Cobalt-Mediated Synthesis of a Versatile Pseudoguaianolide Intermediate

Angel M. Montaña and Kenneth M. Nicholas*

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma 73019

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An efficient stereocontrolled synthesis of hydroxy ketone **24a**, a versatile precursor of various pseudoguaianolides, is described starting from bicyclic ketoacetylene **7**. Synthesis of the latter compound using as a key step alkylation of a suitable silylenol ether by (ethoxypropynylium)$Co_2(CO)_6BF_4$ was described earlier. Annulation of **7** was accomplished by hydration followed by aldol cyclization to ketol **9**. The latter was converted to the key intermediate hydroxy ether **15a** by two different schemes. In one sequence removal of the keto group from **9**, regioselective dehydration, Me_2BBr-induced regioselective cyclic ether cleavage, and stereoselective hydrogenation afforded **15a** efficiently. Alternatively, **9** was first dehydrated regioselectively followed by dithioketalization/desulfurization, which also induced oxacycle cleavage to **22**, which, in turn, underwent stereoselective hydrogenation giving **15a** in good overall yield. Oxidation of **15a** and ethyl ether cleavage afforded the known damsin precursor **24a**.

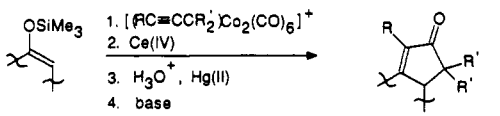
Introduction

The rapidly expanding class of pseudoguaianolide sesquiterpenes[1] has been the focus of a number of synthetic ventures[2,3] because of their challenging stereochemical features and the significant cytotoxic, antitumor, and other biological properties of several members.[4] Various strategies for construction of the bicyclo [3.5.0] skeleton of these compounds have been developed, but very few of these have involved annulation of an appropriately elaborated seven-membered ring, perhaps owing to the paucity of general, stereocontrolled routes to such rings.

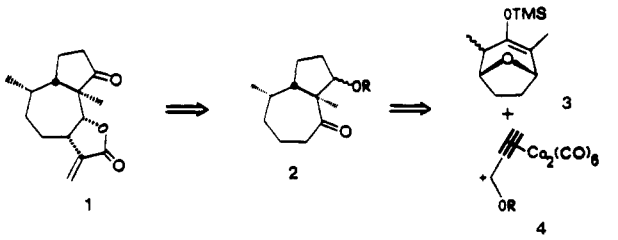
As part of our program to explore the synthetic utility of [propargylium]dicobalt hexacarbonyl complexes,[5] we developed earlier a convenient ketone cyclopentannulation sequence featuring the alkylation of silyl enol ethers by these complexes and subsequent demetalation, alkyne hydration, and aldol cyclization.[6] This methodology was employed in an efficient synthesis of the guaiane cyclocolorenone.[7]

Recently we have turned our attention to an adaptation of this methodology for the synthesis of the pseudoguaiane skeleton according to the retrosynthetic strategy outlined in Scheme I for damsin, **1**. Key elements of this approach are (1) utilization of the Noyori oxyallyl cation/furan cyclization[8] method to supply latent regio- and stereocontrol devices in the seven-membered ring and (2) the use of alkoxy-substituted complexes **4** to provide the requisite oxygen functionality at C10. Our approach to constructing the hydroazulenic skeleton is unusual in being based on annulation of an appropriately functionalized seven-membered ring. An earlier publication described the initial stage of this synthesis[9] (Scheme II) which began with 3-pentanone and provided the bicyclic acetylenic ketone **7** in an overall yield of 57% in seven steps. An important aspect of this phase of the synthesis is the complete exo facial selectivity and good relative diastereoselectivity which occurs in the alkylation of the precursor silyl enol ether by complex **4**. We now report on the continuation of the synthesis concluding with hydroxy ketone **24a**, a demonstrated precursor of damsin, **1**,[10] and other ambrosanolides.[11]

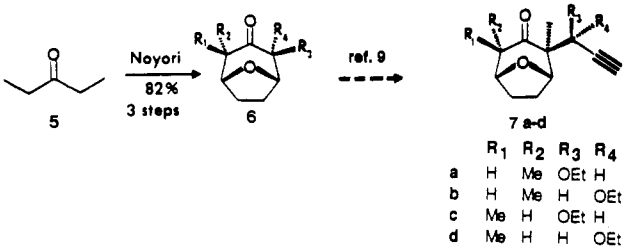
Scheme I



Scheme II



Scheme III



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(2) Apsimon, J. *The Total Synthesis of Natural Products*; J. Wiley: New York, 1982; pp 347–37.
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(8) (a) Noyori, R.; Hayakawa, Y.; Takaya, H.; Murai, S.; Kobayashi, R.; Sonoda, N. *J. Am. Chem. Soc.* **1978**, *100*, 1759. (b) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765. (c) Noyori, R.; Baba, Y.; Makino, S.; Takaya, H. *Tetrahedron Lett.* **1973**, *20*, 1741. (d) Noyori, R.; Makino, S.; Takayo, H. *Tetrahedron Lett.* **1973**, *20*, 1745.
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(11) Kok, P.; De Clercq, P. J.; Vandevalle, M. E. *J. Org. Chem.* **1979**, *44*, 4553.

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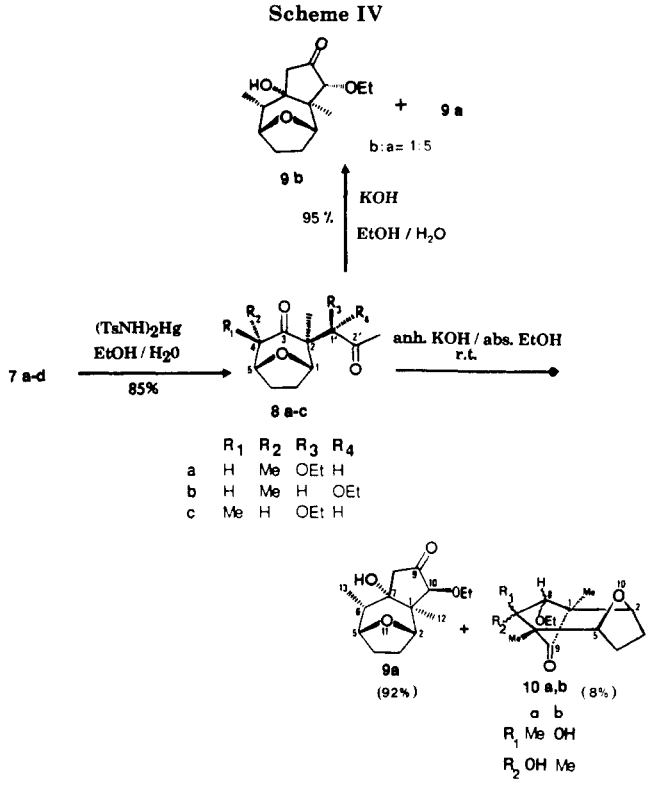
Scheme IV



Results and Discussion

Hydration of the triple bond in the isomeric mixture of **7a–d** (9:36:47:8) was carried out under strictly neutral conditions in the presence of $(p\text{-TolSO}_2\text{NH})_2\text{Hg}$[12] by refluxing in $\text{EtOH}/\text{H}_2\text{O}$ (85:15) (Scheme III). This afforded an 85% yield of a mixture of only three diastereoisomers **8a–c** (18:35:47 by capillary GC/MS and ^{1}H NMR). These isomers could be separated by successive column chromatography and preparative TLC for characterizational purposes, but in our synthetic sequence we were able to utilize the mixture (vide infra). The stereochemistry of each isomer **8a–c** was established from a correlation study of their ^{1}H NMR signals with precursors reported earlier.[9] The assignment of signals was made by COSY-90 experiments and the analysis of multiplicity and coupling constants by ^{1}H homodecoupling experiments. The formation of only three isomers (the starting material contained four) suggests that epimerization (either of the starting materials or products) occurred under the reaction conditions, an hypothesis which was not tested.

Aldol cyclization of **8a–c** (18:35:47) was carried out initially using KOH (pellets, 85%) in 95% EtOH at room temperature (8 h). Under these conditions we obtained a 5:1 mixture of C10 epimers, **9a** and **9b**, in 95% yield (see Scheme IV). These could be separated by flash column chromatography, and their stereochemistry was deduced using ^{1}H and ^{13}C NMR spectroscopy. Analysis of coupling constants and assignment of signals in the ^{1}H NMR spectra were made possible using ^{1}H homodecoupling experiments, COSY-90, long-range COSY, HOMO-2DJ, and phase sensitive RCT (relay coherence transfer) two-dimensional experiments. Double quantum filtered COSY (DQF-COSY) was also very helpful in analyzing the region of the methylene protons. Looking at the chemical shift and multiplicity patterns for H5 (dd) and H13 (s) in both

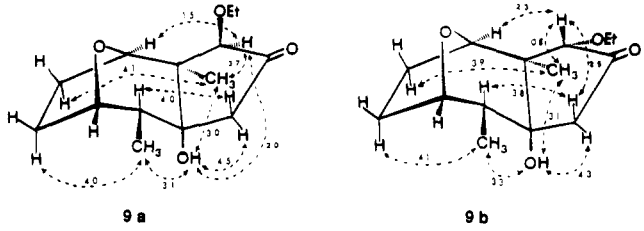


Figure 1.

9a and **9b**, it is possible to establish that both have the same configuration at C6 and C7. On the other hand, it was concluded that they are epimeric at C10, on the following grounds: (1) in **9b** Me-1 is deshielded by the OH and OEt groups due to a 1,3-cis diaxial interaction between them, H-10 is deshielded by interaction with the bridging oxygen, and H2 is deshielded by an electrostatic deshielding interaction with the OEt group; (2) in **9a** Me-1 and H10 are shielded by interaction with one another as well as H2; additionally, a *W* coupling is observed between H10 and the cis-H8 which is not seen in **9b**. Correlation studies of the ^{13}C NMR spectra supported these assignments. The multiplicity of carbon peaks observed in the broadband-decoupled ^{13}C NMR spectrum was established by means of DEPT experiments (APT, off-resonance and HET-2DJ experiments were confirmatory), and the assignments were facilitated by 2D-HETCOR. The main differences between ^{13}C signals of **9a** and **9b** are C10 ($\Delta\delta$ = 19.21), C8 ($\Delta\delta$ = 5.68), C1 ($\Delta\delta$ = 4.29), and C12 ($\Delta\delta$ = 1.73), which can be explained on the basis of the γ-gauche shielding effects which result from inverting the configuration at C10. Phase sensitive NOESY and 1D-NOE experiments corroborated the previous assignments (Figure 1). The stereoselectivity under these nonanhydrous conditions appears to be thermodynamically controlled since **9a** itself was found to produce the same 5:1 isomeric mixture when subjected to identical reaction conditions.

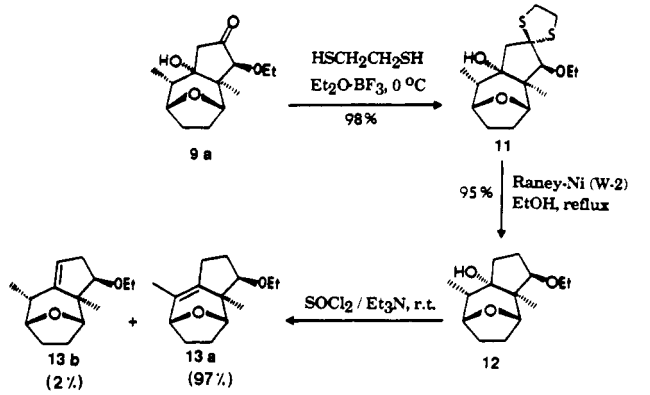
Carrying out the aldol reaction of **8a–c** under strictly anhydrous conditions (absolute EtOH, anhydrous KOH, 20 °C, 8 h) produced ketol **9a** *exclusively* in 92% yield. This surprising and fortuitous result afforded us considerable practical simplification for subsequent stages of the synthesis. Note that from the original mixture of four isomers **7a–d** we now had in hand a single isomer. The remaining 8% of the reaction product was a 3:1 mixture of keto alcohols **10a** (7,8 *l*) and **10b** (7,8 *u*) respectively, resulting from the attack of the less stable tertiary enolate of the cycloheptanone on the acetonyl group of **8a–c**.

Several attempts were made to effect direct aldol condensation, i.e. cyclization followed by dehydration, of **8**. Under more forcing basic conditions (absolute EtOH, anhydrous KOH, reflux, 8 h) only mixtures of **9a,b** were produced. The dehydration process may be both kinetically and thermodynamically unfavorable because the OH group is tertiary, axial, and "endo" and because introduction of a double bond in the tricyclic system would introduce considerable strain. We also tried to accomplish cyclocondensation of **11** under acidic conditions using a variety of Brønsted acids: HCl(c) in EtOH, HCl(g) in CHCl_3, TsOH in PhH, etc. In all cases no cyclization products were produced, even under vigorous conditions (reflux for 20 h), but only epimerization at C4 and C1′ of **8**.

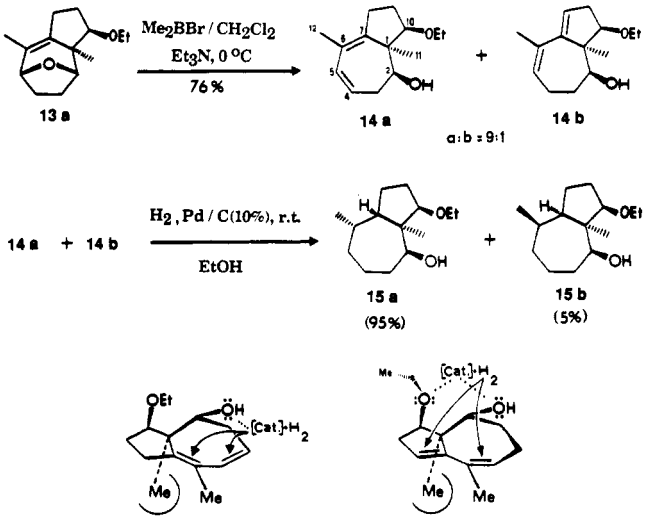
Although dehydration of **8** ultimately proved possible (vide infra), we temporarily turned our attention to relieving some of the strain present in the tricyclic framework by removing the keto function at C9. Accordingly, **9a** was first transformed into the corresponding ethylene dithio-

(12) (a) Boldberg, M. W.; Aeschbacher, R. *Helv. Chim. Acta* **1943**, *26*, 680. (b) Goldberg, M. W.; Aeschbacher, R. *Helv. Chim. Acta* **1939**, *22*, 1185. (c) Ghosh Saha, M. Ph.D. Thesis, Boston College, Boston, MA, 1985, p 166.

Scheme V



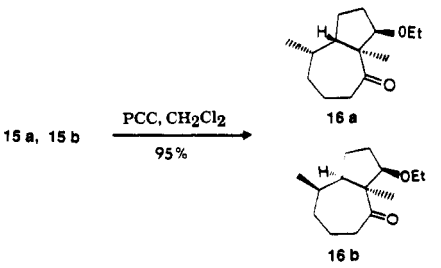
Scheme VI



ketal[13] **11** (Scheme V), in 98% yield, upon treatment with excess 1,2-ethanedithiol and BF_3·OEt_2 in benzene. Neither cleavage of the tetrahydrofuran or the ethyl ethers nor elimination of the OH function occurred under these conditions. Raney Nickel (W-2) reduction[14] of **11** in refluxing ethanol then efficiently provided the crystalline alcohol **12** (95% yield), which was fully characterized spectroscopically. Dehydration of **12** was then accomplished using excess Cl_2SO/NEt_3[15] at room temperature, affording the corresponding olefins **13a** and **13b** (97% and 2% yield), which could be separated by flash column chromatography. The preferred formation of **13a** is presumably thermodynamically favored because the resultant double bond is tetrasubstituted and its presence introduces less strain than that in the five-membered ring of **13b**.

Regiocontrol in the Lewis acid promoted oxygen bridge cleavage of **13a** was now set up by the presence of the activating double bond at the allylic position and probably reinforced by intramolecular coordination of the Lewis acid

Scheme VII



to the neighboring ethoxy group (neighboring orientation effect).[16] Cleavage of the tetrahydrofuran ring in **13a** was carried out using Me_2BBr as Lewis acid[16] in CH_2Cl_2 at 0 °C, giving a 76% yield (unoptimized) of a 9:1 mixture of isomeric dienes **14a** and **14b**, each having the requisite functionality for further synthetic elaboration (Scheme VI). The remaining 24% of the reaction product was a complex mixture of very polar compounds, easily separated from **14a,b** by column chromatography. It is worth noting further that in addition to the excellent regioselectivity observed, complete chemoselectivity was also found. This could reflect the greater basicity[16] of the intracyclic oxygen over the ethoxy one as well as the greater relief of strain accompanying cleavage of the former. The homoannular diene, **14a**, could result from an E2 process (the predominant mechanism in the opening of 2-substituted tetrahydrofurans by Me_2BBr[16]) whereas the heteroannular diene, **14b**, could be derived from an E1 process but experimental support for this hypothesis is presently lacking. Isomers **14a** and **14b** were characterized thoroughly by spectroscopic methods. Assignments of their ^1H NMR spectra were made on the basis of 2D COSY-90 and COSY-45 experiments. In the case of ^{13}C NMR spectra analysis of multiplicity and assignments were assisted by DEPT and 2D-HETCOR experiments respectively.

Hydrogenation of **14a,b** (90:10) was carried out in absolute EtOH under one atmosphere of H_2 using Pd on charcoal (10% w/w) as the catalyst (Scheme VII). The product was a 95/5 mixture of the adducts **15a** and **15b** in quantitative yield. The diastereomers **15a** and **15b** proved difficult to separate, and, accordingly, we used the mixture for subsequent synthetic steps, because separation of the corresponding diastereoisomers was very easy in a later step. However, for characterizational purposes pure samples of **15a** and **15b** were obtained by careful flash column chromatography and preparative TLC. The analysis and assignments of ^1H NMR signals were facilitated by ^1H homodecoupling, 2D-COSY-90, 2D phase-sensitive double quantum filtered-COSY (PS-DQF-COSY), and 2D phase-sensitive relay coherence transfer (PS-RCT) experiments. In **15a** Me-1 and Me-6 appear at higher field than in **15b** due to a 1,3-cis-diaxial shielding interaction. Also, H7 is deshielded by the OH group in **15a** and shielded by Me-1 in **15b**. Moreover, in **15b** the OH group deshields Me-6. These assignments of configuration were further corroborated by phase sensitive 2D-NOESY experiments, observing NOE enhancements between Me-1 and Me-6 in **15a**. In the case of ^{13}C NMR signals, assignments were made possible by DEPT and 2D-HETCOR experiments. The relative configuration at the carbons 1, 2, 6, 7, and 10 in both diastereomers was established by correlation studies of the chemical shift values of the ^1H

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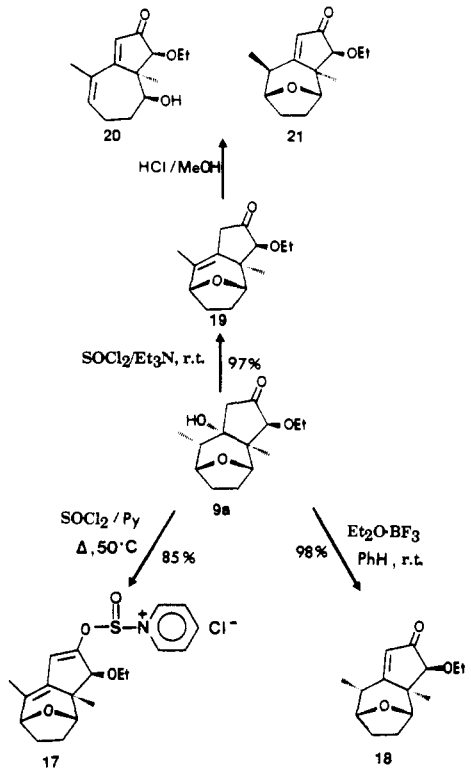
(14) (a) Augustine, R. L. *Reduction Techniques and Application in Organic Synthesis*; M. Dekker Inc.: New York, 1968; p 194. (b) Djerassi, C.; Halpern, O.; Pettit, G. R.; Thomas, G. J. *J. Org. Chem.* **1959**, *24*, 1. (c) Djerassi, C. *Steroid Reactions: An Outline for Organic Chemists*; Holden Day, Inc.: San Francisco, 1963; p 28.

(15) (a) Newman, M. S.; Arkell, A.; Fukunaga, T. *J. Am. Chem. Soc.* **1960**, *82*, 2498. (b) Turner, R. B. *J. Am. Chem. Soc.* **1952**, *74*, 5362. (c) Campbell, J. A.; Babcock, J. C.; Hogg, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 4717. (d) Fieser, L.; Fieser, M. In *Reagents for Organic Syntheses*; John Wiley: New York, 1967; Vol. 1 (pp 394, 670, 878–881), Vol. 5 (p 660), Vol. 7 (p 366).

(16) Guidon, Y.; Thrien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680 and references therein. For another acid-promoted oxacycle cleavage to afford the 5,7-system, see: Rigby, J. J.; Zbur Wilson, J. *J. Org. Chem.* **1987**, *52*, 34.

Scheme VIII

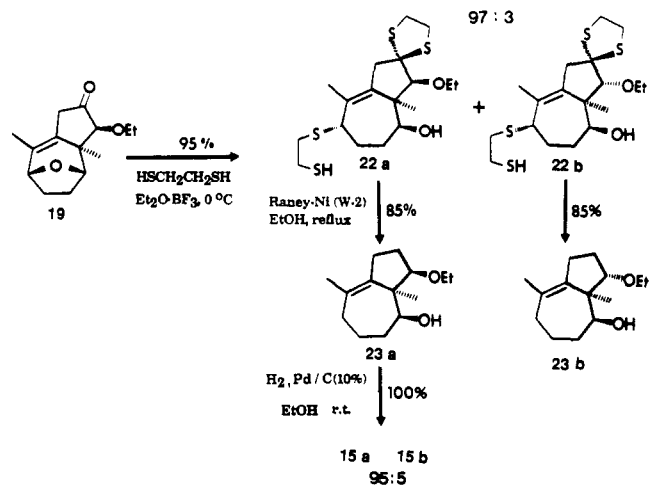


and ^{13}C NMR spectra. The largest differences of δ (ppm) between the isomers were found for protons H2, H7, H10, H11, and H12 and on carbons C11, C12, C6, C7, and C2, whose analysis allowed us to determine for **15a** the relative configurations $1R^*,2S^*,6S^*,7S^*,10R^*$. The highly stereoselective nature of the hydrogenation of **14a**, **14b** is the result of reaction occurring on the presumably less hindered diene face(s) opposite to the pseudoaxial C1-methyl group, possibly assisted by cooperative interaction(s) of the catalysts surface with the donor OH and OEt groups.[17]

Oxidation of **15a** and/or **15b** by pyridinium chlorochromate[18] in CH_2Cl_2 at 20 °C yielded efficiently the corresponding ketones **16a** and **16b** (95:5, 95%, Scheme VII). As previously, for synthetic purposes we worked with the resultant mixture **16a**/**16b** (95:5). But for characterization purposes, we oxidized **15a** and **15b** individually to secure pure samples of **16a** and **16b**. Correlation studies of the ^1H and ^{13}C NMR spectra of **16a** and **16b** showed similar trends as observed in the spectral studies of **15a** and **15b**, corroborating the previous assignments. NOE enhancements were again studied for **16a** and **16b**, observing in **16a** positive enhancements between Me-1 and Me-6 (7% measured by 1D-NOE) and between Me-1 and H10 (4%). In the minor isomer, **16b**, NOE enhancements were observed among Me-1, H6, and H10 but not between Me-1 and Me-6.

Since compound **15a** is a key intermediate in our synthetic route to pseudoguaianolides, we investigated an alternative synthesis of it via intermediate **21** (Scheme VIII). Our first objective in this route to **15a** was the dehydration of **9a** to introduce a nonconjugated $\Delta^{6,7}$ double bond allylic to the oxygen bridge to provide a bias for the eventual regioselective cleavage of the tetrahydrofuran ring. We carried out a systematic study of the reactivity of **9a** toward a large variety of dehydrating agents. Because the OH group at C7 in **9a** is tertiary, axial, and flanked by two methyl groups with a cis relationship, it was anticipated that it would be difficult to remove and that dehydration to the conjugated enone might be a competing process. Indeed, the reaction of **9a** with $SOCl_2$/pyridine was found to be ineffective at 0 °C and room temperature; when forcing conditions were employed (heating to 50 °C), we obtained an 85% yield the pyridinium salt **17**, which stubbornly refused several hydrolysis attempts under various conditions. Alternatively, treatment of **9a** with BF_3·OEt_2 in benzene at room temperature afforded a 98% yield of the conjugated ketone **18**. The stereochemistry of **18** was deduced by examination of molecular models and comparison of the ^1H NMR multiplicity of the H5 resonance and the deshielded resonance of H6 and the shielded one of Me-6 relative to those of its C6 epimer **20** (vide infra). Eventually, using an excess of $SOCl_2$ in NEt_3 at 20 °C, we obtained a 97% yield of the desired nonconjugated compound **19**. Importantly, the configurations at C1 and C10 were preserved during this reaction judging by ^1H NMR chemical shift correlations between **9a** and **19**. Treatment of **19** with concentrated HCl/MeOH at room temperature indicated how activated the C5–O bond is by the allylic unsaturation, affording a 39% yield of the ring-opened diene **21** and a 42% yield of the conjugated ketone **20**. Formation of **20** involves an epimerization process at C-6, which avoids a 1,3-cis-diaxial interaction between Me-1 and Me-6. The stereochemistry indicated for **20** was apparent from the ^1H NMR multiplicity (and coupling constants) of H5 and the positions of both the H6 and Me-6 resonances in comparison with those of epimeric **21**. It is not clear from the experiments to date which dehydrated product **18**, **19**, or **20** is the thermodynamically favored one.

Scheme IX

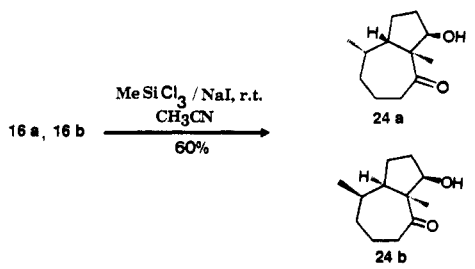


In view of the difficulties of epimerization which occurred in the protolytic cleavage of **19** in the previous experiment, our efforts were directed toward initial removal of the labilizing carbonyl group. When **19** was treated with excess BF_3·OEt_2 in $HSCH_2CH_2SH$ at 0 °C, we were pleased to find that two useful transformations occurred in one step: formation of the ethylene dithioketal at C9 and regioselective cleavage of the tetrahydrofuran ring assisted by the allylic double bond $\Delta^{6,7}$ to afford a 97:3

(17) For other examples of stereoselective hydrogenation of 5,7-ring systems, see: (a) Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312. (b) Kretchmer, R. A.; Thompson, W. J. *Ibid.* **1976**, *98*, 3379.

(18) (a) Piancatelli, G.; Scettri, A.; Auria, M. D. *Synthesis* **1982**, 245. (b) Mijs, W. J.; Jonge, C. R. H. I. *Organic Synthesis by Oxidation with Metal Compounds*; Plenum Press: New York, 1986. (c) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. (d) Fieser, L.; Fieser, M. *Reagents for Organic Synthesis*; J. Wiley: New York, Vol. 6 (p 498), Vol. 7 (p 308), Vol. 8 (p 425), Vol. 9 (p 397), Vol. 10 (p 334), Vol. 11 (p 450), and Vol. 12 (p 417).

Scheme X



mixture of epimers at C10, **22a** and **22b** (95% yield, Scheme IX). Both compounds are useful synthetically because the carbon bearing the ethoxy group (C10) is to become an sp^2 center (keto group) in a later stage of the synthesis. In order to facilitate subsequent spectral interpretations, however, we separated the epimers **22a** and **22b** and carried each foward in the next step of the synthesis.

Reduction of **22a** and/or **22b** by Raney Nickel (W-2) afforded **23a** and/or **23b**, respectively (85% yield), with simultaneous reduction of both the ethylene dithioketal and the allylic thioether functions. Finally, hydrogenation of **23a** under 1 atm of H_2 (20 °C) yielded a 95:5 mixture of **15a** and **15b** in quantitative yield. The observed stereoselectivity is once again accounted for by the least hindered approach of **23a** (opposite to the C1 methyl group) to the catalyst with possible coordinative assistance from the OH and OEt groups. This alternative pathway to prepare **15a** from **9a** via **19** and **22** is one step shorter than the initially described route (via **15a,b**) and has an overall yield 2.4% higher than the former.

Our final goal was to convert keto ether **16a** into the known hydroxy ketone **24a**,[10] a versatile intermediate which has been transformed to a number of ambrosanolides.[10,19] We surveyed the reactivity of **16a,b** (95/5) toward several Lewis acids with the silicon-based ones being found to be the most selective: Me_3SiCl/Na,[20] $MeSiCl_3/NaI$,[21] $SiCl_4/NaI$,[22] etc. The best yield was obtained using $MeSiCl_3/NaI$ in CH_3CN at room temperature for 12 h, which afforded the corresponding alcohols **24a/24b** (95:5, 60% yield, Scheme X). At this particular stage both diastereoisomers were very easy to separate by flash column chromatography. For this reason it is more convenient to work with mixtures of diastereoisomers, starting from **15** up to **24**. We envision that improvements in yield of the ether cleavage step on **16a** could be made by starting the synthetic sequence with $[HC{\equiv}CCHOR]$-$Co_2(CO)_6BF_4$ where R is a more easily removed group than Et (e.g. ^{t}Bu, CH_2Ph, Me).

The product **24a** has the same physical and spectroscopic properties as that synthesized previously by Vandevalle and co-workers[10] and converted into damsin (1),[19] thus completing our formal total synthesis. The overall yield of **24a** starting from 3-pentanone was 19% (14 steps) via intermediate **20** or 17% (15 steps) via **11**. These yields are comparable to Vandevalle's conceptually different route to **24a** and considerably more efficient than one reported by Grieco.[20] Appropriate modifications of the original furan and propargyl components used for synthesis of the seven-membered ring could provide entry to other pseodoguaianolides using the same overall methodology.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were obtained at 300 and 75.4 MHz, respectively. Deuterated NMR solvents were dried over 4-Å molecular sieves, stored, and handled under N_2. ^1H Decoupling and NOE experiments, ^{13}C off resonance, APT, DEPT, as well as two-dimensional phase-sensitive NOESY, HETCOR, COSY-90, long-range COSY, HET2DJ, HOM2DJ, COSNOS, COCONO, and RCT (relay coherence transfer) experiments were performed using standard Varian software. NMR samples for use in NOE experiments were purged thoroughly with nitrogen. For those new compounds in which elemental analyses were not obtained purity was judged to be ≥95% by ^1H NMR (included in the supplementary material) and GC analyses. Analytical and preparative gas chromatography was carried out using 4 ft × $^1/_8$ in. and 6 ft × $^3/_8$ in. OV-101 packed columns, respectively. Preparative TLC was performed over silica gel E. Merck (G-60$PF_{254-366}$) with 20 × 20 cm glass plates (1 mm). Flash column chromatography was carried out with E. Merck silica gel (230–400 mesh) and a pressure of N_2.

Glassware was oven-dried at 120 °C overnight prior to use; solvents were purified and dried by refluxing over drying agents for 2 h prior to distillation under nitrogen.

(1*S,1′*R**,2*R**,4*S**,5*R**)-, (1*S**,1′*S**,2*R**,4*S**,5*R**)-, and (1*S**,1′*R**,2*R**,4*R**,5*R**)-2,4-Dimethyl-2-(1-ethoxy-2-oxo-1-propyl)-8-oxabicyclo[3.2.1]octan-3-ones (8a–c).** To 1 g (4.23 mmol) of **7a–d** (9:36:47:8)[9] dissolved in 125 mL of EtOH/H_2O (85/15) was added 2.3 g (4.23 mmol) of $(TsNH)_2Hg$,[12] and the resulting suspension was refluxed while stirring vigorously for 18 h (monitoring by TLC and GC). The resultant light yellow solution was allowed to reach room temperature and H_2S(g) (generated by reaction of $(NH_4)_2S$ and HCl(aq) was bubbled into the reaction solution for 10 min until it became black ($HgS\downarrow$). The black suspension was filtered through a pad of sand–Celite–alumina using a fritted funnel. The solvent was removed by rotatory evaporation, and 300 mL of ether and 50 mL of brine were added. After shaking vigorously, the aqueous solution was discarded and the ethereal solution was extracted three times with NaOH (aqueous, 1 M) (to remove of $TsNH_2$), washed with brine, and dried over anhydrous $MgSO_4$. Ether was evaporated resulting in 1 g of an oily crude mixture whose analysis by IR, ^1H NMR, and capillary GS/MS (SE, 20m. 50 °C, 10 °C/min, 280 °C) showed no starting material (100% conversion). The crude product contained a mixture of three stereoisomers **8a,b,c** (18:35:47) in 85% yield. For synthetic purposes we used the mixture of diastereoisomers, but it was possible to separate them by successive flash column chromatographies on SiO_2 (100 g SiO_2/g substrate) eluting with mixtures of pentane and ether and/or preparative TLC (SiO_2, hexane/ether 80/20 several developments).

8a: thick oil which crystallizes below 0 °C; IR (neat) 2970, 2930, 2880, 1710, 1470, 1450, 1380, 1350, 1220, 1190, 1100, 1050, 1030, 950, 920, 900, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.53 (1 H, s, H1′), 4.40 (1 H, br d, J = 6.5 Hz, H1), 4.38 (1 H, br dd, J_1 = 4.9 Hz, J_2 = 6.2 Hz, H5), 3.62 (2 H, dq, J_1 = 10.1 Hz, J_2 = 7.1 Hz, H1″), 3.10 (1 H, br dq, J_1 = 4.9 Hz, J_2 = 6.6 Hz, H4), 2.06 (3 H, s, H3′), 1.85–1.50 (4 H, m, $W_{1/2}$ = 86 Hz, H6 and H7), 1.21 (3 H, t, J = 7.1 Hz, H2″), 0.84 (3 H, d, J = 6.6 Hz, Me-4), and 0.78 (3 H, s, Me-2); MS (EI, 12 eV, DIP) m/e (%) 254 (M^+, 8), 211 ($M^+ - CH_3CO$, 2), 208 (24), 168 (17), 165 (26), 153 (19), 140 (12), 125 (16), 122 (15), 113 (11), and 102 (100).

8b: IR (neat) 2970, 2935, 2870, 1710, 1380, 1185, 1100, 1050, 950, and 910 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.46 (1 H, br dd, J_1

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= 4.9 Hz, J_2 = 6.3 Hz, H5), 4.45 (1 H, br s, H1′), 4.41 (1 H, br d, J = 7.01 Hz, H1), 3.60 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.3 Hz, H1″), 3.30 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.3 Hz, H1″), 2.87 (1 H, br dq, J_1 = 6.8 Hz, J_2 = 4.8 Hz, H4), 2.19 (3 H, s, H3′), 2.10–1.55 (4 H, m, $W_{1/2}$ = 140 Hz, H6 and H7), 1.12 (3 H, t, J = 7.0 Hz, H2″), 0.91 (3 H, d, J = 6.8 Hz, Me-4), and 0.89 (s, 3 H, Me-2); MS (EI, 12 eV, DIP) m/e (%) 254 (M^+, 1), 211 ($M^+ - CH_3CO$, 100), 165 (6), 155 (7), 137 (4), 125 (3), 113 (95), and 102 (8).

8c: IR (neat) 2970, 2930, 2870, 1710, 1450, 1380, 1350, 1220, 1190, 1100, 1040, 1030, 950, 930, 900, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.52 (1 H, br d, J = 7.0 Hz, H5), 4.35 (1 H, s, H1′), 4.31 (1 H, d, J = 6.8 Hz, H1), 3.63 (2 H, dq, J_1 = 10.0 Hz, J_2 = 7.0 Hz, H1″), 2.27 (1 H, q, J = 7.7 Hz, H4), 2.14 (3 H, s, H3′), 2.05–1.50 (4 H, m, $W_{1/2}$ = 135 Hz, H6 and H7), 1.38 (3 H, d, J = 7.7 Hz, Me-4), 1.26 (3 H, t, J = 7.0 Hz, H2″), and 0.90 (3 H, s, Me-2); MS (EI, 12 eV, DIP) m/e (%) 254 (M^+, 0.2), 211 ($M^+ - CH_3CO$, 100), 181 (1), 165 (5), 155 (7), 137 (2), 127 (3), 113 (78), 109 (3), 86 (2), and 81 (2). HRMS (EI, 70 eV, DIP) of the mixture **11a,b,c** calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1519. Anal. (of the mixture **11a,b,c**): Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.04; H, 8.59.

(1*R,2*S**,5*R**,6*S**,7*S**,10*S**)- and (1*R**,2*S**,5*R**,6*S**,7*S**,10*R**)-1,6-Dimethyl-10-ethoxy-7-hydroxy-11-oxatricyclo[5.3.0.1^{2,5}]undecan-9-ones (9a,b). A. Aldol Cyclization of 8a–c under Nonanhydrous Conditions.** To a solution of 0.26 g of KOH (pellets, 85%; 3.93 mmol) in 25 mL of EtOH (95%) was added 0.10 g (0.39 mmol) of **8a–c** (18:35:47) dissolved in 5 mL of EtOH (95%), and the mixture was stirred at room temperature under N_2 for 8 h. The reaction mixture was concentrated under reduced pressure, water was added, and the resultant alkaline solution was neutralized with HCl (2 M) and extracted four times with ether. All ethereal fractions were combined, dried over anhydrous $MgSO_4$, filtered through a short pad of neutral alumina, and concentrated to dryness, resulting in 0.1 g of an oily crude mixture of **9a/9b** (5:1) (95% yield). This residue was chromatographed on silica gel using pentane/ether mixtures of increasing polarity. Eluting with 50/50 petroleum ether/ether it was possible to isolate 79 mg of pure **9a** and with P/E 30/70, 16 mg of pure **9b**.

9a: white crystalline solid; mp 105–106 °C (from ether); IR (KBr) 3390 (br), 2970, 2940, 2890, 1745, 1470, 1400, 1260, 1150, 1100, 1035, 1015, 1000, 960, 925, 900, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.48 (1 H, d, J = 1.7 Hz, H10), 4.15 (1 H, dd, J_1 = 7.3 Hz, J_2 = 3.7 Hz, H5), 4.02 (1 H, d, J = 6.8 Hz, H2), 3.98 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.6 Hz, H1′), 3.65 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.6 Hz, H1′), 2.50 (1 H, dd, J_1 = 19.3 Hz, J_2 = 1.7 Hz, H8), 2.04 (1 H, d, J = 19.3 Hz, H8), 2.15 (2 H, m, $W_{1/2}$ = 14 Hz, endo-H4 and endo-H3), 1.95 (1 H, ddq, J_1 = 7.1 Hz, J_2 = 3.7 Hz, J_3 = 1.9 Hz, H6), 1.88 (1 H, m, $W_{1/2}$ = 20 Hz, exo-H3), 1.80 (1 H, m, $W_{1/2}$ = 15 Hz, exo-H4), 1.5 (1 H, s, OH), 1.23 (3 H, t, J = 7.0 Hz, H2′), 0.94 (3 H, d, J = 7.1 Hz, H13), and 0.91 (3 H, s, H12); ^{13}C NMR ($CDCl_3$, ppm) 213.80 (C9), 85.54 (C10), 79.03 (C5), 77.15 (C2), 72.67 (C7), 68.16 (C1′), 49.50 (C1), 48.67 (C8), 41.22 (C6), 24.69 (C3), 23.84 (C4), 15.41 (C2′), 11.43 (C12), and 10.00 (C13); MS (EI, 70 eV, DIP) m/e (%) 254 (M^+, 42), 236 ($M^+ - H_2O$, 7), 210 (16), 192 (25), 181 (19), 168 (68), 165 (15), 156 (42), 153 (16), 151 (12), 139 (34), 137 (21), 127 (31), 125 (38), 123 (75), 112 (100), 109 (33), 99 (58), 85 (69), 81 (55), 79 (22), 69 (34), and 55 (24); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1520. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.14; H, 8.80.

9b: white crystalline solid; mp 150–151 °C (from ether); IR (KBr) 3430 (br), 3000, 2980, 2950, 2940, 2880, 1740, 1460, 1440, 1380, 1350, 1240, 1170, 1130, 1110, 1080, 1040, 1030, 1020, 980, 960, 920, 800, 750, and 690 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.69 (1 H, s, H10), 4.25 (1 H, d, J = 7.8 Hz, H2), 4.12 (1 H, dd, J_1 = 7.6 Hz, J_2 = 3.9 Hz, H5), 4.02 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.6 Hz, H1′), 3.68 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.6 Hz, H1′), 2.79 (1 H, d, J = 18.3 Hz, H8), 2.43 (1 H, d, J = 18.3 Hz, H8), 2.20 (2 H, m, $W_{1/2}$ = 56 Hz, endo-H4 and endo-H3), 2.05 (1 H, br dq, J_1 = 3.9 Hz, J_2 = 7.0 Hz, H6), 1.75 (1 H, m, $W_{1/2}$ = 40 Hz, exo-H3), 1.85 (1 H, m, $W_{1/2}$ = 45 Hz, exo-H4), 1.50 (1 H, br s, OH), 1.26 (3 H, t, J = 7.0 Hz, H2′), 0.99 (3 H, s, H12), and 0.94 (3 H, d, J = 7.0 Hz, H13); ^{13}C NMR ($CDCl_3$, ppm) 213.75 (C9), 104.75 (C10), 79.37 (C5), 78.39 (C2), 71.77 (C7), 66.44 (C1′), 45.21 (C1), 42.99 (C8), 41.29 (C6), 25.26 (C3), 24.34 (C4), 14.94 (C2′), 9.70 (C13), and 9.70 (C12); MS (EI, 12 eV, DIP) m/e (%) 254 (M^+, 2), 236 ($M^+ - H_2O$, 10), 226 ($M^+ - CO$, 10), 210 (20), 192 (25), 181 (20), 168 (70), 156 (35), 139 (40), 127 (31), 123 (80), 112 (100), 99 (60), and 85 (80); HRMS (EI, 12 eV, DIP) calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1517.

B. Aldol Cyclization of 8a–c under Anhydrous Conditions: 9a, ((1*R,2*S**,5*R**,6*S**,7*R**,8*R**)-8-Ethoxy-7-hydroxy-1,6,7-trimethyl-10-oxatricyclo[4.2.1.1^{2,5}]decan-9-one), and 10b ((1*R**,2*S**,5*R**,6*S**,7*S**,8*R**)-8-Ethoxy-7-hydroxy-1,6,7-trimethyl-10-oxatricyclo[4.2.1.1^{2,5}]decan-9-one). ((8*R*,7*S**,6-*S**,5*R**,2*R**,1*R**)-8-Ethoxy-7-hydroxy-1,6,7-trimethyl-10-oxatricyclo[4.2.1.1^{2,5}]decan-9-one).** One gram (3.93 mmol) of **8a–c** (18:35:47) was dried by azeotropic distillation with benzene and dissolved in 50 mL of absolute EtOH. Then 2.2 g (39.3 mmol) of anhydrous KOH dissolved in 250 mL of absolute EtOH was added to the solution of substrate. This reaction mixture was stirred at room temperature under N_2 for 8 h. The solvent was removed in vacuo, and the workup was performed in the same way as previously, resulting in 1 g of a light yellow crystalline crude mixture. Flash column chromatography of the mixture, on silica gel (100 g of SiO_2/g of crude), eluting with mixtures of pentane and ether of increasing polarity afforded 0.92 g (92%) of **9a** (pentane/ether, 30/70), 60 mg (6%) of **10a** (P/E, 50/50), and 20 mg (2%) of **10b** (P/E, 80/20).

10a: IR (KBr) 3500 (OH), 1690, 1470, 1450, 1380, 1350, 1340, 1310, 1300, 1280, 1230, 1200, 1160, 1140, 1115, 990, 1050, 1025, 965, 930, 910, 840, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.33 (2 H, m, $W_{1/2}$ = 15 Hz, H2 and H5), 4.21 (1 H, s, OH), 3.87 (1 H, dq, J_1 = 7.1 Hz, J_2 = 9.2 Hz, H1′), 3.48 (1 H, dq, J = 7.1 Hz, J_2 = 9.2 Hz, H1′), 3.03 (1 H, s, H8), 1.90–1.60 (4 H, m, $W_{1/2}$ = 60 Hz, He and H4), 1.25 (3 H, t, J = 7.1 Hz, H2′), 1.04 (3 H, s, Me-7), 0.96 (3 H, s, Me-1 or Me-6), 0.81 (3 H, s, Me-6 or Me-1); MS (EI, 70 eV, DIP) m/e (%) 254 (4, M^+), 2.08 (14), 165 (30), 153 (12), 139 (18), 137 (21), 125 (35), 113 (33), 109 (25), 102 (100), 85 (29), 83 (17), 74 (12), 69 (13), 55 (17), and 43 (50); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1530.

10b: IR (KBr) 3540 (OH), 2980, 2920, 2780, 1710, 1450, 1440, 1380, 1330, 1300, 1260, 1220, 1100 (sharp), 1050, 1010, 960, 930, 910, and 810 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.20 (2 H, m, $W_{1/2}$ = 15 Hz, H2 and H5), 3.69 (1 H, s, H8), 3.65 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.1 Hz, H1′), 3.55 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.1 Hz, H1′), 3.43 (1 H, s, OH), 1.90–1.60 (4 H, m, $W_{1/2}$ = 30 Hz, H3 and H4), 1.14 (3 H, t, J = 7.0 Hz, H2′), 0.93 (3 H, s, Me-7), 0.87 (3 H, s, Me-6 or Me-1), 0.80 (3 H, s, Me-6 or Me-1); MS (EI, 70 eV, DIP) m/e (%) 254 (M^+, 5), 208 (26, M^+ – EtOH), 165 (49), 152 (22), 139 (25), 137 (36), 125 (43), 123 (24), 113 (50), 109 (29), 107 (13), 102 (100), 99 (44), 95 (19), 85 (44), 83 (27), 69 (20), 55 (25), and 43 (65); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1529.

Epimerization at C10 of 9a under Basic Conditions. Compound **9a** (0.5 g) was dissolved in 20 mL of 1 M KOH ($EtOH/H_2O$, 80/20) and stirred at room temperature under N_2 for 4 days. After the usual workup 0.5 g of a 5:1 mixture of **9a/9b** (by GC and ^1H NMR) was recovered.

Epimerization of 8 under Acidic Conditions. A 1:1 mixture of **8b** and **8c** (0.1 g, 0.39 mmol) was dissolved in 2 mL of EtOH (95%), 0.1 mL of HCl (c = 37%, w/w) was added, and the reaction mixture was stirred under nitrogen at room temperature for 24 h. TLC monitoring of the reaction indicated no change of the starting material, and then the reaction mixture was refluxed for an additional 24 h. The mixture was concentrated, dissolved in ether, washed with aqueous $NaHCO_3$ (0.5 M) and brine, dried ($MgSO_4$), and concentrated, resulting in 0.1 g of an oil consisting of a 3:1 mixture of **8a** and **8b** (by capillary GC and ^1H NMR).

(1*R,2*S**,5*R**,6*S**,7*S**,10*S**)-1,6-Dimethyl-10-ethoxy-7-hydroxy-11-oxatricyclo[5.3.0.1^{2,5}]undecan-9-one Ethylene Dithioketal (11).** Compound **9a** (0.50 g, 1.97 mmol) was dissolved in 25 mL of dry benzene and 10 mL of ethane dithiol under N_2. The solution was cooled to 0 °C, and 0.5 mL (4.06 mmol) of $BF_3{\cdot}OEt_2$ was added by syringe. The reaction mixture was stirred at 0 °C under N_2 for 30 min. Aqueous $NaHCO_3$ (1 M) was added, and the mixture was stirred for 5 min. The crude solution was extracted with ether four times; the ethereal fractions were combined, dried ($MgSO_4$), filtered through a short pad of neutral alumina, and concentrated to dryness by rotatory evaporation and vacuum pump, resulting in 0.64 g of a white crystalline solid

11: mp 90–92 °C (from ether); IR (KBr) 3420 (OH), 2980, 2940, 1460, 1440, 1400, 1280, 1240, 1220, 1100, 1070, 1040, 1000, 960, 900, 800, 770, and 750 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.65 (1 H, s, H10), 4.06 (1 H, dd, J_1 = 3.6 Hz, J_2 = 7.3 Hz, H5), 3.88 (1 H, d, J_1 = 6.9 Hz, H2), 3.84 (1 H, dq, J_1 = 7.0 Hz, J_2 = 9.1 Hz, H1′), 3.64 (1 H, dq, J_1 = 7.0 Hz, J= 9.1 Hz, H1′), 3.23 (4 H, m, $W_{1/2}$ = 49 Hz, SCH_2CH_2S), 2.65 (1 H, d, J = 14.4 Hz, H8), 2.22 (1 H, d, J = 14.4 Hz, H8), 2.04 (1 H, br dq, J_1 = 7.1 Hz, J_2 = 3.6 Hz, H6), 1.80–1.60 (4 H, m, $W_{1/2}$ = 50 Hz, H3 and H4), 1.35 (1 H, br s, OH), 1.16 (3 H, t, J = 7.0 Hz, H2′), 0.91 (3 H, s, H12), and 0.82 (3 H, d, J = 7.1 Hz, H13); ^{13}C NMR ($CDCl_3$, ppm) 87.15 (C10), 79.46 (C5), 77.44 (C2), 76.06 (C7), 68.41 (C1′), 59.99 (C8), 50.69 (C9), 42.25 (C1), 40.11 and 39.22 (SCH_2CH_2S), 39.14 (C6), 24.47 (C3), 24.05 (C4), 15.74 (C2′), 11.63 (C12), and 10.09 (C13); MS (EI, 70 eV, DIP) m/e (%) 330 (22, M^+), 302 (11), 285 (2, M^+ – EtOH), 256 (12), 238 (2, $M^+ - SCH_2CH_2S$), 174 (12), 167 (9), 145 (100), 138 (10), 128 (11), 125 (19), 123 (12), 121 (11), 118 (30), 113 (30), 109 (11), 105 (30), 99 (10), 97 (17), 91 (12), 85 (35), 65 (26), and 55 (20); HRMS (EI, 70 eV, DIP) calcd for $C_{16}H_{26}S_2O_3$ 330.1323, found 330.1329.

Reduction of 11 by Raney Nickel: (1*S,2*S**,5*R**,6*S**,7*S**,10*R**)-1,6-Dimethyl-10-ethoxy-11-oxatricyclo[5.3.0.1^{2,5}]undecan-7-ol (12).** A round-bottomed flask fitted with a magnetic stirring bar and a rubber septum was charged with 11 g of "wet" new Raney nickel W-2 (from a suspension in aqueous NaOH of pH 11). The Raney nickel was washed four times with absolute EtOH by cannula under N_2 and dried, resulting in 10 g of "dry" Raney Nickel. Fifty milliliters of absolute EtOH were added by syringe, and 0.64 g (1.94 mmol) of 11 dissolved also in 50 mL of absolute EtOH was added to the suspension by syringe. The septum was replaced by a condenser fitted with a N_2 inlet, and the reaction mixture was stirred under reflux for 10 h. The reaction was monitored by GC (OV-101/2m; 150 °C, 1 min; 20 °C/min; 250 °C, 30 min) and when conversion was complete, the system was cooled to room temperature. The alcoholic solution was filtered out by cannula. The black residue was resuspended in EtOH and sonicated for 20 min, and the EtOH was extract filtered out by cannula. This operation was repeated four times to recover the product adsorbed on the Nickel powder. All alcoholic extracts were combined together and concentrated to dryness, resulting in a crude oil, which was redissolved in ether and filtered through a short pad of neutral alumina. Solvent was removed affording 0.44 g (95%) of white crystalline solid 12: mp 109–110 °C (from ether); IR (KBr) 3430 (wide, OH), 2950, 2880, 1470, 1440, 1390, 1370, 1350, 1300, 1270, 1240, 1220, 1110 (sharp), 1040, 960, 930, 900, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.39 (1 H, dd, J_1 = 7.8 Hz, J_2 = 8.8 Hz, H10), 4.05 (1 H, dd, J_1 = 3.7 Hz, J_2 = 7.4 Hz, H5), 4.01 (1 H, d, J = 7.5 Hz, H2), 3.52 (2 H, m, $W_{1/2}$ = 40 Hz, H1′), 2.10 (1 H, m, $W_{1/2}$ = 20 Hz, H6), 2.05–1.40 (8 H, m, $W_{1/2}$ = 180 Hz, H3, H4, H8, and H9), 1.16 (3 H, t, J = 6.9 Hz, H2′), 1.15 (1 H, br s, OH), 0.89 (3 H, s, H12), and 0.85 (3 H, d, J = 7.1 Hz, H13); ^{13}C NMR ($CDCl_3$, ppm) 80.31 (C10), 79.64 (C5), 79.01 (C7), 77.84 (C2), 65.51 (C1′), 49.61 (C1), 40.19 (C6), 36.05 (C8), 25.85 (C9), 24.63 (C3), 23.99 (C4), 15.75 (C2′), 11.47 (C12), and 10.07 (C13); MS (EI, 70 eV, DIP) 240 (0.4, M^+), 194 (70), 176 (15), 159 (11), 147 (11), 141 (13), 137 (23), 135 (11), 133 (11), 127 (16), 125 (46), 121 (24), 113 (30), 111 (30), 109 (45), 108 (47), 97 (100), 93 (30), 91 (19), 85 (33), 81 (30), 79 (26), 69 (32), 67 (29), 57 (35), 55 (37), 53 (18), 43 (38), 41 (35), and 29 (42); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1726.

(1*S,2*S**,5*R**,10*R**)- and (1*S**,2*S**,5*R**,6*R**,10*R**)-1,6-Dimethyl-10-ethoxy-11-oxatricyclo[5.3.0.1^{2,5}]undec-6-ene (13a,b).** To 0.43 g (1.82 mmol) of 12 dissolved in 50 mL of absolute ether and 20 mL of dry, freshly distilled Et_3N (from CaH_2) was added 4 mL of $SOCl_2$ (freshly distilled from quinoline) dropwise at 0 °C under N_2 with continuous stirring. After the addition (10 min), the cooling bath was removed and the reaction mixture was stirred at room temperature for 5 h. Ice water was then added to the reaction mixture and extracted four times with ether. All ethereal fractions were combined and successively washed with water, HCl (1 M), water, NaOH (0.5 M, aqueous), and brine. These were dried over anhydrous magnesium sulfate, filtered through a short pad of neutral alumina, and the solvent was evaporated under vacuum at room temperature, resulting in 0.40 g of an oil, which was adsorbed on 30 g of silica gel and placed on top of a chromatographic column (100 g of SiO_2/g of substrate). Elution with a mixture of pentane/ether of increasing polarity afforded after solvent removal 0.39 g (97%) of **13a** and 8 mg (≅2%) of **13b**.

13a: colorless oil; IR (neat) 2970, 2950, 2910, 2890, 1460, 1440, 1380, 1340, 1290, 1260, 1240, 1150, 1110 (sharp), 1060, 1050, 1040, 1010, 960, 930, 900, and 790 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.31 (1 H, d, J = 6.9 Hz, H5), 4.12 (1 H, d, J = 7.2 Hz, H2), 3.64 (1 H, dd, $J_1 \cong J_2$ = 8.0 Hz, H10), 3.48 (2 H, m, $W_{1/2}$ = 48 Hz, H1′), 2.17 (2 H, m, $W_{1/2}$ = 10 Hz, H8), 2.08–1.50 (6 H, m, $W_{1/2}$ = 180 Hz, H3, H4, and H9), 1.60 (3 H, s, H13), 1.14 (3 H, t, J = 7.1 Hz, H2′), and 0.85 (3 H, s, H12); ^{13}C NMR ($CDCl_3$, ppm) 134.02 (C6), 132.58 (C7), 80.22 (C5), 77.50 (C10), 77.09 (C2), 65.11 (C1′), 47.47 (C1), 30.70 (C8), 27.05 (C4), 25.62 (C9), 22.42 (C3), 16.15 (C13), 15.64 (C2′), and 14.98 (C12); MS (EI, 70 eV, DIP) m/e (%) 222 (1, M^+), 207 (47), 178 (17), 164 (12), 149 (12), 147 (15), 135 (28), 133 (30), 121 (80), 116 (12), 109 (14), 107 (39), 105 (40), 93 (38), 91 (51), 79 (45), 77 (38), 67 (15), 65 (17), 55 (20), 53 (19), 43 (33), 41 (40), and 29 (100); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1619.

13b: colorless oil; IR (neat) 3020, 2970, 2880, 1620, 1450, 1370, 1340, 1260, 1120, 1040, 960, 930, 890, 860, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.37 (1 H, m, $W_{1/2}$ = 7 Hz, H8), 4.32 (1 H, m, $W_{1/2}$ = 19 Hz, H5), 4.22 (1 H, d, J = 6.6 Hz, H2), 3.91 (1 H, dd, J_1 = 7.1 Hz, J_2 = 9.4 Hz, H10), 3.55 (2 H, m, $W_{1/2}$ = 47 Hz, H1′), 3.03 (1 H, m, $W_{1/2}$ = 16 Hz, H6), 2.43 (1 H, ddd, J_1 = 3.5 Hz, J_2 = 7.1 Hz, J_3 = 10.5 Hz, H9), 2.20 (1 H, m, $W_{1/2}$ = 25 Hz, H9), 2.10–1.70 (4 H, m, $W_{1/2}$ = 170 Hz, H3 and H4), 1.18 (3 H, t, J = 7.0 Hz, H2′), 1.00 (3 H, d, J = 7.5 Hz, H13), and 0.92 (3 H, s, H12); MS (EI, 70 eV, DIP) m/e (%) 222 (9, M^+), 207 (49, $M^+ - CH_3$), 179 (8), 165 (14), 161 (6), 147 (15), 137 (16), 135 (31), 133 (31), 121 (100), 107 (40), 105 (37), 93 (33), 91 (43), 79 (31), 77 (30), 65 (11), and 55 (12); HRMS (EI, 20 eV, DIP) calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1603.

Cleavage of 13a by Me_2BBr: (1*R,2*S**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]deca-4,6-dien-2-ol (14a) and (1*R**,2*S**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]deca-5,7-dien-2-ol (14b).** To a solution of **13a** (0.15 g, 0.69 mmol) in 2 mL of anhydrous CH_2Cl_2 was added 0.02 mL of dry, freshly distilled NEt_3 under N_2 in a dry and closed system. The solution was cooled to 0 °C, and 0.76 mL of a freshly prepared solution of Me_2BBr in CH_2Cl_2 (2.0 M) was added dropwise over a 5-min period. Then, the reaction mixture was stirred for 3.5 h at 0 °C. When conversion was complete (monitoring by TLC, SiO_2 hexane/ether, 50/50), the reaction was quenched with 0.5 mL of NEt_3, and then the reaction mixture was poured over a stirred aqueous solution of $NaHCO_3$ (0.5 M) and extracted four times with ether. The organic extracts were combined and filtered through a short pad of neutral alumina, and volatiles were evaporated, resulting in 0.16 g of a yellow crystalline crude mixture. The latter was column chromatographed on silica gel (60 g SiO_2/g substrate), eluting with mixtures of pentane/ether of increasing polarity. The fraction of pentane/ether, 80/20, afforded 0.11 g (76%) of a 9:1 mixture of **14a** and **14b** while the more polar subproducts (50 mg) were separated by elution with P/E, 50/50, and ether. The mixture of **14a**/**14b**, for characterizational purposes, was rechromatographed on silica gel (with adsorbed $AgNO_3$, 2% w/w). Eluting with mixtures of pentane and ether afforded pure samples of both isomers.

14a: white crystalline thermally unstable solid; IR (KBr) 3460 (OH), 2980, 2920, 2880, 1650, 1620, 1450, 1370, 1350, 1180, 1155, 1120 (sharp), 1070, 1050, 1030, 950, 920, 870, 830, and 730 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.77 (1 H, dq, J_1 = 12.9 Hz, J_2 = 1.7 Hz, H5), 5.51 (1 H, m, $W_{1/2}$ = 20 Hz, H4), 3.95 (1 H, dd, J_1 = 11.3 Hz, J_2 = 6.1 Hz, H10), 3.75 (1 H, m, $W_{1/2}$ = 25 Hz, H2), 3.60 (1 H, dq, J_1 = 9.3 Hz, J_2 = 7.1 Hz, H1′), 3.48 (1 H, dq, J_1 = 9.3 Hz, J_2 = 7.1 Hz, H1′), 2.50 (2 H, sharp m, $W_{1/2}$ = 14 Hz, H3), 2.42 (1 H, m, $W_{1/2}$ = 35 Hz, H8), 2.15 (1 H, m, $W_{1/2}$ = 25 Hz, H8), 2.05 (1 H, m, $W_{1/2}$ = 30 Hz, H9), 1.75 (3 H, d, J = 1.7 Hz, H12), 1.60 (1 H, m, $W_{1/2}$ = 30 Hz, H9), 1.17 (3 H, t, J = 7.1 Hz, H2′), and 0.76 (3 H, s, H11): ^{13}C NMR ($CDCl_3$, ppm) 142.05 (C7), 130.13 (C6), 129.70 (C5), 127.10 (C4), 82.47 (C10), 68.80 (C2), 65.60 (C1′), 53.50 (C1), 35.23 (C3), 28.22 (C8), 26.85 (C9), 21.41 (C12), 15.69 (C2′), and 15.02 (C11); MS (EI, 12 eV, DIP) m/e (%) 222 (82, M^+), 207 (32), 204 (30), 189 (12), 176 (100), 161 (26), 159 (24), 147 (77), 145 (36), 143 (27), 133 (36), 120 (29), 117 (15), 105 (42), 91

(31), 79 (15), and 55 (11); HRMS (EI, 12 eV, DIP) calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1625.

14b: IR (KBr) 3450 (OH), 2980, 2910, 2870, 1660, 1640, 1620, 1450, 1380, 1345, 1380, 1350, 1180, 1150, 1120 (sharp), 1070, 1050, 950, 915, 870, 830, and 760 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.54 (1 H, dd, J_1 = 1.9 Hz, J_2 = 3.0 Hz, H8), 5.41 (1 H, m, $W_{1/2}$ = 10 Hz, H5), 4.26 (1 H, dd, $J_1 = J_2$ = 7.8 Hz, H10), 3.75 (1 H, m, $W_{1/2}$ = 20 Hz, H2), 360 (1 H, dq, J_1 = 9.4 Hz, J_2 = 7.1 Hz, H1'), 3.50 (1 H, dq, J_1 = 9.4 Hz, J_2 = 7.1 Hz, H1'), 2.60 (1 H, ddd, J_1 = 3.2 Hz, J_2 = 7.6 Hz, J_3 = 16.1 Hz, H9), 2.35 (1 H, m, $W_{1/2}$ = 25 Hz, H3), 2.20 (1 H, m, $W_{1/2}$ = 30 Hz, H9), 2.16 (2 H, m, $W_{1/2}$ = 25 Hz, H4), 1.88 (1 H, m, $W_{1/2}$ = 35 Hz, H3), 1.81 (3 H, dd, J_1 = 1.2 Hz, J_2 = 2.3 Hz, H12), 1.19 (3 H, t, J = 7.1 Hz, H2'), and 1.02 (3 H, s, H11); ^{13}C NMR ($CDCl_3$, ppm) 147.17 (C7), 126.34 (C5), 124.59 (C8), 124.41 (C6), 81.78 (C10), 75.80 (C2), 65.14 (C1'), 56.59 (C1), 34.86 (C9), 28.57 (C4), 26.09 (C3), 25.33 (C12), 15.57 (C2'), and 17.37 (C11); HRMS (EI, 12 eV, DIP) calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1610.

Hydrogenation of 14a,b: (1*R,2*S**,6*S**,7*S**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]decan-2-ol (15a) and (1*R**,2*S**,6*R**,7*R**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo-[5.3.0]decan-2-ol (15b).** To 0.5 g (2.25 mmol) of **14a/14b** (9:1) dissolved in 50 mL of absolute EtOH was added 100 mg of Pd on charcoal (10% w/w). The reaction vessel was pumped and back filled with H_2 three times, and the reaction mixture was kept under strong stirring and atmospheric pressure of H_2 for 2 h. The organic solution was filtered out by cannula, and the product adsorbed on the catalyst was recovered by sonication of a resuspension of the residue in EtOH three times. Solvent was taken out by rotatory evaporation, ether was added, and the ethereal solution was filtered through a short pad of neutral alumina and concentrated to dryness, resulting in 0.51 g (100% yield) of a colorless oil composed of a 95:5 mixture of **15a** and **15b**. Normally, the crude mixture of both isomers was used directly for synthetic purposes, but to obtain pure samples of both isomers for their individual characterization we submitted the crude mixture to a flash column chromatography on silica gel (110 g of SiO_2/g of crude). Elution with mixtures of pentane and ether of increasing polarity led to isolation by P/E, 80:20, of a pure sample of **15a**. A fraction eluted with P/E, 70:30, containing 80% of **15b** was rechromatographed on preparative TLC, eluting with hexane/acetone, 90/10 (several developments), affording a pure sample of **15b**.

15a: colorless oil; IR (neat) 3460 (OH), 2980, 2920, 2880, 1460, 1450, 1370, 1350, 1120 (sharp), 1060, 1030, 1010, 970, 950, and 930 cm^{-1}; MS (EI, 70 eV, DIP) m/e (%) 226 (1, M^+), 193 (31), 180 (15), 165 (13), 162 (21), 155 (6), 151 (8), 147 (11), 139 (43), 136 (18), 123 (17), 125 (8), 121 (18), 119 (6), 115 (10), 108 (29), 98 (14), 97 (22), 95 (22), 93 (21), 91 (13), 85 (100), 81 (93), 79 (24), 77 (12), 72 (12), 69 (20), 67 (25), 57 (44), and 55 (32); ^1H NMR ($CDCl_3$, ppm) 3.89 (1 H, dd, J_1 = 8.3 Hz, J_2 = 8.9 Hz, H10), 3.79 (1 H, m, $W_{1/2}$ = 11 Hz, H_2), 3.54 (1 H, dq, J_1 = 9.5 Hz, J_2 = 6.8 Hz, H1'), 3.41 (1 H, dq, J_1 = 9.5 Hz, J_2 = 6.8 Hz, H1'), 1.96 (1 H, m, H7), 1.91 (1 H, m, H9), 1.74 (2 H, m, H3), 1.51 (1 H, m, H6), 1.44 (1 H, m, H9), 1.15 (3 H, t, J = 6.8 Hz, H2'), 0.85 (3 H, d, J = 6.6 Hz, H12), and 0.84 (3 H, s, H11); ^{13}C NMR ($CDCl_3$, ppm) 12.80 (C11), 15.71 (C2'), 19.15 (C4), 22.15 (C12), 26.35 (C8), 26.57 (C5), 34.25 (C3), 34.83 (C6), 35.91 (C9), 42.49 (C7), 49.84 (C1), 65.11 (C1'), 72.82 (C2), and 82.07 (C10); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{26}O_2$ 226.1933, found 226.1929. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.22; H, 11.61.

15b: colorless oil; IR (neat) 3450 (OH), 2980, 2920, 2880, 1470, 1450, 1380, 1115 (sharp), 1060, 1040, 960, and 930 cm^{-1}; MS (EI, 70 eV, DIP) m/e (%) 226 (1, M^+), 208 (2), 193 (14), 180 (15), 165 (16), 162 (21), 147 (15), 139 (47), 136 (43), 133 (12), 125 (12), 123 (21), 121 (32), 108 (40), 105 (14), 97 (30), 95 (32), 93 (34), 85 (80), 81 (100), 77 (16), 72 (24), 69 (28), 67 (31), 57 (43), and 55 (41); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{26}O_2$ 226.1933, found 226.1935; ^1H NMR ($CDCl_3$, ppm) 3.87 (1 H, dd, J_1 = 8.4 Hz, J_2 = 7.6 Hz, H10), 3.81 (1 H, m, $W_{1/2}$ = 10 Hz, H2), 3.53 (1 H, dq, J_1 = 9.3 Hz, J_2 = 6.9 Hz, H1'), 3.40 (1 H, dq, J_1 = 9.3 Hz, J_2 = 6.9 Hz, H1'), 1.96 (1 H, m, H9), 1.81 (1 H, m, H6), 1.74 (2 H, m, H3), 1.44 (1 H, m, H7), 1.42 (1 H, m, H9), 1.14 (3 H, t, J = 6.9 Hz, H2'), 0.93 (3 H, s, H11), and 0.91 (3 H, d, J = 7.8 Hz, H12); ^{13}C NMR ($CDCl_3$, ppm) 15.20 (C11), 15.65 (C2'), 18.29 (C12), 19.90 (C4), 23.76 (C5), 27.30 (C8), 33.17 (C6), 33.73 (C3), 36.21 (C9), 39.39 (C7), 50.83 (C1), 64.76 (C1'), 74.59 (C2), and 82.38 (C10).

Oxidation of 15a and/or 15b: (1*S,6*S**,7*S**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]decan-2-one (16a) and (1*S**,6*R**,7*R**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]-decan-2-one (16b).** To a suspension of 73 mg (0.34 mmol) of pyridinium chlorochromate in 5 mL of anhydrous CH_2Cl_2 was added 40 mg (0.17 mmol) of **15a** (or **15b**) was added. This reaction mixture was vigorously stirred at room temperature under anhydrous conditions for 2 h, turning from orange into dark brown. Dry ether (20 mL) was added, and the supernatant liquid was decanted from a black gum. The residue was resuspended in ether and sonicated for 15 min, three times. The combined ethereal solutions were passed through a short pad of neutral alumina and concentrated to dryness, resulting in 40 mg of an oily crude mixture, which was submitted to flash column chromatography on silica gel, eluting with pentane ether, 90/10, affording 37 mg (95% yield) of the ketone **16a** (or **16b**).

16a: colorless oil; IR (neat) 2975, 2920, 2860, 1690, 1460, 1420, 1370, 1350, 1320, 1270, 1250, 1120 (sharp), 1050, 1010, 970, and 920 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.29 (1 H, dd, J_1 = 8.8 Hz, J_2 = 8.5 Hz, H10), 3.38 (2 H, m, $W_{1/2}$ = 30 Hz, H1'), 2.72 (1 H, m, $W_{1/2}$ = 28 Hz, H3), 2.46 (1 H, br ddd, J_1 = 15.7, J_2 = 10.1, J_3 = 8.6 Hz, H3), 2.06 (1 H, m, H9), 1.86 (2 H, m, H4), 1.80 (1 H, m, H8), 1.71 (1 H, m, H5), 1.60 (1 H, m, H6), 1.47 (1 H, m, H9), 1.37 (1 H, m, H8), 1.28 (1 H, m, H7), 1.19 (3 H, s, H11), 1.11 (3 H, t, J = 7.1 Hz, H2'), 1.04 (1 H, m, H5), and 0.84 (3 H, d, J = 6.6 Hz, H12); ^{13}C NMR ($CDCl_3$, ppm) 214.97 (C2), 81.83 (C10), 65.25 (C1'), 59.49 (C1), 51.97 (C7), 41.80 (C3), 35.92 (C6), 36.30 (C5), 27.00 (C9), 25.70 (C8), 21.76 (C4), 21.23 (C12), 15.57 (C2'), and 9.72 (C11); MS (EI, 70 eV, DIP) m/e (%) 224 (13, M^+), 209 (100), 195 (70), 181 (20), 178 (40), 163 (10), 153 (25), 149 (10), 139 (14), 137 (17), 135 (29), 125 (33), 121 (26), 109 (32), 97 (40), 95 (25), 93 (25), 85 (46), 81 (40), 79 (27), 77 (13), 69 (29), 67 (22), 57 (28), 55 (30), 53 (2), 43 (15), 41 (22), and 29 (11); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1780. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.99; H, 10.76.

16b: colorless oil; IR (neat) 2980, 2915, 2860, 1690, 1455, 1420, 1350, 1320, 1280, 1115 (sharp), 1060, 1010, 970, and 930 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 3.97 (1 H, dd, J_1 = 8.6 Hz, J_2 = 8.3 Hz, H10), 3.38 (2 H, m, $W_{1/2}$ = 30 Hz, H3), 2.72 (1 H, m, $W_{1/2}$ = 25 Hz, H3), 2.56 (1 H, m, $W_{1/2}$ = 30 Hz, H3), 2.15 (1 H, m, H7), 2.12 (1 H, m, H9), 1.94 (1 H, m, H6), 1.86 (2 H, m, H4), 1.68 (1 H, m, H8), 1.52 (1 H, m, H9), 1.50 (1 H, m, H8), 1.48 (2 H, m, H5), 1.15 (3 H, s, H11), 1.10 (3 H, t, J = 6.9 Hz, H2'), and 0.98 (3 H, d, J = 7.5 Hz, H12); ^{13}C NMR ($CDCl_3$, ppm) 215.87 (C2), 82.62 (C10), 65.52 (C1'), 59.55 (C1), 46.48 (C7), 39.78 (C3), 33.71 (C6), 33.84 (C5), 27.97 (C9), 23.57 (C8), 18.93 (C4), 15.79 (C12), 15.48 (C2'), and 11.45 (C11); MS (EI, 70 eV, DIP) m/e (%) 224 (11, M^+), 209 (100), 195 (71), 181 (29), 178 (78), 163 (27), 153 (33), 149 (16), 139 (22), 135 (69), 125 (57), 123 (22), 121 (35), 111 (11), 109 (50), 107 (35), 105 (11), 97 (71), 95 (35), 93 (34), 91 (17), 86 (16), 85 (62), 83 (18), 82 (19), 81 (65), 79 (32), 69 (38), 67 (29), 57 (32), 55 (33), 53 (12), 43 (16), 41 (24), and 29 (10); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1773. Anal. Calcd for $C_{14}H_{24}O_2$: C, 77.95; H, 10.78. Found: C, 74.81; H, 10.66.

(1*R,2*S**,5*R**,10*S**)-1,6-Dimethyl-10-ethoxy-9-(*N*-pyridiniumylsulfinyl)-11-oxatricyclo[5.3.0.1^{2,5}]undeca-6,8-diene Chloride (17).** To a solution of 1.00 g (3.93 mmol) of **9a** in 25 mL of ether was added 2.00 mL (27.7 mmol) of freshly distilled $SOCl_2$ at once, and the reaction mixture stirred under N_2 at 50 °C for 2 h, monitoring by TLC (hexane/ether, 50:50). Solvent and excesses of pyridine and $SOCl_2$ were removed by pumping (double trap system), resulting in a dark residue which was dissolved in distilled water and extracted successively by hexane, ether, and benzene. The benzene extract after concentration to dryness afforded 1.27 g (85% yield) of a dark brown oil of pure **17**: IR (neat) 3700–3200, 3120, 3070, 2990, 2940, 2890, 1650, 1630, 1580, 1470, 1440, 1370, 1250, 1115, 1020, 960, 930, 880, 800, 770, and 680 cm^{-1}; ^1H NMR (CD_3OD, ppm) 9.01 (2 H, d, J = 6.2 Hz, H2' and H6'), 8.65 (1 H, br, t, J = 7.6 Hz, H4'), 8.17 (2 H, br dd, J_1 =7.6 Hz, J_2 = 6.2 Hz, H3' and H5'), 7.32 (1 H, d, J = 1.4 Hz, H8), 5.20 (1 H, d, J = 1.4 Hz, H10), 4.65 (1 H, d, J = 6.3 Hz, H5), 4.34 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, H2), 3.86 (1 H, dq, J_1 = 8.8 Hz, J_2 = 7.0 Hz, H1''), 3.68 (1 H, dq, J_1 = 7.0 Hz, J_2 = 8.8 Hz, H1''), 2.30–1.60 (4 H, m, $W_{1/2}$ = 150 Hz, H3 and H4), 1.93 (3 H, s, Me-6), 1.21 (3 H, s, Me-1), 1.15 (3 H, t, J = 7.0

Hz, H2″); ^{13}C NMR (C_6D_6, ppm) 175.61 (C9), 145.69 (C4′), 142.84 (C2′ and C6′), 142.20 (C7), 135.00 (C6), 129.48 (C3′ and C5′), 128.24 (C8), 84.75 (C10), 77.59 (C5), 76.69 (C2), 67.16 (C1″), 56.23 (C1), 28.73 (C3), 27.87 (C4), 19.03 (C13), 17.54 (C12), and 15.77 (C2″); MS (FAB, 3-NBA, FB$^+$) m/e (%) 298 (M^+ – SOCl, 100), 255 (6), 222 (10), 199 (50), 177 (80), 160 (5), 147 (7), and 105 (40).

(1*R,2*S**,5*R**,10*S**)-1,6-Dimethyl-10-ethoxy-11-oxatricyclo[5.3.0.1^{2,5}]undec-7-en-9-one (18).** To a solution of 50 mg (0.20 mmol) of **9a** in 1 mL of dry benzene was added 0.05 mL (0.41 mmol) of BF_3·OEt_2 at once by microsyringe, and the reaction mixture kept under N_2 with continuous stirring at room temperature for 12 h (monitoring by TLC: SiO_2, hexane–ether, 50:50, two developments). Solvent and excess BF_3·OEt_2 were removed in vacuo, resulting in a crude oil which was dissolved in ether and washed successively with aqueous $NaHCO_3$ (0.1 M) and water and dried by anhydrous $MgSO_4$. Filtration through a short pad of neutral alumina and evaporation of solvent afforded 45 mg (98% yield) of a colorless oil of pure **18**: IR (neat) 2970, 2940, 2880, 1720, 1610, 1480, 1455, 1380, 1340, 1255, 1185, 1125, 1035, 1015, 950, 880, and 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 5.91 (1 H, s, H8), 4.48 (1 H, ddd, J_1 = 8.1 Hz, J_2 = 6.6 Hz, J_3 = 1.8 Hz, H5), 4.41 (1 H, d, J = 6.3 Hz, H2), 3.99 (1 H, s, H10), 3.97 (1 H, dq, J_1 = 6.8 Hz, J_2 = 9.0 Hz, H1′), 3.67 (1 H, dq, J_1 = 6.8 Hz, J_2 = 9.0 Hz, H1′), 3.47 (1 H, br dq, J_1 = 8.1 Hz, J_2 = 7.6 Hz, H6), 2.10–1.70 (4 H, m, $W_{1/2}$ = 18 Hz, H4 and H3), 1.27 (3 H, t, J = 6.6 Hz, H2′), 1.13 (3 H, d, J = 7.6 Hz, H13), and 1.06 (3 H, s, H12); ^{13}C NMR ($CDCl_3$, ppm) 205.54 (C9), 182.17 (C7), 127.17 (C8), 90.74 (C10), 79.79 (C5), 75.84 (C2), 67.29 (C1′), 51.85 C1), 38.77 (C6), 29.39 (C4), 22.56 (C3), 22.56 (C13), 16.73 (C12), and 15.44 (C2′); MS (EI, 70 eV, DIP) m/e (%) 236 (11, M^+), 221 (4), 211 (2), 208 (13), 192 (100), 179 (25), 174 (10), 168 (38), 165 (39), 156 (21), 151 (60), 148 (33), 139 (22), 135 (43), 128 (23), 125 (32), 119 (52), 112 (64), 109 (38), 107 (43), 99 (45), 91 (55), 85 (56), 81 (66), 69 (63), and 55 (87); HRMS (EI, 20 eV, DIP) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1422.

(1*R,2*S**,5*R**,10*S**)-1,6-Dimethyl-10-ethoxy-11-oxatricyclo[5.3.0.1^{2,5}]-6-undecen-9-one (19).** One gram (3.93 mmol) of **9a** was dissolved in 40 mL of dry benzene and 4 mL (28.7 mmol) of anhydrous NEt_3. The system was purged with N_2, and 2 mL (27.4 mmol) of freshly distilled $SOCl_2$ was added portionwise along 2 h, under N_2 and with continuous stirring at room temperature. After the last addition of $SOCl_2$ the reaction mixture was kept stirring for 1 more hour (monitoring by TLC and GC). Aqueous HCl (1 M) was added, and the crude mixture extracted with ether four times. The ethereal extracts were combined together, dried over anhydrous $MgSO_4$, filtered through a short pad of neutral alumina, and concentrated to dryness, resulting in an oily crude mixture, which was flash chromatographed on column of silica gel (110 g SiO_2/g crude), eluting with mixture of pentane/ether of increasing polarity. Elution with pentane/ether, 80/20, afforded 0.9 g (97% yield) of white crystalline **19**: mp 55–56 °C (from pentane); IR (KBr) 2980, 2930, 2880, 1750, 1440, 1400, 1380, 1180, 1160, 1120, 1100, 1070, 1040, 1030, 1010, 970, 940, 920, and 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 4.32 (1 H, d, J = 6.9 Hz, H5), 4.23 (1 H, d, J = 7.1 Hz, H2), 3.98 (1 H, dq, J_1 = 9.5 Hz, J_2 = 7.0 Hz, H1′), 3.95 (1 H, s, H10), 3.62 (1 H, dq, J_1 = 9.5 Hz, J_2 = 7.0 Hz, H1′), 2.85 (1 H, d, J = 20.8 Hz, H8), 2.73 (1 H, dd, J_1 = 20.8 Hz, J_2 = 1.9 Hz, H8), 2.35–1.75 (4 H, m, $W_{1/2}$ = 125 Hz, H3 and H4), 1.68 (3 H, d, J = 1.9 Hz, H13), 1.22 (3 H, t, J = 7.0 Hz, H2′), and 0.93 (3 H, s, H12); ^{13}C NMR ($CDCl_3$, ppm) 213.63 (C9), 137.42 (C6), 125.44 (C7), 87.17 (C10), 77.18 (C5), 76.66 (C2), 67.67 (C1′), 48.38 (C1), 37.19 (C8), 30.80 (C4), 25.56 (C3), 16.58 (C13), 15.52 (C12), and 15.38 (C2′); MS (EI, 70 eV, DIP) m/e (%) 236 (M^+, 100), 221 (6, $M^+ - CH_3$), 218 (2, $M^+ - H_2O$), 208 (8, $M^+ - CO$), 191 (10, M^+ – EtO), 190 (46, M^+ – EtOH), 179 (21), 165 (12), 162 (54), 151 (23), 147 (11), 133 (30), 121 (16), 106 (14), 101 (12), and 84 (18); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1415. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.56.

Reaction of 19 with HCl(g)/MeOH: (1*R,2*S**,5*R**,6*S**,10*S*)-1,6-Dimethyl-10-ethoxy-11-oxatricyclo[5.3.0.1^{2,5}]-7-undecen-9-one (21) and (6*S**,7*R**,8*S**)-2,7-Dimethyl-8-ethoxy-6-hydroxybicyclo[5.3.0]deca-2,10-dien-9-one (20).** Concentrated HCl (0.5 mL, 37% w/w) was added at once by syringe to a solution of 90 mg (0.38 mmol) in **19** in 5 mL of MeOH, and the reaction mixture was stirred under N_2 at room temperature for 24 h, monitoring by TLC (SiO_2; hexane–ether, 50:50). Solvent was taken out by pump, and the remaining oil was dissolved in ether, washed with brine, dried by anhydrous $MgSO_4$, filtered through a short pad of neutral alumina, and concentrated to dryness by vacuum, resulting in a crystalline crude mixture which was flash chromatographed on column of silica gel (110 g SiO_2/g of crude), eluting with mixtures of pentane and ether. Elution with P/E, 70:30, afforded 38 mg (42% yield) of pure **20** while pentane/ether, 30:70, eluted 35 mg (39% yield) of pure **21**.

20: colorless oil; IR (neat) 2980, 2930, 2880, 1720, 1615, 1480, 1460, 1380, 1340, 1260, 1125, 1020, 960, 940, and 880 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 5.87 (1 H, d, J = 2.2 Hz, H8), 4.42 (1 H, d, J = 7.1 Hz, H2), 4.04 (1 H, d, J = 6.8 Hz, H5), 4.01 (1 H, s, H10), 4.02 (1 H, dq, J_1 = 9.3 Hz, J_2 = 6.9 Hz, H1′), 3.70 (1 H, dq, J_1 = 9.3 Hz, J_2 = 6.9 Hz, H1′), 2.43 (1 H, dq, J_1 = 7.0 Hz, J_2 = 2.2 Hz, H6), 2.20–1.70 (4 H, m, $W_{1/2}$ = 22 Hz, H3 and H4), 1.30 (3 H, d, J = 7.0 Hz, H13), 1.27 (3 H, t, J = 6.9 Hz, H2′), and 1.05 (3 H, s, H12); ^{13}C NMR ($CDCl_3$, ppm) 205.71 (C9), 182.26 (C7), 124.61 (C8), 89.76 (C10), 80.66 (C5), 80.29 (C2), 67.33 (C1′), 52.47 (C1), 40.68 (C6), 32.27 (C4), 24.33 (C3), 20.12 (C13), 17.78 (C12), and 15.45 (C2′); UV (EtOH) λ_{max} 231 nm, ϵ = 12 000; MS (EI, 70 eV, DIP) m/e (%) 236 (30, M^+), 192 (100), 179 (35), 163 (40), 151 (60), 148 (60), 135 (45), 119 (58), 107 (45), 91 (58), 77 (40), and 55 (55); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1415.

21: crystalline solid which melts at room temperature; IR (neat) 3460 (br, OH), 2970, 2930, 2875, 1700, 1630, 1590, 1550, 1450, 1400, 1380, 1270, 1260, 1220, 1120, 1070, 920, 870, 810, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 5.96 (1 H, s, H10), 5.89 (1 H, m, $W_{1/2}$ = 12 Hz, H3), 4.34 (1 H, s, H8), 4.15 (1 H, dq, J_1 = 9.1 Hz, J_2 = 7.0 Hz, H1′), 3.98 (1 H, m, $W_{1/2}$ = 20 Hz, H6), 3.98 (1 H, m, $W_{1/2}$ = 20 Hz, H6), 3.73 (1 H, dq, J_1 = 9.1 Hz, J_2 = 7.0 Hz, H1′), 2.40–1.70 (4 H, m, $W_{1/2}$ = 200 Hz, H4 and H5), 1.95 (3 H, br s, $W_{1/2}$ = 5 Hz, H11), 1.26 (3 H, t, J = 7.0 Hz, H2′), and 1.18 (3 H, s, H12); MS (EI, 70 eV, DIP) m/e (%) 236 (18, M^+), 218 (37, $M^+ - H_2O$), 175 (29), 161 (35), 147 (26), 133 (27), 105 (28), 91 (44), 79 (23), 77 (32), 55 (37), and 44 (100); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1410.

Reaction of 19 with HSCH$_2$CH$_2$SH/BF$_3$·OEt$_2$: (3*S,6*S**,7*R**,8*S**)-2,7-Dimethyl-1,1-(1,2-ethylenedithio)-8-ethoxy-6-hydroxy-3-((2-mercaptoethyl)thio)bicyclo[5.3.0]-dec-1-ene (22a) and (3*S**,6*S**,7*R**,8*R**)-2,7-Dimethyl-1,1-(1,2-ethylenedithio)-8-ethoxy-6-hydroxy-3-((2-mercaptoethyl)thio)bicyclo[5.3.0]dec-1-ene (22b).** Compound **19** (0.43 g, 1.8 mmol) was dissolved in 25 mL of dry benzene, 10 mL of 1,2-ethanedithiol was added, and the solution cooled to 0 °C under N_2. Then, 0.5 mL (4.06 mmol) of BF_3·OEt_2 was added by syringe, and the reaction mixture was kept stirring under N_2 at 0 °C for 2 h (monitoring by TLC: SiO_2; hexane/ether, 50:50, three developments). Solvent and excess $HSCH_2CH_2SH$ and BF_3·OEt_2 were removed in vacuo (double trap system, 0.1 mm). The resultant oil (0.80 g) was dissolved in ether and washed with aqueous $NaHCO_3$ (0.1 M), dried by anhydrous $MgSO_4$, and concentrated to dryness, resulting in 0.7 g (95% yield) of a mixture of **22a** and **22b** (97:3). The epimers were separated by a short column chromatography on silica gel, eluting with mixtures of pentane and ether (40:60, 30:70) to afford 0.68 g of **22a** and 0.02 mg of **22b**.

22a: malodorous colorless oil; IR (neat) 3420 (OH), 2970, 2920, 2880, 2560 (SH), 1430, 1380, 1260, 1205, 1115, 960, and 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 4.43 (1 H, s, H8), 3.98 (1 H, dq, J_1 = 9.3 Hz, J_2 = 7.1 Hz, H1′), 3.80 (1 H, dq, J_1 = 9.3 Hz, J_2 = 7.1 Hz, H1′), 3.60 (1 H, m, $W_{1/2}$ = 13 Hz, H8), 3.38 (1 H, m, $W_{1/2}$ = 30 Hz, H3), 3.25 (4 H, m, $W_{1/2}$ = 32 Hz, SCH_2CH_2S), 3.16 (1 H, m, $W_{1/2}$ = 15 Hz, H10), 3.08 (1 H, m, $W_{1/2}$ = 15 Hz, H10), 2.78 (4 H, m, $W_{1/2}$ = 25 Hz, SCH_2CH_2S), 2.40–1.80 (2 H, m, $W_{1/2}$ = 140 Hz, H4), 1.72 (3 H, br s, H11), 1.68 (2 H, m, $W_{1/2}$ = 50 Hz, H5), 1.25 (3 H, s, H12), and 1.23 (3 H, t, J = 7.1 Hz, H2′); MS (EI, 70 eV, DIP) 406 (2, M^+), 267 (14), 125 (23), 121 (18), 105 (24), 97 (18), 93 (14), 91 (15), 77 (10), 65 (10), and 61 (100); HRMS (EI, 70 eV, DIP) calcd for $C_{18}H_{30}O_2S_4$ 406.1130, found 406.1139.

22b: malodorous white crystalline solid; mp 149–150 °C (from MeOH); IR (KBr) 3450 (br, OH), 2970, 2920, 2880, 2390 (SH), 1450, 1430, 1420, 1375, 1210, 1150, 1120 (sharp), 1080, 1060, 1050, 960, and 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 4.59 (1 H, s, H8), 4.00

(1 H, dq, J_1 = 9.7 Hz, J_2 = 7.0 Hz, H1'), 3.82 (1 H, dq, J_1 = 9.7 Hz, J_2 = 7.0 Hz, H1'), 3.69 (1 H, ddd, J_1 = 9.0 Hz, J_2 = 8.3 Hz, J_3 = 5.5 Hz, H6), 3.41 (1 H, dd, J_1 = 9.5 Hz, J_2 = 4.4 Hz, H3), 3.27 (4 H, m, $W_{1/2}$ = 28 Hz, SCH_2CH_2S), 3.12 (1 H, dd, J_1 = 19 Hz, J_2 = 1.2 Hz, H10), 2.90 (1 H, dd, J_1 = 19 Hz, J_2 = 1.2 Hz, H10), 2.75 (4 H, m, $W_{1/2}$ = 11 Hz, SCH_2CH_2SH), 2.50 (1 H, m, $W_{1/2}$ = 30 Hz, H4), 2.16 (1 H, m, $W_{1/2}$ = 30 Hz, H4), 1.75 (3 H, d, J = 1.2 Hz, H11), 1.72 (2 H, m, $W_{1/2}$ = 40 Hz, H5), 1.45 (1 H, d, J = 9.0 Hz, OH), 1.32 (3 H, s, H12), and 1.24 (3 H, t, J = 7.0 Hz, H2'); MS (EI, 70 eV, DIP) 406 (21, M^+), 313 (33), 267 (100), 249 (10), 238 (10), 223 (23), 219 (13), 207 (19), 194 (10), 191 (13), 173 (19), 163 (26), 157 (12), 149 (22), 145 (29), 133 (33), 131 (32), 129 (24), 121 (22), 119 (24), 115 (25), 107 (27), 105 (95), 97 (20), 91 (62), 77 (35), and 61 (48). Anal. Calcd for $C_{18}H_{30}O_2S_4$: C, 53.16; H, 7.43. Found: C, 53.14; H, 7.48.

Reduction of 22a (22b) by Raney Nickel: (1*R,2*S**,10*R**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]dec-6-en-2-ol (23a) and (1*R**,2*S**,10*S**)-1,6-Dimethyl-10-ethoxybicyclo[5.3.0]dec-6-en-2-ol (23b).** To 10 g of dry Raney Nickel W-2 (washed as described previously), placed under N_2 into a closed flask, a solution of 0.5 g (1.2 mmol) of **22a** (or **22b**) in 100 mL of absolute ethanol was added by syringe, and the reaction mixture was stirred and refluxed under N_2 for 12 h, monitoring by TLC (SiO_2, hexane/ether, 50/50, two developments). After the usual workup, 0.3 g of crude oil was obtained, which was submitted to flash column chromatography on silica gel to afford upon elution with pentane/ether (90/10), 0.23 g (85% yield) of **23a** (or **23b**).

23a: colorless oil; IR (neat) 3460 (OH), 2980, 2920, 2880, 1450, 1370, 1350, 1110 (sharp), 1020, 980, 950, 940, and 850 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 3.94 (1 H, apparent t, $J_1 \cong J_2$ = 7.5 Hz, H10), 3.80 (1 H, m, $W_{1/2}$ = 15 Hz, H2), 3.56 (1 H, dq, J_1 = 9.3 Hz, J_2 = 6.9 Hz, H1'), 3.40 (1 H, dq, J_1 = 9.3 Hz, J_2 = 6.9 Hz, H1'), 2.50–2.10 (4 H, m, $W_{1/2}$ = 80 Hz, H5 and H8), 2.05–1.40 (6 H, m, $W_{1/2}$ = 160 Hz, H9, H5 and H4), 1.67 (3 H, br s, H12), 1.13 (3 H, t, J = 6.9 Hz, H2'), and 0.91 (3 H, s, H11); MS (EI, 70 eV, DIP) m/e (%) 224 (3, M^+), 209 (24, $M^+ - CH_3$), 206 (17), 178 (25), 163 (11), 153 (18), 150 (10), 145 (11), 135 (20), 125 (55), 121 (30), 107 (100), 97 (31), 93 (30), 91 (25), 81 (27), 79 (25), 77 (17), 76 (15), and 55 (34). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.93; H, 10.95.

23b: colorless oil; IR (neat) 3460 (OH), 2980, 2915, 2890, 1450, 1375, 1110 (sharp), 1015, 980, and 860 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.07 (1 H, dd, J_1 = 6.0 Hz, J_2 = 11.5 Hz, H10), 3.70 (1 H, m, $W_{1/2}$ = 15 Hz, H2), 3.62 (1 H, dq, J_1 = 9.2 Hz, J_2 = 6.9 Hz, H1'), 3.48 (1 H, dq, J_1 = 9.2 Hz, J_2 = 6.9 Hz, H1'), 2.50–2.20 (4 H, m, $W_{1/2}$ = 60 Hz, H5 and H8), 2.05–1.40 (6 H, m, $W_{1/2}$ = 140 Hz, H3, H4, and H9), 1.63 (3 H, br s, H12), 1.16 (3 H, t, J = 6.9 Hz, H2'), and 0.97 (3 H, s, H11); MS (EI, 70 eV, DIP) m/e (%) 224 (3, M^+), 179 (13), 178 (92), 163 (17), 150 (10), 145 (20), 137 (13), 134 (100), 131 (9), 125 (16), 121 (58), 107 (80), 106 (21), 94 (69), 91 (34), 81 (37), 77 (23), 67 (25), and 55 (34); HRMS (EI, 70 eV, DIP) calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1780.

Hydrogenation of 23a. To 0.25 g (1.11 mmol) of **23a** dissolved in 20 mL of EtOH was added 60 mg of Pd on charcoal (10% w/w), and the system was purged with H_2. The suspension was stirred under 1 atm of H_2 at room temperature for 12 h, affording after the usual workup 0.25 g (quantitative yield) of a 95:5 mixture of **15a** and **15b**.

Reaction of 16a,b with $MeSiCl_3$/NaI: (1*S,6*S**,7*S**,10*R**)-1,6-Dimethyl-10-hydroxybicyclo[5.3.0]decan-2-one (24a) and (1*S**,6*R**,7*R**,10*R**)-1,6-Dimethyl-10-hydroxybicyclo[5.3.0]decan-2-one (24b).** To a solution of 0.23 g (1.02 mmol6) of **16a,b** (95:5) (free of moisture) in 2 mL of dry CH_3CN was added 0.21 g (1.42 mmol) of strict anhydrous NaI, and the system was purged and stirred under N_2 until a homogeneous dissolution was obtained. At this point, 0.2 mL (1.70 mmol) of freshly distilled $MeSiCl_3$ was added by syringe, and the reaction mixture was stirred at room temperature for 12 h, monitoring by TLC (SiO_2; hexane/ether, 40:60). Solvent was evaporated, ether was added, and the ethereal solution was washed consecutively with aqueous $NaHCO_3$ (0.5 M) twice and saturated aqueous $Na_2S_2O_3$ once, finally dried with $MgSO_4$, and concentrated to dryness, resulting in 0.25 g of a colorless oil which was flash chromatographed on silica gel (110 g SiO_2/g crude), eluting with mixtures pentane/ether of increasing polarity, to afford with 70:30 P/E 114 mg (57% yield) of **24a** and with 50:50 P/E 6 mg (3% yield) of **24b**.

24a: white crystalline solid; mp 61–62.5 °C (from ether) (lit.[10] mp 61 °C); IR (KBr) 3400 (OH), 1690, 1450, 1410, 1370, 1345, 1320, 1270, 1250, 1210, 1120 (sharp), 1065, 1010, 965, and 920 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.06 (1 H, ddd, J_1 = 9.8, J_2 = 9.0, J_3 = 1.8 Hz, H10), 3.00 (1 H, d, J = 1.8 Hz, OH), 2.55 (1 H, dddd, $J_1 \cong J_2$ = 4.5, J_3 = 1.2, J_4 = 16.8 Hz, H3), 2.40 (1 H, m, $W_{1/2}$ = 30 Hz, H3), 1.95–1.10 (10 H, m, $W_{1/2}$ = 250 Hz, H4, H5, H6, H7, H8, and H9), 1.06 (3 H, s, H11), and 0.91 (3 H, d, J = 6.5 Hz, H12); MS (EI, 70 eV, DIP) m/e (%) 196 (10, M^+), 181 (42, $M^+ - CH_3$), 178 (37, $M^+ - H_2O$), 167 (6), 163 (8), 153 (34), 139 (100), 135 (25), 125 (21), 121 (37), 109 (51), 97 (86), 91 (11), 85 (10), 81 (49), 77 (12), 69 (54), and 55 (85); HRMS (EI, 70 eV, DIP) calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1467. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.15.

24b: IR (CCl_4) 3450 (OH), 1690, 1450, 1420, 1380, 1320, 1280, 1250, 1210, 1120, 1065, 1015, and 920 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 4.03 (1 H, ddd, J_1 = 9.5 Hz, J_2 = 9.3 Hz, J_3 = 1.5 Hz, H10), 3.00 (1 H, d, J = 1.5 Hz, OH), 2.78 (1 H, ddd, J_1 = 19.0, J_2 = 11.4 Hz, J_3 = 3.9 Hz, H3), 2.63 (1 H, m, $W_{1/2}$ = 20 Hz, H3), 2.00–1.10 (10 H, m, H4, 5, 6, 7, 8, 9), 1.17 (3 H, s, H11), and 0.81 (3 H, d, J = 7.3 Hz, H12); MS (EI, 70 eV, DIP) m/e (%) 196 (5, M^+), 181 (40, $M^+ - CH_3$), 178 (30, $M^+ - H_2O$), 167 (10), 163 (15), 153 (30), 139 (100), 135 (20), 125 (30), 121 (30), 109 (55), 97 (80), 91 (10), 85 (10), 81 (50), 77 (10), 69 (54), and 55 (85). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.51; H, 10.19.

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Supplementary Material Available: ^1H NMR spectra for compounds **9b**, **10a,b**, **11**, **12**, **13a,b**, **14a,b**, **15b**, **17**, **18**, **20**, **21**, **22a**, and **23b** (18 pages). Ordering information is given on any current masthead page.