2 Hz, 1 H), 4.71 (t, J = 5.7 Hz, 1 H, secondary hydroxyl) 5.02 (d, J = 5.4 Hz, 1 H, tertiary hydroxyl), 6.28 (d, J = 9 Hz, 1 H), 6.91–6.98 (overlapping s and d, 2 H), 7.61 (d, J = 9 Hz, 1 H), 7.99 (d, J = 9 Hz, 1 H); mass spectrum, m/e 236.0689 (M^+, calcd for $C_{12}H_{12}O_5$ 236.0685).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.87; H, 5.01.

7-(2-Oxoethoxy)coumarin (6). A mixture of 0.5 g (2 mmol) of diol **33**, 19 mL of 25% aqueous dioxane (v/v) and 1.2 g (4.27 mmol) of sodium periodate was stirred at ambient temperature for 40 h. The organic material was extracted into ethyl acetate, washed with water and brine, and finally dried over magnesium sulfate. Removal of the solvent in vacuo yielded 310 mg (76%) 7-(2-oxoethoxy)coumarin (**6**), which was recrystallized from cyclohexane–ethyl acetate: mp 124–127 °C (lit.[19,26] mp 130 °C); IR (KBr) 2885–2995 (w, br), 1665–1700 (s, br), 1590 (s), 1290 (m), 1235 (m), 900 (w), 825 (m) cm^{-1}; NMR (60 MHz, $(CD_3)_2SO$) δ 5.00 (br s, 2 H), 6.30 (d, J = 9 Hz, 1 H), 6.85–7.10 (m, 2 H), 7.65 (d, J = 9 Hz, 1 H), 8.00 (d, J = 9 Hz, 1 H), 9.70 (s, 1 H); mass spectrum, m/e 204.0438 (M^+, calcd for $C_{11}H_8O_4$ 204.0422).

7-[[3-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl)-2-hydroxybutyryl]oxy]-2*H*-1-benzopyran-2-one (34). To a flask which had been flame dried under a stream of nitrogen was added 85 μL (0.6 mmol) of diisopropylamine and 10 mL of tetrahydrofuran. After the mixture was cooled to −15 °C, 0.25 mL (0.6 mmol; 2.4 M solution) of *n*-butyllithium was added and the mixture stirred 5 min. The temperature was then lowered to −78 °C, and a solution of 92 mg (0.66 mmol) of 2,2-dimethyl-5-ethyl-3(2*H*)-furanone (**5**) in 2.0 mL of tetrahydrofuran was added dropwise. After the mixture was stirred 30 min, a solution containing 187 mg (0.92 mmol) of 7-(2-oxoethoxy)coumarin (**6**) in 8.0 mL of tetrahydrofuran was added very slowly over a 30-min

(26) 7-(2-Oxoethoxy)coumarin exists as the monohydrate which tends to lower and broaden the melting point range (see ref 5a).

period. Stirring was continued for 1 h at -78 °C. Without removal of the cooling bath, the solution was warmed to 10 °C over 1.5 h. The mixture was then poured into ethyl acetate, washed with ammonium chloride and brine, and dried over magnesium sulfate. Preparative thin-layer chromatography [1000-μm silica gel plate, elution with 20% ether–methylene chloride (v/v)] afforded 92 mg (53%) of a diastereomeric mixture of alcohols **34** isolated as a yellow foam: IR ($CHCl_3$) 3200–3600 (m, br), 1650–1750 (s, br) 1610 (s), 1580 (m, sh), 1200–1250 (s, br), 1140 (m), 830 (m) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.32–1.43 (2 s and d overlapping, 9 H), 2.61 (br s, 1 H), 2.95–3.08 (m, 1 H), 3.98–4.12 (m, 2 H), 4.20, 4.21 (2 br s, 1 H), 5.51, 5.54 (2 s, 1 H), 6.50 (d, J = 11 Hz, 1 H), 6.66–6.76 (m, 2 H), 7.26 (d, J = 11 Hz, 1 H), 7.51 (d, J = 11 Hz, 1 H); mass spectrum, m/e 344.1287 (M^+, calcd for $C_{19}H_{20}O_6$ 344.1260).

7-[[3-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl)-2-butenyl]oxy]-2*H*-1-benzopyran-2-one (3, 35). To a solution of 119 mg (0.35 mmol) of **34** in 12 mL of benzene were added 84.4 mg (0.41 mmol) of dicyclohexylcarbodiimide and 40 mg (0.4 mmol) of purified cuprous chloride. The mixture was refluxed 26 h and then filtered through a pad of magnesium sulfate. Removal of the benzene in vacuo followed by preparative thin-layer chromatography [1000-μm silica gel plate, elution with 20% ether–methylene chloride (v/v)] afforded a 1:1 mixture of E and Z isomers of geiparvarin (30% based on recovered alcohol).

The E isomer (**3**; 14.5 mg, R_f 0.38) was recrystallized from methanol (mp 157–158 °C) and proved to be identical in all respects with geiparvarin, possessing the following spectral data: IR ($CHCl_3$) 2800–3000 (m), 1675–1710 (s, br), 1600 (s), 1550 (s), 1350–1400 (m), 1285 (m), 1180 (s), 1165 (s), 1130 (m), 1015 (m, br), 835 (s) cm^{-1}; NMR(360 MHz, $CDCl_3$) δ 1.42 (s, 6 H), 2.03 (d, J = 0.84 Hz, 3 H), 4.82 (d, J = 5.4 Hz, 2 H), 5.61 (s, 1 H), 6.17 (d, J = 9 Hz, 1 H), 6.64 (t, J = 5.4 Hz, 1 H), 6.70, 6.75 (s and d, J = 9 Hz, 2 H), 7.29 (d, J = 9 Hz, 1 H), 7.53 (d, J = 9 Hz, 1 H), NMR (60 MHz, $CDCl_3$) δ 1.40 (s, 6 H), 2.10 (d, J = 15 Hz, 3 H), 4.80 (d, J = 6 Hz, 2 H), 5.60 (s, 1 H), 6.25 (d, J = 9 Hz, 1 H), 6.70–7.00 (m, 3 H), 7.30 (d, J = 9 Hz, 1 H), 7.65 (d, J = 9 Hz, 1 H); mass spectrum, m/e 326.1168 (M^+, calcd for $C_{19}H_{18}O_5$ 326.1154) [lit.[5a] mp 160–161 °C; NMR[5b] (60 MHz, $CDCl_3$) δ 1.4 (s, 6 H), 2.1 (d, J = 1 Hz, 3 H), 4.87 (d, J = 6 Hz, 2 H), 5.6 (s, 1 H), 6.3 (d, J = 9.5 Hz, 1 H), 6.6–7.0 (m, 3 H), 7.3 (d, J = 9.5 Hz, 1 H), 7.61 (d, J = 9.5 Hz, 1 H).

The Z isomer (**35**; 17.3 mg, R_f 0.42) recrystallized from methanol as a fluffy white solid: mp 149–150 °C IR ($CHCl_3$) 2800–3000 (m), 1675–1720 (s, br), 1600 (s), 1550 (s), 1340–1400 (m), 1290 (m), 1175 (m), 1135 (m), 1020 (m, br), 840 (s) cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.47 (s, 6 H), 2.06 (d, J = 1.5 Hz, 3 H) 5.02 (d, J = 4. 3 Hz, 2 H), 5.58 (s, 1 H), 6.08 (t, J = 4.3 Hz, 1 H), 6.26 (d, J = 9 Hz, 1 H), 6.78 (s, 1 H), 6.83 (d, J = 9 Hz, 1 H), 7.39 (d, J = 9 Hz, 1 H), 7.64 (d, J = 9 Hz, 1 H); mass spectrum, m/e 326.1143 (M^+, calcd for $C_{19}H_{18}O_3$ 326.1154).

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Registry No. 3, 36413-91-9; **5**, 18458-23-6; **6**, 16851-02-8; **13**, 55816-60-9; **14**, 75767-42-9; **15**, 75767-43-0; **16** (isomer 1), 74796-27-3; **16** (isomer 2), 74796-32-0; **17** (isomer 1), 74796-28-4; **17** (isomer 2), 74796-33-1; **18** (isomer 1), 74796-26-2; **18** (isomer 2), 74796-31-9; **19** (isomer 1), 74796-29-5; **19** (isomer 2), 74796-34-2; **20**, 75767-44-1; **21**, 74796-38-6; **22**, 74796-39-7; **23**, 74796-40-0; **24**, 74796-41-1; **25**, 74796-36-4; **26**, 74796-37-5; **27**, 74796-42-2; **28**, 74796-43-3; **31**, 93-35-6; **32**, 31005-03-5; **33**, 22919-21-7; **34** (isomer 1), 74796-30-8; **34** (isomer 2), 74796-35-3; **35**, 74796-44-4; 3-hydroxy-3-methyl-2-butanone, 115-22-0; propionaldehyde, 123-38-6; acetaldehyde, 75-07-0; benzaldehyde, 100-52-7; *trans*-cinnamaldehyde, 14371-10-9; allyl bromide, 106-95-6.

Microbial Stereodifferentiating Reduction and Absolute Configuration of 8-Deltacyclanone and 4-Brendanone.[1] An Application of the Quadrant Rule

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Incubation of (±)-8-deltacyclanone (**11**) and (±)-4-brendanone (**16**) with *Curvularia lunata* furnished a 9:7:1 mixture of (+)-ketone **11**, (−)-endo alcohol **12**, and exo alcohol **14** and a 2:1 mixture of (−)-ketone **16** and (−)-endo alcohol **17**, respectively. The CD spectra as well as the NMR spectra of these metabolites permitted assignment of their absolute configurations which were found to be compatible with those predicted on application of the quadrant rule to these racemic ketone substrates.

In previous papers,[2] we have reported the microbial stereodifferentiating reduction of various racemic C_2 ketones[3] including 9-*twist*-brendanone (**1**), 2-brexanone (**2**), D_3-trishomocubanone (**3**), and the biphenyl-bridged ketone (**4**) (Chart I) with *Curvularia lunata* and *Rhodotorula rubra* and summarized the results in a "C_2-ketone rule"[4]

Chart I

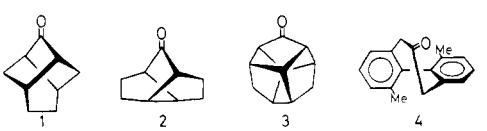
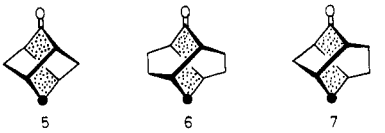


Chart II



which states that these microbes preferentially reduce the P–C_2 ketone enantiomers possessing the larger parts of

(1) Presented at the 41th Annual Meeting of the Chemical Society of Japan, Osaka, Apr 1980; Abstracts, Vol. II, p 1137.

(2) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 667–8. (b) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Org. Chem.* **1979**, *44*, 4588–93.

(3) In this paper, ketones are conveniently classified according to their symmetry: C_s ketones belong to the C_s point group and have the plane of symmetry coincident with the carbonyl plane; C_2 ketones belong to the C_2 point group and have the C_2 axis coincident with the carbonyl axis; C_1 ketones have no symmetry element passing through the carbonyl axis.

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