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Conformational Analysis of 4,8-Dimethyl-3(*E*),8(*E*)-decadien-10-olide (*E*,*E*-Suspensolide), a Key Component of the Pheromones of the Male Caribbean and Mexican Fruit Flies

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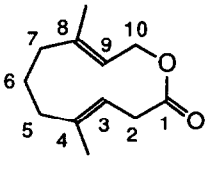
Abstract: Molecular modeling and NMR studies of suspensolide (1), a major component of the sex and aggregation pheromones of the Caribbean, *A. suspensa* [Loew], and Mexican, *A. ludens* [Loew], fruit flies reveal two major conformers with the methyls *syn*.

Tropical and subtropical fruit flies of the genus *Anastrepha* [Tephritidae] comprise a fairly extensive group of various species distributed worldwide.[1] Of these, the Caribbean, *A. suspensa* [Loew], and Mexican, *A. ludens* [Loew], flies are major pests of commercially valuable fruits in Central and North America. A promising way to assess and control the population of insect species such as these is by use of their sex and/or aggregation pheromones as species specific attractants. While the Caribbean and Mexican fruit flies are non-sympatric, the males of both species exhibit parallel courtship and calling behaviors and release a remarkably similar multicomponent pheromone blend that is used to form leks and attract the females for mating.[2,3] The individual components, identified to date from the total volatiles emitted by sexually mature males of both species, are suspensolide[4] (1), anastrephin[5,6] (2), epianastrephin[5,6] (3), (Z)-3-nonenol, (Z,Z)-3,6-nonadien-1-ol,



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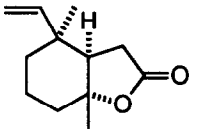

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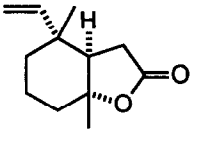

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α-farnasene, β-bisabolene, and (E)-α-bergamatene.[2,3] Of these components the relative ratio of the three sesquiterpenes varies widely between the two species and apparently constitutes the major difference in their pheromonal blends other than the singular presence of the minor monoterpenes (Z)-β-ocimene and limonene in the volatiles of *A. suspensa* and *A. ludens*, respectively.[2a] The relative ratio of the lactones **1-3**, however, is strikingly consistent for both species given the variability in volatile emissions based on age of flies, time of day, temperature, light incidence, etc.

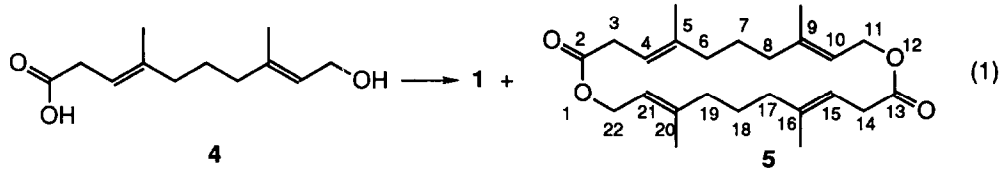
Since lactones **1-3** comprise a major portion of the two multicomponent sex pheromones, they, together with the minor two C-9 alcohols, offer a cogent explanation for the morphosyntactic similarity in the behavior of *A. suspensa* and *A. ludens* fruit flies. Biosynthetically, these lactones and the three sesquiterpenes mentioned above are apparently derived from farnesol.[2a] The final step in the biosynthetic production of bicyclic lactones **2** and **3** may involve a stereoselective acid catalyzed rearrangement of the monolide **1**. This unique rearrangement has recently been reported by us to produce a 1:2.3 ratio of lactones **2** and **3**, a result closely mimicking the natural ratio of the bicyclic isomers.[7,8]

In this paper we report conformational studies of (E,E)-suspensolide (**1**) by ^{1}H NMR with interpretive support by molecular modeling. Besides the intrinsic interest in understanding the conformational vicissitudes of **1** and their possible importance in the rearrangement of **1** to **2** and **3**, this study should also provide invaluable information for understanding of the structure of the pheromone receptors in the species of *A. suspensa* and *A. ludens*. To our best knowledge this is the first conformational analysis of a natural 11-membered lactone.[9,10]

Results and Discussion

Synthesis. Monolide 1 was obtained by macrolactonization of the linear hydroxy acid **4**[4,5b] in the presence of DEAD and triphenylphosphine[11] (eq 1). Numerous macrolactonization approaches[12] were attempted in this and previous work[4] with less than satisfying results. Interestingly, in the synthesis of **1** by the DEAD/Ph_3P method the application of high dilution techniques versus direct mixing of the reagents at the concentration level of 10 mM produced similar yields of suspensolide, but in the latter reaction, in addition to **1** (19%), the diolide **5** was formed in a 5% yield.

Diolide **5** was fully characterized by NMR and HRMS. Both the ^{13}C NMR and ^{1}H NMR spectra of **5** exhibited the symmetry associated with two identical units of the dimeric molecule. The NMR spectra of **5** were little affected by changes in temperature in the range of +23°C to -90°C, as expected for the molecule with a large degree of conformational freedom.



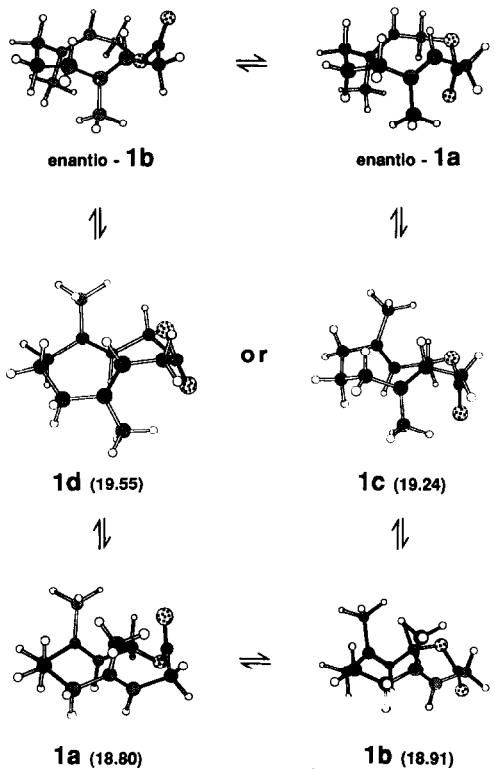
4 **5** (1)

Conformational Search of 1. In sharp contrast to the simplicity of the ^1H NMR temperature spectra of **5**, the spectra of **1** taken in a range of +50°C to -90°C are complex (Figure 1). The spectral patterns are consistent with the presence of interconverting conformers which undergo equilibration (Figure 1C). The broad absorption for the $C10H_2$ has been noted previously[4a,b] and explained,[4a] without elaboration, in terms of an "inside-outside" exchange of these diastereotopic methylene protons of **1**.

In order to focus the spectral changes with temperature we have conducted a detailed conformational analysis of **1** using a steric energy minimization program[13] operating with the MODEL MM2 force field. Both a grid search and a statistical Monte Carlo method were used. The Monte Carlo method proved to be more efficient and reliable in this study and in similar conformational analyses of cyclic flexible molecules,[14] and we now use this method in preference to the grid search. These methodologies, using many different starting geometries, consistently revealed the presence of four unique conformers, **1a-d**, within a 1 kcal window of the global minimum[15] (Scheme I).

The calculations indicated two conformers **1a** and **1b**, both having a *syn*-relationship of the two methyl groups, to be most important over the temperature range studied. These two conformers differ in the

Scheme I. Equilibration of the calculated conformers **1a-d** and their energies (kcal/mol)



configuration of the carbonyl group and ring oxygen. In the lowest energy conformer **1a** the carbonyl is *syn* to the methyls, and the lactone function itself adopts a twisted *s-trans* orientation[16] with the torsional angle around the ring oxygen-carbonyl bond of 50°. While pure stereoelectronic effects would favor co-planar *s-trans* conformation of the lactone function,[17,18] this stereochemistry would induce prohibitive steric repulsions between the carbonyl and the methyls. The deviation of the lactone moiety from co-planarity minimizes the *syn* steric interactions with and between the methyl groups.

The carbonyl is *anti* to the methyl groups, and the lactone function itself adopts a twisted *s-cis* orientation[16] in the less stable conformer **1b**. The calculations showed the torsional angle around the ring oxygen-carbonyl bond to be about 50°. A similar analysis revealed that this molecular twist minimizes severe steric interactions between C2β- and C10β-hydrogens in the co-planar arrangement of the lactone unit.

In the minor conformers **1c,d** the methyls are *anti*, and the carbonyl and C4-methyl are *syn*; however, the trimethylene moiety adopts a different conformation in **1c** and **1d**. Interestingly, both conformers **1c** and **1d** adopt a similar twisted *s-trans* conformation of the lactone function indicated by the computations for the most stable conformer **1a**. These results strongly suggest that stereoelectronic effects are of primary importance for conformations of the sterically strained macrolide **1**. The strong preference toward *s-trans* conformations of esters and conformationally flexible macrolides has been noted previously in a number of theoretical and experimental studies, due primarily to stereoelectronic effects.[17,18]

Because of the dissymmetry of **1** each of the conformers can exist in a mirror image form. The conformers can undergo interconversion by partial, sequential ring inversions at the carbonyl, C3-vinyl, C8-vinyl, and trimethylene portions of the molecule. A possible mechanistic pathway which makes use of the conformational analysis for the interconversion and enantiomerization of the more populated *syn* **1a** and **1b** conformers is given in Scheme I. While their equilibration requires inversion of the lactone moiety, the enantiomerization involves rotations of the C3-vinyl and C8-vinyl portions which most likely occur sequentially. The latter conformational changes involve the intermediacy of *anti* conformers.

NMR. A complete assignment in the ^{13}C NMR spectrum of **1** at 23°C has been reported.[4a,b] The spectrum consists of ten lines with the overlapping signals for C5, C7 and C4Me, C8Me. The number of ^{13}C absorptions increased to twenty three at -90°C suggesting the presence of two stable conformers at this temperature. Analysis of the ^1H NMR spectrum of **1** taken in acetone-d_6 at -90°C (Figure 1A) also revealed two sets of absorptions in the ratio of 52:48. The spectrum taken in ether-d_{10} at -90°C was more complex (not shown), although the sets of absorptions corresponding to those in acetone-d_6 were of a similar ratio (60:40) but were accompanied by other weak signals (ca 5%). The latter signals apparently corresponded to additional conformers because after concentration of the ether followed by dilution with acetone-d_6 the ^1H NMR spectrum obtained at -90°C was identical with that given in Figure 1A. These results are clearly consistent with the presence of two major stable conformers at -90°C the ratio of which is affected by solvent. Presumably the more abundant conformer would have the lower polarity because its concentration increases in ether which is a less polar solvent (dielectric constant ε=4.3) than acetone (ε=21).

On the basis of detailed NMR analysis (*vide infra*) taken in conjunction with the modeling studies we assign the less polar and more populated structure to **1a** and the more polar, but less populated conformer to **1b**. The structure assignments for **1a** and **1b** was fully supported by relayed coherence transfer (RCT), NOE, and decoupling experiments at -90°C. These techniques facilitated complete assignment of all nonoverlapping

signals in the spectrum (Figure 1A). The only overlapping signals are the trimethylene protons, and they are not crucial for the stereochemical identification.

For each conformer the $C2H_2$ resonances are well separated from other signals, and are in the expected chemical shift range. A relatively large difference between the assigned chemical shifts for C2Hα and C2Hβ in **1b** and the negligible difference for the respective proton signals in **1a** are fully consistent with anisotropic effects of the carbonyl group[19] in the computer derived conformations. The RCT spectrum combined with integration results distinguished two groups of interacting protons, C4(Me)-C3(H)-C2(H_2) and C8(Me)-C9(H)-C10(H_2), for each conformer.

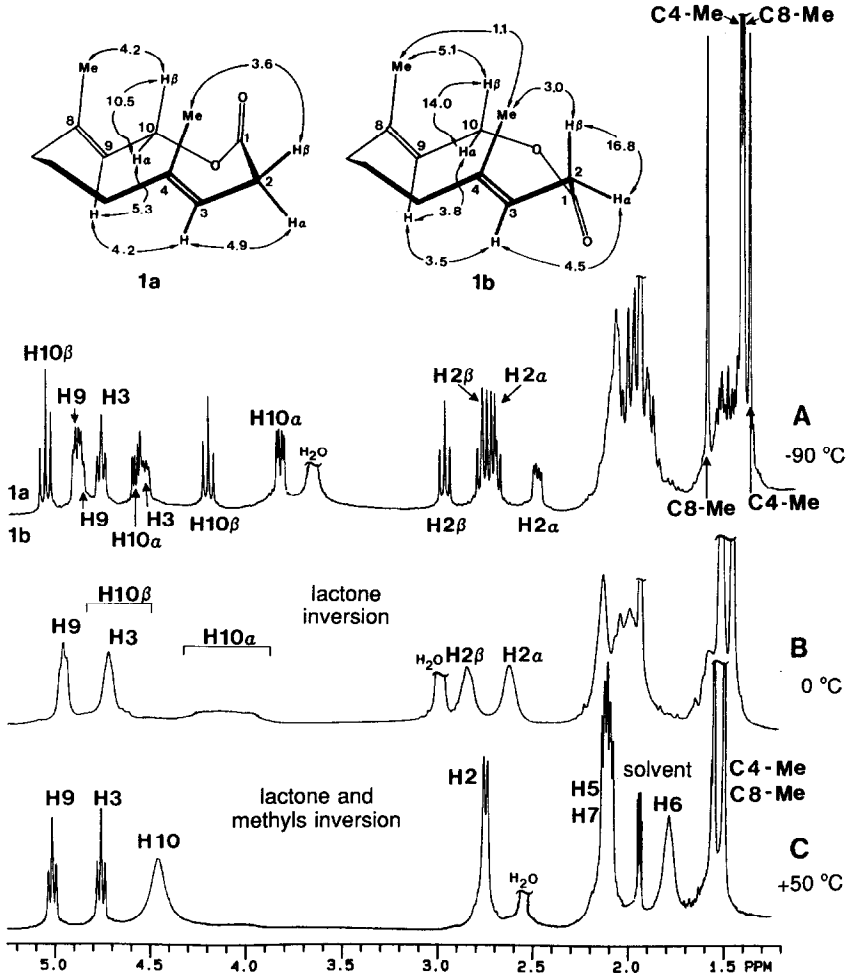


Figure 1. ^1H NMR spectra of **1** taken in acetone-d_6 at the indicated temperatures. The chemical shift assignments at -90 °C (A) for conformers **1a** and **1b** are given above and below the spectrum, respectively. The insert shows averaged percentages of NOE enhancement between protons.

The subsequent assignments of chemical shifts for protons in each of the two conformers, **1a** and **1b**, including stereochemistry was achieved by using NOE experiments. For example, irradiation of C8Me of **1b** gave an NOE enhancement for the adjacent C10-Hβ and a weak, but unambiguous, signal for C4Me, as expected for the *syn* stereochemistry. The irradiation of C4Me in **1b** gave NOE signals for C8Me and C2Hβ. The latter result is in excellent agreement with the initial assignment of the chemical shift for C2Hβ, which was based on the anisotropic effect of the carbonyl group in the computer derived stereochemistry of **1b**. Other protons were identified in a similar way, always with the irradiations conducted at each of the interacting protons. The observed magnetization transfer between vinyl protons C3H and C9H in **1b** is a strong argument for their *syn* relationship. Similar NOE results for C3H and C9H of **1a** are also consistent with the *syn* relationship of these protons, as derived from the modeling studies.

The obtained assignments for methyl singlets in the spectra of **1a** and **1b** are in good agreement with the stereochemistries of these conformers derived from computer modeling. The chemical shift for C8Me of **1b** is at a normal position because this methyl is not affected by magnetic anisotropic effects in the molecule. By contrast, the C4Me of **1b** experiences shielding by a C8=C9 bond.[19] The carbonyl group is approximately antiperiplanar to both methyls in **1b** and, because of the large distance and geometry, the carbonyl exerts no stereoelectronic effect on these methyls. On the other hand, the carbonyl is nearly synperiplanar to the methyls in **1a** and close enough to these methyls to exert a shielding effect.[19] The experimental proton assignments and stereochemistries for **1a** and **1b** were additionally supported by analysis of a COSY spectrum and decoupling experiments.[20]

The third and fourth most populated conformations **1c** and **1d** from calculations for idealized conditions *in vacuo* have the methyls in an *anti* relationship. Signals for these conformers could not be identified in the ^{1}H NMR spectrum taken in acetone-d_6, a polar solvent, at -90°C indicating that their relative abundance was less than 5%. As already mentioned, the ^{1}H NMR spectrum of the same sample taken in ether-d_{10}, the less polar solvent, at -90°C showed additional, relatively weak resonances in the vicinity of those for **1a** and **1b**. These absorptions may well be attributable to the *anti* conformers, such as **1c** and **1d**.

The presence of only two conformers **1a** and **1b** in acetone-d_6 at -90°C was the rationale for conducting temperature studies in this solvent. The spectral changes with increasing temperature (Figures 1B and 1C) are consistent with the suggested conformational dynamics of Scheme I. As the temperature increases, two coalescence temperatures are sequentially observed on the NMR time scale. Between -40°C and -20°C conformers **1a** and **1b** undergo interchange in a slow process that involves flipping of the lactone grouping signified by the carbonyl changing faces of the molecule. This interconversion of **1a** and **1b** primarily causes coalescence of the respective pairs of proton signals **1a**-H2α···**1b**-H2α, **1a**-H2β···**1b**-H2β, **1a**-H10α···**1b**-H10α, and **1a**-H10β···**1b**-H10β. The methyl absorptions are also affected, as expected for changes in the anisotropic effect of the carbonyl. The carbonyl exchange is essentially complete at -20°C on the NMR time scale, and no further significant changes in the spectrum are observed up to 0°C (Figure 1B). At higher temperatures above 0°C (Figure C) the conformers undergo enantiomerization. This interconversion between **1a**/enantio-**1a** and **1b**/enantio-**1b** results in the α-β exchange for the C2 and C10 protons.[21] The enantiomerization involves rotation of both vinyl methyls, presumably outward and notably sequentially, and will involve intermediate *anti* conformations. These may be **1c** and **1d** as suggested in Scheme I or other intermediate conformations sufficiently high in energy to have populations which are insignificant for observation by NMR.

In summary, both the molecular modeling and extensive NMR studies are consistent with a complex conformational equilibrium of suspensolide (**1**). A remarkable result is that the two most stable conformers have the methyls *syn*. These conformers undergo interconversion and enantiomerization through intermediacy of less stable *anti* conformers, the relative abundance of which is too low to be characterized by NMR. An interesting observation is the remarkable similarity of the molecular shapes of bicyclic lactones **2, 3** and the two most stable conformers of **1**, all of which have bulky groups *syn*. It is tempting to suggest that these lactones **1-3** can interact with the same receptor in the expression of their pheromonal activity.

Experimental Section

Macrolactonization of 10-Hydroxy-4,8-dimethyl-3(E),8(E)-decadienoic acid (4). A solution of **4** (74 mg, 0.35 mmol), DEAD (92 mg, 0.53 mmol), and triphenylphosphine (138 mg, 0.53 mmol) in anhydrous benzene (30 mL) was stirred at 23°C for 12 h. Concentration of the mixture on a rotary evaporator at 23°C was followed by chromatography on silica gel with benzene as eluent to give in order of elution **1** (13 mg, 19%), and **5** (3.4 mg, 5%).

4,4-Dimethyldeca-3(E),8(E)-dien-10-olide (Suspensolide, 1). The purity of the sample was greater than 96% by GC [a poly(dimethylsiloxane)-coated capillary column, 60m x 0.32mm, 150°C]. The ^{1}H NMR ($CDCl_3$, 23°C), ^{13}C NMR (C_6D_6, 23°C), and GC-MS (EI, 70eV) spectra were identical with those reported.[4c,6a,b] **Conformer 1a at -90°C**: ^{1}H NMR (acetone-d_6) δ 1.43 (s, C8-Me), 1.44 (s, C4-Me), 1.47-1.60 (m, H6), 1.85-2.15 (m, H5 and H7), 2.73 [dd, J(H2α-H2β) = 11.6 Hz, J(H2α-H3) = 7.6 Hz, H2α], 2.80 [dd, J(H2α-H2β) = 11.6 Hz, J(H2β-H3) = 8.8 Hz, H2β], 3.86 [dd, J(H10α-H10β) = 10.8 Hz, J(H9-H10α) = 4.4 Hz, H10α], 4.79 [dd, J(H2β-H3) = 8.8 Hz, J(H2α-H3) = 7.6 Hz, H3], 4.92 [dd, J(H9-H10β) = 11.4 Hz, J(H9-H10α) = 4.4 Hz, H9], 5.09 [dd, J(H9-H10β) = 11.4 Hz, J(H10α-H10β) = 10.8 Hz, H10β]. **Conformer 1b at -90°C**: ^{1}H NMR (acetone-d_6) δ 1.40 (s, C4-Me), 1.62 (s, C8-Me), 1.47-1.60 (m, H6), 1.85-2.15 (m, H5 and H7), 2.52 [dd, J(H2α-H2β) = 10.8 Hz, J(H2α-H3) = 4.8 Hz, H2α], 3.00 [t, J(H2α-H2β) = J(H2β-H3) = 10.8 Hz, H2β], 4.24 [dd, J(H9-H10β) = 11.2 Hz, J(H10α-H10β) = 10.8 Hz, H10β], 4.57 [dd, J(H2β-H3) = 10.8 Hz, J(H2α-H3) = 4.8 Hz, H3], 4.61 [dd, J(H10α-H10β) = 10.8 Hz, J(H9-H10α) = 5.2 Hz, H10α], 4.91 [dd, J(H9-H10β) = 11.2 Hz, J(H9-H10α) = 5.2 Hz, H9]. **Conformers 1a and 1b at -90°C**: ^{13}C NMR (acetone-d_6) δ 14.90, 14.97, 15.08, 15.39 (Me4 and Me8); 25.94, 25.97 (C6); 34.99, 36.68 (C2); 41.31, 41.71, 41.82, 42.35 (C5 and C7); 60.95, 61.31 (C10); 114.39, 117.36 (C3); 120.16, 120.68 (C9); 142.89, 143.76 (C8); 143.76, 145.65 (C4); 168.94, 171.12 (C1).

5,9,16,20-Tetramethyl-1,12-dioxa-4(E),9(E),15(E),20(E)-cyclodocosatetraen-2,13-dione (5). Mp 42-44°C; ^{1}H NMR (acetone-d_6), 25°C) δ 1.41 (quint., 4H, J = 7.2 Hz, H7 and H18), 1.50 (s, 6H, C9-Me and C20-Me), 1.57 (s, 6H, C5-Me and C16-Me), 1.86 (t, 8H, J = 7.2 Hz, H6, H8, H17, and H19), 2.87 (d, 4H, J = 7.6 Hz, H3 and H14), 4.43 (d, 4H, J = 7.6 Hz, H11 and H22), 5.16 (t, 2H, J = 7.6 Hz, H10 and H21), 5.19 (t, 2H, J = 7.6 Hz, H4 and H15); a similar ^{1}H NMR spectrum (δ ± 0.03 ppm) is observed at -90°C; ^{13}C NMR ($CDCl_3$, 25°C) δ 16.15, 16.35 (Me5, Me9, Me16, and Me20), 24.88 (C7 and C18), 34.61 (C3 and C14), 38.16, 38.27 (C6, C7, C17, and C19), 61.39 (C11 and C22), 116.31 (C4 and C15), 118.56 (C10 and C21), 138.45 (C9 and C20), 142.06 (C5 and C16), 172.16 (C2 and C13); MS (70eV) m/z 81(100), 93(25), 107(24), 121(30), 135(47), 194(42), 388(2, M^+); HRMS m/z 388.2618 ($C_{24}H_{36}O_4$ requires 388.2614).

NMR. All spectra were taken on a Varian VXR-400 spectrometer operating at 400 MHz and 100 MHz for ^1H and ^{13}C, respectively, with Me_4Si as the internal reference. The accuracy for the reported coupling constants is ±0.3 Hz. All ^1H spectra were taken with an optimized spectral width of 1728 Hz. The RCT[22,23] spectrum was accumulated with the following parameters; 90° pulse width, acquisition time of 0.592 s, relaxation delay of 3.5 s, interval delay (τ) of 35 μs, relay of 1, 2048 data points, 1024 increments of 24 transients with 2 steady state pulses, and zero filled to 2048 data points in both dimensions. The NOE[23] difference spectra were taken in interleave mode with a 90° pulse width, relaxation delay ≥ 5 x T_1 (typically 20 s to 30 s). For each peak the irradiation power was optimized to deliver only enough power for saturation.

Conformational Search. A conformational search of **1** was carried out using the program, BAKMDL (KS 2.96) on a VAX and using BKM[13] the Unix version running on a IBM Risc 6000 320 . This program is a steric energy minimization program which uses the MODEL MM2 force field and operates in batch mode. The conformational search was carried out using a stochastic search procedure. The calculations were carried out with full force field screening for bad 1,5 C-C VDW interactions, and a minimum cutoff distance of 3.5Å. The structure was examined starting from different geometries and in all cases the collection of conformations was the same with the exception of a grid search. We have found that the statistical Monte Carlo method is superior to a grid search for the collection of low energy conformations.

The generation of geometries for finding the low energy conformation were done by a mixed random-search method, searching on bonds and internal coordinates. The search is biased towards the low-energy regions of conformational space by choosing starting geometries for each step in the conformational search from among previously determined low-energy conformers.[14] Tendencies of the search method to concentrate in certain regions of conformational space at the expense of others is reduced by uniform usage of stored structures as starting geometries and by using varying numbers or torsional rotations in each step.[24]

The search was stopped when duplicate conformers had been found 35 times in a row. Conformers were checked for duplication via a superimposition routine that will classify as identical any two structures in which every non-volatile atom superimposes to within 0.25 Å of its counterpart. The original collection of conformers was put through the compare routine twice. This procedure first removes and then replaces the volatile hydrogens thereby slightly altering each structure which is then reminimized.

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References and Notes

1. (a) Nation, J.L. In *World Crop Pests: Fruit Flies, Their Biology, Natural Enemies and Control*; Robinson, A.S., Hooper, G., Eds.; Elsevier Science Publishers B.V.: Amsterdam, 1989; Vol. 3A, pp. 189-205; and references cited therein. (b) Nation, J.L. *J. Chem. Ecol.* **1990**, *16*, 553-572.
2. Pheromone of *A. suspensa*: (a) Rocca, J.R.; Nation, J.L.; Strekowski, L.; Battiste, M.A. *J. Chem. Ecol.* (in press). (b) Reference 1b. (c) Chuman, T.; Sivinski, J.; Heath, R.R.; Calkins, C.O.;

Tumlinson, J.H.; Battiste, M.A.; Wydra, R.L.; Strekowski, L.; Nation, J.L. *Tetrahedron Lett.* **1988**, *29*, 6561-6564. (d) Battiste, M.A.; Strekowski, L.; Vanderbilt, D.P.; Visnick, M.; King, R.W.; Nation, J.L. *Tetrahedron Lett.* **1983**, *24*, 2611-2614.

3. Pheromone of *A. ludens*: (a) Reference 2a. (b) Reference 1a. (c) Robacker, D.C.; Hart, W.G. *Ann. Entomolog. Soc. Amer.* **1985**, *78*, 488. (d) Stokes, J.B.; Uebel, E.C.; Warthen, J.D.; Jacobson, M.; Flippen-Anderson, J.L.; Gilardi, R.; Spishakoff, L.M.; Wilzer, K.R. *J. Agric. Food Chem.* **1983**, *31*, 1162-1167.
4. For syntheses of **1**, see: (a) Battiste, M.A.; Rocca, J.R.; Wydra, R.L.; Tumlinson, J.H.; Chuman, T. *Tetrahedron Lett.* **1988**, *29*, 6565-6568. (b) Mori, K.; Nakazono, Y. *Liebigs Ann. Chem.* **1988**, 167-174. (c) Nakazono, Y.; Komata, T.; Senda, S.; Tachikawa, T.; Konno, M. Jpn. Kokai Tokkyo Koho JP 02,212,482 (C.A. **1991**, *114*, 23674j).
5. For syntheses of racemic **2** and **3**, see: (a) Reference 4b. (b) Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1984**, 729. (c) Reference 2d.
6. The natural lactones **2** and **3** isolated from cultured *A. suspensa* males are scalemic (not single enantiomers), enantiomerically enriched (ee~10%) with the 3aS,7aS-(-)-enantiomer. For a facile resolution of the racemic mixture, see: Strekowski, L.; Visnick, M.; Battiste, M.A. *J. Org. Chem.* **1986**, *51*, 4836-4839.
7. Battiste, M.A.; Strekowski, L.; Coxon, J.M.; Wydra, R.L.; Harden, D.B. *Tetrahedron Lett.* **1991**, *32*, 5303-5304.
8. Lactones **2** and **3** are also formed in a Lewis acid catalyzed cyclization of a linear hydroxy acid **4** (ref. 5b) from which monolide **1** is derived by macrolactonization. The cyclization of **4** produces **2** and **3** in the ratio of 1:1 and, therefore, this reaction is an unlikely biosynthetic route to the bicyclic lactones.
9. Ferrulactone I, an isomer of suspensolide, is another example of a pheromone component. For the isolation from the volatiles of *Cryptolestes ferrugineus* [Stephens] and synthesis, see: (a) Wong, J.W.; Verigin, V.; Oehlschlager, A.C.; Borden, J.H.; Pierce, H.D.; Pierce, A.M.; Chong, L. *J. Chem. Ecol.* **1983**, *9*, 451-460. (b) Oehlschlager, A.C.; Wong, J.W.; Verigin, V.G.; Pierce, H.D. *J. Org. Chem.* **1983**, *48*, 5009-5017.
10. For reviews on the stereochemistry of larger-ring lactones, see: (a) Shenin, Yu. D. *Antibiot. Khimioter.* **1991**, *36*, 48-51. (b) Nakagawa, A.; Omura, S. In *Structure and Stereochemistry of Macrolides*; Omura, S., Ed.; Academic Press: Orlando, Florida, 1984; pp. 37-84.
11. Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, *28*, 2455-2458.
12. For reviews, see: (a) Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 5218-5223. (b) Karim, M.R.; Sampson, P. *J. Org. Chem.* **1990**, *55*, 598-605.
13. The steric energy minimization program BAKMDL was provided by Professor Kosta Steliou, University of Montreal. BKM, the Unix version running on an IBM Risc 6000 320, was obtained from Serina Software.
14. (a) Saunders, M.; Houk, K.N.; Wu, Y.-D.; Still, W.C.; Lipton, M.; Chang, G.; Guida, W.C. *J. Am. Chem. Soc.* **1990**, *112*, 1419-1427. (b) Howard, A.E.; Kollman, P.A. *J. Med. Chem.* **1988**, *31*, 1669-1675.

15. Eight additional conformers, four of them with the methyls *syn* and four with the methyls *anti* were found within a 3 kcal window of the global minimum. None of the structures of the higher energy *syn* conformers, as obtained from the modeling studies, was consistent with the NMR data. The population distribution of the calculated conformers is 43.6 (**1a**), 32.2 (**1b**), 13.0 (**1c**), 5.6 (**1d**), and 5.6% (the eight additional conformers) at -90°C, and 32.7 (**1a**), 27.1 (**1b**), 15.5 (**1c**), 9.1 (**1d**), and 15.6% (the eight additional conformers) at +23°C.
16. This nomenclature refers to the spatial relationship of the two alkyl substituents at the -C(O)O- function, as described in ref. 17. The *s-trans* and *s-cis* co-planar conformations are indicated as *Z* and *E*, respectively, in ref. 18.
17. Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, *110*, 7858-7868.
18. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp. 54-100.
19. Silverstein, R.M.; Bassler, G.C.; Morril, J.C. *Spectrometric Identification of Organic Compounds*; 4th ed.; Wiley: New York, 1981; pp. 188-189.
20. Theoretical analysis of vicinal couplings from the application of a modified Karplus equation was of a limited value because of problems with parameterization for substituents: (a) Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783-2792. (b) Garbisch, E.W. *J. Am. Chem. Soc.* **1964**, *86*, 5561-5564.
21. It is not possible to determine if the enantiomerization occurs from **1a** or **1b** or for both because the temperature of the conformational interconversion **1a**⇌**1b** occurs at lower temperature.
22. Eich, G.; Bodenhausen, G.; Ernst, R.R. *J. Am. Chem. Soc.* **1982**, *104*, 3731-3732.
23. Derome, A.E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: New York, 1987.
24. Chang, G.; Guida, W.C.; Still, W.C. *J. Am. Chem. Soc.* **1989**, *111*, 4379-4386.