Evaluation of the Claisen Rearrangement of 2-Cyclohexenols for the Stereoselective Construction of a Terpene Synthon

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A variety of stereocontrolled propanoate Claisen rearrangement procedures was applied to 2-cyclohexenol and the *trans*-6-methyl-substituted derivative. The ester–enolate procedure afforded the *RS,SR* diastereomers **6a** and **8a** predominantly, regardless of enolate geometry, indicating a preference for the boatlike conformation in rearrangement of the ketene acetals in which the methyl and cyclohexenyloxy groups are trans. Similar boat specificity is seen on rearrangement of (*E*)-ketene *N,O*-acetals. A model is proposed to explain the alternating chair–boat specificity. Evaluation of these reactions with *cis*-6-methyl-2-cyclohexenol was foiled by poor yields of rearranged products. An alternative, highly stereoselective route to both diastereomers of *p*-menth-1-en-9-ol was developed by using kinetically controlled alkylation and epimerization of a bicyclic lactone intermediate to control the stereochemistry.

The Claisen rearrangement has become a powerful tool in the stereocontrolled construction of acyclic systems,[1] particularly since the development of methods for production of either geometric isomer of the vinyl ether (ketene acetal) moiety.[2] The strong preference for a chairlike conformation in the transition state for rearrangement of acyclic systems serves to relate the stereochemistry of the sp^2-hybridized centers of the starting material and the sp^3-hybridized centers in the product in a predictable fashion.[3] We were interested in extending this process to cyclohexenol derivatives in order to develop a general solution to one of the stereochemical problems in terpene synthesis: that of side chain stereochemistry. The juvabiones (**1**),[4] chrysomelidial (**2a**),[5] and dehydroiridodial (**2b**;[6] see Chart I) are examples of targets which require this type of stereocontrol and illustrate the need for a route to either diastereomer.

Of numerous previous syntheses of these molecules,[7] only the routes to epijuvabione reported by Ficini[7a] and Evans[7b] are stereoselective. Several of the syntheses rely on the *p*-menth-1-en-9-ols, (**3**;[7c,j,m] or related compounds[7h,i]) as intermediates, although they were produced as a stereoisomeric mixture (60:40, *RR/RS*) by hydroboration/oxidation of limonene.[8,9] We chose these compounds as initial targets to evaluate the potential of the Claisen rearrangement for the construction of systems such as **1** and **2**.

In spite of recent interest in the Claisen rearrangement and in acyclic stereocontrol, only Lythgoe et al. have reported examples in cyclohexenol systems in which *acyclic* stereorelationships are generated.[10] They found with some complex substrates that rearrangement takes place via the *boat* conformation, instead of the expected chair. More recently, Ireland et al. have noted that the boat can also be favored in rearrangement of cyclic, carbohydrate-derived, allylic alcohols.[11] Finally, in connection with their work on epijuvabione, Evans and Nelson saw a preference for the boatlike transition state in the related oxy-Cope rearrangement of certain cyclohexene derivatives.[7b]

Claisen Rearrangement of 2-Cyclohexenols. Application of Ireland's "ester–enolate" Claisen rearrangement procedures[2b] to 2-cyclohexenyl propanoate (Table I) led to some surprising results: the *RS,SR* isomer **6a** is the favored product of rearrangement of *both* geometric isomers of the ketene acetal intermediate **5**. The Johnson "ortho ester" procedure[12] also affords predominantly the same isomer, although with diminished selectivity as expected for the higher reaction temperature. Clearly, one of the ketene acetal isomers (cyclohexenyloxy and methyl cis) rearranges predominantly via the chair and the other via the boat. To our knowledge, this represents the first example of a Claisen rearrangement which reverses transition state conformation on reversal of enol double bond stereochemistry. Since our initial report[1a] of this phenomenon, Ireland and Daub have described a similar observation with a dihydropyran substrate.[11]

The condensation of an allylic alcohol with a ketene *N,O*-acetal such as 1-ethoxy-1-(diethylamino)propene ("ortho amide" method) leads to Claisen rearrangement via the (*Z*)-ketene *N,O*-acetal.[2a] Application of this reaction to 2-cyclohexenol results in an equimolar mixture of the diastereomeric amides, indicating that the chair- and boatlike transition states are similar in energy in this case. A striking difference is observed on rearrangement of the corresponding (*E*)-ketene *N,O*-acetal, generated on con-

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(2) (a) W. Sucrow and W. Richter, *Chem. Ber.*, **104**, 3679 (1971); D. Felix, K. Geschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969); (b) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); (c) P. A. Bartlett and W. F. Hahne, *J. Org. Chem.*, **44**, 882 (1979); J. Ficini and C. Barbera, *Tetrahedron Lett.*, 6425 (1966).

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(4) J. F. Manville, *Can. J. Chem.*, **53**, 1579 (1975).

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(6) K. Yoshihara, T. Sakai, and T. Sakan, *Chem. Lett*, 433 (1978).

(7) Epijuvabione: (a) J. Ficini, J. d'Angelo, and J. Noiré, *J. Am. Chem. Soc.*, **96**, 1213 (1974); (b) D. A. Evans and J. V. Nelson, *ibid.*, **102**, 774 (1980); (c) B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *ibid.*, **92**, 336 (1970). Both juvabiones: (d) A. J. Birch, P. L. McDonald, V. H. Powell, *J. Chem. Soc.* C, 1469 (1970); (e) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968); (f) K. S. Ayyar and G. S. Krishna Rao, *Can. J. Chem.*, **46**, 1467 (1968); (g) A. A. Drabkina and Y. S. Tsizin, *J. Gen. Chem. USSR (Engl. Transl.)*, **43**, 691 (1973); (h) E. Negishi, M. Sabanski, J.-J. Katz, and H. C. Brown, *Tetrahedron*, **32**, 925 (1976); (i) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **99**, 3101 (1977). Chrysomelidial: (j) J. Meinwald and T. H. Jones, *ibid.*, **100**, 1883 (1978); (k) T. H. Jones, M. S. Blum, and H. M. Fales, *Tetrahedron Lett.*, 1701 (1980); (l) K. Kon and S. Isoe, *ibid.*, 3399 (1980). Dehydroiridodial: (m) see ref 6.

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(9) While our work was in progress, a stereoselective route to both diastereomers of racemic *p*-menth-1-en-ol by using bicyclic intermediates was reported: S. D. Larsen and S. A. Monti, *Synth. Commun.*, **9**, 141 (1979).

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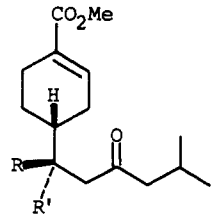
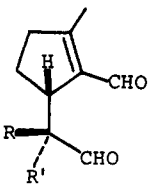
Chart I



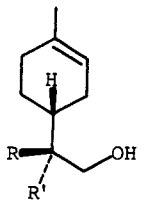
1a R=Me, R'=H: *Juvabione*

1b R=H, R'=Me: *Epijuvabione*



2a R=Me, R'=H: *Chrysomelidial*

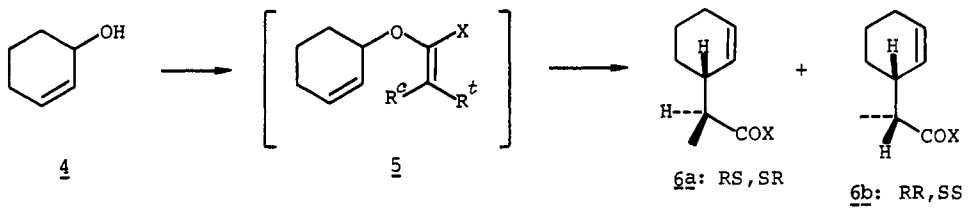
2b R=H, R'=Me: *(ent)-Dehydroiridodial*



3a R=Me, R'=H: *RS-p-menth-1-en-9-ol*

3b R=H, R'=Me: *RR-p-menth-1-en-9-ol*

Table I



4 5 6a: RS,SR 6b: RR,SS

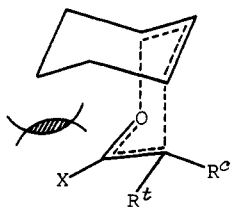
entry	conditions	favored intermediate X	favored intermediate R^c	favored intermediate R^t	ratio[a] of 6a/6b	favored transition state	yield,[b] %
1	ester-enolate[c] in THF	$OSiR_3$	Me	H	85:15	chair	47
2	ester-enolate[c] in 23% HMPA/THF	$OSiR_3$	H	Me	75:25	boat	36
3	ortho ester[d]	OEt	(Me, H)		70:30		48
4	ortho amide[e]	NEt_2	Me	H	50:50		36
5	ynamine[f]	NEt_2	H	Me	>90:10	boat	62

[a] Determined by ^{13}C NMR. [b] Isolated yield of purified product. [c] Treatment of propanoate ester with LDA in the indicated solvent and with the following: −78 °C, $ClSi(t\text{-}Bu)Me_2$, Δ, H_3O^+. [d] $EtC(OEt)_3$, $o\text{-}NO_2PhOH$, 150 °C. [e] $MeCH{=}C(OEt)NEt_2$, xylene, Δ. [f] $MeC{\equiv}CNEt_2$, xylene, Δ.

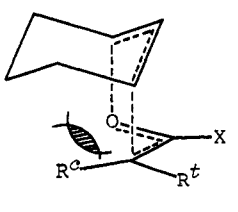
densation of 2-cyclohexenol with 1-(diethylamino)propyne in refluxing xylene (ynamine method).[2c] In this case a 9:1 mixture favoring the RS,SR isomer **6a** is obtained. Again, a trans relationship between the methyl and cyclohexenyloxy groups leads to a strong preference for the boat.

Both the *cis*- and *trans*-6-methyl-2-cyclohexenols were studied as well, as precursors to the *p*-menth-1-en-9-ols (**3**). Similar trends were observed for the trans isomer (Table II). Unfortunately, the cis isomer gave very low yields of rearranged material under all of the conditions, and meaningful isomer ratios could not be obtained. The propensity for elimination and other side reactions to intervene in the Claisen rearrangement of more sterically congested allylic alcohols has been noted previously.[1b,2,13]

To explain the alternation of chair- and boatlike transition states for these rearrangements, structures B and C can be considered. Two types of steric interactions can



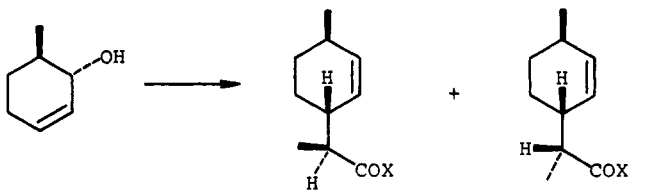
C



B

be envisaged for the bicyclic systems. In the chair form C, substituent X interacts unfavorably with the tri-

Table II[a]



7 8a: RS,SR 8b: RR,SS

entry	conditions	ratio[a] of 8a/8b	favored transition state	yield,[b] %
1	ester-enolate[c] in THF	80:20	chair	41
2	ester-enolate[c] in 23% HMPA/THF	60:40	boat	30
3	ynamine[d]	85:15	boat	36

[a] Determined by ^{13}C NMR. [b] Isolated yield of purified product. [c] Treatment of propanoate ester with LDA in the indicated solvent and with the following: −78 °C, $ClSi(t\text{-}Bu)Me_2$, Δ, H_3O^+. [d] $MeC{\equiv}CNEt_2$, xylene, Δ.

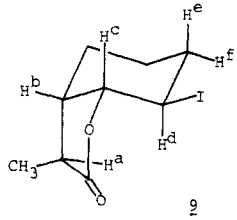
methylene portion of the cyclohexenyl ring. In the absence of other effects, this leads to a preference for the alternative boat conformation B (entries 2 and 5, Table I; and 2 and 3, Table II).

On the other hand, when R^c = methyl, the boat conformation is destabilized by the eclipsing interaction between this methyl and an allylic methylene group. This latter effect is dominant when X = OSi (entry 1 in Tables

(13) A. F. Thomas and G. Ohloff, *Helv. Chim. Acta*, **53**, 1145 (1970); M. W. Rathke and D. F. Sullivan, *Synth. Commun.*, **3**, 67 1973).

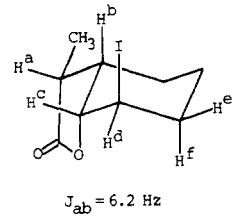
I and II 2); when X is the bulkier diethylamino group (entry 4, Table I), a mixture of isomers is obtained. The interpretations of Lythgoe[10] and Ireland[11] are also in accord with this picture.

Assignment of Stereochemistry. The stereochemistry of the rearranged products was determined by NMR analysis of the isomeric halo lactones **9**–**11**. A 7:3 mixture of the acids **6a** (X = OH) and **6b** (X = OH) obtained from the ortho ester rearrangement affords lactones **9** and **10**



J_{ab} = 10 Hz
J_{bc} = 6.5 Hz
J_{cd} = 8 Hz
J_{de} = 10.5 Hz
J_{df} = 4 Hz

9

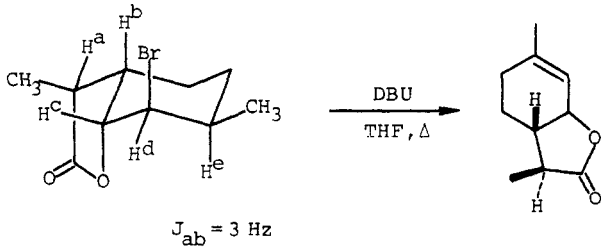


J_{ab} = 6.2 Hz
J_{bc}, J_{cd}, J_{de}, J_{df} ≤ 4 Hz

10

on treatment with iodine in acetonitrile.[14] The major isomer **9** was obtained by fractional crystallization of the crude mixture. The minor isomer **10** remained as an oil. The coupling constants of H^d in isomer **9** define the conformation of the *cis*-6,5 system to be as depicted. Furthermore, the coupling constant $J_{a,b}$ = 10 Hz for isomer **9** is fully consistent with the dihedral angle of 165° estimated from Dreiding models.[15] The corresponding coupling constants for the isomer **10** show that it has the other conformation of the bicyclic system (iodine axial). In addition, the coupling constant J_{ab} = 6.2 Hz is compatible with a dihedral angle of 40° predicted for **10** and incompatible with the angle of 85° expected for the opposite methyl configuration. Hydrolysis of the ester **6** (X = OEt) to the acid and conversion of the acid to the amide **6** (X = NEt_2) served to establish the stereochemistry of those products as well.

The stereochemistry of the methyl-substituted isomers **8a** and **8b** was similarly established by conversion of the major isomer **8a** (X = OH) to the bromo lactone **11** (NBS in chloroform). The low coupling constant (J_{cd} ≤ 4 Hz) indicates that this compound also has the axial halogen conformation, but in contrast to **10**, the coupling constant J_{ab} = 3 Hz reflects the exo configuration of the crucial methyl group. Additionally, elimination of HBr by treatment of **11** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) leads to the unsaturated lactone **12a**, which was



J_{ab} = 3 Hz
J_{bc}, J_{cd}, J_{de} ≤ 4 Hz

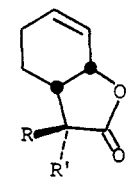
11 **12a**

produced unambiguously by another route (see below). Experiments with epimeric mixtures indicated that no epimerization of the crucial methyl group was taking place under these conditions.

Stereocontrol via Lactone Alkylation. Although the results presented above served to define some of the directive effects which operate during the Claisen rearrangement of cyclohexenyl systems, the low yields obtained, the modest stereoselectivity observed, and the inability to produce either stereoisomer detract from the utility of the approach. We therefore developed another route to the diastereomeric lactones **12a** and **12b** and thence to the *p*-menth-1-en-9-ols (see Scheme I).

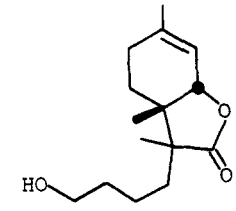
Orthoacetate Claisen rearrangement of a 3:1 mixture of *trans*- and *cis*-6-methyl-2-cyclohexenols[16] leads to a trans/cis mixture of methylcyclohexenylacetic acids **13** in 60% yield after ester hydrolysis. Bromolactonization of this material (quantitative yield) and DBU-induced elimination (xylene at reflux) convert both isomers to the unsaturated lactone **15**, thus obviating the necessity for separating stereoisomers at any stage. Forcing conditions are nonetheless required in order to effect the unfavorable syn elimination from the minor isomer. Alkylation of the lithium enolate of **15** with methyl iodide provides the *exo*-methyl isomer **12a** essentially stereospecifically. The same strategy for stereocontrol has been employed in a number of similar systems.[17] The epimeric lactone **12b** is obtained on kinetically controlled protonation of the enolate of **12**; proton delivery from the less congested exo face affords the *endo*-methyl derivative in 20:1 ratio and quantitative yield. Thermodynamically controlled epimerization (*t*-BuOK/*t*-BuOH) leads to a 4:1 mixture favoring the exo isomer **12a**.

A similar sequence of reactions starting with cyclohexenol led to the epimeric lactones **17a** and **17b**. DBU-induced elimination of HI from the iodo lactones **9** and **11**, respectively, gave the same compounds, confirming the NMR-based stereochemical assignments.



17a: R=Me, R'=H

17b: R=H, R'=Me

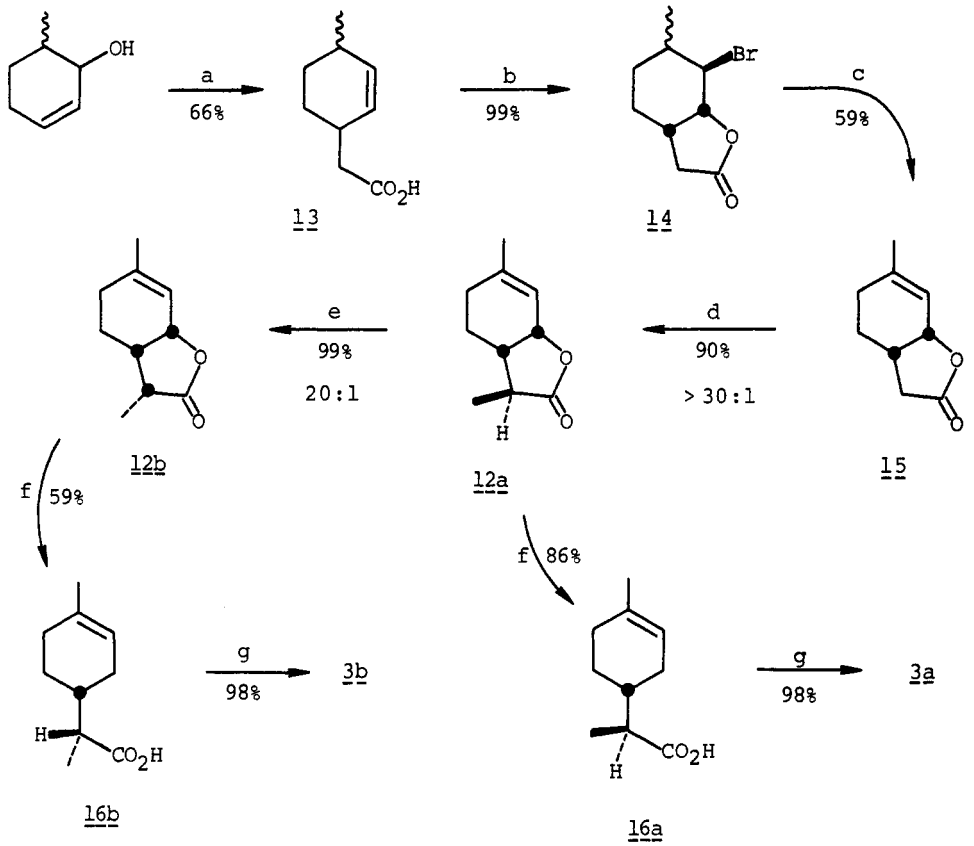


18

Dissolving-metal reduction of the allylic lactones can lead to both the desired product ("1,2-cleavage") as well as to the isomer derived from allylic rearrangement ("1,4-cleavage"). For example, in reduction of the lactones **18** with calcium in ammonia, Welch found ratios for 1,2-cleavage/1,4-cleavage which varied from 1:2 to 2:1, depending on the configuration α to the carbonyl.[17a] We found for lactones **12a** and **12b** that cleavage with calcium in ammonia (with THF and HMPA as cosolvents) leads predominantly to the desired products, with a regioselectivity that increases with time, implying isomerization of the di- to the trisubstituted isomer by the calcium amide generated during the reaction. On prolonged reaction, however, some epimerization of the chiral center α to the carboxylate is also seen. Inclusion of *tert*-butyl alcohol as a cosolvent prevents this epimerization while still affording

(14) P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
(15) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley, New York, 1972, p 273.
(16) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4604 (1956).
(17) (a) S. C. Welch, A. S. C. P. Rao, C. G. Gibbs, and R. Y. Wong, *J. Org. Chem.*, **45**, 4077 (1980); (b) A. E. Greene, *J. Am. Chem. Soc.*, **102**, 5337 (1980); (c) J. A. Marshall and P. G. M. Wuts, *ibid.*, **100**, 1627 (1978); (d) P. A. Grieco and J. J. Reap, *Tetrahedron Lett.*, 1097 (1974).

Scheme I[a]



[a] (a) $MeC(OEt)_3$, o-NO_2PhOH, 150 °C; OH^-, MeOH. (b) NBS, $CHCl_3$. (c) DBU, xylene, Δ. (d) LDA, THF, −78 °C, CH_3I. (e) LDA, THF, −78 °C, AcOH. (f) Ca, NH_3, HMPA, THF, t-BuOH. (g) $LiAlH_4$, ether.

the desired products with good regioselectivity (>4:1). Finally, lithium aluminum hydride reduction of the carboxylic acids gives the isomeric *p*-menth-1-en-9-ols (3) in nearly quantitative yield.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Ether and THF were distilled from sodium/benzophenone immediately prior to use. Boiling and melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 710A spectrometer. ^1H NMR spectra were obtained on the following spectrometers: Varian T-60, Varian EM-390, UCB-180 (180-MHz FT instrument). ^{13}C NMR spectra were obtained with a Nicolet TT-23 spectrometer (25.14 MHz). All spectra were obtained in $CDCl_3$, and all ^1H NMR data are presented as follows: chemical shift (parts per million downfield from internal Me_4Si), multiplicity, number of protons, coupling constants in hertz. Unless otherwise specified, analytical samples were obtained by preparative GLC on a Varian Aerograph A-90P instrument equipped with a 10% SE-30 column. Microanalyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley.

(2*RS*)-2-[(1*SR*)-2-Cyclohexenyl]propanoic Acid (6a, X = OH) via the Ester Enolate Procedure. The *tert*-butyldimethylsilyl enol ether of 2-cyclohexenyl propanoate was prepared and rearranged in THF or 23% HMPA/THF by following the procedure of Ireland, Mueller, and Willard[2b] to give the acids 6 (X = OH). Yields and isomer ratios [after bulb-to-bulb distillation, 120 °C (0.1 torr)] are indicated in Table I: IR (film) 1700, 2890 cm^{-1}; ^1H NMR δ 1.15–1.43 (m, 6), 1.24 (d, 3), 2.6 (m, 2), 5.65 (m, 2), 10.6 (br s, 1); ^{13}C NMR δ 12.92, 21.50, 24.94, 37.90, 44.08, 128.65, 129.17, 182.53. Minor peaks attributable to the isomer **6b** (X = OH) were seen in the ^{13}C NMR at δ 13.34, 27.08, 127.67, and 182.66. Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 70.04; H, 8.97.

(2*RS*)-2-[(1*RS*,*SR*)-2-Cyclohexenyl]-*N*,*N*-diethylpropanamide (6a, X = NEt_2) via the Ynamine Procedure. We have described this procedure in ref 2c.

6a and 6b (X = NEt_2) via the Ortho Amide Procedure. The conditions reported by Sucrow and Richter[2a] were employed with 1-ethoxy-1-(diethylamino)propene in refluxing xylene to give a 36% yield of a 1:1 mixture of the diasteromeric amides **6a** and **6b** (X = NEt_2).[2c]

(2*RS*)-2-[(1*SR*,4*SR*)-4-Methyl-2-cyclohexenyl]propanoic Acid (8a, X = OH) via the Ester–Enolate Procedure. Using the procedure of Ireland, Mueller, and Willard,[2b] *trans*-6-methyl-2-cyclohexenyl propanoate was deprotonated in THF, silylated, and rearranged to give the diastereomeric acids 8 (X = OH) in the yields and ratios indicated in Table II, after bulb-to-bulb distillation [125 °C (0.1 torr)]: IR (film) 1705, 2970 cm^{-1}; ^1H NMR δ 1.0 (d, 3), 1.1 (d, 3), 1.15–1.4 (m, 4), 1.82 (m, 1), 2.5 m, 2), 5.52 (m, 2), 10.6 (br s, 1); ^{13}C NMR (**8a**, X = OH) δ 12.82, 21.61, 25.10, 30.54, 31.27, 38.26, 44.14, 128.36, 182.50. Additional peaks in the ^{13}C NMR were seen for the minor isomer (**8b**, X = OH): δ 13.11, 27.04, 43.94, 126.81, 135.45. Anal. Calcd for $C_{10}H_6O_2$: C, 71.39; H, 9.59. Found: C, 71.05; H, 9.39.

(2*RS*)-*N*,*N*-Diethyl-2[(1*SR*,4*SR*)-4-Methyl-2-cyclohexenyl]propanamide (8a, X = NEt_2) via the Ynamine Procedure. A solution of 0.5 g (4.4 mmol) of *trans*-6-methyl-2-cyclohexenol[16] in 5 mL of xylene was added by syringe pump to a refluxing solution of 0.59 g (5.3 mmol) of 1-(diethylamino)propyne in 45 mL of xylene over a 10-h period. After an additional 2 h, the solvent was evaporated at reduced pressure and 0.36 g (36% yield) of an 85:15 mixture of **8a** and **8b** (X = NEt_2) was isolated by bulb-to-bulb distillation [75 °C (0.1 torr)]: IR (film) 1630 cm^{-1}; ^1H NMR δ 1.0–1.4 (m, 12), 1.5–2.2 (m, 5), 2.5 (m, 3), 3.36 (2 q, 4), 5.41 (m, 2); ^{13}C NMR δ 12.90, 14.66, 15.10, 21.45, 26.16, 30.38. 31.01, 38.68, 40.27, 40.72, 41.84, 128.99, 133.98, 175.2. Minor peaks attributable to isomer **8b** (X = NEt_2) were seen in the ^{13}C NMR: δ 15.72, 27.42, 29.51, 38.00, 39.75, 128.89, 134.57. Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 74.91; H, 11.17; N, 6.22.

(3*RS*,3a*RS*,7*SR*,7a*SR*)-3a,4,5,6,7,7a-Hexahydro-7-iodo-3-methyl-2(3*H*)-benzofuranone (9) and (3*RS*,3a*SR*,7*RS*,7-a*RS*)3a,4,5,6,7,7a-Hexahydro-7-iodo-3-methyl-2(3*H*)-benzo-

furanone (10). A solution of 70 mg (0.45 mmol) of a 2:1 mixture of acids **6a** (X = OH) and **6b** (X = OH) and 23 mg (0.90 mmol) of I_2 in 1 mL of acetonitrile was kept in the dark at 21 °C for 24 h. After being partitioned between ether and saturated $NaHCO_3$, the organic layer was washed with saturated $Na_2S_2O_3$ and saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to give 70 mg (56% yield) of iodo lactones **9** and **10**. Recrystallization of the crude mixture from ether/hexane gave **9** as the major isomer: mp 98.5–99.5 °C; IR ($CHCl_3$) 1780 cm^{-1}; ^1H NMR (180 MHz) δ 1.0–1.5 (m, 6), 1.24 (d, 3, J = 6.8), 1.75 (dddd, 1, J = 6.4, 6.4, 6.4, 10.1, H^b), 2.47 (dq, 1, J = 10.1, 6.8, H^a), 4.10 (ddd, 1, J = 4.14, 8.05, 10.5, H^d), 4.70 (dd, 1, J = 6.38, 7.96, H^c); ^{13}C NMR δ 13.20, 21.98, 24.69; 27.76, 34.95, 37.57, 42.51, 83.12. Anal. Calcd for $C_9H_{13}O_2I$: C, 38.59; H, 4.65; I, 45.31. Found: C, 38.68; H, 4.68; I, 45.34.

Concentration of the mother liquor gave the minor isomer **10** as an oil: ^1H NMR (180 MHz) δ 1.15 (d, 3, J = 7.15), 1.0–1.5 (m, 6), 1.80 (dddd, 1, J = ≤3, ≤3, ≤3, 6.2, H^b), 2.78 (dq, 1, J = 6.2, 7.15, H^a), 4.65 (ddd, 1, J = ≤3, ≤3, ≤3, H^d), 4.83 (dd, 1, J = ≤3, ≤3, H^c).

(3*RS*,3a*RS*,6*SR*,7*SR*,7a*SR*)-3a,4,5,6,7,7a-Hexahydro-7-bromo-3,6-dimethyl-2(3*H*)-benzofuranone (11). A solution of 164 mg (0.97 mmol) of acid **8a** (X = OH) and 0.2 g (1.2 mmol) of NBS in 5 mL of $CHCl_3$ was kept in the dark at 21 °C for 8 h, diluted with ether, washed with water, saturated $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to provide 239 mg (97% yield) of crystalline bromo lactone **11**: mp 75–76 °C; IR ($CHCl_3$) 1780 cm^{-1}; ^1H NMR (180 MHz) δ 1.15 (d, 3), 1.08–2.88 (m, 5), 1.93 (d, 3, J = 7.34), 2.98 (dddd, 1), 3.15 (dq, 1, J = 3, 7.34, H^a), 4.48 (dd, 1, J = 3, 3), 4.73 (dd, 1, J = 4, 4); ^{13}C NMR δ 13.14, 18.55, 25.49, 25.64, 31.60, 38.69, 42.54, 57.14, 79.77, 178.74. An analytical sample was recrystallized from ether/hexane. Anal. Calcd for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12; Br, 32.33. Found: C, 48.82; H, 6.10; Br, 32.36.

***trans*- and *cis*-(4-Methyl-2-cyclohexenyl)acetic Acid (13).** A solution of 59.6 mmol of a 3:1 mixture of *trans*- and *cis*-6-methyl-2-cyclohexenol, 67.7 g (417 mmol) of triethyl orthoacetate, and a catalytic amount of 2,4-dinitrophenol was kept at 150 °C in a flask equipped with a short-path distillation apparatus. After 1 equiv of ethanol had been evolved, excess reagent was distilled from the product. The residue was hydrolyzed in a solution of 4.0 g (71.5 mmol) of KOH in 75 mL of MeOH containing 18 mL of water at reflux for 24 h. After the mixture was diluted with water and washed with ether, the aqueous layer was acidified and extracted twice with ether. The organic layer was washed with water and saturated NaCl, dried ($MgSO_4$), and concentrated to afford 5.46 g (60% yield) of a 3:1 trans/cis mixture of acids **13** after bulb-to-bulb distillation [60 °C (0.1 torr)]: IR (film) 1705, 3000 cm^{-1}; ^1H NMR δ 1.0 (d, 3), 1.1–2.6 (m, 8), 5.5 (m, 2), 10.5 (br s, 1); ^{13}C NMR (trans isomer) δ 21.49, 28.79, 30.35, 30.78, 32.43, 40.73, 128.95, 134.57, 179.19; ^{13}C NMR (cis isomer) δ 21.17, 25.88, 27.86, 29.61, 31.46, 40.29, 128.80, 134.57, 179.19. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.22; H, 9.00.

(3a*RS*,6*RS*,*SR*,7*SR*,7a*SR*)-3a,4,5,6,7,7a-Hexahydro-7-bromo-6-methyl-2(3*H*)-benzofuranone (14). Prepared in 99% yield by the same procedure as described above for **13**: IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR δ 1.1 (d, 3), 1.25–2.9 (m, 8), 4.5 (m, 1), 4.7 (m, 1); ^{13}C NMR (trans isomer) δ 20.00, 25.77, 27.23, 30.58, 30.92, 38.01, 56.99, 81.71, 175.69; ^{13}C NMR (cis isomer) δ 20.24, 27.67, 30.67, 35.68, 36.89, 60.15, 84.47. An analytical sample was prepared by chromatography (silica gel/ether–hexane). Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.28. Found: C, 46.51; H, 5.66; Br, 34.32.

(3a*RS*,7a*SR*)-3a,4,5,7a-Tetrahydro-6-methyl-2(3*H*)-benzofuranone (15). A solution of 1.15 g (4.94 mmol) of the isomeric mixture of bromo lactones **14** and 0.88 mL (5.9 mmol) of DBU in 25 mL of xylene was heated at vigorous reflux (oil bath temperature 150 °C) for 2 h. After evaporation of the solvent and bulb-to-bulb distillation [130 °C (0.58 torr)] of the residue, 442.5 mg (59% yield) of unsaturated lactone **15** was obtained: IR (film) 1770 cm^{-1}; ^1H NMR 1.4–2.0 (m, 4), 1.79 (s, 3), 2.3 (dd, 1), 2.5 (m, 1), 2.7 (dd, 1), 4.8 (m, 1), 5.2 (m, 1); ^{13}C NMR 23.07, 23.24, 27.29, 32.28, 34.66, 76.11, 117.09, 142.24, 175.98. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.85; H, 8.00.

(3*RS*,3a*RS*,7a*SR*)-3a,4,5,7a-Tetrahydro-3,6-dimethyl-2-(3*H*)-benzofuranone (12a). To a stirred soltuion of 1.43 mmol of LDA in 5 mL of THF at −78 °C was added a solution of 197 mg (1.3 mmol) of lactone **15** in 0.5 mL of THF over a 5-min period. After 15 min at −78 °C, 221 mg (1.56 mmol) of methyl iodide was added, and, after 2.5 min, the mixture was brought to room temperature. The solution was partitioned between ether and water, and the organic layer was washed with saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to give 193 mg (90% yield) of lactone **12a** after bulb-to-bulb distillation [118 °C (0.1 torr)]: IR (film) 1770 cm^{-1}; ^1H NMR δ 1.23 (d, 3), 1.73 (s, 3), 1.6–2.6 (m, 7), 5.69 (br s, 1), 5.89 (m, 1); ^{13}C NMR δ 13.85, 22.23, 23.41, 25.88, 37.57, 40.30, 75.20, 118.75, 140.64. Anal. Calcd For $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.17; H, 8.51.

(3*RS*,3a*SR*,7a*RS*)-3a,4,5,7a-Tetrahydro-3,6-dimethyl-2-(3*H*)-benzofuranone (12b). To a stirred solution of 0.5 mmol of LDA in 5 mL of THF at −78 °C was added a solution of 75 mg (0.45 mmol) of lactone **12a** in 0.5 mL of THF over a 5-min period. After 15 min, an excess of glacial acetic acid was added and the mixture was brought to room temperature and partitioned between water and ether. The ether layer was washed with saturated NaCl, dried ($MgSO_4$), and concentrated to give 74 mg (99% yield) of the epimeric lactone **12b** as a 20:1 mixture of isomers: ^{13}C NMR δ 9.09, 19.62, 23.50, 28.85, 37.82, 40.11, 74.57, 117.06, 143.80.

(2*RS*)-2-[(1*SR*)-4-Methyl-3-cyclohexenyl]propanoic Acid (16a). To a solution of 106 mg (0.64 mmol) of lactone **12a** in 2 mL of HMPA, 10 mL of THF, 4 mL of *tert*-butyl alcohol, and 100 mL of liquid NH_3 (distilled from Na) at −78 °C was added 41 mg (1.02 mmol) of calcium metal. The mixture was brought to −33 °C for 1 h, quenched with 100 mL of water, and brought to pH 1 with HCl and ice. After extraction with pentane (4 × 25 mL), the combined organic layer was washed with water and saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Bulb-to-bulb distillation [160 °C (0.4 torr)] of the residue afforded 87 mg (86% yield) of acid **16a**: IR (film) 1705, 2950 cm^{-1}; ^1H NMR δ 1.18 (d, 3), 1.41–2.6 (m, 8), 5.36 (m, 1); minor peaks in the spectrum indicated <20% contamination with the double bond isomer **8a** and its 4′-methyl epimer; ^{13}C NMR δ 13.93, 23.26, 25.73, 29.66, 30.05, 36.42, 44.12, 120.06, 133.99, 182.53. No peaks attributable to 2-methyl epimers could be seen in the ^{13}C NMR. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.41.

(2*RS*)-2-[(1*RS*)-4-Methyl-3-cyclohexenyl]propanoic Acid (16b). In a similar manner lactone **12b** was reduced to afford a 59% yield of acid **16b**: ^{13}C NMR δ 13.92, 23.29, 27.47, 28.44, 30.23, 36.41, 44.66, 119.11, 133.98.

***p*-Menth-1-en-9-ols (3).** To a suspension of 132 mg (3.48 mmol) of $LiAlH_4$ in 25 mL of ether was added 0.47 g (2.78 mmol) of a 3:1 mixture of **16a** and **16b** (arising from nonstereospecifically produced lactone **12**) at such a rate as to maintain gentle reflux. After an additional 30 min, excess $Na_2SO_4 \cdot 10H_2O$ was added, and the slurry was stirred for 45 min. After being filtered and dried ($MgSO_4$), the mixture was concentrated under reduced pressure, and 0.42 g (98% yield) of a 3:1 mixture of the *p*-menth-1-en-9-ol isomers **3a** and **3b** was obtained after bulb-to-bulb distillation [111 °C (0.2 torr)]: ^1H NMR δ 0.92 (d, 3), 0.97–2.1 (m, 11), 2.9 (m, 1), 3.5 (m, 3, CH_2OH), 5.3 (m, 1); ^{13}C NMR (**3a**) δ 13.38, 23.09, 25.23, 29.60, 30.42, 35.13, 39.69, 65.64, 120.63, 133.54; ^{13}C NMR (**3b**) δ 12.99, 23.09, 27.41, 30.56, 34.99, 39.88, 67.76, 120.57, 133.48. ^{13}C NMR comparison of this mixture with a 2:3 mixture of **3a** and **3b** produced on hydroboration of limonene[8] established the validity of our stereochemical assignments.

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Registry No. 3a, 70518-83-1; **3b**, 70518-81-9; **6a** (X = OH), 78168-26-0; **6b** (X = OH), 78168-27-1; **6a** (X = NEt_2), 78168-28-2; **6b** (X = NEt_2), 78168-29-3; **8a** (X = OH), 78168-30-6; **8b** (X = OH), 78215-30-2; **8a** (X = NEt_2), 78168-31-7; **8b** (X = NEt_2), 78215-31-3; **9**, 78168-32-8; **10**, 78168-33-9; **11**, 78168-34-0; **12a**, 78168-35-1; **12b**, 78168-36-2; **13** (isomer 1), 78168-37-3; **13** (isomer 2), 78168-38-4; **14** (isomer 1), 78168-39-5; **14** (isomer 2), 78168-40-8; **15**, 78168-41-9; **16a**, 78215-32-4; **16b**, 78215-33-5; 1-ethoxy-1-(diethylamino)propene, 78168-42-0; *trans*-6-methyl-2-cyclohexenyl propanoate, 78168-43-1; *trans*-6-methyl-2-cyclohexenol, 40523-67-9; *cis*-6-methyl-2-cyclohexenol, 40523-66-8.