Quararibea Metabolites. 4.[1] Total Synthesis and Conformational Studies of (±)-Funebrine and (±)-Funebral

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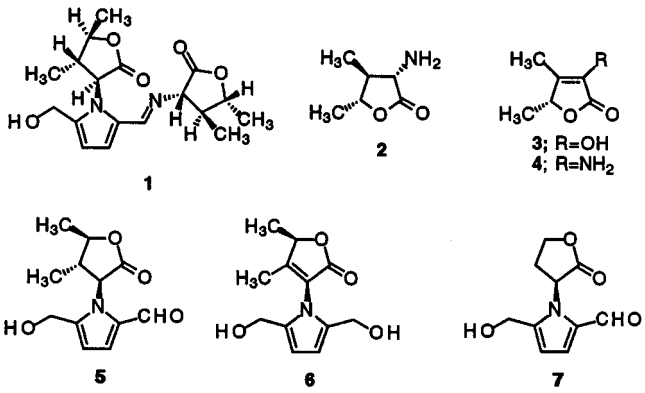
Received July 28, 1998

Syntheses of racemic forms of the main secondary metabolites of *Quararibea funebris*, (±)-funebrine, (±)-funebral, and their biogenetic precursor (±)-(2*S*,3*S*,4*R*)-γ-hydroxyalloisoluecine lactone have been developed. In synthetic studies, a new variation of the Paal−Knorr condensation employing titanium isopropoxide was utilized to construct the pyrrole lactone moiety. Two efficient synthetic approaches to the key (±)-γ-amino lactone have been developed, one based on Claisen chemistry and the other on addition reactions to the butenolide ring of β-angelicalactone. The restricted rotation around the C(sp^3)−N(sp^2) bond in the pyrrole lactone structures of (±)-funebrine, (±)-funebral, and related aldehydes has been probed by conformational dynamic studies, and the barriers for interconversion between conformations have been measured by full NMR line-shape analysis. Molecular mechanics (MMX) and a ^{1}H−^{1}H NOE study indicate a distinct preferred conformation for (±)-funebrine.

Quararibea funebris (Llave) Vischer (Bombacaceae)[2] is a moderately large tree indigenous to southeastern Mexico and Guatemala. It derives its specific name from the fact that the Zapotec people of Oaxaca, Mexico, conducted funeral rites beneath its branches. The strongly odorous flowers of the tree have been used as a flavor additive in chocolate drinks from pre-Columbian times, and in local folk medicine the plant has served as a cough remedy and antipyretic, to control menstrual disorders and psychopathic fears, and as a hallucinogen.[3] Our interest in *Q. funebris* first arose from a report[4] of alkaloids in its flowers and from Schultes's intriguing observation[3] that the dried flowers and leaves have a characteristic spicy odor that persists even in long-stored herbarium specimens. Our investigation of the secondary metabolites of *Q. funebris* dried flowers yielded a family of compounds, **1**−**4**, from polar fractions. Enol lactone **3** and enamine **4** are responsible for the odor of the flowers. The saturated lactone **2** and its parent amino acid, (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine, were obtained along with the pyrrole alkaloid funebrine (**1**).[5] The stereochemistry shown in **1**−**4** is based on the presumed derivation of **1**, **3**, and **4** from **2**.[5] Subsequent investigations disclosed two related metabolites, funebral (**5**)[6] and funebradiol (**6**).[7] All these *Quararibea* metabolites are structurally unusual. Indeed the only similar natural pyrrole isolated thus far is the bisnorfunebral derivative **7**. This compound was obtained by Lynn[8] from pea seedlings (*Pisum sativum L.*), where it was identified as a regulator of cellular cycles.



Funebrine (**1**) is a structurally unique alkaloid, and its discovery also represents the first characterization of an alkaloid in the family Bombaceae. Since alkaloids are known to exhibit a wide range of physiological activity,[9] and extraction of the flowers of *Q. funebris* yielded insufficient funebrine (**1**) and funebral (**5**) for full biological evaluation, we initiated a synthetic program.

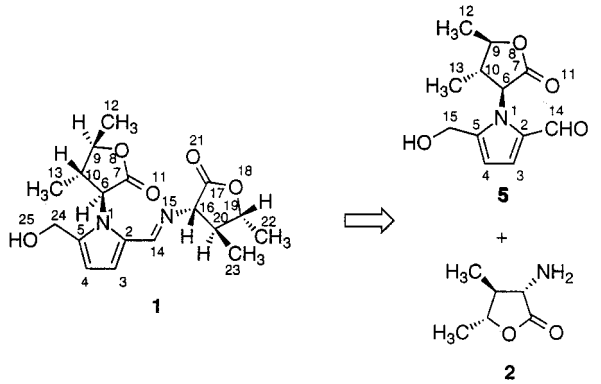
The existence of an imine bond in funebrine (**1**) suggests C14−N15 bond disconnection to give funebral (**5**) and γ-hydroxyalloisoleucine lactone (**2**) (Scheme 1).[10] The known lability of imines suggests this reaction should be the last in the synthesis of funebrine.

Funebral (**5**) has a pyrrole ring with a N-substituted lactone, the lactone being identical to lactone **2**, and formyl and hydroxymethyl substituents at positions 2 and 5 of the pyrrole, respectively. Various ways to incorporate the *N*-, 2-, 5-substituents on a pyrrole ring

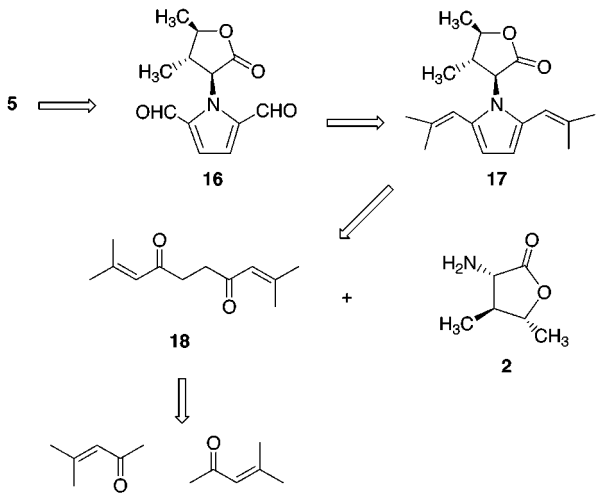
(1) For part 3, see Yu, S-X.; LeQuesne, P. W. *Tetrahedron Lett*. **1995**, *36*, 6205.
(2) For a thorough taxonomic discussion, see Alverson, W. S. *Taxon* **1989**, *38*, 377.
(3) Schultes, R. E. *Bot. Mus. Leafl*. **1957**, *17*, 247.
(4) Rosengarten, F. *Bot. Mus. Leafl*. **1977**, *25*, 184.
(5) Raffauf, R. F.; Zennie, T. M.; Onan, K. D.; Le Quesne, P. W. *J. Org. Chem*. **1984**, *49*, 2714.
(6) Zennie, T. M.; Cassady, J. M.; Raffauf, R. F. *J. Nat. Prod*. **1986**, *49*, 695.
(7) Zennie, T. M.; Cassady, J. M. *J. Nat. Prod*. **1990**, *53*, 1611.
(8) Lynn, D. D.; Jaffe, K.; Cornwall, M.; Tramontano, W. *J. Am. Chem. Soc*. **1987**, *109*, 5858.
(9) Dalton, D. R. *The Alkaloids*; Marcel Dekker Inc: New York, Basel, 1979.
(10) The numbering system here originated from the earlier X-ray result; see ref 5.

10.1021/jo981501u CCC: $18.00
Published on Web 04/01/1999

Scheme 1



Scheme 2



were investigated (see below), but eventually Lynn's strategy[8] of chemoselective reduction of one of the aldehyde groups in the 2,5-diformyl-*N*-substituted pyrrole **16** was adopted. Dialdehyde **16** was obtained by oxidation of the diene **17**, which was conveniently synthesized by Paal−Knorr condensation between γ-diketone **18** and lactone **2** (Scheme 2).

Synthesis of (±)-amino lactone **2** was achieved by two routes. The first, shown in Scheme 3, is based on highly stereoselective ester enolate Claisen chemistry developed by Bartlett and co-workers.[11] The key rearrangement of ester **8** took place with >20:1 stereoselectivity in favor of the desired isomer, based on peak area ratio of the methyl doublets in proton NMR. Direct iodolactonization of acid **9** gave a cyclic carbamate as the major product, since the *tert*-butoxycarbonyl protecting group of **9** preferentially participated in the cyclization. We therefore adjusted the protecting group of **9** to phthaloyl by hydrolysis with trifluoroacetic acid to yield the amine salt **10**, which was subsequently refluxed with phthalic anhydride in the presence of triethylamine. The methyl ester derivative **12** was used instead of acid **11** in the iodolactonization step because high stereoselectivity was achieved under thermodynamic control.[12] Reduction of the iodomethyl compound **13** with tributylstannane gave, after acid hydrolysis of the phthaloyl group, the hydrochloride **15** of the desired amino lactone **2**.

In a second approach (Scheme 4), we considered that the butenolide ring of β-angelicalactone (**19**) would offer a convenient platform for arranging the substituents of **2** in the desired *trans*,*trans*-relationship.[13] Treatment of β-angelicalactone (**19**) first with lithium tris(thiophenyl)-methide and then with trisyl azide gave **20**, which was reduced with Raney nickel to give **2**. Despite the brevity and stereospecificity of this route, the final reduction step and workup were low-yielding, and the approach is at present less efficient than that of Scheme 3, which now proceeds in ca. 20% yield from t-BOC-glycine.

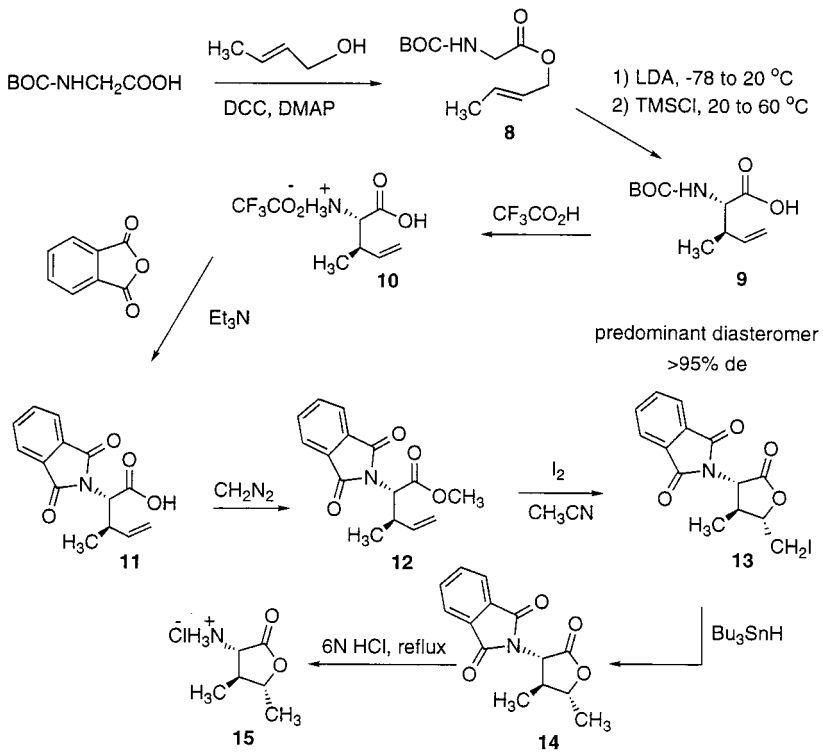
Our first approach to funebral (**5**) (Scheme 5), which made use of the chemistry of Scheme 3 but employed *N*-pyrrolylacetic acid instead of protected glycine, failed because we did not find iodolactonization conditions to which the pyrrole ring was unreactive. Esterification of acid **21** with *trans*-crotyl alcohol proceeded normally to give **22**, which after rearrangement via **23** and methylation to give **24** was subjected unsuccessfully to a variety of iodolactonization reaction conditions. We then turned to pyrrole lactone **25**, obtained from amino lactone hydrochloride **15** and 2,5-dimethoxytetrahydrofuran (Scheme 6). We hoped that this compound would undergoVilsmeier−Haack formylation to give first the mono- and then the diformylated derivative **26** and **16** (Scheme 6). Compound **26** was formed without difficulty, but its ^{1}H NMR spectrum clearly showed restricted rotation around the interannular N1−C6 bond. This finding augured poorly for successful formylation at the remaining α-carbon of the pyrrole. In fact, Vilsmeier−Haack reaction of **26** gave only small quantities of the α,γ-diformyl product. If compound **26** exists as a rotameric pair at room temperature, funebral (**5**) itself should do the same. The original sample of natural funebral comprised only 0.54 mg, and its ^{1}H NMR spectrum did not clearly disclose doubled signals arising from restricted rotation. A second isolation of funebral has now given material whose ^{1}H NMR spectrum showed the existence of two rotamers in a 9:1 ratio in $CDCl_3$.

We then considered Lynn's method for the synthesis of *N*-substituted-α,α′-diformylpyrroles, i.e., ozonolysis of a bisisobutenyl compound such as **17**. Such pyrroles can be prepared by Paal−Knorr reactions between amines and 2,9-dimethyldeca-2,8-diene-4,7-dione (**18**),[27] which itself was obtained by Cu(II)-mediated oxidative dimerization of mesityl oxide. Attempted Paal−Knorr reactions between amino lactone **2** and **18** employing various literature procedures either returned starting material or led to decomposition. Molecular models suggested that the target pyrrole **17** should be sterically crowded, probably also having restricted rotation at room temperature. In this case its formation in the Paal−Knorr reaction should be relatively slow. We therefore sought a catalyst for the Paal−Knorr reaction that would strongly coordinate the oxygen atoms of the diketone and yield neutral reaction products, which would not catalyze polymerization of the pyrrole. Titanium(IV) isopropoxide suggested itself as a suitable catalyst, and a series of model reactions shown in Table 1 demonstrated its utility.[14]

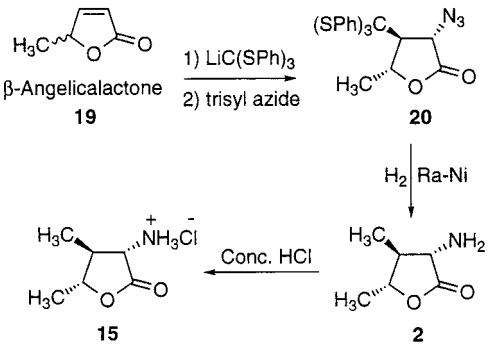
Condensation of amino lactone **2** with **18** in the presence of titanium(IV) isopropoxide gave pyrrole **17** (Scheme 7). ^{1}H and ^{13}C NMR spectra of **17**, as expected, showed significant restricted rotation around the interannular N1−C6 bond. Treatment of this compound with

(11) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.
(12) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.
(13) Chen, S.-Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2168.
(14) Yu, S-X. M.S. Thesis, Northeastern University, Boston, 1995.

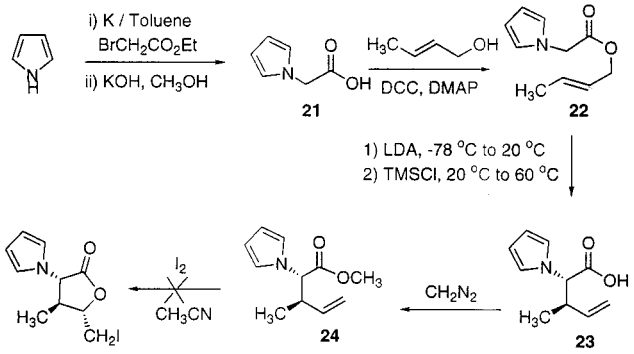
Scheme 3



Scheme 4



Scheme 5



Scheme 6

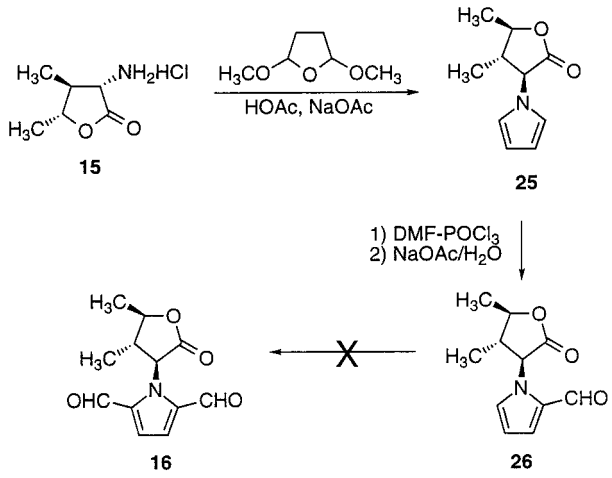
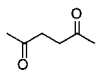
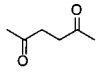
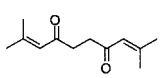
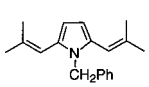


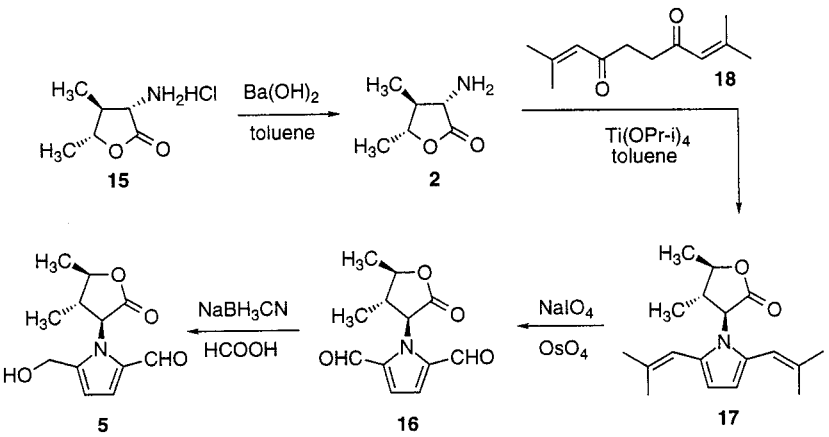
Table 1. Paal–Knorr Synthesis of N,2,5-Trisubstituted Pyrroles Using Titanium(IV) Isopropoxide

Amines	Diketones	Condition	Products	Yield
$PhCH_2NH_2$		Benzene, 20°C, 0.5h		91%
$(CH_3)_3CNH_2$		Benzene, 80°C, 12h		22%
$PhCH_2NH_2$		Benzene, 80°C, 4h		63%

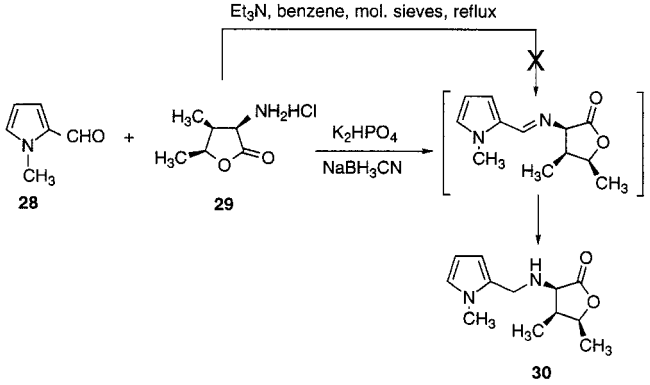
osmium tetraoxide and sodium metaperiodate gave dialdehyde **16**, which, on reduction with sodium cyanoborohydride, gave funebral (**5**) having identical spectral characteristics to the natural product.

Synthesis of (±)-funebrine (**1**) from (±)-funebral (**5**) presented two challenges. First, reaction of (±)-lactone **2** with (±)-funebral (**5**) could potentially yield (±)-funebrine and its diastereomer; secondly, formation of the imine bond might be slow on account of steric crowding. To understand better the chemistry of the imine bond present in funebrine (**1**), the reaction between the model compound *N*-methyl-2-formylpyrrole (**28**) and the easily obtainable (*SRR*,*RSS*)-amino lactone hydro-

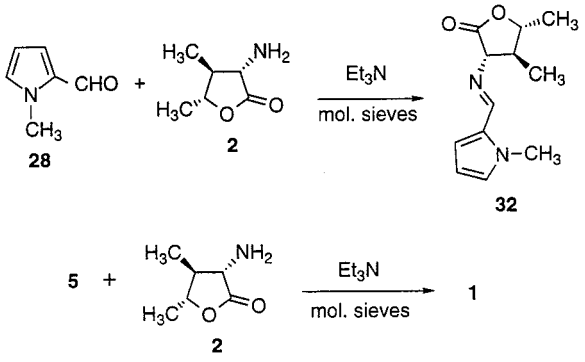
Scheme 7



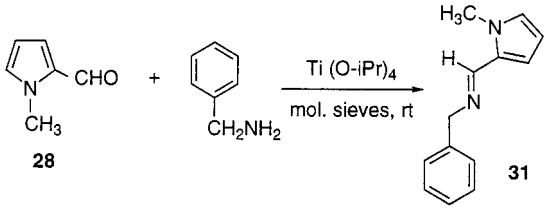
Scheme 8



Scheme 9



Scheme 10



chloride **29**[28] was investigated (Scheme 8). Attempted condensation of **28** and **29** in benzene with molecular sieves and triethylamine under reflux[15] gave an inseparable mixture, the ^{1}H NMR spectrum of which showed no evidence of condensation having taken place. Using a procedure similar to Olsson's,[16] hydrochloride **29**, after neutralization with dipotassium hydrogen phosphate, was treated with sodium cyanoborohydride in methanol in the presence of aldehyde **28**. A ninhydrin- and Ehrlich-positive compound was formed after 48 h of stirring and workup, which, after separation of components, gave the reductive amination product **30**.

The free (±)-amino lactone **2** was generated from the hydrochloride without opening the sensitive lactone ring by adding the solid **15** to mixed 1:1 chloroform and saturated sodium bicarbonate solution. When aldehyde **28**, in a slurry of molecular sieves and triethylamine in anhydrous chloroform,[17] was treated with the free base of (±)-amino lactone **2**, an unstable imine **32** was formed after stirring overnight at room temperature. Under similar conditions, **2** condensed with **5** to give **1** (60%) after refluxing in chloroform for four days (Scheme 9). The identity of the synthetic (±)-funebrine was confirmed by mass spectral analysis, ^{13}C NMR data, and comparison of the ^{1}H NMR spectrum with that of the naturally derived sample.

As mentioned above, condensation between **2** and (±)-funebral (**5**) might have been expected to produce a mixture of (±)-funebrine and a diastereomer, "(±)-Ψ-funebrine", in which the absolute configurations of the component lactone rings are opposite rather than the same. Careful search of the condensation reaction products revealed only (±)-funebrine, recovered starting materials, and traces of a compound which from its ^{1}H NMR spectrum was clearly a decomposition product. Molecular mechanics calculations (vide infra) of funebrine and "Ψ-funebrine" showed that the most stable conformation of the latter is less stable by 2 kcal/mol than the most stable conformation of funebrine. Since imine formation is a reversible reaction, formation of the thermodynamically more stable funebrine would be favored.

Incidentally, titanium tetraisopropoxide was observed to catalyze the formation of an imine bond between aldehyde **28** and benzylamine (Scheme 10). The Schiff's base **31** was formed in 83% yield after 12 h at 20 °C. However, titanium tetraisopropoxide did not induce imine bond formation between (±)-funebral and amino lactone **2**, probably because of complexation between titanium and the lactone oxygens.

The pyrrole lactone structure central to funebrine, funebral, and their synthetic precursors presents a structural situation in which crowding introduced by

(15) Brunner, H.; Reiter, R.; Riepl, G. *Chem. Ber.* **1984**, *17*, 1330.
(16) Olsson, K. Pernemalm, P. *Acta Chem. Scand.* **1979**, *B33*, 125.
(17) Scott, M. K.; Martin, G. E.; DiStefano, D. L.; Fedde, C. L.; Kukla, M. J.; Barrett, D. L.; Baldy, W. J.; Elgin, R. J., Jr.; Kesslick, J. M.; Mathiasen, J. R.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1992**, *49*, 2168.

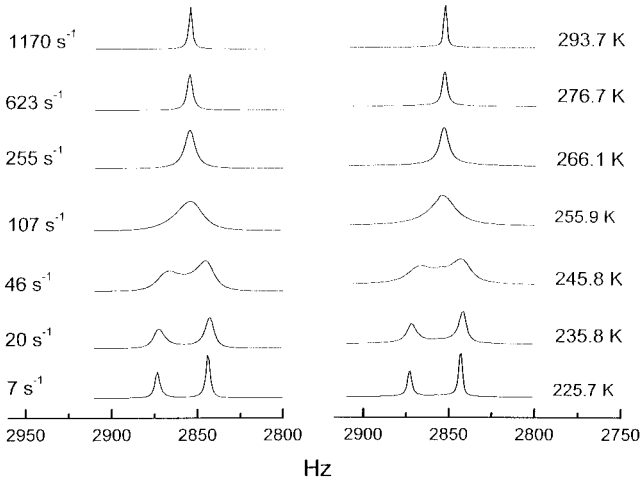


Figure 1. Experimental 300 MHz ^{1}H NMR spectra of the aldehyde signal from **26** at various temperatures are in the right column, and DNMR5 simulations at different exchange rates are in the left column.

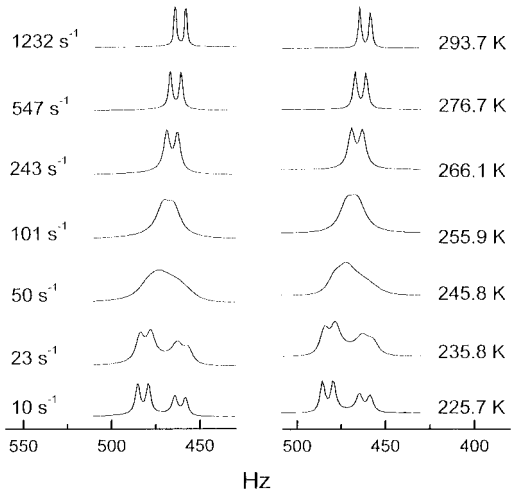


Figure 2. Experimental 300 MHz ^{1}H NMR spectra of the C12-CH_3 signal of **26** are in the right column, and DNMR5 simulations are in the left column.

substituents at the 2- and 5-positions of the pyrrole results in restricted conformational motion about the C6−N1 bond. While the sixfold barrier for an unhindered rotation about a bond linking tetrahedral and trigonal planar centers is ordinarily very small, the conformations available to the pyrrole lactones are restricted and the barrier for rotation about the C(sp^3)−N(sp^2) bond is substantial. We find evidence in variable temperature ^{1}H NMR studies for the existence of distinct conformations for the pyrrole lactones **26**, **16**, **5**, and **1**, and we have measured the barriers for interconversion between the conformations by full NMR line-shape analysis. Molecular mechanics (MMX) studies[18] provide a further basis for defining these conformations.

For the monoaldehyde **26** just one signal is seen for each ^{1}H nucleus in the ambient temperature 300 MHz spectrum. Upon cooling, signals broaden and decoalesce eventually into two sets of signals for two unequally populated conformers. At 226 K, the ratio is about 3:2 in $CDCl_3$. The exchange process is most easily analyzed from the singlet aldehyde signal that becomes two singlets, and in the C12-CH_3 doublet signal that becomes two doublets at low temperature. DNMR5 lineshape analyses[19] of these two signals are shown in Figures 1 and 2. (The numbering scheme for all atoms discussed in regard to NMR data is given in Scheme 1.) The dynamical information from the two signals agrees very well. The rates are most likely to be determined accurately from spectra in which there is significant line-broadening, and, accordingly, the rate constants agree within 10% for the intermediate temperatures from 226 K and 266 K. Agreement for the narrower spectra at higher and lower temperatures is still good. Combining the data from both sources in an Eyring plot of log k/T vs $1/T$ gives the activation parameters for the conversion from the major conformer to the minor conformer: $\Delta G^{\ddagger}$(300 K), 13.1 ± 0.2 kcal/mol; $\Delta H^{\ddagger}$ 9.4 kcal/mol; and $\Delta S^{\ddagger}$, -12 eu.

For the dialdehyde **16**, two aldehyde ^{1}H signals of equal area are seen in the ambient temperature 300 MHz spectrum, corresponding to nonequivalence of the aldehyde groups induced by slow rotation about the C−N bond linking the pyrrole and lactone portions. Indeed, the equal-area signals, along with the lack of a second set of signals for lactone resonances, establish firmly that the dynamic NMR observations are not due to hindered rotation about the bond linking the formyl group to the pyrrole ring. Coalescence of the aldehyde signals occurs at elevated temperatures in spectra of a solution of **16** in tetrachloroethane-d_2. Line-shape analysis yields a barrier of $\Delta G^{\ddagger}$(300 K), 17.2 ± 0.3 kcal/mol, with a $\Delta H^{\ddagger}$ of 13.3 kcal/mol and a $\Delta S^{\ddagger}$ of -13.1 eu.

Funebral (**5**) shows two sets of NMR signals in an approximately 8:1 ratio in ambient temperature 300 MHz ^{1}H spectra in a tetrachloroethane-d_2 solution, indicating two different conformations. Raising the temperature leads to coalescence of all doubled signals. Complete line-shape analysis of the aldehyde signal gives activation parameters for the conversion from the more stable conformer to the less stable conformer: $\Delta G^{\ddagger}$(300 K), 17.2 ± 0.2 kcal/mol; $\Delta H^{\ddagger}$ 12.3 kcal/mol; and $\Delta S^{\ddagger}$ -16.4 eu.

Funebrine (**1**) appears to be similar to **5** and **16** in the magnitude of the rotational barrier about the pyrrole lactone C−N bond, but it shows an even more pronounced conformational preference than for funebral (**5**). In acetone-d_6, the ratio of the major to the minor conformation is 13.5:1 at ambient temperature. In $CDCl_3$, the minor conformer was not detected in a low-noise ^{1}H NMR spectrum, and so the ratio was estimated to be ≥50:1. Signal broadening was evident in a ^{1}H spectrum in acetone-d_6 when the temperature was raised to 45 °C, but the dynamics were not pursued further because of the low boiling point of acetone and because the lopsided conformational preference would render questionable the accuracy of the line-shape analysis.

The conformational preferences for funebrine and Ψ-funebrine were studied via molecular mechanics using the MMX forcefield. The searches for global minima were carried out by systematic variation of the dihedral angles involving rotation about the N1−C6, C5−C24, C2−C14, C14−N15, and N15−C16 bonds. The dihedral driver routines were not used because it was discovered that

(18) Gajewski, J. J.; Gilbert, K. E.; McKelvie, H. In *Advances in Molecular Modelling*; Liotta, D., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2. PCMODEL, V. 6.0, Serena Software: Box 3076, Bloomington, IN.

(19) A locally modified version of the DNMR5 (Stephenson, D. S.; Binsch, G.) program further adapted by C. B. LeMaster, C. L. LeMaster, and N. S. True. Program no. QCMP059, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN 47405.

there are relatively few low-lying minima in this crowded molecule. Rotation through 360° for most of the bonds produce just two minima. Further, the lactone ring conformation is well-defined because of the *trans-trans* alignment of the three substituents on the five-membered ring. The lowest energy conformation for funebrine is depicted in Figure 3. This conformation is 2.3 kcal/mol lower in energy than the lowest found for the diastereomeric Ψ-funebrine. It is also lower by nearly 3.0 kcal/mol than any other conformers for funebrine that involve different placements of the imine bond or lactone rings. There are a few additional low energy conformers involving rotations of the CH_2OH group, but the predicted orientation of the hydroxyl oxygen, and indeed the entire structure, correspond precisely to the conformation found for the solid state in an X-ray crystal structure.[5]

As shown in Figure 3, the conformation appears to have a fairly close approach of the two lactone rings. However, the lactone shapes are complementary and not particularly crowded since the methyls of the pyrrole lactone are above the plane of the pyrrole ring as shown while the methyls of the imine lactone are below the plane. The closest approach is 3.33 Å between the methine proton at C20 in the imine lactone and the C12 methyl carbon attached to the pyrrole lactone. (See Scheme 1 for atom numbers.) Dipole−dipole interactions probably play an important role in determing the conformational preference. In particular, the imine nitrogen N15 is predicted to be only 2.84 Å from the C7 carbonyl carbon of the pyrrole lactone, its closest approach to any of the carbons or oxygens of that lactone.

Strong support for the actual existence of funebrine in the conformation shown in Figure 3 comes from steady-state, difference NOE measurements and from the chemical shift of the C6-H methine signal. Preirradiation (for 10 s) of the imine hydrogen C14-H produced a positive NOE of 6.8% at C16-H and 6.4% at C3-H in a $CDCl_3$ solution (no other NOE's were detected in this experiment). As shown in Figure 3, the imine C14-H is predicted to be at the middle of a nearly planar "double-U" segment with distances of 2.37 Å to C16-H of the imine lactone and 2.64 Å to the pyrrole C3-H. The high NOE's are certainly consistent with the "double-U" alignment and are otherwise difficult to explain. Attempts to detect an inter-ring NOE between the C20-H of the imine lactone and C12 methyl yielded ambiguous results because of the overlap of C12 and C22 methyl signals.

The orientation of the pyrrole lactone ring in funebrine is established by the chemical shift of the C6-H signal that exhibits a remarkable 2.25 ppm shift difference between the major and minor conformations. The C6-H signal for the predominant conformer occurs at a rather ordinary δ 5.18 in acetone-d_6 (δ 5.03 in $CDCl_3$), while C6-H for the minor conformer is strongly deshielded at δ 7.43. These shifts correspond to having the C6-H approximately anti to C2 and its attached imine group in the major conformer (Figure 3), and approximately syn in the minor conformer. The syn alignment brings C6-H close to the imine nitrogen and results in strong deshielding. These assignments are based on comparison with similar chemical shift behavior in the aldehydes **5**, **16**, and **26**.

The C6-H signal is diagnostic of the conformation of the pyrrole lactone with respect to the carbonyl group in **5**, **16**, and **26**, as shown in Figure 4. In the dialdehyde

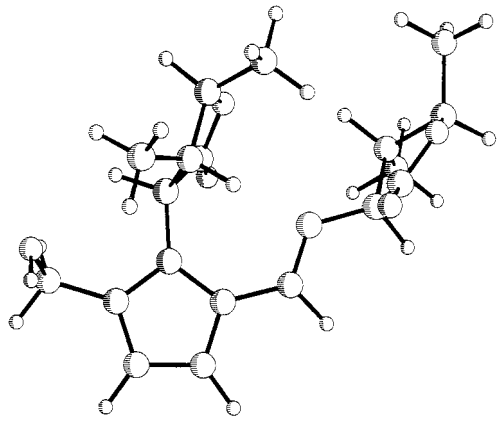


Figure 3. The lowest energy conformer of funebrine predicted in MMX calculations.

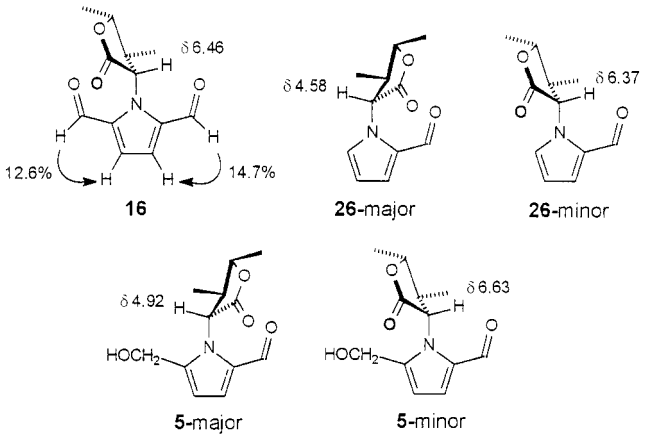


Figure 4. The chemical shifts at C6-*H* and conformations of pyrrole aldehydes related to funebrine.

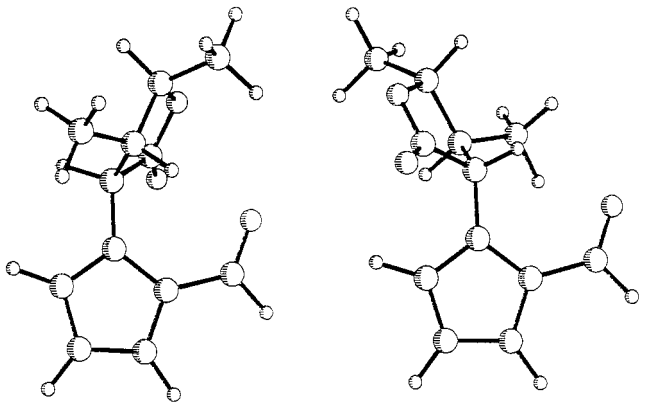


Figure 5. MMX structures of the observed major (left) and minor (right) conformations of **26**.

16, the C6-H methine must be near one of the two carbonyls, and the nucleus is deshielded to δ 6.46. That the carbonyl oxygens of **16** are oriented syn with respect to the pyrrole nitrogen was established by steady state, difference NOE measurements on a degassed $CDCl_3$ solution: preirradiation (10 s) of the δ 9.84 aldehyde signal gave a 14.7% enhancement to C3-H at δ 7.08, and irradiation at δ 9.75 gave a 12.6% effect to C4-H at δ 7.15. (Saturation of the closely spaced aldehyde signals was not completely selective, but the qualitative conclusion is clear. Saturation of both aldehyde signals resulted in a positive NOE of only 2.2% at C6-H, most likely due

to rotation through minor conformers during the long preirradiation.) For **26**, the minor conformer has C6-H at δ 6.37 and thus is assigned as having C6-H syn to the aldehyde based on similarity to the shift in the dialdehyde. The C6-H occurs at δ 4.58 in the major conformer. Similarly, for funebral (**5**), C6-H occurs at δ 6.63 in the minor conformer but at only δ 4.92 in the major conformer.

The geometry assignments deduced above from NMR data are consistent with MMX calculations that predict approximately syn and anti alignments for C6-H in the two conformations. For example, the major and minor conformations predicted from **26** are shown in Figure 5. The MMX structures for **26** are nearly isoenergetic, with the observed minor conformer favored by 0.1 kcal/mol in the calculations. In either structure, rotation of the aldehyde group by about 180° raises the energy by about three kcal/mol.

In summary, total syntheses of (±)-funebral and (±)-funebrine have been achieved that involve a new variation of the Paal−Knorr condensation to construct the pyrrole lactone moiety. Condensation between (±)-funebral and the racemic amino lactone **2** produced only (±)-funebrine and not the possible diastereomeric (±)-Ψ-funebrine. Molecular mechanics calculations indicate that funebrine is more stable than Ψ-funebrine and also predict that the most stable conformation for funebrine is the same as the one found in the solid state. NMR chemical shift and NOE measurements support the conclusion that this predicted conformation is strongly favored in $CDCl_3$ solution, although less than 10% of a minor conformer can be detected in acetone-d_6. The barrier to rotation about the pyrrole lactone C−N bond in funebral (**5**) is 17.2 kcal/mol and funebrine (**1**) has a similarly high barrier for this rotation.

Experimental Section

Materials and Methods. Microanalyses were by Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were recorded using KBr pellets or in CCl_4. Chromatography refers to flash chromatography on silica gel according to the method of Still.[20] *trans*-Crotyl *N*-t-Boc-glycinate (**8**),[21] 2-(*N*-t-Boc)-3-methylpent-4-enoic acid (**9**),[22] (*SSS*,*RRR*)-3,4-dihydro-2-(iodomethyl)-3-methyl-4-phthalimidofuran-5[2*H*]-one (**13**)[12] and 2,4,6-triisopropylbenzenesulfonyl azide[23] were prepared by procedures previously reported. Ethereal diazomethane was prepared by an established procedure.[24] Toluene and Et_3N were distilled from calcium hydride and stored over 4 Å molecular sieves. THF and Et_2O were distilled from sodium/benzophenone ketyl prior to use. DMF and $CHCl_3$ were dried over 4 Å molecular sieves in several batches. All other reagents were used as purchased.

Trifluoroacetate Salt of (*SR*,*RS*)-2-Amino-2-(*N*-t-Boc-)-3-methylpent-4-enoic Acid (10). Compound **10** was prepared from (*SR*,*RS*)-2-amino-2-(*N*-t-Boc-)-3-methylpent-4-enoic acid **9**[22] (10.96 g, 47.97 mmol) by using the procedure of ref 22. The crude trifluoroacetate salt was purified by recrystallization from methanol/water yielding a colorless solid (10.7 g, 92%): mp 154−156 °C; IR (KBr) cm^{-1} 3450,3300, 2250, 1600; ^1H NMR (D_2O) δ 1.0 (d, J = 7.0 Hz, 3H), 2.75 (m, 1H), 3.84 (d, J = 4.2 Hz, 1H), 5.13 (m, 2H), 5.65 (m, 1H).

(*SR*,*RS*)-3-Methyl-2-phthalimidopent-4-enoic Acid (11). Compound **11** (mixed with <5% of its diastereomer) was prepared from the trifluoroacetate salt of **10** (6.24 g, 25.6 mmol) by using the procedure of ref 22. It was obtained as a colorless solid (4.79 g, 73%): mp 129−132 °C; IR (KBr) cm^{-1} 3500 (br), 1775, 1725; ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 7.0 Hz, 3H), 3.34 (m, 1H), 4.81 (d, J = 8.2 Hz, 1H), 5.13 (m, 2H), 5.90 (m, 1H), 7.71∼7.86 (m, 4H), 10.7 (bs, 1H); minor isomer: 1.25 (d, J = 6.7 Hz), 3.12 (m), 4.66 (d, J = 9.5 Hz), 4.8−4.98 (m), 5.51−5.63 (m); ^{13}C NMR ($CDCl_3$) δ 16.6, 37.3, 55.9, 115.7, 123.6, 131.4, 134.2, 139.7, 167.6, 173.5; minor isomer: 18.0, 38.3, 45.0, 116.9, 139.0, 167.3; MS: 259 [M^+].

Methyl (*SR*,*RS*)-2-Phthalimido-3-methylpent-4-enolate (12). Compound **11** (0.65 g, 2.5 mmol) in dry Et_2O was added to excess ethereal diazomethane (16.6 mmol) and stirred at 0 °C for 2 h. Excess diazomethane was destroyed by the dropwise addition of acetic acid. The ethereal solution was washed with sat. $NaHCO_3$ solution (2 × 5 mL), dried (Na_2SO_4), and evaporated to give **12** (0.56 g, 76%) as a chromatographically homogeneous amber oil which could be used in the next step without further characterization: IR ($CHCl_3$) cm^{-1} 3010, 2920, 1750; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7.0 Hz, 3H), 3.35 (m, 1H), 3.89 (s, 3H), 4.48 (d, J = 8.8 Hz, 1H), 5.05−5.2 (m, 2H), 5.85−6.05 (m, 1H), 7.60−7.86 (m, 4H); minor isomer: 1.25 (d, J = 6.7 Hz), 3.34 (m), 3.82 (s), 4.68 (d), 4.85−5.0 (m), 5.55−5.70 (m); ^{13}C NMR ($CDCl_3$) δ 16.6, 37.3, 55.9, 115.7, 123.6, 131.4, 134.2, 139.7, 167.6, 173.5; minor isomer: 18.0, 38.3, 45.0, 116.9, 139.0, 167.3; MS: 273 [M^+], 241 [$M^+ - 32$], 218 [$M^+ - 45$], 190 [$M^+ - 83$], 126 [$M^+ - 147$].

(*SSS*,*RRR*)-3,4-Dihydro-2-(iodomethyl)-3-methyl-4-phthalimidofuran-2[5*H*]-one (13). Compound **13** (mixed with <5% of its diastereomer) was prepared from **12** (12 g, 44 mmol) by using the procedure of ref 12. The crude product was recrystallized (ethyl acetate/hexane) to yield pure **13** (12.22 g, 72%): mp 187−190 °C; IR (KBr) cm^{-1} 2960, 2940, 1775, 1720; ^1H NMR ($CDCl_3$) δ 1.3 (d, J = 7.2 Hz, 3H), 2.87 (m, 1H), 3.47 (m 1H), 3.58 (m, 1H), 4.18 (m, 1H), 4.81 (d, J = 11.6 Hz, 1H), 7.75−7.95 (m, 4H); minor isomer: 1.0 (d), 4.35 (m); ^{13}C NMR ($CDCl_3$) δ 13.5, 15.5, 40.9, 55.4, 82.2, 123.8, 131.5, 134.6, 166.8, 169.7; minor isomer: 12.0, 37.0, 79.3; MS: 385 [M^+], 258 [$M^+ - 127$].

(*SSR*,*RRS*)-3,4-Dihydro-4,5-dimethyl-3-phthalimidofuran-2[5*H*]-one (14). Compound **13** (1.3 g, 3.38 mmol) was dissolved in 20 mL of dry THF. Tri-*n*-butyltin hydride (5.41 g, 18.6 mmol) was added via syringe, and the reaction mixture was stirred at 20 °C for 20 h. The solvent was then evaporated, and the residue was dissolved in 15 mL of CH_3CN. The solution was extracted with hexane (8 × 5 mL) until TLC and NMR showed no tin compound present. The CH_3CN phase was evaporated at reduced pressure to give a pale yellow solid as crude product which upon recrystallization from ethyl acetate/hexane gave a colorless solid (0.806 g, 93%): mp 175−177 °C; IR (KBr) cm^{-1} 2920, 1775, 1720; ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 6.60 Hz, 3H), 1.53 (d, J = 6.2 Hz, 3H), 2.83 (m, 1H), 4.25 (m, 1H), 4.71 (d, J = 11.8 Hz, 1H), 7.73−7.86 (m, 4H); minor isomer: 0.95 (d), 1.40 (d), 2.72 (m), 5.02 (d); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.7, 41.9, 55.6, 80.5, 123.7, 131.6, 134.4, 166.5, 170.9; MS: 259 [M^+], 220 [$M^+ - 39$], 200 [$M^+ - 59$]; Anal. calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.02; N, 5.41. Found: C, 64.67; H, 5.00; N, 5.30.

(*SSR*,*RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2-[5*H*]-one Hydrochloride (15). Compound **14** (0.806 g, 3.31 mmol) was refluxed with 6 N HCl (10 mL) at 110 °C for 14 h. The reaction mixture was cooled to 20 °C and extracted with Et_2O (4 × 25 mL). The aqueous layer was then evaporated to dryness. The crude product was further purified by recrystallization from CH_3OH/Et_2O and dried in vacuo over KOH for 24 h to yield a colorless solid (0.417 g, 81%) identical in all respects except optical rotation with the hydrochloride of the natural amino lactone **2**: mp 205−207 °C; ^1H NMR (D_2O) δ 1.21 (d, J = 6.6 Hz, 3H), 1.42 (d, J = 6.2 Hz, 3H), 2.25−2.40 (m, 1H), 4.12 (d, J = 11.7 Hz, 1H), 4.33−4.45 (dq, J = 9.6, 6.2 Hz, 1H); minor isomer: 1.10 (d), 1.40 (d), 2.72 (m), 4.60 (d); ^{13}C NMR (D_2O) δ 15.1, 20.0, 45.5, 58.5, 85.0, 176.2. Anal. Calcd

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for $C_6H_{12}NO_2Cl \cdot 1/2\ H_2O$: C, 41.26; H, 7.45; N, 8.02. Found: C, 40.99; H, 7.37; N, 8.32.

1-{(*SSR,RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2[5*H*]-one}-2,5-diformyl Pyrrole (16). Osmium(VIII) oxide (7.2 mg, 0.028 mmol) and then, in several portions over a 30-min period, sodium metaperiodate (363.7 mg, 1.70 mmol) were added at 20 °C to a stirred solution of **17** (122 mg, 0.425 mmol) in a mixture of dioxane (6.5 mL) and water (3.5 mL). The reaction was allowed to proceed for 20 h, after which TLC analysis indicated complete consumption of the starting material. The reaction mixture was filtered and extracted thoroughly with diethyl ether (50 mL). The combined organic layers were washed, dried (Na_2SO_4), and concentrated under vacuum. Chromatography (2:1; hexane/ethyl acetate, v/v) of the crude product gave pure **16** as colorless needles (44 mg, 44%): mp 121.5−122.5 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.5 Hz, 3H), 1.61 (d, J = 6.1 Hz, 3H), 2.66 (ddq, J = 11.5, 9.5, 6.5 Hz, 1H), 4.30 (dq, J = 9.5, 6.1, 1H), 6.46 (d, J = 11.6 Hz, 1H), 7.08 (d, J = 4.2 Hz, 1H), 7.15 (d, J = 4.2 Hz, 1H), 9.75 (s, 1H), 9.84 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.5, 44.3, 62.0, 80.5, 123.9, 124.4, 136.0, 136.3, 171.2, 181.6, 182.9. This product was immediately reduced as described below.

1-{(*SSR,RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2[5*H*]-one}-2,5-bis(isobutenyl)pyrrole (17). To a suspension of **15** (360.4 mg, 2.18 mmol) in 8 mL of dry toluene was added $Ba(OH)_2 \cdot 8H_2O$ powder (186.5 mg, 1.09 mmol). The mixture was stirred at 20 °C for 2 h. In a separate flask, a solution of **18**[27] (422.5 mg, 2.18 mmol) and titanium tetraisopropoxide (631.6 mg, 2.18 mmol) in 8 mL of dry toluene was stirred at 20 °C. The two solutions were then mixed and heated under reflux for 24 h. Water was removed by a Dean−Stark trap. The reaction mixture was cooled to 20 °C and solvent evaporated under reduced pressure. The brown solid residue was subjected to chromatography (8% ethyl acetate/hexane, v/v), to give crude **17** which recrystallized from hexane as a pale yellow solid (148 mg, 24%): mp 71.5−72.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 6.6 Hz, 3H), 1.46 (d, J = 6.2 Hz, 3H), 1.84 (s, 6H), 1.86 (s, 3H), 1.89 (s, 3H), 2.48 (m, 1H), 4.16 (m, 1H), 4.66 (d, J = 11.8 Hz, 1H), 5.80 (s, 1H), 5.93 (s, 1H), 6.03 (br, 1H), 6.09 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.3, 20.0, 26.3, 26.4, 44.8, 61.2, 80.0, 108.7, 110.5, 114.4, 115.6, 129.1, 131.7, 136.6, 139.2, 173.6. This was immediately subjected to osmium tetraoxide−periodate cleavage.

(*RSR,SRS*)-3,5-Dihydro-3-azido-5-methyl-4-[tris(phenylthio)methyl]furan-2[5*H*]-one (20). To a solution of tris(phenylthio)methane (1.56 g, 4.59 mmol) in freshly distilled THF (10 mL) at −78 °C, was added *n*-butyllithium (1.96 mL of 2.5 M solution in hexane). After 30 min, β-angelicalactone[25] (0.375 g, 0.343 mL, 3.82 mmol) in THF (5 mL) was added dropwise during 30 min at −78 °C, and the mixture was stirred for an additional 4 h at the same temperature. A solution of trisyl azide (1.53 g, 4.90 mmol) in THF (15 mL) was added to the lactone solution at −78 °C via a cannula. After 20 min, the reaction was quenched by the addition of acetic acid (0.88 mL, 15.3 mmol) followed by warming on a water bath to 20 °C over 30 min. After addition of ethyl acetate (25 mL) and washing with satd sodium bicarbonate (3 × 30 mL), the organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give a crude pale yellow solid. Flash chromatography (ethyl acetate/hexane, 0−50%) yielded (0.819 g, 45%) compound **20** as a chromatographically pure colorless powder which was carried to the next step immediately: mp 128−130 °C; IR (KBr) cm^{-1} 3080, 2990, 2110, 1780, 1475, 1440; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 6.45 Hz, 3H), 2.55 (t, 1H), 4.67 (d, J = 2.7 Hz, 1H), 4.97 (dq, J = 2.8, 6.5 Hz, 1H), 7.39 (m, 9H), 7.66 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 22.8, 57.6, 61.3, 77.2, 78.1, 128.9, 130.0, 130.1, 136.3, 172.6.

(*SSR,RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2-[5*H*]-one (2). In a 50 mL three-necked flask was placed a solution of **20** (400 mg, 840 mmol) in 15 mL of THF. Raney nickel (2 g, in 50% water slurry) washed with absolute ethanol three times and suspended in 10 mL of THF was added to the flask. The mixture was stirred mechanically for 4 h at reflux temperature (60−65 °C) under a hydrogen atmosphere. The reaction was cooled to 20 °C, and 3 mL of concd NH_4OH was added with stirring. The clear THF solution was transferred to a new flask, and the Raney nickel particles were washed three times with a mixture of THF (22 mL) and concd NH_4OH (3 mL). The combined THF−NH_4OH solution was evaporated under reduced pressure. The residue was dissolved in 20 mL of diethyl ether and extracted with water (3 × 10 mL). The organic layer was treated with concd HCl (2 mL) and extracted with H_2O (3 × 25 mL). The combined aqueous phase was evaporated to dryness under reduced pressure, giving compound **15** (16 mg, 15%) identical to that prepared above.

(*E*)-2-Butenyl-1-pyrrolyl Acetate (22). 1-Pyrrolylacetic acid **21**[26] (0.254 g, 2.03 mmol), was mixed in dry ether (30 mL) with *trans*-crotyl alcohol (0.146 g, 2.03 mmol), dicyclohexylcarbodiimide (0.419 g, 2.03 mmol), and a catalytic amount of *p*-(*N,N*-dimethylamino)pyridine (0.5 mg). The mixture was stirred for 24 h at room temperature. After removal of the precipitated dicyclohexylurea, the solution was washed with saturated sodium bicarbonate (2 × 10 mL) solution, dried ($MgSO_4$), filtered, and evaporated to give 0.431 g of crude product. This was flash chromatographed on silica gel (ether: petroleum ether 1/20, 1/11, ether 100%) to give compound **22** as a yellow oil (0.248 g, 68%): IR ($CHCl_3$) cm^{-1} 3100, 2980, 2960, 1725; ^{1}H NMR ($CDCl_3$) δ 1.70 (d, J = 7.0 Hz, 3H), 4.55 (d, J = 6.9 Hz, 2H), 4.60 (s, 2H), 5.58 (m, 1H), 5.79 (m, 1H), 6.19 (d, J = 2.1 Hz, 2H), 6.65 (d, J = 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.7, 50.6, 66.1, 108.9, 121.6, 124.3, 132.3, 168.5; MS: 179 [M$^+$].

(*SR,RS*)-2-(1-Pyrrolyl)-3-methylpent-4-enoic Acid (23). *n*-Butyllithium (2.0 M in hexane, 0.747 mL, 1.49 mmol) was added to diisopropylamine (0.151 g, 0.209 mL, 1.49 mmol) in dry THF (8 mL) at 0 °C, stirred for 5 min, and cooled to −78 °C, after which ester **22** (0.223 g, 1.25 mmol) in THF (2 mL) was added dropwise with stirring. After the mixture had been stirred for 10 min, trimethylsilyl chloride (0.150 g, 0.175 mL, 1.40 mmol) was added, and the solution was stirred for 5 min before being allowed to warm to 21 °C over 30 min. The mixture was then warmed to 55−60 °C for 1 h, cooled, dilute with ether (10 mL), and extracted with 2 N NaOH (4 × 10 mL). The aqueous layer was acidified to pH 2 with concentrated hydrochloride acid and extracted with chloroform (4 × 15 mL). The chloroform extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 0.144 g (64%) of **23** as an oily mixture of diastereomers (>95% of **23**) which solidified to a colorless wax on standing: ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 6.8 Hz, 3H), 3.08 (m, 1H), 4.38 (d, J = 9.1 Hz, 1H), 4.96−5.10 (m, 1H), 6.15 (t, J = 2.1 Hz, 2H), 6.74 (t, J = 2.1 Hz, 2H), 11.60 (br s, 1H); minor isomer: 0.87 (d, J = 6.8 Hz, 3H), 4.28 (d, J = 10.4 Hz, 1H), 5.08−5.24 (m, 2H), 5.64−5.76 (m, 1H), 6.19 (t, J = 2.1 Hz, 2H), 6.79 (t, J = 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.7, 40.4, 67.0, 108.6, 116.8, 120.7, 137.5, 176.0; minor isomer: 16.4, 41.7, 67.0, 108.9, 117.4, 120.5, 138.0, 175.9; MS: 179 [M$^+$].

(*SR,RS*)-2-(1-Pyrrolyl)-3-methylpent-4-enoate (24). Acid **23** (0.134 g, 0.749 mmol) was treated with excess diazomethane dissolved in ether (20 mL) at 0 °C. After 30 min of stirring, the mixture was kept at room temperature, when excess of diazomethane was allowed to evaporate. The reaction mixture (ether layer) was washed with saturated sodium bicarbonate solution (2 × 15 mL), dried ($MgSO_4$), and evaporated to give 80 mg of **24** (62.5%, based on 15 mg of recovered acid **23** from the aqueous phase) as a yellow oily mixture of diastereomers which was relatively unstable and immediately utilized in attempted iodolactonization: ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.6 Hz, 3H), 3.03 (m, 1H), 3.79 (s, 3H), 4.37 (d, J

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= 10.1 Hz, 1H), 4.92−5.10 (m, 1H), 5.47−5.62 (m, 1H), 6.17 (t, J = 2.1 Hz, 2H), 6.79 (t, J = 2.1 Hz, 2H); minor isomer: 0.86 (d, J = 6.8 Hz, 3H), 3.70 (s, 3H), 4.30 (d, J = 10.6 Hz, 1H), 5.10−5.24 (m, 2H), 5.64−5.77 (m, 1H), 6.20 (t, J = 2.1 Hz, 2H), 6.83 (t, J = 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.6, 40.8, 52.4, 67.1, 108.4, 116.4, 120.6, 137.8, 170.3; minor isomer: 16.4, 42.1, 52.1, 67.2, 108.6, 116.8, 120.3, 138.4; MS: 193 [M^+].

1-(*SSR*,*RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2[5*H*]-one Pyrrole (25). A mixture of **15** (0.77 g, 4.65 mmol), sodium acetate (3.480 g, 25.6 mmol), and 2,5-dimethoxytetrahydrofuran (0.60 mL, 4.65 mmol) in acetic acid (5 mL) was refluxed for 1.5 h. After cooling to room temperature, the reaction mixture was diluted with water (50 mL). The resulting solution was extracted with ethyl acetate (50 mL, 3 × 25 mL) and washed with saturated aqueous sodium bicarbonate solution (3 × 30 mL) and water (25 mL). After drying (Na_2SO_4) the combined organic extracts, evaporation of the solvent under reduced pressure gave a dark brown oil. Flash column chromatography (ethyl acetate in hexane, 20−60%) yielded compound **25** as a pale yellow oil (0.724 g, 87%): IR ($CHCl_3$) cm^{-1} 3100, 2950, 1785, 1500, 1200; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.5 Hz, 3H), 1.43 (d, J = 6.2 Hz, 3H), 2.25 (m, 1H), 4.11 (dq, J = 6.5, 3.3 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 6.20 (t, J = 2.1 Hz, 2H), 6.66 (t, J = 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.3, 18.2, 46.4, 65.0, 79.2, 109.2, 119.8, 172.3. Anal. Calcd for $C_{10}H_{12}NO_2$: C, 67.42; H, 6.74; N, 7.86. Found: C, 67.94; H, 7.46; N, 7.58.

1-{(*SSR*,*RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2[5*H*]-one}-2-formyl Pyrrole (26). To an ice-cooled flask containing *N*,*N*-dimethylformamide (0.85 mL, 11.0 mmol) was added phosphorus oxychloride (1.0 mL, 11.0 mmol) dropwise. Stirring was continued at ambient temperature for 30 min, followed by the addition of a small portion of dichloroethane (3 mL). The reaction mixture was cooled to 0 °C, and the pyrrole **25** (0.565 g, 3.15 mmol) in dichloroethane (3 mL) was added slowly. Following the addition, the reaction mixture was refluxed for 1 h and cooled to 20 °C. A 10 % aqueous sodium acetate solution (25 mL) was added dropwise, and the reaction solution was refluxed for an additional 30 min. After cooling to 20 °C, the lower layer was removed, and the remaining aqueous solution was extracted with saturated sodium carbonate solution (4 × 20 mL) and water (15 mL) and dried (Na_2SO_4). Evaporation of the solvent under aspirator pressure gave a pale brown oil which upon purification by flash column chromatography (ethyl acetate in hexane, 20−50%) yielded compound **26** as a pale yellow crystalline solid (0.354 g, 54.2%): mp 77−79 °C; IR ($CHCl_3$) cm^{-1} 3025, 2980, 1790, 1660, 1220; ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 6.5 Hz, 3H), 1.53 (d, J = 6.2 Hz, 3H), 2.74 (m, 1H), 4.41 (dq, J = 6.5, 3.3 Hz, 1H), 6.33 (dd, J = 4.0, 2.7 Hz, 1H), 7.03 (dd, J = 4.0, 1.5 Hz, 1H), 7.06 (m, 1H), 9.52 (s, 1H); minor isomer: 0.62 (d), 1.41 (d), 3.05 (m), 4.81 (m); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.4, 40.8, 59.2, 81.9, 110.9, 126.1, 130.8, 131.6, 171.7, 179.4. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.60; H, 6.46; N, 6.62.

3-[2′-(1′-Methylpyrrol)methylamino]-4,5-dimethylfuran-2[5*H*]-one (30). A solution of amino lactone·HCl **29**[28] (100 mg, 0.60 mmol) in water (5.0 mL) was neutralized to pH 7 with K_2HPO_4, and $NaBH_3CN$ (31 mg, 0.50 mmol) was added, followed by aldehyde **28** (56 mg, 0.50 mmol) dissolved in methanol (25 mL). The mixture was stirred at 20 °C for 48 h, diluted with water (10 mL), carefully saturated with $NaHCO_3$, and immediately extracted with CH_2Cl_2 (3 × 60 mL). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered, and evaporated at aspirator pressure to give 124 mg of crude product. Preparative TLC (silica gel, ethyl acetate/hexane, 3:7, v/v) of the crude product gave 9 mg of aldehyde **28** and product **30** (58 mg, 51%) as a yellowish brown oil: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 7.0 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.75 (br, 1H), 2.44 (m, 1H), 3.55 (d, J = 6.8 Hz, 2H), 3.68 (s, 3H), 3.89 (q, J = 8.2 Hz, 1H), 4.50 (dq, J = 6.8, 4.2 Hz, 1H), 6.05 (d, J = 3.0 Hz, 2H), 6.60 (t, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.2 (q), 15.4 (q), 33.7 (q), 38.6 (d), 44.2 (t), 61.5 (d), 76.7 (d), 106.4 (d), 108.7 (d), 122.8 (d), 129.7 (s), 177.2 (s); MS: 222 [M^+]. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.6. Found: C, 64.60; H, 8.20; N, 12.45.

1-Methyl-2-(*N*-benzyl formimidoyl)pyrrole (31). To a slurry of aldehyde **28** (200 mg, 1.833 mmol) and 5 Å molecular sieves (0.7 g) in dry $CHCl_3$ (1.8 mL) was added titanium(IV) isopropoxide (260 mg, 0.916 mmol) dropwise. After stirring for 10 min at 20 °C, benzylamine (196 mg, 1.833 mmol) in dry $CHCl_3$ (1.8 mL) was introduced to the mixture. The reaction mixture was stirred at 20 °C for 18 h and filtered through Celite. The solid was washed with $CHCl_3$ thoroughly (10 mL), and the chloroform solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 2:1, v/v) to give the mixed isomers of **31** (301 mg, 83%) as an orange semisolid: mp 28−30 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.72 (s, 2H), 6.18 (dd, J = 4.0, 4.8 Hz, 1H), 6.52 (dd, J = 4.4, 4.8 Hz, 1H), 6.70 (br, 1H), 7.21−7.45 (m, 5H), 8.24 (s, 1H); minor conformer: 3.62, 4.83, 7.80, 8.40; ^{13}C NMR ($CDCl_3$) δ 36.8, 65.5, 108.1, 116.7, 126.8, 127.7, 128.0, 128.4, 129.9, 140.4, 153.4.

1{(*SSR*,*RRS*)-3,4-Dihydro-3-amino-4,5-dimethylfuran-2[5*H*]-one}-2-formyl-5-(hydroxymethyl)pyrrole (5). Compound **16** (24 mg, 0.10 mmol) was dissolved in 1 mL of dioxane and mixed with 100 μL of HCOOH and 100 mL of H_2O. Then $NaBH_3CN$ (6.4 mg, 0.10 mmol) was added, and the mixture was stirred at 20 °C for 4 h. After neutralization to pH 7.0 by the addition of $NaHCO_3$ (219 mg), the mixture was extracted thoroughly with diethyl ether (50 mL). The combined organic layer was washed with H_2O and brine and dried (Na_2SO_4). The dried ether solution was evaporated under reduced pressure to give a yellow solid as crude product (20.4 mg, 84%) which was further purified by chromatography (1:1, ethyl acetate: hexane, v/v) to give pure **5** (13 mg, 54%) as colorless crystals, identical except for optical rotation with the natural product: mp 129−130 °C (from diethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.6 Hz, 3H), 1.60 (d, J = 6.6 Hz, 3H), 2.01 (br, 1H), 2.70 (m, 1H), 4.20 (dq, J = 10.8, 6.8 Hz, 1H), 4.62 (d, J = 14.2 Hz, 1H), 4.70 (d, J = 14.2 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 6.27 (d, J = 4.0 Hz, 1H), 7.01 (d, J = 4.0 Hz, 1H), 9.41 (s, 1H); minor conformer: δ 1.06, 2.53, 4.18, 6.36, 6.63, 6.94, 9.48; ^{13}C NMR ($CDCl_3$) δ 14.8, 18.8, 43.6, 56.7, 62.8, 81.0, 111.2, 126.4, 132.3, 142.7, 172.3, 179.0; minor conformer: 14.0, 17.4, 46.7, 61.6, 113.4, 180.5.

(*SSR*,*RRS*)-Dihydro-3-{2-(hydroxymethyl)-5-[*N*-[(*SSR*-,*RRS*)-tetrahydro-4,5-dimethyl-2-oxo-3-furyl]formimidoyl]-pyrrol-1-yl}-4,5-dimethyl-2-(3*H*)-furanone (1). A slurry of **5** (98 mg, 0.4135 mmol) and 5 Å molecular sieves (3.8 g) in 2 mL of dry $CHCl_3$ was treated with a solution of **2** (220 mg, 1.705 mmol) in 3 mL of dry $CHCl_3$. After 5 min, Et_3N (128 μL, 0.4142 mmol) was added to the mixture. The reaction mixture was then held at 60−65 °C with stirring for 4 days. After cooling to 20 °C, the mixture was filtered through diatomaceous earth. The solid was thoroughly washed with $CHCl_3$ (30 mL), and the chloroform solution was concentrated under reduced pressure. The residue was then subjected to column chromatography on silica gel (5% methanol in chloroform, v/v) to give **1** (86.5 mg, 60%), identical in every respect except optical rotation with funebrine: mp 168−169 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.5 Hz, 6H), 1.45 (d, J = 6.3 Hz, 3H), 1.48 (d, J = 6.2 Hz, 3H), 1.70 (br, 1H), 2.50 (m, 1H), 3.17 (m, 1H), 3.60 (d, J = 10.8 Hz, 1H), 4.16 (m, 2H), 4.60 (d, J = 13.8 Hz, 1H), 4.69 (d, J = 13.7 Hz, 1H), 5.03 (d, J = 11.7 Hz, 1H), 6.22 (d, J = 3.8 Hz, 1H), 6.61 (d, J = 3.8 Hz, 1H), 7.98 (s, 1H); ^{1}H NMR (acetone-d_6) δ 1.07 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.43 (d, J = 6.8 Hz, 3H), 2.43 (m, 1H), 3.78 (d, J = 10.9 Hz, 1H), 4.23 (m, 2H), 4.33 (t, J = 5.45 Hz, 1H), 4.65 (d, J = 5.45 Hz, 1H), 5.18 (d, J = 10.8 Hz, 1H), 6.20 (d, J = 3.9 Hz, 1H), 6.64 (d, J = 3.9 Hz, 1H), 8.05 (s, 1H); minor conformer: 1.16 (d), 1.45 (d), 4.00 (d), 6.26 (d), 6.60 (d), 7.43 (d), 8.25 (s); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.6, 18.2, 18.8, 42.7, 46.2, 57.0, 57.1, 63.0, 76.3, 80.7, 80.9, 110.4, 120.5, 130.4, 139.4, 155.3, 172.7, 174.8; ESI-MS (*m*/*z*): 349.6 (78.0%) [M + H]$^+$, 331.6 (100%) [M + H − H_2O]$^+$; daughter ions of 349.6:349.1, 331.2, 258.9, 231.3, 220.2, 192.3, 174.4, 160.0, 147.8, 146.4, 132.6, 119.5, 112.9, 94.1, 69.1, 57.0, 43.6, 26.3, 14.9.

Acknowledgment. We are grateful to Dr. Thomas Zennie for informing us of his recent study of the ^{1}H NMR spectrum of natural funebral. We thank the Barnett Innovative Research Fund and Telor Ophthalmic Pharmaceuticals Inc. for financial support, Professor Paul Vouros and Drs. Jianmei Ding, Meg Annan, and Jim Kyranos for mass spectra, and Professor David Jebaratnam for discussions.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compound **11**−**17**, **20**, **22**−**24**, **26**, **30**−**31**, (±)-**1**, (±)-**5**, and ^{1}H NMR spectra of compound **10**, (±)-2. Dynamic lineshape analysis data are given for compounds **5** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO981501U