12 (9 mg) and the ^1H NMR spectra were recorded after each addition. The chemical shift of each signal was measured for each addition of shift reagent and the induced shift ($\Delta\delta$) corresponding to the addition of 1 equiv of shift reagent was determined by least-squares analysis (Table I). The distance (r_{calcd}) between a proton and praseodymium atom was calculated using the relationship $\Delta\delta = k/r^3$ (this approximation for $\Delta\delta = k(3\cos^2\theta - 1)/r^3$ is valid when the O-Pr-H angle (θ) is less than 20°) and compared with distances measured (r_{meas}) using a Dreiding model. In practice, this was accomplished by assuming approximate distances between the praseodymium atom and the three rigidly positioned protons on the cyclopropane ring to obtain a starting position for the praseodymium atom, that was modified as more protons were considered. The calculated distances between the praseodymium atom and protons at C-2 and C-9 corresponded to the distances measured when the lactone ring is in a pseudo-boat conformation. The stereochemistry at C-6 was determined by measuring the oxygen-praseodymium distances. The smallest Pr-O distance for this isomer was 2.5 Å, a normal value, while for the alternate isomer it was ~4.0 Å, an abnormally large distance.[6] In this conformation, the induced shifts for the protons on the ethyl group could not be explained by the simple formula since $\theta > 30°$. The hydroxymethylene protons also required a correction for θ. The calculated distances (r_{calcd}) and measured distances (r_{meas}) must differ by less than 10% for a valid correlation.

(B) Aliquots (5 μL) of $Eu(fod)_3$ shift reagent (33.5 mg) in deuteriochloroform (100 μL) were added to a solution of the alcohol **14** (5 mg) in deuteriochloroform and ^1H NMR spectra were recorded after each addition. The induced shifts ($\Delta\delta$) corresponding to the addition of 1 equiv of shift reagent were calculated by least-squares analysis (Table II). Using the techniques described above, a good correlation between r_{calcd} and r_{meas} was obtained for the isomer shown. For the protons at C-7, the H-Eu-O angle (θ) was measured at ~30°. Recalculation of r_{calcd} for $\theta = 30°$ gave a very good fit with the measured distance.

Alcohol 13: IR ($CHCl_3$) 3450, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 1.37 (d, 3 H, J = 6 Hz), 1.75 (br s, -OH), 2.14 (q, 2 H, J = 7 Hz), 2.44 (dq, 1 H, J = 9, 7, 7, 7 Hz), 2.61 (dt, 1 H, J = 19, 9, 9 Hz), 4.13 (br s, 2 H), 4.15 (dq, 1 H, J = 9, 6, 6, 6 Hz), 5.23 (d, 1 H, J = 10 Hz); mass spectrum m/e 198 (M^+).

Alcohol 14: IR ($CHCl_3$) 3400, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 7 Hz), 1.45 (d, 3 H, J = 6 Hz), 1.88 (m, 1 H, J = 10, 9, 5, 4 Hz), 1.99 (s, -OH), 2.61 (dq, 1 H, J = 10, 7, 7, 7 Hz), 3.75 (dd, 1 H, J = 11, 5 Hz), 3.82 (dd, 1 H, J = 11, 4 Hz), 4.41 (dq, 1 H, J = 9, 6, 6, 6 Hz); mass spectrum m/e 144 (M^+).

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Registry No. **3**, 1896-62-4; **4**, 70941-32-1; **5**, 70941-33-2; **6**, 70941-34-3; **7**, 70941-35-4; **8**, 70941-36-5; **9**, 70981-88-3; **10**, 70941-37-6; **11**, 70941-38-7; **12**, 70941-39-8; **13**, 70941-40-1; **14**, 70941-41-2.

(6) For examples see Sievers, R., Ed. "Nuclear Magnetic Resonance Shift Reagents"; Academic Press: New York, 1973.

Santolinolide B [(2*R*,3*S*,4*S*)-4-Hydroxy-2,5-dimethyl-3-vinyl-5-hexenoic Acid Lactone]. A New Irregular Monoterpene from *Artemisia tridentata tridentata*

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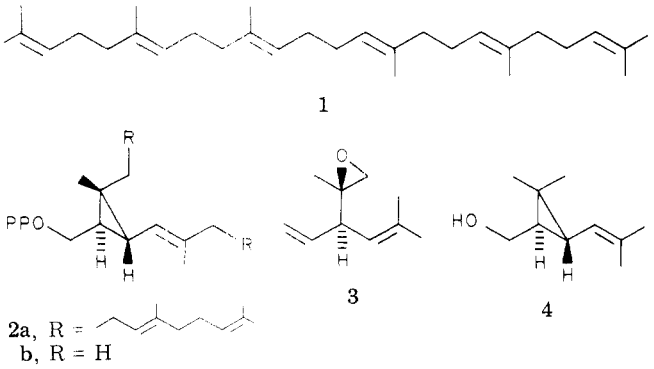
The neutral pentane extract of the leaves and flower heads of big sage (*Artemisia tridentata tridentata*) contains a new non-head-to-tail monoterpene lactone, santolinolide B (**12**). The steam distillate from the plant material contains a mixture of santolinolides A (**11**), B (**12**), B′ (**14**), and C (**13**). The absolute stereochemical structures of these diastereomers have been established.

In recent years there has been interest generated in the biosynthesis of irregular monoterpenes serving as a model for the biogenesis of the important triterpene squalene (**1**) and its immediate precursor, presqualene pyrophosphate (**2a**). It has been hypothesized that (1*R*,3*R*)-chrysanthemyl pyrophosphate (**2b**), a C-10 analogue of presqualene pyrophosphate, is the biosynthetic precursor of the non-head-to-tail monoterpenes.[1] The isolation and absolute stereochemistry of several monoterpenes lent support to this hypothesis;[2-5] however, the occurrence of (2*S*,3*R*)-santolina epoxide (**3**) is stereochemically inconsistent with the proposed biogenetic route.[6] If chrysanthemyl pyrophosphate is indeed the precursor of the irregular monoterpenes, then it must also occur as the 1*R*,3*S* cis diastereomer since optically pure (1*R*,3*R*)-*trans*-chrysanthemol (**4**) has been isolated from *Artemisia ludoviciana*.[4]



We have been screening plants of the Anthemidae tribe of the Compositae family for *cis*-chrysanthemol,[7,8] and as

(1) W. W. Epstein and C. D. Poulter, *Phytochemistry*, **12**, 737 (1973).
(2) C. D. Poulter, R. J. Goodfellow, and W. W. Epstein, *Tetrahedron Lett.*, 71 (1972).
(3) J. Shaw, T. A. Noble, and W. W. Epstein, *J. Chem. Soc., Chem. Commun.*, 590 (1975).
(4) K. Alexander and W. W. Epstein, *J. Org. Chem.*, **40**, 2576 (1975).
(5) T. A. Noble and W. W. Epstein, *Tetrahedron Lett.*, 3931 (1977).
(6) T. A. Noble and W. W. Epstein, *Tetrahedron Lett.*, 3933 (1977).

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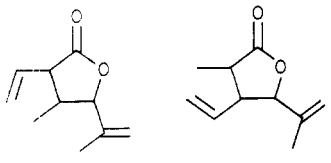
possible sources of cell-free enzyme systems to be used in the study of the more complex, but presumably analogous squalene biosynthetic pathway.

We now wish to report the isolation and structures, including absolute stereochemistry, of four new diastereomeric monoterpene lactones from *Artemisia tridentata tridentata*, big sage. Plants were collected from two sites, one near Price, Utah, and the other near Lehi, Utah. The lactones isolated from the Price material unfortunately proved to be almost racemic while the Lehi material yielded optically pure compounds. Since all of the early work involved the Price material, the following discussion is not limited to the more biosynthetically relevant compounds from Lehi sagebrush.

Results and Discussion

Essential oils, from steam distillation of the ground leaves and stems of *A. tridentata tridentata* collected near Price, Utah, were saponified to yield a lactone fraction after a conventional acid–base workup. GLC analysis indicated the presence of four components, although silica gel TLC in several different solvent systems showed only a single spot. One of the components, representing 58% of the mixture, was isolated by preparative GLC and proved to be a colorless oil with no appreciable rotation and molecular formula $C_{10}H_{14}O_2$. The spectral data suggested γ-lactone, vinyl [$-CH{=}CH_2$], and isopropenyl [$-C(CH_3){=}CH_2$] functionalities. The 3-H doublet at δ 1.27 in the ^1H NMR can be assigned to a methyl group either α or β to the carbonyl, and the 1-H ABX pattern at δ 4.50 is consistent with a trisubstituted lactone juncture. Double resonance experiments showed the vinyl and lactone juncture protons were not coupled.

With this information in hand two gross structures can be drawn, **5** and **6**; however there exists biogenetic pre-

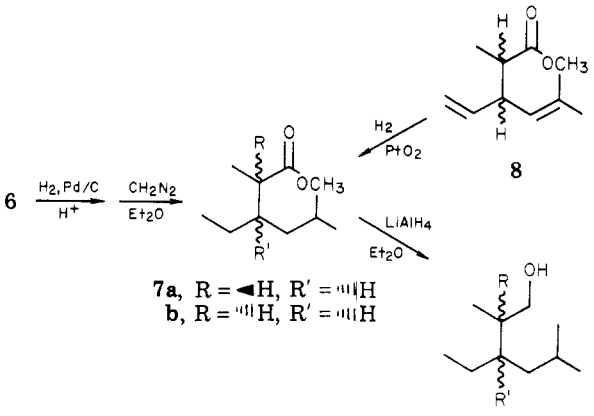


5 6

cedence for **6**, which possesses the known santolinyl skeletal system.[1,3,5,6]

The correctness of structure **6** for lactone A was confirmed by chemical degradation to a known compound (Scheme I). Hydrogenolysis of the lactone over Pd/C followed by esterification with diazomethane yielded an oil **7** with IR and ^1H NMR spectral properties and a GLC retention time characteristic of the ester obtained from hydrogenation of methyl santolinate (**8**).[3] The ^1H NMR spectrum of the degradation product possesses splitting patterns in the δ 0.75–1.90 region that are virtually identical with those of the 2*S*,3*R* saturated ester **7a**, and clearly different from those of the 2*R*,3*R* diastereomer **7b**. The above considerations are also important because the saturated esters from methyl santolinate were inseparable with respect to GLC. Reduction of **7** with $LiAlH_4$ gave alcohol **9** as an oil, $[\alpha]_D$ −2.5°. The sign and magnitude of the rotation indicate a 62:38 enantiomeric ratio of the 2*S*,3*R*/2*R*,3*S* alcohols, respectively, based upon the known rotation of optically pure alcohol **9a**.[6]

Scheme I

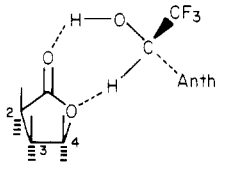


9a, R = ◀H, R' = ▮H
$[\alpha]_D$ −10.8°
b, R = ▮H, R' = ▮H
$[\alpha]_D$ +27.7°

The optical purity of lactone A was also determined by NMR using a chiral shift reagent. Nonequivalence of two separate signals is seen in the ^1H NMR spectrum upon introduction of (*S*)(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol.[9,10] The methyl singlet at δ 1.76 was resolved into two singlets separated by 3.9 Hz, and the peak height ratio of the upfield to the downfield signal is 57:43, respectively.[11] The complex doublet at δ 4.50 also shows nonequivalence in the presence of the shift reagent. Two overlapping doublets appear (J = 9.3 Hz) separated by 5.6 Hz, and the upfield to downfield signal ratio is 43:57, respectively, indicating the expected enantiomeric excess.

The assignment of relative stereochemistry at C-4 of lactone A was achieved by analysis of the ^1H NMR. The proton at C-4 is split into the X portion of an ABX system. Irradiation of the olefinic region at δ 5.12 produced no change in the splitting pattern; however irradiation of the two proton multiplet at δ 2.50 collapsed the X multiplet to a clean singlet. These results suggest that the protons occurring as the δ 2.50 multiplet are responsible for both the vicinal and long-range spin–spin coupling interactions. The protons attached to C-2 and C-3 have been assigned to this signal. In order for appreciable long-range coupling to occur through four saturated bonds, a near planar zigzag configuration is required[12] which is possible only if the protons on C-2 and C-4 are cis with respect to each other.

Further examination of the ^1H NMR spectrum obtained in the presence of the chiral shift reagent verified this assignment. The shift reagent is thought to coordinate with γ-lactones as shown in **10**.[9] An α-substituent at C-4



10

would be expected to be shifted upfield due to the shielding effect of the aromatic system, while the $-CF_3$ moiety would deshield β-substituents at that center. Upon

(7) Plants producing pyrophosphates might be expected to have the corresponding alcohols due to the ubiquitous occurrence of phosphatases in these systems.

(8) W. W. Epstein, L. R. McGee, C. D. Poulter, and L. L. Marsh, *J. Chem. Eng. Data*, 21, 500 (1976).

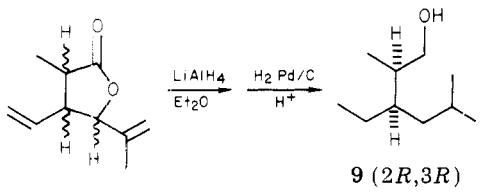
(9) W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, 42, 1370 (1977).

(10) We would like to thank Dr. William Pirkle for a sample of the chiral shift reagent used in this study.

(11) The ratio is approximate since the signals were not base line separated.

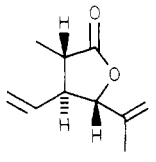
(12) S. Sternhell, *Rev. Pure Appl. Chem.*, 14, 15 (1964).

Scheme II



B 9 (2*R*,3*R*)

coordination with the shift reagent, the larger $-CH_3$ singlet occurs upfield and the larger -H doublet downfield with respect to the smaller signals. This implies that the predominant 2*S*,3*S* enantiomer has a β-hydrogen and an α-isopropenyl group at C-4, or the 2*S*,3*S*,4*S* configuration **11**.



11 (2*S*,3*S*,4*S*)

Further preparative gas chromatography of the lactone mixture resulted in the isolation of an inseparable two-component mixture and a second pure compound. The similarity of spectral data to that from lactone A indicates that all four components of the mixture are diastereomeric lactones.

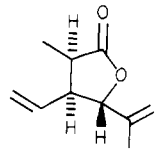
Due to the presence of two epimerizable centers in the lactone, it was thought that the mixture could be the result of the isolation procedure. Under milder conditions, discussed in detail below, lactone B was isolated as the predominant diastereomer with no GLC evidence of lactones B′ and C. Thus, these santolinolides are indeed artifacts of the steam distillation.

The ground leaves and flower heads of a sample of *A. tridentata tridentata* collected near Lehi, Utah, were continuously extracted with pentane. The essential oil was analyzed via silica gel TLC and shown to contain a spot with the same R_f value as the lactones. GLC coinjection studies gave evidence that one of the diastereomeric lactones greatly predominated over the others in the crude plant oil. Repeated silica gel chromatography yielded a colorless oil which was shown to be 96% lactone B by GLC. The lactone was purified by preparative GLC to yield an oil, $[\alpha]_D$ +64°.

An analysis of the spectral data indicated that lactone B corresponded to one of the diastereomers of lactone A, and was therefore assigned the same gross structure. Both the structure and absolute stereochemistry at C-2 and C-3 were confirmed utilizing the degradative pathway of Scheme II.

The lactone was reduced with $LiAlH_4$ and the crude product was hydrogenolyzed to give the saturated alcohol **9** (85% pure). Since epimerization at C-2 was avoided throughout the reaction sequence, the sign of the rotation would indicate the configuration at that center. Based upon the rotations of compounds **9a** and **9b**, the isolated alcohol, $[\alpha]_D$ +25.9°, corresponds to a 94% optically pure product with the 2*R*,3*R* configuration.

The configuration at C-4 was established using ^1H NMR data and epimerization results. The lack of appreciable long-range coupling between H-2 and H-4 suggests that they are trans to one another. The coupling of the signal at δ 4.63 which appears as a doublet (J = 5.2 Hz) implies that H-3 is trans to H-4, and thus a 3*S*,4*S* configuration results.[13] Since lactone B could be epimerized to lactone A in refluxing 10% NaOH, all the evidence supports structure **12** for lactone B with the absolute configuration indicated.

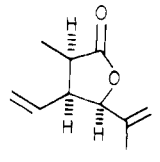


12 (2*R*,3*S*,4*S*)

Whereas the neutral extraction of Lehi *A. tridentata tridentata* produced primarily one lactone component, steam distillation of the Lehi material yielded a mixture of the four diastereomeric lactones. An equilibration of lactone B occurs during the steam distillation process since the essential oils contain the four isomers prior to acid–base workup, as evidenced by GLC coinjection studies.

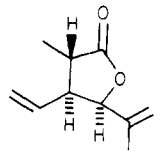
Lactone A was isolated from the Lehi equilibration mixture by preparative GLC, $[\alpha]_D$ -9.4°, and its optical purity was determined in the presence of the chiral shift reagent. There is no evidence of nonequivalence in either the EM-390 or SC-300 ^1H NMR spectra, indicating that the Lehi plant material produces optically pure lactone B. This result is contrary to that of the Price sage, which yields a partially racemic product.

The stereochemistry of the two remaining diastereomers isolated from the Lehi equilibration mixture was deduced as follows. Lactone C, $[\alpha]_D$ -12.8°, was isolated by preparative GLC as a solid with a melting point near room temperature. The configuration at C-3 should be unaffected throughout equilibration of lactone B, and there is evidence of long-range coupling between the C-2 and C-4 protons in the ^1H NMR, suggesting they are cis oriented. This implies that lactone C possesses the all cis 2*R*,3*S*,4*R* absolute configuration **13**.



13 (2*R*,3*S*,4*R*)

Lactone B′ was isolated as an inseparable two-component mixture with lactone B (B:B′ = 63:37), $[\alpha]_D$ +28.2°. An analysis of the ^1H NMR spectrum clearly shows the presence of two doublets corresponding to the C-4 protons of lactones B and B′ at δ 4.45 (J = 5.2 Hz) and 4.75 (J = 8.0 Hz), respectively. The lack of long-range coupling between H-2 and H-4 of lactone B′, and the fact that this isomer is produced when lactone C is epimerized in base, is consistent only with structure **14** for lactone B′.



14 (2*S*,3*S*,4*R*)

The CD spectra of the lactones isolated from the Lehi mixture provide data which support the absolute stereochemical assignments reported here. Lactones A and B′ display positive circular dichroism maxima at 217 and 221 nm, while lactones B and C show negative curves with

(13) B. Tursch, J. C. Braekman, D. Daloze, M. Herin, and R. Karlsson, *Tetrahedron Lett.*, 3769 (1974).

minima at 219 and 218 nm, respectively.[14] These results are in complete agreement with the assignments made.[15]

According to the revised hypothesis concerning irregular monoterpene biosynthesis, (1*R*,3*S*)-*cis*-chrysanthemyl pyrophosphate should be the precursor of these lactones, since they possess the *S* configuration at C-3. We are continuing the screening process for *cis*-chrysanthemol, and for a suitable plant system which efficiently biosynthesizes non-head-to-tail monoterpenes.

Experimental Section

^{1}H NMR spectra were recorded on Varian EM-390, XL-100, and SC-300 spectrophotometers. ^{13}C spectra were recorded on the Varian XL-100 instrument operating on 25.1 MHz. IR spectra were obtained from a Beckman Acculab 3 spectrophotometer, and UV spectra from a Perkin-Elmer 299 spectrophotometer. Optical rotations were measured at ambient temperatures on a Perkin-Elmer 141 polarimeter in a 1-dm cell. CD spectra were recorded on a Cary 60 spectrophotometer in a 1-cm cell. GC/MS data was obtained from a Varian MAT 112-S instrument fitted with a 6 ft × $^1/_8$ in. glass Carbowax 20 M (1%) column. TLC analyses were performed on silica gel G (E. Merck) with detection by an anisaldehyde/HOAc/H_2SO_4 spray reagent. Column chromatography was done on Baker 60–200 mesh silica gel, and medium-pressure liquid chromatography (MPLC) was done on 0.032–0.063 mm Woelm silica gel using a Milton Roy minipump, 1.5 × 100 cm and 2.5 × 100 cm Altex columns. All solvents were distilled prior to MPLC use, and spectral grade solvents were used for NMR (Me_4Si standard) and optical rotation measurements. A Varian Aerograph Series 1200 gas chromatograph with a flame ionization detector was used for GLC analyses. The analytical columns employed were 39 ft × $^1/_8$ in. and 9 ft × $^1/_8$ in. Carbowax 20 M (10%) on silanized 100–120 mesh Anakrom AB, and a 38 ft × $^1/_8$ in. Tween-80 (6%) on silanized 80–100 mesh Anakrom AB, all in silanized aluminum tubing. Preparative GLC was performed on an Aerograph A-90-P chromatograph with a thermal conductivity detector using a 25 ft × $^3/_8$ in. Carbowax 20 M (10%) on silanized 60–80 mesh Chromosorb P aluminum column. Microanalysis was performed by Chemalytics Inc., Tempe, Arizona.

Collections. *Artemisia tridentata tridentata* was collected from two locations: Price, Utah, April 21, 1974; and Lehi, Utah, November 11, 1977. The University of Utah Herbarium contains pressed samples of the material used in this study.

Extractions and Isolations. The material from Price, Utah, was steam-distilled as a yellow oil and 5.0 g was saponified for 2 h in refluxing 10% NaOH (50 mL) and MeOH (25 mL). The cooled solution was extracted with Et_2O (3 × 25 mL) and the combined organic phases were washed with saturated $NaHCO_3$ (3 × 25 mL), H_2O (1 × 10 mL), and saturated NaCl (1 × 10 mL) before drying over anhydrous $MgSO_4$. Concentration in vacuo yielded 261.5 mg of a yellow oil which consisted of lactones A (58%), B/B′ mixture (39%, 63:37), and C (3%). TLC analysis of the mixture with EtOAc/hexanes (20:80) indicated the presence of one spot with R_f 0.45.

Lactone A (11): isolated as a clear oil via preparative GLC; $[\alpha]_D$ 0° (*c* 0.026, $CHCl_3$); MS (EI) *m/e* 68 (100%), 67 (22), 53 (8), 69 (7), 96 (4), 79 (2), 138 (2, M^+ − CO), 77 (2), 91 (2); IR (neat) 3095, 1770, 1655, 1385, 980, 930, and 890 cm^{-1} (shoulder); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (3 H, d, *J* = 6.7 Hz), 1.76 (3 H, s), 2.50 (2 H, m), 4.50 (1 H, ABX), 5.12 (4 H, m), 5.71 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 13 (q), 17 (q), 41 (d), 53 (d), 85 (d), 115 (t), 119 (t), 135 (d), 140 (s), 178 (s).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.36; H, 8.54.

Lactone B/B′ mixture (12 and 14): obtained as an inseparable mixture via preparative GLC.

Lactone C (13): isolated via preparative GLC as a clear oil; MS (EI) *m/e* 68 (100%), 67 (34), 41 (16), 39 (13), 53 (11), 69 (6), 40 (4), 77 (3), 79 (3), 138 (3); IR (CCl_4) 3050, 1775, 1650, 1380, 925, 910, and 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (3 H, d, *J* = 7.2 Hz), 1.65 (3 H, s), 2.90 (1 H, m), 3.11 (1 H, m), 4.78 (1 H, m), 5.07 (4 H, m), 5.44 (1 H, m).

Continuous Pentane Extraction of Lehi *Artemisia tridentata*. The ground leaves and flower heads (fresh and frozen) were continuously extracted with pentane for 2–10 days. The combined extracts were concentrated in vacuo and distilled under reduced pressure (1.45 mmHg, 38–56 °C) to yield a yellow oil (1% dry weight). TLC analysis with EtOAc/hexanes (20:80) indicated the presence of a lactone component with R_f 0.45. The crude oil was chromatographed on a silica column with EtOAc/hexanes (20:80), and the fractions containing the R_f 0.45 spot were combined, concentrated, and subjected to MPLC through silica gel with EtOAc/hexanes (20:80) followed by MPLC with CH_2Cl_2. The isolation was monitored by TLC and GLC. Concentration of the desired fractions yielded a clear oil which was shown to be 96% lactone B and 4% lactone A* by analytical GLC.

Lactone B (12): isolated as a colorless oil by preparative GLC (0.02% dry weight); $[\alpha]_D$ +64.0° (*c* 0.023, $CHCl_3$); MS (EI) *m/e* 68 (100), 67 (30), 41 (13), 39 (9), 53 (9), 69 (6), 40 (4), 79 (3), 91 (3), 138 (3); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.18 (3 H, d, *J* = 7.4 Hz), 1.78 (3 H, s), 2.88 (2 H, m), 4.63 (1 H, d, *J* = 5.2 Hz), 5.12 (4 H, m), 5.72 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 11, 18, 38, 48, 85, 113, 119, 134, 141, 179; UV_{max} (EtOH) 207 nm (ε 369); CD (*c* 0.09, EtOH), 25 °C, $[\theta]_{250}$ 0, $[\theta]_{219}$ −1.77 × 10^3.

Steam Distillation of Lehi *A. tridentata*. The ground leaves and flower heads were placed in a 12-L round-bottom flask equipped with a side arm Two condensers were attached in series to the side arm, and 1 L of saturated $NaHCO_3$ was added to the contents of the flask. Steam was allowed to percolate through the plant material for 10 h, and the condensate was collected, extracted with Et_2O, and concentrated to yield a yellow oil.

Lactone A (11): isolated as a colorless oil by preparative GLC; $[\alpha]_D$ −9.4° (*c* 1.69, $CHCl_3$); UV_{max} (EtOH) 207 nm (ε 364); CD (*c* 0.19, EtOH), 25 °C, $[\theta]_{250}$ 0, $[\theta]_{217}$ +3.50 × 10^3.

Lactone B/B′ mixture (12 and 14): isolated as an inseparable mixture by preparative GLC: $[\alpha]_D$ +28.2° (*c* 1.6, $CHCl_3$); UV_{max} (EtOH) 207 nm (ε 356); CD (*c* 0.07, EtOH), 25 °C, $[\theta]_{250}$ 0, $[\theta]_{221}$ −0.282 × 10^3; ^{1}H NMR (CCl_4, 90 MHz) δ 1.10 (3 H, d, *J* = 7.4 Hz), 1.15 (3 H, d, *J* = 7.0 Hz), 1.80 (3 H, s), 1.87 (3 H, s), 2.60 (4 H, m), 4.45 (1 H, d, *J* = 5.2 Hz), 4.75 (1 H, d, *J* = 8.0 Hz), 5.05 (8 H, m), 5.75 (2 H, m).

Lactone C (13): isolated as a colorless solid by preparative GLC; $[\alpha]_D$ −12.8° (*c* 1.2, $CHCl_3$); UV_{max} (EtOH) 207 nm (ε 382); CD (*c* 0.09, EtOH), 25 °C, $[\theta]_{250}$ 0, $[\theta]_{218}$ −6.30 × 10^3.

Hydrogenolysis and Esterification of Lactone A (11) (Price). To a solution of the lactone (127 mg, 0.77 mmol) in 10 mL of MeOH and 1 drop of concentrated $HClO_4$ was added 80 mg of Pd/C (5%) and the mixture was shaken for 16 h under 5 psi H_2. The mixture was filtered, taken up in Et_2O, washed with H_2O (2 × 10 mL) and saturated NaCl (1 × 10 mL), and dried over anhydrous $MgSO_4$. The ethereal solution was subjected to excess diazomethane, concentrated, and analyzed by GLC. The first of two components (61:39) was isolated via preparative GLC: $[\alpha]_D$ +7.56° (*c* 0.026, $CHCl_3$); IR (neat) 1736, 1470, 1390, 1370, and 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.75–1.10 (12 H, $-CH_3$), 1.10–1.90 (6 H, m), 2.48 (1 H, m), 3.63 (3 H, s). The latter peak was not collected.

Hydrogenation of (2*R*,3*S*)-Methyl Santolinate (8). To a solution of the ester (74 mg, 0.41 mmol) in 13 mL of glacial HOAc was added 17 mg of PtO_2 and the mixture was shaken for 1 h under 30 psi H_2, filtered, and taken up in pentane. The solution was washed with H_2O (3 × 15 mL) and saturated $NaHCO_3$ (2 × 2 mL), dried over anhydrous $MgSO_4$, and concentrated to yield 70 mg (0.38 mmol) of a clear oil (93%): IR (neat) 1738, 1470, 1390, 1370, and 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.75–1.10 (12 H, $-CH_3$), 1.10–1.80 (6 H, m), 2.48 (1 H, m), 3.66 (3 H, s).

Hydrogenation of (2*R*,3*R*)-Methyl Santolinate. The preceding reduction procedure was followed for the 2*R*,3*R* ester (64 mg, 0.35 mmol, 71%): IR (neat) 1736, 1470, 1390, 1370, and 1202 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.70–1.06 (12 H, $-CH_3$), 1.10–1.77 (6 H, m), 2.50 (1 H, m), 3.60 (3 H, s).

$LiAlH_4$ Reduction of Price Methyl Ester 6. The ester (21 mg, 0.11 mmol) was dissolved in anhydrous Et_2O and added dropwise to a stirred solution of $LiAlH_4$ (32 mg, 0.84 mmol) in Et_2O. The reaction was quenched after 0.5 h with saturated

(14) The sign of the curve associated with lactone B′ was determined by difference from the B/B′ mixture.

(15) A. F. Beecham, *Tetrahedron Lett.*, 2355, 3591 (1968).

NH_4Cl (200 μL), stirred an additional 0.5 h, filtered, and dried over anhydrous $MgSO_4$. The solvent was removed and the oil was purified by preparative GLC to yield 13 mg (0.08 mmol) of a colorless oil (73%): $[\alpha]_D$ −2.48° (c 0.013, $CHCl_3$); IR (neat) 3320, 1470, 1390, 1370, 1030, 915, and 745 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.80–0.93 (12 H, $-CH_3$), 1.00–1.85 (8 H, m), and 3.48 (2 H, m).

$LiAlH_4$ Reduction of the 2*R*,3*S* Ester 6a. The ester (30 mg, 0.16 mmol) was reduced as above to yield a clear oil (94%): IR (neat) 3340, 1465, 1380, 1360, 1250, 1020, and 790 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.80–0.93 (12 H, $-CH_3$), 1.00–1.85 (8 H, m), and 3.47 (2 H, m).

Epimerization of Lactone A (11). The lactone (20 μL), 2 mL of MeOH, and 3 mL of 10% NaOH were refluxed for 1 h. The mixture was acidified with dilute HCl and extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. Concentration in vacuo followed by GLC analysis revealed two components with retention times of 24.1 and 27.3 min (38 ft Tween-80) corresponding to lactones A and B, respectively.

Epimerization of Lactone Mixture B/B′ (12 and 14). The same procedure as above was followed. The GLC coinjection studies and GC/MS data were consistent with the formation of lactones A (24.1 min) and C (32.6 min).

Epimerization of Lactone C (13). The same epimerization procedure was followed, and the GLC coinjection studies and GC/MS data verified the observation that lactone B′ (27.9 min) was produced.

$LiAlH_4$ Reduction of Lehi Lactone B (12). The lactone (90 mg, 0.54 mmol) was dissolved in anhydrous Et_2O and added dropwise to a stirred solution of $LiAlH_4$ (15 mg, 0.39 mmol) in Et_2O. After 1 h the reaction was quenched with excess $Na_2SO_4 \cdot 10H_2O$ and allowed to stir an additional 0.5 h. The solution was filtered and concentrated to yield 112 mg of an oil.

Hydrogenolysis of the Crude Diol. To a solution of the previous product (112 mg) in 30 mL of MeOH and 1 mL of 10% $HClO_4$ was added 60 mg of Pd/C (5%), and the mixture shaken for 24 h under 10 psi H_2. The mixture was filtered, taken up in pentane, and concentrated to yield 59 mg of an oil. Preparative GLC purification yielded 9.6 mg (0.06 mmol) of the desired alcohol **9** (11% from **12**). The alcohol was 85% pure by analytical GLC: $[\alpha]_D$ +25.9° (c 0.096, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.80–1.08 (12 H, $-CH_3$), 1.15–1.85 (7 H, m), 2.13 (1 H, s), 3.50 (2 H, m).

Epimerization of Lactone B (12). The same general epimerization procedure was followed as for lactone A. The appearance of lactone A (24.1 min) was supported by GLC coinjection studies and GC/MS data.

^1H NMR Nonequivalence Studies. Price lactone A (**11**; 24 mg, 0.145 mmol), (*S*)(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (120 mg, 0.435 mmol), and 0.73 mL of CCl_4 were placed in a 5-mm NMR tube and the spectrum was recorded. Lehi lactone A (**11**; 14 mg, 0.084 mmol), (*S*)(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (70 mg, 0.254 mmol), and 0.42 mL of CCl_4 were placed in a 5 mm NMR tube and the spectrum was recorded after the shift reagent was completely dissolved.

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Transannular Reactions of Dibenzo[*a*,*d*]cycloalkenes. 1.[1a] Synthesis of Dibenzo[*a*,*d*]cycloocten-6,12-imines and Dibenzo[*a*,*d*]cyclohepten-5,10-imines

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A strategy for the synthesis of dibenzo[*a*,*d*]cycloocten-6,12-imines based on the initial construction of a hydrocarbon framework containing the appropriate functionality for transannular nitrogen ring closure was developed. The key to this approach was the synthesis of the symmetrical diketone, 5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene-6,12-dione (**15**). Reductive amination of **15** occurred regioselectively at the 6 position giving rise directly to the dibenzocycloocten-6,12-imine ring system by transannular carbinolamine formation. The diketone **15** was converted through the oxime **26** to the hydroxylamine **28**. Thermal cyclization of **28** to **29** established a second transannular route to the dibenzo[*a*,*d*]cycloocten-6,12-imines. This latter method also was used successfully for the synthesis of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imines. The proximity of functional groups at the 6 and 12 positions of dibenzo[*a*,*d*]cyclooctanes which favored nitrogen bridging reactions also promoted other transannular reactions such as the facile conversion of **26** to **27**.

A number of heterocyclic molecules of medicinal interest contain a tricyclic hydrocarbon framework with a nitrogen-bridged central ring flanked by two aromatic rings to form at least one benzhydryl bridgehead carbon (Figure 1).[1a-e] The simplest construction of this type and the only one with two such carbons is 9,10-dihydroanthracen-9,10-imine. Recently, we described a broad analysis of the cycloaddition approach to this heterocycle.[1b] The next higher homologue, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine,[1c-d] has received limited attention in the literature and the larger 5,6,7,12-tetrahydrodibenzo[*a*,*d*]cycloocten-6,12-imines have not been reported. Described here are efficient syntheses of both of these ring systems. In each case the strategy was to construct the required hydrocarbon framework containing the appropriate functionality for subsequent transannular nitrogen ring closure. The methods set forth below were developed

(1) (a) Part 2: B. E. Evans, P. S. Anderson, M. E. Christy, C. D. Colton, D. C. Remy, K. E. Rittle, and E. L. Engelhardt, *J. Org. Chem.*, following paper in this issue; (b) P. S. Anderson, M. E. Christy, C. D. Colton, W. Halczenko, G. S. Ponticello, and K. L. Shepard, *ibid.*, **44**, 1519 (1979); (c) Roussel Uclaf, U.S. Patent 3 892 756 (1975); (d) J. H. Dygos, *J. Heterocycl. Chem.*, **13**, 1355 (1976); (e) D. C. Remy, P. S. Anderson, M. E. Christy, and B. E. Evans, *J. Org. Chem.*, **43**, 4311 (1978).

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