with the present results. The reduction of the reactivity of the enolate anion upon association with a water molecule may be the result of an enhancement of the diffuse character of the charge and of a drastic lowering of the HOMO energy of the enolate anion. Although the influence of hydration on the HOMO energy of an enolate anion is not known, it has been shown for several anions in the gas phase that solvation leads to a (0.5–1.3 eV)[58,59] higher energy required to remove an electron from the anion which can be associated with a lowering of HOMO energy.

"Boiling off" of water molecules during the gas-phase reactions of hydrated reactant ions is not an uncommon phenomenon, since it has been shown frequently that reactions of mono- and polyhydrated reactant ions may result in complete or partial desolvation of the ionic products.[34,37,38,44,45] Yet, it is not always clear if the evaporation of water molecules is fueled by the energy gained upon formation of the reaction encounter complex or by the energy released in the ion/molecule reaction which takes place in the solvated reaction complex.

Although the related phenomenon of ligand or solvent switching for solvated gaseous ions is well-known, the question remains if the exchange of the water molecule for a perfluorocarbon molecule which is assumed to precede the reaction between the presently studied enolate anions and the perfluorocarbon molecule is energetically accessible. The thermodynamics of this solvent switching process is not known. However, it has been shown in both theoretical[56,60] and experimental[40,61,62] studies that the electrostatic bonding between Cl^- and hexafluorobenzene is ca. 8 kJ mol^{-1} more favorable than the clustering of Cl^- with H_2O, which indicates that the assumed solvent switching step in the presently studied reactions is not energetically blocked. Yet, evaporation of the water molecule from the encounter complex can be expected to cool off the reaction complex as a result of which the excess internal energy may be lower than for the same complex formed upon encounter of the unsolvated enolate anion and the unsaturated fluorocarbon molecule. In spite of this anticipated difference in excess internal energy, only for the reactions with hexafluorobenzene a small shift in the reaction selectivity towards addition via the oxygen nucleophilic center has been detected upon association of the enolate anion with a water molecule. This seemingly insensitivity for variation of the excess internal energy of the reaction complex may be due to a relatively small or similar activation entropy of the two reaction channels. This is supported by the observation that translational excitation up to 100 eV of the unsolvated enolate anion from acetone showed no significant shift of the reaction selectivity in the reaction with hexafluorobenzene. Nevertheless, it would be much more conclusive to study the temperature dependence of the ambident chemical behavior of the unsolvated enolate anions.

Acknowledgment. The authors wish to thank the Netherlands Organization for Scientific Research (NWO/SON) for financial support.

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Total Synthesis of Some Marasmane and Lactarane Sesquiterpenes

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A general and efficient synthetic route to the marasmane sesquiterpenes (±)-isovelleral (**2**) and (±)-stearoylvelutinal (**1b**) is described. Total syntheses of two other naturally occurring sesquiterpenes, deconjugated anhydrolactarorufin A (**5**) and lactarorufin A (**6**), were achieved using an acid-catalyzed ring expansion of lactone **25**. All four syntheses are highly stereoselective and do not require the use of any protecting groups. Finally, the protic acid-catalyzed degradation of velutinal (**1a**) was investigated in an effort to chemically induce the biologically important conversion of velutinal (**1a**) to isovelleral (**2**). The experimental results thus obtained indicate that an enzymatic mechanism for the key transformation of velutinal (**1a**) into isovelleral (**2**) is more plausible than one that is acid-catalyzed.

Marasmane and lactarane sesquiterpenes, representative examples of which are shown below, have been isolated from basidiomycetes of several genera, including *Marasmius*, *Lactarius*, and *Russula*.[2] Some of these sesquiterpenes appear to be part of a complicated chemical defense mechanism in which fatty acid esters (**1b,c**) of the unstable hemiacetal velutinal (**1a**) serve as inactive forms of the ammunition.[3] For example, injury of a specimen of *Lactarius velereus* causes rapid enzymatic hydrolysis of ester **1b** to **1a**, which is further transformed by an unknown mechanism, enzymatic or chemical, into the strongly antifungal and antibacterial sesquiterpene dialdehydes isovelleral (**2**)[4] and velleral (**4**).[5] Compounds **2** and **4** impart a pungent taste to the fungi, and **2** is a potent insect and opossum antifeedant.[6] Furthermore, **2** shows significant mutagenic activity in the Ames *Salmonella*/microsome assay and may be a contributing

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(2) For a review of marasmane and lactarane sesquiterpenes, see: Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199.
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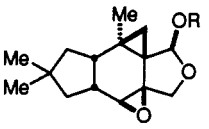
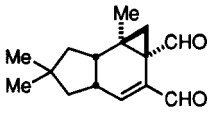
mutagen in other species of *Russulaceae*, such as *Lactarius rufus*, *Lactarius necator*, *Russula aeruginea*, *Russula consobrina*, and *Russula foetens*.[7]

Marasmane Sesquiterpenes



R=H: **1a**
R=stearoyl: **1b**
R=6-ketostearoyl: **1c**



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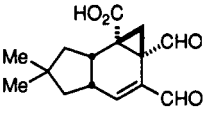
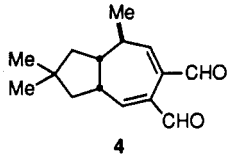


3

Lactarane Sesquiterpenes



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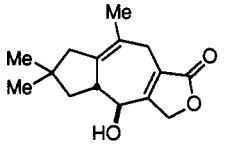

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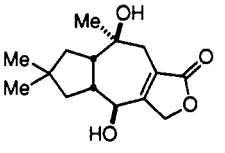
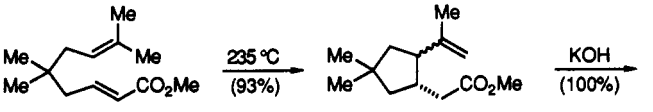


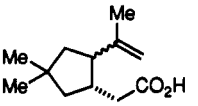
6

A significant amount of research has been devoted to the synthesis of marasmane sesquiterpenes. However, most of the studies have been directed toward the synthesis of marasmic acid (**3**).[8] Far less attention has been given to the synthesis of isovelleral (**2**),[9] and no approaches to the total synthesis of velutinal (**1a**) or its esters have been reported. The two objectives of this study were (1) to develop one general synthetic route that could be used for the synthesis of both isovelleral (**2**) and stearoylvelutinal (**1b**) with complete control of stereochemistry at all stereocenters and (2) to investigate the in vitro conversion of **1a** into **2**. This report outlines the retrosynthetic analysis, the eventual total syntheses of isovelleral and stearoylvelutinal as well as deconjugated anhydrolactarorufin A (**5**) and lactarorufin A (**6**), and an in vitro study of the conversion of **1a** into **2**.

Total Synthesis of (±)-Isovelleral (2). The synthesis began with the preparation of the *gem*-dimethylcyclopentylacetic acid **9**. Pyrolytic cyclization of dienic ester **7** (a 20:1 mixture of *E* and *Z* isomers)[10] provided in 93% yield **8** (a 70:30 mixture of cis and trans isomers), which was saponified to give **9** in quantitative yield.

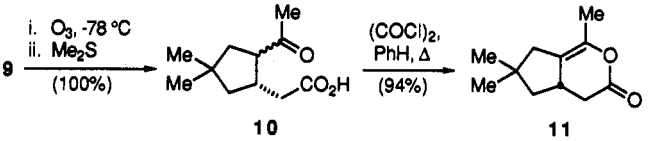


7 **8**
cis:trans=70:30

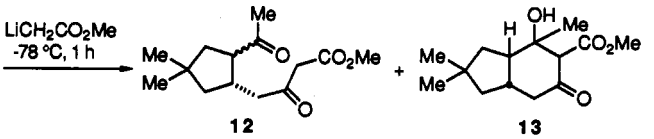


9
cis:trans=70:30

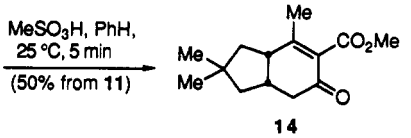
The next synthetic task was conversion of **9** into unsaturated β-keto ester **14**. The route adopted was oxidative cleavage of the olefin, two-carbon homologation to a diketo ester, and subsequent cyclization and dehydration to give the required unsaturated β-keto ester. A considerable amount of experimentation[11] led to the four-step sequence shown below. Ozonolysis of **9** gave quantitatively keto acid **10** which was treated with oxalyl chloride in refluxing benzene to provide enol lactone **11** in 94% yield. Treatment of **11** with methyl α-lithioacetate[12] provided an inseparable mixture of diketo esters **12** and aldol product **13** in nearly quantitative yield. The aldol product **13** appears to be a single diastereomer on the basis of ^{1}H NMR spectral data of the mixture of **12** and **13**. However, because **13** could not be separated from keto esters **12**, it could not be rigorously characterized, so the relative stereochemistry at three of its four stereocenters remains undefined. Without purification, the mixture of **12** and **13** was treated with various acid catalysts to effect cyclization and dehydration to **14**. Benzene was found to be the most suitable solvent for this reaction; the reaction proceeded very slowly and in low yield in THF solution, presumably because of competing protonation of the solvent. Treatment with *p*-toluenesulfonic acid or sulfuric acid in refluxing benzene gave low yields of **14** (36% and 14%, respectively). Because of the low solubility of these acids in benzene, elevated temperatures are required to solubilize the acid catalyst, and under these conditions, significant product decomposition may occur. Methanesulfonic acid, however, is much more soluble in benzene, so the reaction can occur rapidly and at room temperature. Using this catalyst for the cyclization/dehydration reaction, the desired unsaturated keto ester **14** was isolated in 50% overall yield from enol lactone **11**.



10 **11**



12 **13**



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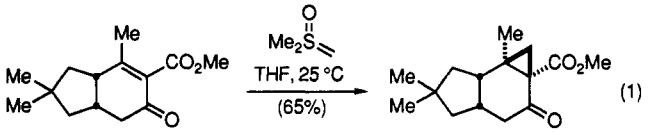
(10) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386.
(11) Two unsuccessful synthetic sequences were investigated, the details of which are described in the supplementary material.
(12) Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102.

Table I. Conversion of Keto Ester 14 to Cyclopropane 15

entry	solvent	temp (°C)	time (min)	yield of 15 (%)
1	DMSO	25	180	24
2	DMSO	50	15	50
3	THF	25	30	65
4	THF	67	5	65

After having accomplished an efficient synthesis of **14**, the conversion to cyclopropane **15** (R = Me) was investigated. Treatment of **14** with the Corey–Chaykovsky reagent[13] provided the desired cyclopropane **15** in varying yields, depending on the solvent and reaction temperature used (eq 1). Several experiments involving variation of

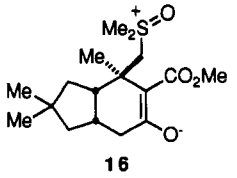


14 15 (1)

the solvent and reaction temperature were carried out for the purpose of optimizing the yield of **15** produced in this reaction. The results of these experiments are summarized in Table I.

The relative stereochemistry of **15** was assigned on the basis of a 2D NOESY NMR experiment.[14] The observed NOE enhancements between protons H_A and H_C and between H_C and H_D not only confirm that the cyclopropane ring is on the same face of the cyclohexane ring as the ring juncture protons H_C and H_D, but also that the six- and five-membered rings are cis-fused (vide infra).

The smooth cyclopropanation of **14** is uncommon, as the dimethylsulfoxonium methylide usually deprotonates ketones with enolizable α-protons.[15] Undoubtedly, there is some enolization occurring because the yields obtained are slightly lower than those obtained in the reaction of dimethylsulfoxonium methylide with α,β-unsaturated ketones,[13] and once enolization has occurred, the substrate is lost since the enolate of **14** appears to be very prone to decomposition.[16] It is clear from the data in Table I that THF is superior to DMSO as the solvent for this reaction. Furthermore, greater yields of **15** are obtained under conditions in which the reaction is completed as rapidly as possible (entry 1 vs 2). It is possible that the intermediate sulfoxonium enolate **16** is more highly stabilized in DMSO than in THF due to the greater polarity of DMSO. If **16** has greater stability in DMSO, it is likely that ring closure to cyclopropane **15** is not as rapid relative to the reverse reaction to give **14** and dimethylsulfoxonium methylide. Once the reverse reaction has occurred, the re-formed **14** may undergo readdition of the dimethylsulfoxonium methylide or enolization. It is expected that this would be the case as well at the lower temperatures at which the reaction did not proceed as rapidly. The increased reversibility of this reaction would eventually lead to more total enolization and decomposition of **14** and a corresponding decrease in the yield of **15**. This explanation appears to be in accord with the observed experimental results.



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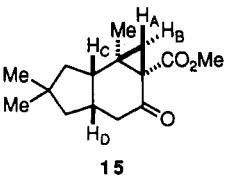
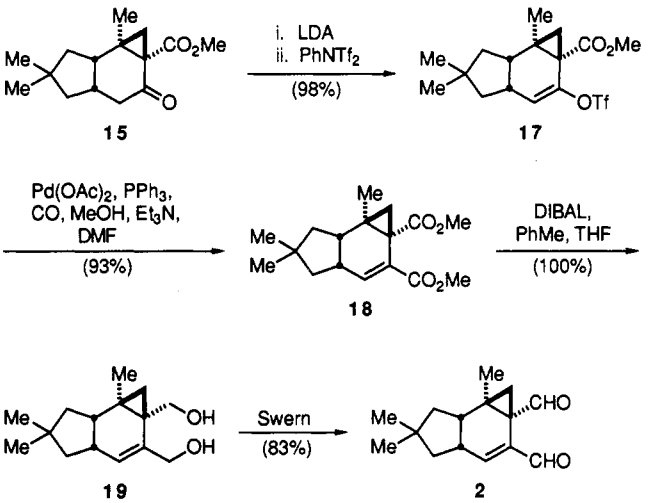


15

The final task necessary for the completion of the total synthesis of **2** was the one-carbon homologation of the ketone carbonyl and manipulation of the appropriate functionality. The route chosen was conversion of the ketone to the enol triflate followed by palladium-catalyzed methoxycarbonylation to give a diester, thus providing the necessary dicarbonyl functionality and positioning the unsaturation correctly. The diester would be reduced to the diol, which would, in turn, be oxidized to provide (±)-**2**.[17] Hence, sequential treatment of **15** with LDA and *N*-phenyltrifluoromethanesulfonamide[18] afforded **17** in 98% yield. Palladium-catalyzed methoxycarbonylation of **17**[19] provided diester **18** in 93% yield. Reduction of **18** with an excess of diisobutylaluminum hydride (DIBAL) gave in quantitative yield diol **19**, which was oxidized in 83% yield by the Swern protocol[20] to obtain (±)-isovelleral (**2**),[21] identical by 500-MHz ^{1}H NMR spectrometry to a sample of (+)-isovelleral.[22]



15 17 18 19 2

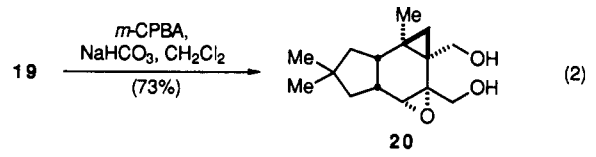
This highly stereoselective total synthesis of (±)-isovelleral (**2**) requires 14 steps from commercially available 3-methyl-2-butenal and proceeds in 15% overall yield. This corresponds to an 87% yield per step. A noteworthy feature of this synthesis is that it does not require the use of any protecting groups.

Total Synthesis of (±)-Stearoylvelutinal (1b). Stearoylvelutinal (**1b**) as a synthetic target provides two synthetic challenges not provided by **2**. First, if intermediates such as diester **18** or diol **19** are to be used in a synthesis of **1b**, a regioselective reduction of one of two ester carbonyls (or regioselective oxidation of one or two carbinol carbons) must be achieved. Second, a stereoselective epoxidation must be accomplished. A synthetic plan that addresses both of these challenges was chosen, starting from diol **19**. Epoxidation of **19** was expected to

(13) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(14) Copies of all COSY and NOESY NMR spectra are given in the supplementary material.
(15) Cholest-4-en-3-one, for example, suffers complete enolization at C-2 when treated with this reagent (see ref 10).
(16) Very low yields and incomplete conversion were observed in the cyclization of **12** and **13** to **14** under basic conditions (sodium methoxide in methanol) presumably because of enolate formation and decomposition.
(17) This four-step transformation was first investigated in a model study, the details of which are described in the supplementary material.
(18) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(19) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(20) Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(21) The total synthesis of (±)-isovelleral (**2**) has been communicated, see: Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3004.
(22) We are grateful to Professor B. Wickberg (University of Lund) for providing us with samples of natural isovelleral (**2**) and stearoylvelutinal (**1b**).

occur from the exo face of the hydrindan ring system to provide an epoxide which could undergo a regioselective oxidation of the cyclopropylcarbinol[23] to furnish velutinal (**1a**). Acylation of **1a** with stearoyl chloride would then provide **1b**.

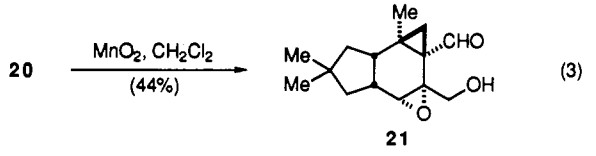
Epoxidation of **19** was accomplished by treatment with *m*-CPBA in CH_2Cl_2 buffered by sodium bicarbonate. However, the undesired diastereomer **20** was obtained in 73% yield (eq 2). Treatment with $VO(acac)_2$ and *tert*-



(2)

20

butyl hydroperoxide[24] or with dimethyldioxirane[25] provided the same diastereomer, **20**. The issue of the stereochemistry of the epoxide in **20** was resolved by oxidation of the cyclopropylcarbinol. Treatment of **20** with manganese dioxide provided the hydroxy aldehyde **21** in 44% yield (eq 3). The 500-MHz ^1H NMR spectrum of **21** shows that it is clearly not (±)-velutinal and is consistent with the proposed structure. Therefore, it is clear that the epoxy diol precursor has the relative stereochemistry shown in structure **20**.



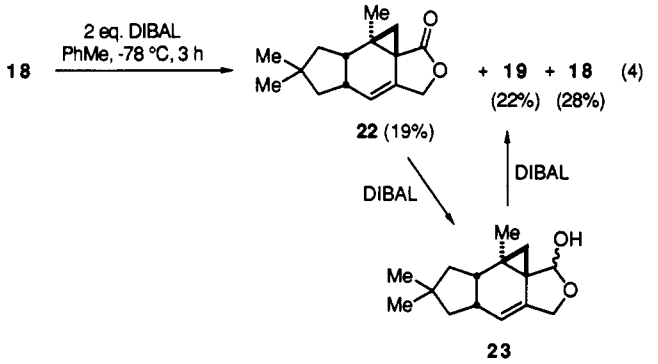
(3)

21

It is not completely clear what is responsible for the extremely high stereoselectivity observed in the conversion of **19** to **20**. A steric effect is unlikely because both faces of the alkene appear to be equally hindered on the basis of molecular models. A directing effect on the part of the homoallylic alcohol is a possibility, although direction by a homoallylic alcohol is not expected to provide the high degree of stereoselectivity that is observed. It is most likely the case that a stereoelectronic effect is responsible for the observed stereoselectivity. The allylic ring juncture methine hydrogen is in a pseudoaxial position and is virtually perpendicular to the π-system of the alkene. This arrangement has been described by Houk[26] as the "perpendicular model". Epoxidation of an alkene in such an arrangement is expected to occur from the face opposite to that of the pseudoaxial hydrogen because of σ^*-π hyperconjugation. This argument has been used to explain a highly stereoselective epoxidation of a similar system in which steric or electrostatic effects cannot participate.[27]

Because the epoxidation of **19** provided the epoxide stereochemistry opposite to that which was desired, we chose to investigate the epoxidation of a system in which the final ring containing what will eventually become the lactol functionality in **1a** has been closed. Lactone **22** would provide such a system. Epoxidation of **22** was expected to occur from the same face as is located the cyclopropane ring to provide a cis-fused oxahydrindan ring system and avoid the formation of the thermodynamically less favorable trans-fused ring system. Although this is an issue of thermodynamics, this difference in torsional strain energies can be realized in the transition state of the epoxidation reaction, as is evidenced in Danishefsky's total synthesis of coriolin.[28]

For the initial preparation of lactone **22**, we chose to investigate the regioselective reduction of diester **18**. Regioselective reductions of diesters to lactones[29] or lactols[30] have been accomplished by treatment with DIBAL[31] or sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al (Aldrich) or VITRIDE).[32] Upon treatment of **18** with either of these reagents, only treatment with DIBAL gave detectable amounts of the desired product. Treatment of a toluene solution of **18** with 2 molar equiv of DIBAL at −78 °C gave lactone **22**, diol **19**, and recovered diester **18** in 19%, 22%, and 28% yields, respectively (eq 4). Because there was only one lactone regioisomer formed in this reaction, it is probable that the formation of the diol is the result of further reduction of **22** to provide isovellerol (**23**)[33], which is expected to undergo a rapid reduction by DIBAL to diol **19**.



(4)

23

Although the aforementioned reaction did provide some of the desired product, it is far too inefficient to be synthetically useful. Therefore, we found it necessary to conduct the selective reduction on a dicarbonyl compound in which the two carbonyls are of different functionality. A considerable amount of experimentation with a model system[34] led to the three-step synthesis of **22** and the completion of the total synthesis of stearoylvelutinal (**1b**), shown below. Treatment of enol triflate **17** with a catalytic amount of tetrakis(triphenylphosphine)palladium(0), tri-*n*-butyltin hydride, and an excess of lithium chloride in THF at 50 °C under 3 atm of carbon monoxide pressure gave aldehyde **24** in 88% yield. Reduction of **24** with sodium borohydride and cerium(III) chloride[35] followed by lactonization with *p*-toluenesulfonic acid in benzene provided **22** in 93% yield. With an efficient synthesis of

(23) Crombie, L.; Crossley, J. *J. Chem. Soc.* **1963**, 4983.

(24) (a) Tanaka, H.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. (c) Mihelich, E. D. *Tetrahedron Lett.* **1979**, 4729.

(25) (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (c) Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (d) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (e) Adam, W.; Hadjiarapoglou, L.; Wang, X. *Tetrahedron Lett.* **1989**, *30*, 6497.

(26) Houk, K. N. *Pure Appl. Chem.* **1983**, *55*, 277.

(27) Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. *Tetrahedron Lett.* **1989**, *30*, 3935.

(28) (a) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097. (b) Danishefky, S.; Zamboni, R. *Tetrahedron Lett.* **1980**, 3439.

(29) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1988**, *29*, 37.

(30) Kraiss, G.; Povarny, M.; Scheiber, P.; Nador, K. *Tetrahedron Lett.* **1973**, 2359.

(31) For a review of the use of this reagent as a reducing agent, see: Winterfeldt, E. *Synthesis* **1975**, 617.

(32) Malek, J.; Cerny, M. *Synthesis* **1972**, 217.

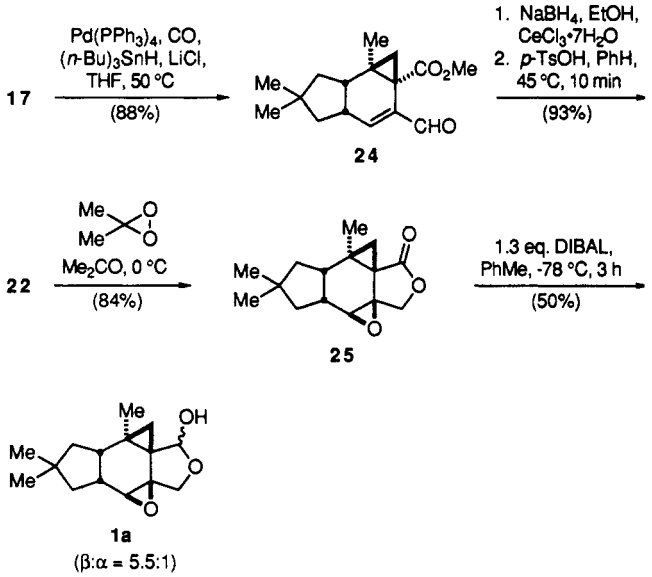
(33) Isovellerol (**23**) is a related fungal isolate, presumably a product of in vivo reduction of isovelleral (**2**). See refs 3 and 7 and: Sterner, O.; Bergman, R.; Kesler, E.; Nilsson, L.; Olowadiya, J.; Wickberg, B. *Tetrahedron Lett.* **1983**, *24*, 1415.

(34) Some of these experiments are described in the supplementary material.

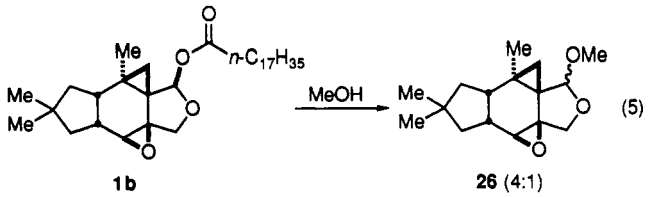
(35) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

22 having been completed, we then investigated the epoxidation of 22. This was initially accomplished with *m*-CPBA. Treatment of 22 with *m*-CPBA in CH_2Cl_2 buffered by sodium bicarbonate gave the desired epoxy lactone 25 in 50% yield as a single diastereomer. Although this reaction did provide the desired product, the reaction was sluggish and could not be driven to completion. Furthermore, product decomposition was a significant problem and 50% was the highest yield obtained under these conditions when 25% of the starting lactone 22 was recovered. However, treatment with the more mild reagent dimethyldioxirane[25] gave 25 in 84% yield, again as a single diastereomer. Furthermore, this reaction was not complicated by decomposition of the product under the reaction conditions.

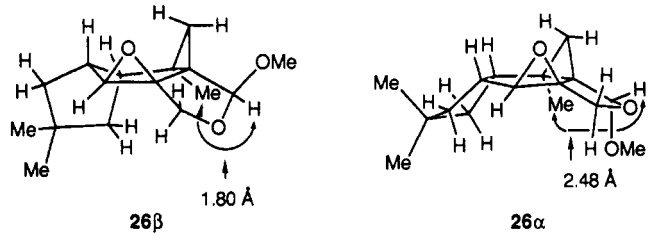
The reduction of 25 to velutinal (1a), the synthetic precursor to stearoylvelutinal (1b), was then investigated. Initial experiments involved treatment with DIBAL[31] or with Red-Al/ethanol.[36] Both reagents effected the desired reaction. However, reduction with DIBAL gave a yield of 1a superior to that obtained with Red-Al/ethanol. Therefore, we chose to concentrate on the DIBAL reduction for purposes of optimization. There are several side products formed in this reaction, some of which may be a result of overreduction of 1a. In fact, when 1 molar equiv of DIBAL was used, some starting lactone 25 was recovered, indicating the consumption of greater than 1 mol of DIBAL/mol of 25. Therefore, to maximize the yield of 1a produced in this reaction, a series of experiments were carried out using varying amounts of DIBAL, ranging from 1.0 to 1.5 molar equiv in increments of 0.1 molar equiv. We found that 1.3 molar equiv of DIBAL gave the optimal yield of 50% of 1a as a 5.5:1 mixture of β- and α-anomers. The 50% yield is somewhat misleading in that the ^{1}H NMR spectrum of the product mixture prior to purification indicated that the product is 75–80% pure 1a by integration. It was necessary to purify the synthetic velutinal for subsequent experiments, and the only means by which it could be purified is silica gel chromatography. Unfortunately, velutinal is known to decompose significantly on silica gel.[37] Therefore, the low isolated yield of velutinal obtained is probably due to product decomposition occurring during the purification process.



We were surprised to find that the synthetic velutinal (1a) existed as a 5.5:1 mixture of isomers at the anomeric center (as determined by ^{1}H NMR) because it has been reported that velutinal exists as only one isomer having the β-stereochemistry at the anomeric center.[38] Free velutinal was first prepared by basic ethanolysis of stearoylvleutinal (1b).[33] When we repeated this experiment on an authentic sample of natural 1b, the product we isolated was identical to the synthetic material obtained from the DIBAL reduction of lactone 25 in that it existed as a 5.5:1 mixture of isomers at the anomeric center as determined by ^{1}H NMR. In addition to the misrepresentation of 1a as a single diastereomer, the stereochemical assignment of this diastereomer was somewhat suspicious. In actuality, the stereochemical assignment of velutinal was made on the basis of NOESY NMR spectral data of the methyl acetal of velutinal (26) and not velutinal. The acetal, which was prepared by neutral methanolysis of 1b, was reported to exist as only one diastereomer having the β-stereochemistry at the anomeric center.[38] When we repeated this experiment, we obtained an inseparable 4:1 mixture of diastereomers isomeric at the anomeric center (eq 5).



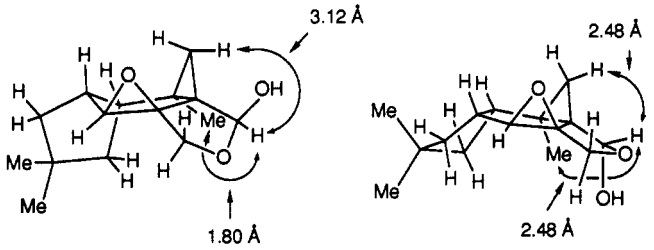
The stereochemical assignment of acetal 26 was made on the basis of an observed NOE enhancement between the acetal proton and adjacent methyl group in structure 26β. The two structures 26β and 26α shown below are minimized structures obtained using an MM2 molecular mechanics program.[39] It is important to note that the calculated interatomic distances between the acetal proton and the methyl group for the β- and α-isomers of 26 are 1.80 and 2.48 Å, respectively. Both of these interatomic distances are well within the 3-Å limit for detection of NOE enhancements in small molecules.[40] Therefore, the stereochemical assignment of 26 was made on the basis of an NOE enhancement that could be observed in either α- or β-isomer. Also noteworthy is that the calculated energy difference between 26α and 26β is 0.85 kcal/mol favoring 26β. This energy difference corresponds to a 4.2:1 equilibrium ratio at room temperature, which is in excellent agreement with the 4:1 ratio observed experimentally.



We sought to unambiguously determine the stereochemistry of both the major and minor isomers of 1a. Toward this end, the 2D NOESY NMR spectrum of the synthetic 1a was obtained.[14] The observed NOE en-

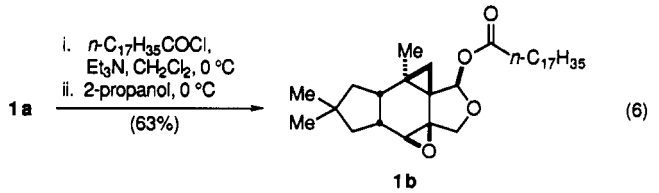
(36) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526.
(37) Sterner, O.; Bergman, R.; Kihlberg, J.; Oluwadiya, J.; Wickberg, B.; Vidari, G.; De Bernardi, M.; De Marchi, F.; Fronza, G.; Vita-Finzi, P. *J. Org. Chem.* **1985**, *50*, 950.
(38) Favre-Bonvin, J.; Gluchoff-Faisson, K.; Bernillon, J. *Tetrahedron Lett.* **1982**, *23*, 1907.
(39) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637. For a discussion of the MMX-enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Advances in Molecular Modeling*; JAI Press: Vol. 2, in press.
(40) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: New York, 1987; p 183.

hancement between the hemiacetal proton and the adjacent methyl group in the major isomer (1aβ) does not allow for the unambiguous stereochemical assignment of either isomer. However, in the minor isomer (1aα) an NOE enhancement between the hemiacetal proton and the exo proton on the cyclopropane ring is observed in addition to the NOE enhancement observed between the hemiacetal proton and the adjacent methyl group (see structures 1aβ and 1aα, minimized using an MM2 molecular mechanics program, below). This NOE enhancement would be virtually impossible to observe for the β-isomer because the calculated interatomic distance between the hemiacetal proton and the exo proton on the cyclopropane ring in this isomer is beyond the 3-Å limit[40] at 3.12 Å. The results of this NOESY NMR experiment are very hard evidence that the major isomer of velutinal is of the β-stereochemistry at the anomeric center (1aβ) and the minor isomer is of the α-stereochemistry (1aα). Also, it is noteworthy that the calculated energy difference between the two velutinal isomers is 1.00 kcal/mol favoring 1aβ. This energy difference corresponds to a 5.4:1 equilibrium ratio of 1aβ:1aα at room temperature, which is in excellent agreement with the experimentally observed ratio of approximately 5.5:1.



1aβ (major) 1aα (minor)

The fact that 1a exists as a mixture of stereoisomers at the anomeric center presents an interesting problem if we wish to synthesize stearoylvelutinal (1b) by acylation of 1a. Since it is known that 1b exists as only one isomer,[41] a selective acylation of one isomer of velutinal or a more rapid acylation of one isomer with concomitant equilibration of the two isomers would be necessary for a stereoselective synthesis of 1b. Our experimental results indicate that the latter is the case at least for the acylation of 1a with stearoyl chloride under basic conditions. Treatment of 1a with 2 molar equiv of stearoyl chloride and triethylamine followed by treatment with 2-propanol after all of the velutinal mixture had been consumed provided (±)-1b as a single diastereomer in 63% yield (eq 6). The purpose of the addition of 2-propanol after all



(6)

of the velutinal mixture had been consumed was to consume the excess stearoyl chloride that is necessary the drive the reaction with 1a to completion. The synthetic (±)-stearoylvelutinal (1b) was identical by 500-MHz ^{1}H NMR spectrometry to a sample of natural (+)-stearoylvelutinal provided by Professor B. Wickberg.[21]

The 63% yield obtained in this reaction is slightly misleading in that it might lead one to believe that the other diastereomer of stearoylvelutinal is contained within the remaining 37% of the mass balance. This, however, is not the case. In actuality, the transformation proceeds with quantitative conversion of 1a to 1b. But, in order to achieve this, it is necessary to use a 2-fold excess of stearoyl chloride. The remainder of the stearoyl chloride is converted upon addition to 2-propanol to isopropyl stearate, which cannot be separated from 1b by means other than silica gel chromatography. Unfortunately, 1b, like 1a, decomposes on silica gel.[36] In fact, the ^{1}H NMR spectrum of the product mixture prior to purification shows the presence of only 1b as a single diastereomer which has been assigned the β-stereochemistry (vide infra), and isopropyl stearate. Hence, it is apparent that 1aβ undergoes acylation by stearoyl chloride much more rapidly than does 1aα and that the equilibrium between 1aα and 1aβ is rapid because the entire acylation process is complete in less than 5 min at 0 °C. Furthermore, the comparatively low yield (63%) of 1b obtained in this reaction can be attributed to product decomposition during the purification process.

The relative stereochemistry of the ester moiety in 1b has been assigned as β. However, this assignment was based on an analogy to the methyl acetal of velutinal (26β). In an effort to obtain some stereochemical information on 1b, the 2D NOESY NMR spectrum was obtained.[14] Because a sample of the α-isomer is not available, an analysis similar to that used in the stereochemical assignment of the two velutinal isomers, 1aα and 1aβ, cannot be used for the stereochemical assignment of 1b. However, it is noteworthy that the NOESY spectrum of 1b closely resembles the NOESY spectrum of 1aβ in that an NOE enhancement is observed between the acetal proton and the adjacent methyl group and not between the acetal proton and the exo proton on the cyclopropane ring. Although this evidence is not conclusive, it is strongly suggestive of the β-stereochemical assignment of the ester moiety in 1b.

This highly stereoselective synthesis of (±)-stearoylvelutinal (1b) requires 16 steps from commercially available 3-methyl-2-butenal and proceeds in 4% overall yield. The comparatively low overall yield, however, is largely due to product decomposition during the purification process in the final two steps. Finally, an important feature of this synthesis, like the synthesis of (±)-isovelleral (2), is that it does not require the use of any protecting groups.

Protic Acid-Catalyzed Rearrangements of the Velutinal Skeleton. The transformation of velutinal (1a) into isovelleral (2) is believed to be the key transformation in the chemical defense system of fungi of the genera *Lactarius* and *Russula*.[3,42] It has been proposed that this transformation is enzymatic[3,42,43] although the exact mechanism is not known. The silica gel induced degradation of 1a and its derivatives 1b, 1c, and 26 in methanol has been investigated.[37,44] A plethora of products was isolated from these degradations, although isovelleral (2) was not seen.

In an effort to chemically induce the conversion of 1a into 2, a system that should more closely mimic the conditions existing within the fungus was chosen. An aqueous system was used with methanol as a cosolvent to facilitate the solubility of 1a. The reactions were conducted at a range of pH levels, varying from 1 to 6 in increments of 1 pH unit. At the higher pH levels (pH 5 and 6), there was essentially no difference in the product distribution

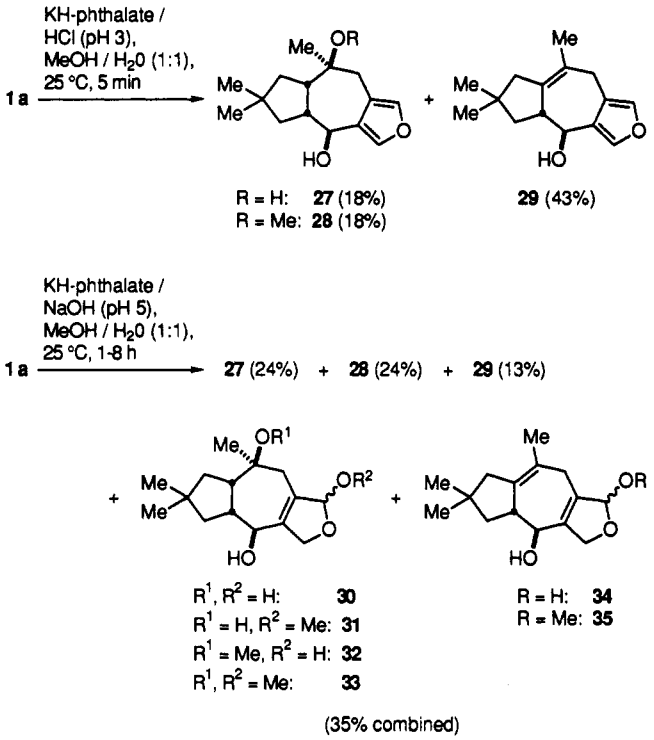
(41) The 500-MHz ^{1}H NMR spectrum of natural stearoylvelutinal (1b) shows only one compound is present.

(42) Sterner, O.; Bergman, R.; Franzen, C.; Wickberg, B. *Tetrahedron Lett.* **1985**, *26*, 3163.

(43) De Bernardi, M.; Fronza, G.; Scilingo, A.; Vidari, G.; Vita-Finzi, P. *Tetrahedron* **1986**, *42*, 4277.

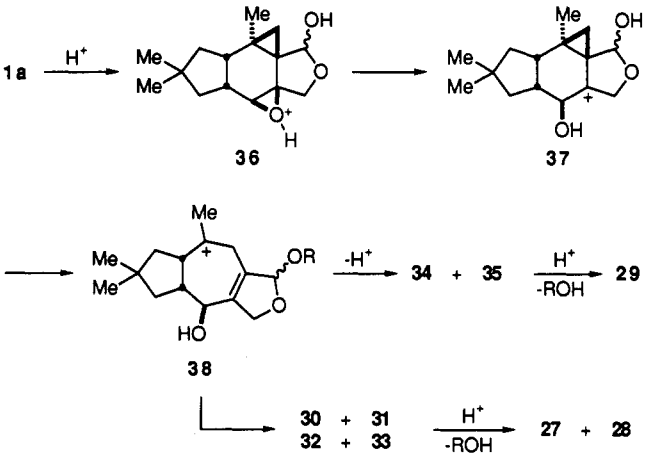
(44) Kihlberg, J.; Bergman, R.; Nilsson, L.; Sterner, O.; Wickberg, B. *Tetrahedron Lett.* **1983**, *24*, 4631.

between the two runs, but the decomposition of **1a** was more rapid at pH 5. At the lower pH levels (pH 1–3), the product distribution was essentially the same among the three runs, and the rate of decomposition of **1a** again increased with increasing acidity. There was, however, a disparity between the product distribution obtained at high pH and that obtained at low pH. For the purpose of comparison of product distributions at high and low pH, the reactions were run on a scale sufficient for the isolation and characterization of the products at pH 5 (potassium hydrogen phthalate/NaOH buffer) and pH 3 (potassium hydrogen phthalate/HCl buffer). At pH 3, furans **27**, **28**, and **29** were isolated in 18%, 18%, and 43% yields, respectively. At pH 5, the same three furans, **27**, **28**, and **29**, were isolated in 24%, 24%, and 13% yields, respectively. However, also isolated at pH 5 was a mixture of hydroxy- and methoxydihydrofurans **30**–**35** in 35% combined yield. The formation of isovelleral (**2**) was not observed under either sets of conditions.[45]



The hydroxy- and methoxydihydrofurans are obvious precursors to the furans **27**, **28**, and **29** via elimination of water or methanol. Interestingly, the elimination to the furans is never complete at pH 5 regardless of the reaction time. An equilibrium between the hydroxy- and methoxydihydrofurans and the furans does not exist because the furans, when separately resubmitted to the reaction conditions, do not interconvert or revert to the hydroxy- and methoxydihydrofurans. A reasonable explanation for this result is not available, although it is possible that formation of a dimeric complex between hydroxy- and methoxydihydrofurans or the formation of a complex between the hydroxy- and methoxydihydrofurans and the furans or constituents of the buffer system render them unreactive toward acid-catalyzed elimination of water or methanol. Also noteworthy is that only three furans are formed in these reactions, in sharp contrast to the nine furans formed in the silica gel induced degradation of velutinal.[37,44] Presumably, the acidic template provided by the silica gel surface or cavities is necessary for the formation of these other furans.

The proposed mechanism[3,37,46] for the conversion of **1a** to the observed furans and hydroxy- and methoxydihydrofurans involves protonation of **1a** to provide **36** which would give cyclopropylcarbinyl system **37** upon opening of the epoxide. Ring expansion from **37** would furnish tertiary carbocation **38**. An elimination of a proton from **38** would provide the hydroxy- and methoxydihydrofurans **34** and **35**, which can undergo a protonation and elimination of water or methanol to give furan **29**. Alternatively, trapping of **38** by water or methanol would provide hydroxy- and methoxydihydrofurans **30**–**33**, which can undergo protonation and elimintion of water or methanol to give furans **27** and **28**.



Protic Acid-Catalyzed Rearrangement of Lactone 25. Synthesis of (±)-Deconjugated Anhydrolactarorufin A (5) and (±)-Lactarorufin A (6). Lactone **25** was found to undergo a ring-expansion reaction similar to that observed for velutinal (**1a**) when treated with protic acids, although much more harsh conditions were required. Treatment of **25** with the pH 3 and pH 5 buffered aqueous methanol solutions resulted in essentially no reaction within the reaction times used in the decomposition of **1a** under these conditions. It is possible that this difference in reactivity between **25** and **1a** is due to a decreased basicity of the lone pairs on the epoxide, and a corresponding decrease in the rate of their protonation as compared to those on the epoxide of **1a**, because of the inductive effect of the lactone carbonyl. However, subjection of **25** to more acidic conditions (catalytic sulfuric acid in THF) provided (±)-deconjugated anhydrolactarorufin A (**5**)[47,48] in 82% yield. Within 3 days on standing, **5** was converted into the conjugated isomer **39**. For the purpose of characterization, **5** was converted to acetate ester **40** (acetic anhydride, pyridine, and catalytic 4-(dimethylamino)pyridine; 98% yield), which was not prone to isomerization. Acetate **40** was identical by 500-MHz ^{1}H NMR spectrometry to a sample of deconjugated anhydrolactarorufin A acetate derived from natural

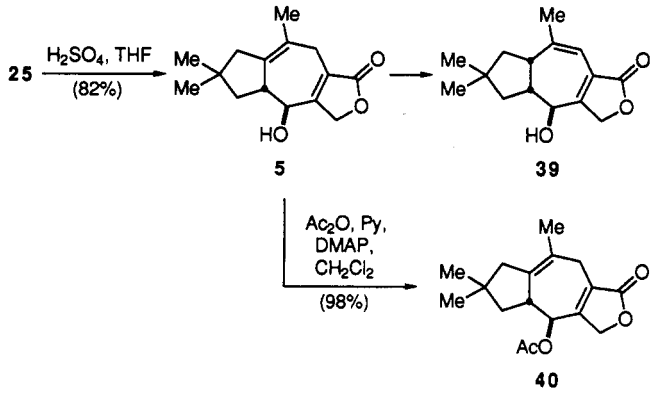
(45) The conversion of **1a** into **2** was observed only upon treatment of **1a** with less than 1 molar equivalent of DIBAL or treatment of **25** with greater than 1.3 molar equiv of DIBAL. The formation of trace amounts of **2** was observed under these conditions, although these reactions proceeded with only limited reproducibility. The mechanism of this transformation may be similar to the base-catalyzed mechanism proposed by Hansson and Sterner for the transformation of **26** into **2**: Hansson, T.; Sterner, O. *Tetrahedron Lett.* **1991**, 2541.

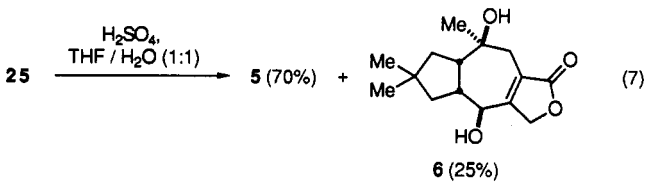
(46) De Bernardi, M.; Vidari, G.; Vita-Finzi, P.; Gluchoff-Fiasson, K. *Tetrahedron Lett.* **1982**, *23*, 4623.

(47) (a) Widen, K.; Seppa, E. *Phytochemistry* **1979**, *18*, 1226. (b) Pyysalo, H.; Seppa, E.; Widen, K. *J. Chromatogr.* **1980**, *190*, 466. (c) Seppa, E.; Widen, K. *Ann. Bot. Fennici* **1980**, *17*, 56.

(48) (a) Daniewski, W. M.; Kocor, M.; Krol, J. *Roczniki Chem.* **1976**, *50*, 2095. (b) Daniewski, W. M.; Kocor, M.; Krol, J. *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* **1975**, *23*, 637.

sources.[49] Degradation of **25** with a catalytic amount of sulfuric acid in a 1:1 mixture of THF and water gave **5** as the major product in 70% yield, but (±)-lactarorufin A (**6**)[47] could be isolated in up to 25% yield (eq 7). The synthetic (±)-lactarorufin A was identical by 500-MHz ^{1}H NMR spectrometry to a sample of natural (+)-lactarorufin A provided by Professor W. M. Daniewski.[49]





Conclusion. A general and efficient synthetic route to the marasmane sesquiterpenes (±)-isovelleral (**2**) and (±)-stearoylvelutinal (**1b**) has been developed. Total syntheses of two other naturally occurring sesquiterpenes, deconjugated anhydrolactarorufin A (**5**) and lactarorufin A (**6**), were achieved using an acid-catalyzed ring expansion of lactone **25**. All four syntheses are highly stereoselective and do not require the use of any protecting groups. Finally, we have determined on the basis of our experimental results that an enzymatic mechanism for the key transformation of velutinal (**1a**) into isovelleral (**2**) is more plausible than one that is acid-catalyzed.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Benzene, toluene, methylene chloride, triethylamine, and diisopropylamine were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from barium oxide and stored over 3-Å molecular sieves. Methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide, respectively, immediately prior to use. The concentration of commercially available solutions of *n*-butyllithium in hexanes was periodically checked by titration using the procedure of Gilman.[50] Ozone was generated using a Welsbach ozone generator. All reactions involving organometallic reagents or strong bases (e.g. LDA) were conducted under an atmosphere of dry nitrogen or dry argon in oven-dried glassware. Boiling points and melting points (Pyrex capillary) are uncorrected. IR spectra were measured as films unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were obtained at 500 and 125 MHz, respectively. When NMR spectra were obtained on mixtures of stereoisomers, some of the resonances overlap. Therefore, the correct number of resonances may not be listed. All NMR spectra were obtained as solutions in $CDCl_3$. All extracts were dried over anhydrous magnesium sulfate, and solvents were removed with a Buchi rotary evaporator at aspirator pressure. Flash chromatography using Kieselgel 60 silica gel refers to the method of Still, Kahn, and Mitra.[51]

***cis*- and *trans*-(±)-Methyl 4,4-Dimethyl-2-(1-methylethenyl)cyclopentaneacetate (8).** A sample of a 20:1 cis:trans mixture of **7** (18.27 g, 86.9 mmol) was degassed (3 freeze–pump–thaw cycles) in a Pyrex bomb and heated at 235 °C under an atmosphere of argon for 24 h. Distillation (57–59 °C, 0.005 mmHg) gave 16.95 g (93%) of **8** as a colorless liquid which consisted of a 70:30 mixture of cis and trans isomers: IR 1740 cm^{-1}; ^{1}H NMR δ 1.01 (s, 3), 1.04 (s, 3), 1.05 (s, 3), 1.11 (s, 3), 1.16 (dd, 1, *J* = 9.9, 12.7), 1.33 (dd, 1, *J* = 4.2, 13.5), 1.39–1.44 (m, 1), 1.47 (dd, 1, *J* = 6.4, 12.6), 1.56–1.62 (m, 2), 1.68 (s, 3), 1.72 (s, 3), 1.73 (t, 1, *J* = 10.5), 1.80 (dd, 1, *J* = 7.1, 12.7), 2.03 (dd, 1, *J* = 10.9, 15.4), 2.07–2.09 (m, 1), 2.20 (dd, 1, *J* = 4.5, 15.4), 2.25–2.28 (m, 2), 2.45 (dd, 1, *J* = 4.1, 15.0), 2.62–2.68 (m, 1), 2.71–2.76 (m, 1), 3.63 (s, 3), 3.65 (s, 3), 4.66 (s, 1), 4.73 (s, 2), 4.81 (s, 1); ^{13}C NMR δ 18.88, 23.12, 30.85, 31.17, 31.32, 31.60, 35.80, 36.67, 36.79, 37.56, 38.75, 39.16, 43.15, 46.47, 46.54, 47.59, 48.44, 51.24, 51.32, 53.80, 110.89, 111.02, 145.39, 145.96, 173.78, 174.25. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.43; H, 10.57.

***cis*- and *trans*-(±)-4,4-Dimethyl-2-(1-methylethenyl)-cyclopentaneacetic Acid (9).** To a stirring solution of 7.25 g (34.5 mmol) of **8** in 35 mL of methanol was added 35 mL of 3 M aqueous KOH. After being stirred at room temperature for 22 h, the mixture was extracted with 70 mL of ether and the organic layer was extracted with 35 mL of 3 M aqueous KOH. The combined aqueous layers were acidified to pH 2 with concentrated HCl then extracted with two 100-mL portions of CH_2Cl_2. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to give 6.77 g (100%) of **9** as a colorless oil which consisted of a 70:30 mixture of cis and trans isomers: IR 3500–2300, 1710 cm^{-1}; ^{1}H NMR δ 1.02 (s, 3), 1.04 (s, 3), 1.05 (s, 3), 1.12 (s, 3), 1.18 (dd, 1, *J* = 9.8, 12.5), 1.38 (dd, 1, *J* = 4.1, 13.5), 1.42–1.44 (m, 1), 1.48 (dd, 1, *J* = 6.4, 12.6), 1.56–1.63 (m, 2), 1.68 (s, 3), 1.73 (s, 3), 1.76 (dd, 1, *J* = 7.5, 13.5), 1.85 (dd, 1, *J* = 7.0, 12.8), 2.03–2.09 (m, 2), 2.22–2.30 (m, 3), 2.52 (dd, 1, *J* = 3.5, 15.5), 2.60–2.67 (m, 1), 2.72–2.77 (m, 1), 4.68 (s, 1), 4.74 (s, 2), 4.83 (s, 1), 11.76 (bs, 2); ^{13}C NMR δ 18.92, 23.13, 30.90, 31.22, 31.37, 31.64, 35.90, 36.74, 36.85, 37.41, 38.72, 38.91, 43.18, 46.40, 46.53, 47.50, 48.46, 53.75, 111.17, 111.27, 145.20, 145.81, 180.21, 180.61. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.71; H, 10.23.

***cis*- and *trans*-(±)-2-Acetyl-4,4-dimethylcyclopentaneacetic Acid (10).** A solution of 8.47 g (43.2 mmol) of **9** in 430 mL of 1:1 methanol/CH_2Cl_2 was cooled to −78 °C and ozone was bubbled through the solution until the solution turned faintly blue. Dry nitrogen was then bubbled through the solution until the blue color disappeared (about 5 min). Methyl sulfide (85 mL) was added, and the solution was allowed to stir at −78 °C for 5 min and then warmed to room temperature. The solution was concentrated, and the residue was dissolved in 430 mL of ether. The solution was washed with 430 mL of 0.1 M aqueous HCl, and the aqueous layer was extracted with 430 mL of ether. The combined organic layers were washed with saturated brine, dried, filtered, and concentrated to give 8.56 g (100%) of **10** as a colorless oil which consisted of a 70:30 mixture of cis and trans isomers: IR 3630–2750, 1705 cm^{-1}; ^{1}H NMR δ 1.00 (s, 3), 1.03 (s, 3), 1.06 (s, 3), 1.09 (s, 3), 1.24 (dd, 1, *J* = 9.6, 12.8), 1.43 (dd, 1, *J* = 9.6, 12.7), 1.52 (dd, 1, *J* = 8.8, 12.7), 1.65–1.69 (m, 4), 1.84–1.89 (m, 1), 2.15 (s, 6), 2.31 (dd, 1, *J* = 7.6, 15.2), 2.36 (dd, 1, *J* = 7.5, 16.5), 2.47 (dd, 1, *J* = 5.8, 15.2), 2.59 (dd, 1, *J* = 8.0, 16.5), 2.69–2.80 (m, 3), 3.31 (q, 1, *J* = 8.4); ^{13}C NMR δ 29.14, 29.27, 29.69, 29.92, 30.28, 31.56, 35.57, 37.02, 37.38, 38.07, 38.36, 39.26, 43.84, 44.79, 47.16, 47.25, 52.52, 57.79, 178.39, 179.01, 210.32, 211.94. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.78; H, 9.25.

(±)-4a,5,6,7-Tetrahydro-1,6,6-trimethylcyclopenta[*c*]-pyran-3(4*H*)-one (11). To a stirring solution of 8.56 g (43.2 mmol) of **10** in 120 mL of dry benzene was added 7.3 g (57.7 mmol) of oxalyl chloride. The solution was slowly heated to reflux. After

(49) We are grateful to Professor W. M. Daniewski (Polish Academy of Sciences) for providing us with samples of natural deconjugated anhydrolactarorufin A acetate (**40**) and lactarorufin A (**6**).

(50) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.

(51) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

22 h at reflux, the mixture was concentrated to give a brown oil. The crude product was Kugelrohr distilled (57 °C, 0.02 mmHg) to give 7.78 g (94%) of 11 as a colorless oil: IR 1760, 1725 cm^{-1}; ^1H NMR δ 1.02 (s, 3), 1.13 (s, 3), 1.17 (t, 1, J = 10.9), 1.80–1.84 (m, 4), 2.11–2.17 (m, 3), 2.79 (dd, 1, J = 5.4, 15.4), 2.88–2.96 (m, 1); ^{13}C NMR δ 16.01, 28.27, 29.20, 35.26, 35.98, 39.42, 41.41, 47.52, 119.96, 141.39, 170.11. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.31; H, 8.84.

***cis*-(±)-Methyl 2,3,3a,6,7,7a-Hexahydro-2,2,4-trimethyl-6-oxo-1*H*-indene-5-carboxylate (14).** To a stirring solution of 3.33 g (32.9 mmol, 4.61 mL) of diisopropylamine in 50 mL of dry THF, cooled to 0 °C, was added 15.94 mL (32.9 mmol) of a 2.06 M solution of *n*-butyllithium in hexanes. After 10 min, the solution was cooled to −78 °C, and 2.44 g (32.9 mmol, 2.62 mL) of methyl acetate was added dropwise over 7 min. After an additional 30 min, a solution of 5.93 g (32.9 mmol) of 11 in 5 mL of THF was added all at once. The solution was allowed to stir at −78 °C for 1 h and then warmed to room temperature, and 70 mL of saturated aqueous NH_4Cl was added. The organic layer was washed with saturated brine, dried, filtered, and concentrated to give 7.78 g of a slightly yellow oil. The oil was dissolved in 600 mL of dry benzene, and 12.25 g (8.25 mL) of methanesulfonic acid was added all at once. After the mixture was stirred vigorously for 5 min, 600 mL of saturated aqueous $NaHCO_3$ was added. The organic layer was washed with saturated brine, dried, filtered, and concentrated to give a slightly yellow oil. The crude product was purified by flash chromatography on 300 g of 230–400-mesh silica gel, eluting with 20% ethyl acetate in hexanes, to give 3.89 g (50%) of 14 as a slightly yellow oil: IR 1740, 1675, 1630 cm^{-1}; ^1H NMR δ 1.07 (s, 3), 1.12 (s, 3), 1.32 (dd, 1, J = 6.4, 13.3), 1.61 (dd, 1, J = 10.3, 12.7), 1.75 (dd, 1, J = 7.6, 13.3), 1.93 (dd, 1, J = 7.6, 12.7), 1.96 (s, 3), 2.39 (dd, 1, J = 9.3, 16.1), 2.50 (dd, 1, J = 6.5, 16.1), 2.56–2.73 (m, 1), 2.79–2.84 (m, 1), 3.82 (s, 3); ^{13}C NMR δ 21.03, 30.31, 30.79, 36.51, 38.45, 40.34, 44.44, 45.48, 46.51, 52.12, 131.52, 161.26, 167.41, 195.17. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.86; H, 8.72.

(1a*α*,3a*β*,6a*β*,6b*α*)-(±)-Methyl Octahydro-5,5,6b-trimethyl-2-oxocycloprop[*e*]indene-1a(1*H*)-carboxylate (15). To 3.29 g (13.9 mmol) of 14 was added 27.5 mL (14.9 mmol) of a 0.54 M solution of dimethylsulfoxonium methylide in THF.[52] The resulting solution was allowed to stir at room temperature for 30 min. Water (25 mL) was added, and the mixture was extracted with two 30-mL portions of ether. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to give a pale yellow oil. The oil was purified by flash chromatography on 400 g of 230–400-mesh silica gel, eluting with 12% ethyl acetate in hexanes, to give 2.26 g (65%) of 15 as a white solid: mp 56–57 °C; IR ($CHCl_3$) 1735, 1690 cm^{-1}; ^1H NMR δ 1.05 (s, 3), 1.13 (s, 3), 1.16 (s, 3), 1.27 (dd, 1, J = 2.1, 13.6), 1.46 (t, 1, J = 12.8), 1.47 (d, 1, J = 5.5), 1.60 (d, 1, J = 5.5), 1.72 (dd, 1, J = 7.2, 13.6), 1.75 (dd, 1, J = 6.4, 12.8), 2.09 (dd, 1, J = 9.8, 17.6), 2.23–2.28 (m, 1), 2.36 (dd, 1, J = 7.3, 17.6), 2.50 (dt, 1, J = 6.4, 12.8), 3.75 (s, 3); ^{13}C NMR δ 19.78, 24.18, 31.85, 32.09, 32.96, 34.87, 37.22, 40.04, 42.16, 44.03, 44.11, 47.87, 52.42, 169.38, 204.77. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.83; H, 8.94.

(1a*α*,3a*β*,6a*β*,6b*α*)-(±)-Methyl 3a,4,5,6,6a,6b-Hexahydro-5,5,6b-trimethyl-2-[[(trifluoromethyl)sulfonyl]oxy]cycloprop[*e*]indene-1a(1*H*)-carboxylate (17). To a stirring solution of 468.5 mg (4.63 mmol, 0.65 mL) of diisopropylamine in 4.2 mL of THF, cooled to 0 °C, was added dropwise 1.70 mL (4.21 mmol) of a 2.48 M solution of *n*-butyllithium in hexanes. After 10 min, the solution was cooled to −78 °C and a solution of 957.8 mg (3.83 mmol) of 15 in 2.1 mL of THF was added slowly over 5 min. After 40 min, a solution of 1.476 g (4.13 mmol) of *N*-phenyltrifluoromethanesulfonimide in 4.5 mL of THF was added slowly over 2 min. The solution was allowed to warm to room temperature and stir for 1 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with 10 mL of ether. The organic layer was washed with two 10-mL portions of water and then with 10 mL of saturated brine, dried, filtered, and concentrated to give a yellow-orange oil. The crude product was purified by flash chromatography on 45 g of 230–400-mesh silica gel, eluting with 3% ethyl acetate in hexanes, to give 1.43 g (98%) of 17 as a slightly yellow oil: IR 1745, 1680 cm^{-1}; ^1H NMR δ 1.04 (s, 3), 1.06 (s, 3), 1.19 (s, 3), 1.27 (d, 1, J = 5.1), 1.40–1.46 (m, 2), 1.69 (d, 1, J = 5.1), 1.68–1.72 (m, 1), 1.86 (dd, 1, J = 8.2, 13.4), 2.53 (dt, 1, J = 7.5, 12.5), 2.58–2.62 (m, 1), 3.76 (s, 3), 5.28 (d, 1, J = 2.3); ^{13}C NMR δ 19.70, 27.95, 31.36, 31.48, 32.77, 37.34, 37.67, 40.61, 44.72, 47.39, 52.38, 118.40, 118.42 (q, J_{C-F} = 320), 145.17, 168.77. Anal. Calcd for $C_{15}H_{21}F_3SO_5$: C, 50.26; H, 5.54. Found: C, 50.05; H, 5.52.

(1a*α*,3a*β*,6a*β*,6b*α*)-(±)-Dimethyl 3a,4,5,6,6a,6b-Hexahydro-5,5,6b-trimethylcycloprop[*e*]indene-1a,2(1*H*)-dicarboxylate (18). A solution of 286.3 mg (0.75 mmol) of 17, 151.5 mg (1.5 mmol, 0.21 mL) of triethylamine, 960 mg (30 mmol, 1.21 mL) of methanol, 5.0 mg (22.5 μmol) of palladium(II) acetate, and 11.8 mg (45 μmol) of triphenylphosphine in 3 mL of DMF was purged with carbon monoxide for 5 min, and then allowed to stir at room temperature under a balloon of carbon monoxide for 2 h. The mixture was poured into 30 mL of ether and washed with two 30-mL portions of water, 30 mL of saturated brine, dried, filtered, and concentrated to give a brown oil. The crude product was purified by flash chromatography on 44 g of 230–400-mesh silica gel, eluting with 12% ethyl acetate in hexanes, to give 210.7 mg (93%) of 18 as a white solid: mp 88.5–89.5 °C; IR ($CHCl_3$) 1735, 1650 cm^{-1}; ^1H NMR δ 0.98 (d, 1, J = 4.7), 1.03 (s, 3), 1.04 (s, 3), 1.15 (s, 3), 1.30 (t, 1, J = 12.0), 1.50 (dd, 1, J = 2.3, 13.3), 1.60 (d, 1, J = 4.7), 1.63–1.68 (m, 1), 1.88 (dd, 1, J = 8.5, 13.3), 2.51–2.57 (m, 2), 3.67 (s, 3), 3.74 (s, 3), 6.39 (d, 1, J = 2.0); ^{13}C NMR δ 19.79, 26.90, 28.60, 29.74, 31.09, 31.44, 37.42, 38.57, 40.49, 44.92, 46.99, 51.82, 51.85, 130.38, 139.37, 167.10, 173.32. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.22; H, 8.43.

(1a*α*,3a*β*,6a*β*,6b*α*)-(±)-3a,4,5,6,6a,6b-Hexahydro-5,5,6b-trimethylcycloprop[*e*]indene-1a,2(1*H*)-dimethanol (19). To a stirring solution of 123 mg (0.42 mmol) of 18 in 1.1 mL of THF, cooled to −78 °C, was added dropwise 2.24 mL (3.37 mmol) of a 1.5 M solution of diisobutylaluminum hydride in toluene. The solution was allowed to warm to room temperature and stir for 30 min. The solution was cooled to 0 °C, and 564.3 mg (13.44 mmol) of NaF was added, followed by dropwise addition of 3 mL of water. The mixture was allowed to warm to room temperature. The mixture was diluted with 30 mL of water and extracted with two 35-mL portions of ethyl acetate. The combined extracts were dried, filtered, and concentrated to give 100.7 mg (100%) of 19 as a white solid: mp 134–135 °C; IR ($CHCl_3$) 3560–3300 cm^{-1}; ^1H NMR δ 0.61 (d, 1, J = 4.1), 0.87 (d, 1, J = 4.1), 1.01 (s, 6), 1.28 (s, 3), 1.30–1.35 (m, 1), 1.61–1.65 (m, 1), 1.76 (dd, 1, J = 7.8, 13.2), 2.43–2.47 (m, 2), 2.79 (bs, 1), 3.07 (bs, 1), 3.50 (d, 1, J = 12.4), 4.15–4.21 (m, 2), 4.34 (d, 1, J = 11.1), 5.22 (s, 1); ^{13}C NMR δ 20.63, 26.46, 27.00, 27.97, 31.76, 31.96, 37.55, 38.41, 42.31, 44.96, 47.97, 64.12, 66.84, 130.15, 138.77. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.15; H, 10.63.

(±)-Isovelleral (2). To a stirring solution of 65.3 mg (0.51 mmol, 45 μL) of oxalyl chloride in 1.2 mL of CH_2Cl_2, cooled to −78 °C, was added dropwise 80.4 mg (1.03 mmol, 73 μL) of DMSO. After 2 min, a solution of 30.4 mg (0.13 mmol) of 19 in 0.4 mL of CH_2Cl_2/DMSO (3/1) was added dropwise over 5 min. After an additional 15 min, 236.6 mg (2.34 mmol, 0.33 mL) of triethylamine was added, and the mixture was allowed to stir at −78 °C for 5 min and then warm to room temperature. The mixture was passed through a plug of 230–400-mesh silica gel, eluting with 25% ethyl acetate in hexanes, and the eluent was concentrated to give a yellow oil. The oil was purified by flash chromatography on 2 g of 230–400-mesh silica gel, eluting with 15% ethyl acetate in hexanes, to give 24.7 mg (83%) of 2 as a white solid: mp 80–81 °C; IR ($CHCl_3$) 1715, 1690, 1640 cm^{-1}; ^1H NMR δ 0.95 (d, 1, J = 4.5), 1.06 (s, 3), 1.08 (s, 3), 1.13 (s, 3), 1.20 (t, 1, J = 12.3), 1.59 (dd, 1, J = 2.4, 13.5), 1.76 (dd, 1, J = 6.7, 12.3), 1.91 (d, 1, J = 4.5), 2.00 (dd, 1, J = 8.8, 13.5), 2.66–2.75 m, 2), 6.47 (d, 1, J = 2.2), 9.49 (s, 1), 9.75 (s, 1); ^{13}C NMR δ 18.66, 26.92, 31.12, 31.64, 34.18, 34.56, 37.51, 39.57, 41.78, 45.59, 46.92, 140.35, 153.57, 192.31, 197.86. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.56; H, 8.85.

(1a*α*,2a*β*,3*β*,3a*β*,6a*β*,6b*α*)-(±)-Octahydro-5,5,6b-trimethyl-5,6-epoxycycloprop[*e*]indene-1a,2(1*H*)-dimethanol (20). To

(52) The THF solution of dimethylsulfoxonium methylide was prepared by treatment of trimethylsulfoxonium chloride with KH in refluxing THF for 4 h. The white precipitate was removed by vacuum filtration. The concentration of the ylide in THF was determined by addition of an aliquot of the ylide solution to water and titration with a standard 0.1 N HCl solution to the phenolphthalein end point.

a stirring solution of 59 mg (0.25 mmol) of **19** in 2.5 mL of CH_2Cl_2, cooled to 0 °C, was added 33.6 mg (0.4 mmol) of solid $NaHCO_3$, followed by 56 mg (0.325 mmol) of *m*-chloroperoxybenzoic acid. After 1 h, 2.5 mL of saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with two 5-mL portions of CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated to give a colorless oil. The oil was purified by flash chromatography on 6 g of 230–400-mesh silica gel, eluting with 2:1 ethyl acetate/hexanes, to give 45.8 mg (73%) of **20** as a white solid: mp 95–96 °C; IR ($CHCl_3$) 3620–3100 cm^{-1}; ^1H NMR δ 0.50 (s, 1, J = 4.7), 0.75 (d, 1, J = 4.7), 0.99 (s, 3), 1.11 (s, 3), 1.14 (s, 3), 1.48–1.55 (m, 2), 1.60 (dd, 1, J = 3.9, 13.4), 1.81 (dd, 1, J = 9.5, 13.4), 2.22–2.27 (m, 1), 2.42 (dt, 1, J = 7.9, 12.1), 2.59 (bs, 1), 2.85 (bs, 1), 2.92 (d, 1, J = 2.1), 3.73–3.79 (m, 2), 3.94–4.00 (m, 2); ^{13}C NMR δ 21.36, 21.56, 25.21, 28.59, 30.17, 30.60, 35.19, 37.60, 42.74, 44.51, 46.84, 61.87, 62.73, 64.36, 65.58. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.70; H, 9.96.

(1aα,2aβ,3β,3aβ,6aβ,6bα)-(±)-5,6-Epoxy-2-(hydroxymethyl)octahydro-5,5,6b-trimethyl-1*H*-cycloprop[*e*]indene-1a-carbaldehyde (21). To a stirring solution of 12.3 mg (0.05 mmol) of **20** in 0.5 mL of CH_2Cl_2 was added 0.25 g of activated MnO_2 powder. After 19 h, the slurry was filtered through a bed of Celite, and the filter cake was washed thoroughly with ethyl acetate. The filtrate was concentrated to give a colorless oil. The crude product was purified by flash chromatography on 1 g of 230–400-mesh silica gel, eluting with 1:2 ethyl acetate/hexanes, to give 5.4 mg (44%) of **21** as a colorless oil: IR ($CHCl_3$) 3640–3100, 1705 cm^{-1}; ^1H NMR δ 1.01 (s, 3), 1.11 (d, 1, J = 4.7), 1.126 (s, 3), 1.133 (s, 3), 1.51 (dd, 1, J = 6.9, 11.7), 1.56–1.58 (m, 1), 1.60 (d, 1, J = 4.7), 1.69 (dd, 1, J = 3.9, 13.5), 1.83–1.88 (m, 2), 2.27–2.32 (m, 1), 2.46–2.51 (m, 1), 3.02 (d, 1, J = 2.3), 3.73 (dd, 1, J = 8.7, 12.3), 4.02 (dd, 1, J = 4.2, 12.3), 9.72 (s, 1); ^{13}C NMR δ 20.24, 24.38, 30.13, 30.66, 33.02, 34.83, 37.45, 38.74, 42.65, 44.37, 46.61, 58.43, 62.78, 63.17, 200.64; M_r calcd for $C_{15}H_{22}O_3$ 250.1570, found 250.1558.

(1aα,3aβ,6aβ,6bα)-(±)-Methyl 2-Formyl-3a,4,5,6,6a,6b-hexahydro-5,5,6b-trimethyl-1*H*-cycloprop[*e*]indene-1a-carboxylate (24). A solution of 680.9 mg (1.78 mmol) of **17**, 82.3 mg (71.2 μmol) of $Pd(PPh_3)_4$, and 226.4 mg (5.34 mmol) of LiCl in 11 mL of THF was pressurized to 3 atm with carbon monoxide, and then the pressure was released. The pressurize/depressurize sequence was repeated once more. The vessel was again pressurized to 3 atm and stirred for 3 min, and then the pressure was released. A solution of 570 mg (1.96 mmol, 0.53 mL) of tri-*n*-butyltin hydride in 4.5 mL of THF was taken up in a 5-mL gas-tight syringe, and the syringe was connected to the reaction vessel through a septum via a 25-guage needle. The syringe was placed in a syringe pump, and the reaction vessel was pressurized to 3 atm with carbon monoxide and heated to 50 °C in an oil bath. The tri-*n*-butyltin hydride solution was added at the rate of 1.6 mL/h. After addition was complete, stirring at 50 °C was continued for 22 h. The pressure was then released from the reaction vessel, the yellow solution was poured into 40 mL of ether, and the resulting solution was washed with three 15-mL portions of water and then with 15 mL of saturated brine. The organic layer was dried, filtered, and concentrated to give a yellow oil. The oil was dissolved in 55 mL of ether and stirred vigorously with 55 mL of 50% saturated aqueous KF for 15 min. The white precipitate was removed by filtration, and the organic layer was dried, filtered, and concentrated to give a brown oil. The crude product was purified by flash chromatography on 14 g of 230–400-mesh silica gel, eluting with 15% ethyl acetate in hexanes, to give 413 mg (88%) of **24** as a slightly yellow oil which crystallized upon standing: mp 50–52 °C; IR ($CHCl_3$) 1730, 1685 cm^{-1}; ^1H NMR δ 0.88 (d, 1, J = 4.9), 1.05 (s, 3), 1.06 (s, 3), 1.15 (s, 3), 1.30 (t, 1, J = 12.2), 1.55 (dd, 1, J = 2.5, 13.4), 1.57 (d, 1, J = 4.9), 1.69 (dd, 1, J = 6.9, 12.2), 1.96 (dd, 1, J = 8.8, 13.4), 2.60–2.67 (m, 2), 3.69 (s, 3), 6.29 (d, 1, J = 2.0), 9.39 (s, 1); ^{13}C NMR δ 19.46, 26.47, 27.73, 27.80, 30.98, 31.48, 37.49, 39.25, 41.09, 44.93, 46.90, 51.89, 140.87, 150.53, 171.86, 191.60; M_r calcd for $C_{16}H_{22}O_3$ 262.1570, found 262.1560.

(1α,7β,11β,12α)-(±)-3-Oxa-9,9,12-trimethyltetracyclo[10.1.0.0^{1,5}.0^{7,11}]tridec-5-en-2-one (22). To a stirring solution of 758.5 mg (2.89 mmol) of **24** and 1.185 g (3.18 mmol) of $CeCl_3 \cdot 7H_2O$ in 8 mL of absolute ethanol was added a solution of 120.3 mg (3.18 mmol) of sodium borohydride in 6 mL of absolute ethanol. After 15 min, 15 mL of saturated aqueous NH_4Cl and 3 mL of water were added. The mixture was extracted with four 30-mL portions of ether. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to give a yellow oil. The oil was dissolved in 30 mL of benzene, and 22 mg (0.116 mmol) of *p*-toluenesulfonic acid was added. The mixture was heated at 45 °C for 15 min, saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with 30 mL of ether. The combined organic layers were dried, filtered, and concentrated to give a yellow-orange oil. The crude product was purified by flash chromatography on 20 g of 230–400-mesh silica gel, eluting with 8% ethyl acetate in hexanes to give 626.9 mg (93%) of **22** as a colorless oil which crystallized upon standing: mp 33–34 °C; IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 0.98 (s, 3), 1.02 (s, 3), 1.17 (t, 1, J = 12.2), 1.40–1.42 (m, 2), 1.46 (s, 3), 1.55–1.59 (m, 2), 1.81 (dd, 1, J = 7.6, 13.3), 2.46–2.51 (m, 2), 4.86 (dt, 1, J = 2.2, 13.0), 4.91 (ddd, 1, J = 2.5, 3.9, 13.0), 4.99 (d, 1, J = 1.4); ^{13}C NMR δ 16.96, 27.59, 30.89, 31.94, 32.00, 33.13, 37.24, 38.60, 42.71, 43.80, 47.82, 69.16, 118.13, 133.46, 177.80. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.52; H, 8.54.

(1α,5aα,7aα,8β,12β,13aα)-(±)-3,6-Dioxa-10,10,13-trimethylpentacyclo[11.1.0.0^{1,5}.0^{5,7}.0^{8,12}]tetradecan-2-one (25). To a stirring solution of 575 mg (2.48 mmol) of **22** in 1 mL of acetone, cooled to 0 °C, was added 67.5 mL of a 0.04 M solution of dimethyldioxirane in acetone.[53] After 45 min, the solution was concentrated, and the residue was taken up in ether, dried, filtered, and concentrated to give a white solid. The solid was dissolved in ether, adsorbed to 3 g of 230–400-mesh silica gel, placed on top of a column of 20 g of 230–400-mesh silica gel, and eluted with 12% ethyl acetate in hexanes to give 514.4 mg (84%) of **25** as a white solid: mp 107–108 °C; IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR δ 1.03–1.04 (m, 1), 1.06 (s, 3), 1.08 (s, 3), 1.27 (d, 1, J = 4.8), 1.35 (d, 1, J = 4.8), 1.37 (s, 3), 1.66 (dd, 1, J = 1.1, 13.8), 1.76 (ddd, 1, J = 1.2, 6.4, 12.7), 1.84 (dd, 1, J = 8.1, 13.8), 1.97 (dt, 1, J = 1.3, 6.4), 2.36 (dt, 1, J = 6.4, 13.0), 2.86 (d, 1, J = 1.1), 4.42 (d, 1, J = 11.1), 4.63 (d, 1, J = 11.1); ^{13}C NMR δ 17.48, 24.44, 25.61, 31.71, 31.83, 32.81, 36.65, 38.44, 44.40, 45.90, 46.18, 56.69, 63.15, 69.07, 175.88. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H. 8.12. Found: C, 72.58; H, 8.24.

(±)-Velutinal (1a). To a stirring solution of 90.5 mg (0.36 mmol) of **25** in 1.8 mL of toluene, cooled to −78 °C, was added dropwise 0.38 mL (0.47 mmol) of a 1.26 M solution of diisobutylaluminum hydride in toluene over 6 min. After 3 h, 2 mL of a saturated aqueous potassium sodium tartrate was added, followed by 5 mL of water. The mixture was allowed to warm to room temperature and then extracted with two 25-mL portions of ethyl acetate. The combined extracts were dried, filtered, and concentrated to give a colorless oil. The crude product was purified by flash chromatography on 3.7 g of 230–400-mesh silica gel, eluting with 30% ethyl acetate in hexanes, to give 45.6 mg (50%) of **1a** as a colorless oil which consisted of an inseparable 5.5:1 mixture of β and α anomers: IR ($CHCl_3$) 3500–3100 cm^{-1}. **Compound 1aβ**: ^1H NMR δ 0.56 (d, 1, J = 5.2), 0.83 (d, 1, J = 5.2), 1.04 (s, 3), 1.05 (s, 3), 1.06–1.14 (m, 1), 1.16 (s, 3), 1.58 (dd, 1, J = 1.4, 13.7), 1.64 (ddd, 1, J = 1.1, 6.4, 12.7), 1.80 (dd, 1, J = 8.2, 13.7), 1.92 (dt, 1, J = 1.3, 6.5), 2.23 (dt, 1, J = 6.4, 13.0), 2.79 (d, 1, J = 0.8), 3.19 (d, 1, J = 6.8), 4.11 (d, 1, J = 10.3), 4.25 (d, 1, J = 10.3), 5.28 (d, 1, J = 6.8); ^{13}C NMR δ 17.40, 20.35, 23.85, 31.58, 31.73, 32.44, 36.79, 38.61, 43.36, 45.93, 46.48, 58.09, 66.12, 68.44, 99.49. **Compound 1aα**: Most of the ^1H NMR resonances belonging to **1aα** are obscured by the resonances belonging to **1aβ**. Therefore, it is impossible to accurately tabulate all of the ^1H NMR spectral data for **1aα**. The ^1H and ^{13}C NMR resonances belonging to **1aα** not obscured by resonances belonging to **1aβ** are tabulated: ^1H NMR δ 0.65 (d, 1, J = 4.7), 0.95 (d, 1, J = 4.7), 1.03 (s, 3), 1.06 (s, 3), 1.20 (s, 3), 2.74 (d, 1, J = 3.0), 2.85 (s, 1), 3.90 (d, 1, J = 10.5), 4.52 (d, 1, J = 10.5), 5.52 (d, 1, J = 3.0); ^{13}C NMR δ 20.35, 20.46, 22.68, 24.08, 31.26, 31.42, 36.72, 38.76, 43.79, 46.25, 46.63, 55.71, 67.57, 69.44, 102.44; M_r calcd for $C_{15}H_{22}O_3$ 250.1570, found 250.1558.

(±)-Stearoylvelutinal (1b). To a stirring solution of 24.2 mg (0.1 mmol) of **1a** in 0.5 mL of CH_2Cl_2, cooled to 0 °C, was added 19.6 mg (0.19 mmol, 27 μL) of triethylamine, followed by 55.6 mg

(53) The acetone solution of dimethyldioxirane was prepared according to the procedure of Adam: See ref 25c.

(0.18 mmol, 62 μL) of stearoyl chloride. After 5 min, 11 mg (0.18 mmol, 14 μL) of 2-propanol was added. After an additional 5 min, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with two 5-mL portions of ether. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to give an oily white solid. The crude product was purified by flash chromatography on 3 g of 230–400-mesh silica gel, eluting with 5% ethyl acetate in hexanes, to give 31.5 mg (63%) of **1b** as a colorless oil which crystallized upon standing: mp 38–39 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR δ 0.48 (d, 1, J = 5.4), 0.86 (d, 1, J = 5.4), 0.88 (t, 3, J = 6.8), 0.98–1.09 (m, 1), 1.04 (s, 3), 1.06 (s, 3), 1.22 (s, 3), 1.25–1.30 (bs, 28), 1.58–1.66 (m, 4), 1.80 (dd, 1, J = 8.2, 13.7), 1.90–1.92 (m, 1), 2.22 (dt, 1, J = 6.4, 13.0), 2.34 (t, 2, J = 7.5), 2.82 (s, 1), 4.16 (d, 1, J = 10.1), 4.26 (d, 1, J = 10.1), 6.24 (s, 1); ^{13}C NMR δ 14.11, 17.42, 20.37, 22.67, 24.80, 24.89, 29.08, 29.24, 29.34, 29.44, 29.57, 29.62, 29.64, 29.65, 29.68 (4 C), 31.18, 31.61, 31.81, 31.90, 34.51, 36.75, 38.56, 43.31, 45.77, 46.42, 58.39, 65.52, 69.82, 99.44, 173.50. Anal. Calcd for $C_{33}H_{56}O_4$: C, 76.70; H, 10.92. Found: C, 77.03; H, 11.11.

(4β,4aβ,7aβ,8β)-(±)-4,4a,5,6,7,7a,8,9-Octahydro-4,8-dihydroxy-6,6,8-trimethylazuleno[5,6-*c*]furan (27), (4β,4aβ,7aβ,8β)-(±)-4,4a,5,6,7,7a,8,9-Octahydro-4-hydroxy-8-methoxy-6,8,8-trimethylazuleno[5,6-*c*]furan (28), and (4β,4aβ)-(±)-4,4a,5,6,7,9-Hexahydro-4-hydroxy-6,6,8-trimethylazuleno[5,6-*c*]furan (29). A solution of 21.5 mg (0.086 mmol) of **1a** in 2.5 mL of a 1:1 mixture of methanol and pH 4.7 potassium hydrogen phthalate/NaOH buffer was allowed to stir at room temperature for 5 min. Saturated aqueous $NaHCO_3$ (2.5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined extracts were dried, filtered, and concentrated to give 20.2 mg of a colorless oil. The oil was purified by flash chromatography on 4.3 g of 230–400-mesh silica gel, eluting with a solvent gradient running from 13% ethyl acetate in hexanes up to 38% ethyl acetate in hexanes, to give 3.9 mg (18%) of **27** as a colorless oil, 4.1 mg (18%) of **28** as a white solid, and 8.6 mg (43%) of **29** as a colorless oil. **Compound 27**: IR ($CHCl_3$) 3580, 3520–3230 cm^{-1}; ^1H NMR δ 1.03 (s, 3), 1.04 (s, 3), 1.24–1.33 (m, 2), 1.28 (s, 3), 1.48 (ddd, 1, J = 1.4, 6.9, 12.6), 1.63 (ddd, 1, J = 1.3, 7.7, 12.6), 2.56–2.62 (m, 1), 2.68–2.73 (m, 1), 2.72 (d, 1, J = 16.5), 2.94 (dd, 1, J = 1.6, 16.5), 3.50 (bs, 1), 4.69 (d, 1, J = 5.8), 7.21 (s, 1), 7.37 (d, 1, J = 1.6); ^{13}C NMR δ 28.69, 30.40, 31.52, 33.05, 36.54, 44.73, 44.88, 46.30, 51.36, 67.46, 73.76, 118.60, 127.42, 141.28 (2 C); M_r Calcd for $C_{15}H_{23}O_3$ (MH^+) 251.1648, found 251.1641. **Compound 28**: mp 107–110 °C dec; IR ($CHCl_3$) 3520–3190 cm^{-1}; ^1H NMR δ 1.015 (s, 3), 1.021 (s, 3), 1.12 (t, 1, J = 12.4), 1.18 (s, 3), 1.26 (dd, 1, J = 10.2, 12.9), 1.42 (ddd, 1, J = 1.8, 6.5, 12.2), 1.68 (ddd, 1, J = 1.8, 8.5, 12.9), 2.67 (dq, 1, J = 1.5, 10.0), 2.80 (dd, 1, J = 1.7, 17.3), 2.84–2.90 (m, 1), 2.92 (dd, 1, J = 0.6, 17.3), 3.20 (s, 3), 4.60 (dd, 1, J = 4.4, 11.2), 5.49 (d, 1, J = 11.2), 7.18 (s, 1), 7.39 (s, 1, J = 1.7); ^{13}C NMR δ 24.41, 27.70, 27.97, 29.89, 36.76, 45.16, 45.50, 46.93, 48.85, 48.94, 66.79, 80.73, 118.35, 127.52, 140.01, 142.10; M_r calcd for $C_{16}H_{24}O_3$ 264.1726, found 264.1733. **Compound 29**: IR ($CHCl_3$) 3640–3540 cm^{-1}; ^1H NMR δ 0.90 (s, 3), 1.14 (s, 3), 1.55 (dd, 1, J = 8.7, 12.6), 1.69 (d, 1, J = 7.2), 1.74 (s, 3), 1.92 (ddd, 1, J = 2.1, 7.8, 12.6), 2.06 (d, 1, J = 13.8), 2.20 (d, 1, J = 15.1), 2.93 (q, 1, J = 8.8), 2.95 (d, 1, J = 16.7), 3.37 (d, 1, J = 16.7), 4.41 (dd, 1, J = 7.2, 9.7), 7.15 (s, 1), 7.43 (t, 1, J = 1.4); ^{13}C NMR δ 21.93, 27.60, 28.97, 29.59, 37.21, 45.99, 46.39, 48.63, 70.64, 120.934, 127.76, 129.12, 136.93, 138.07, 140.69. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.37; H, 8.89.

(±)-Deconjugated Anhydrolactarorufin A (5). To a stirring solution of 10.0 mg (0.04 mmol) of **25** in 0.8 mL of THF was added 3 μL of H_2SO_4. After 15 min, 1 mL of saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with two 5-mL portions of ether. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to give a colorless oil. The crude product was purified by flash chromatography on 2 g of 230–400-mesh silica gel, eluting with 2:1 hexanes/ethyl acetate, to give 8.2 mg (82%) of **5** as a colorless oil: IR ($CHCl_3$) 3710–3250, 1750 cm^{-1}; ^1H NMR δ 0.93 (s, 3), 1.14 (s, 3), 1.49 (dd, 1, J = 9.2, 12.3), 1.74 (s, 3), 1.92 (ddd, 1, J = 2.2, 7.8, 12.3), 2.09 (d, 1, J = 15.2), 2.27 (d, 1, J = 15.2), 2.90 (d, 1, J = 20.4), 2.96–3.02 (m, 1), 3.14 (d, 1, J = 20.4), 4.24–4.26 (m, 1), 4.72–4.77 (m, 1), 4.95–4.99 (m, 1); ^{13}C NMR δ 22.68, 27.17, 28.69, 30.33, 37.10, 45.51, 46.86, 48.12, 70.65, 71.25, 124.20, 127.12, 136.22, 161.03, 174.86; M_r calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1414.

(±)-Deconjugated Anhydrolactarorufin A Acetate (40). To a stirring solution of 8.3 mg (0.033 mmol) of **5** in 0.16 mL of CH_2Cl_2, cooled to 0 °C, was added 6.8 mg (0.066 mmol, 6.3 μL) of acetic anhydride, 5.3 mg (0.066 mmol, 5.4 μL) of pyridine, and a crystal of 4-(dimethylamino)pyridine. After 15 min, the mixture was diluted with 10 mL of ether and washed with 0.1 N aqueous HCl followed by washing with saturated aqueous $NaHCO_3$. The organic layer was dried, filtered, and concentrated to give a colorless oil. The crude product was purified by flash chromatography on 2 g of 230–400-mesh silica gel, eluting with 15% ethyl acetate in hexanes, to give 9.5 mg (98%) of **40** as a colorless oil which crystallized upon standing: mp 91–92 °C; IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR δ 0.90 (s, 3), 1.10 (s, 3), 1.34 (dd, 1, J = 9.2, 12.6), 1.76 (s, 3), 1.79 (ddd, 1, J = 2.2, 7.8, 12.7), 2.10–2.16 (m, 1), 2.13 (s, 3), 2.26 (d, 1, J = 15.2), 2.95 (d, 1, J = 20.3), 3.12–3.20 (m, 2), 4.62 (t, 1, J = 1.6), 5.55 (dd, 1, J = 1.4, 11.0); ^{13}C NMR δ 20.55, 22.59, 27.08, 28.48, 30.30, 37.04, 45.02, 45.19, 46.69, 69.83, 71.77, 126.17, 127.85, 135.88, 157.28, 170.53, 174.06; M_r calcd for $C_{17}H_{23}O_4$ (MH+) 291.1597, found 291.1605.

(±)-Deconjugated Anhydrolactarorufin A (5) and (±)-Lactarorufin A (6). To a stirring solution of 10.0 mg (0.04 mmol) of **25** in 0.4 mL of THF and 0.4 mL of water was added 3 μL of H_2SO_4. After 15 min, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with two 2-mL portions of ether. The combined extracts were dried, filtered, and concentrated to give a colorless oil. The crude product was purified by flash chromatography on 2 g of 230–400-mesh silica gel, eluting with 1:1 ethyl acetate/hexanes to give 7.0 mg (70%) of **5** as a colorless oil and 2.7 mg (25%) of **6** as a white solid. **Compound 6**: mp 194–196 °C dec; IR ($CHCl_3$) 3580, 3540–3180, 1750 cm^{-1}; ^1H NMR δ 1.01 (s, 3), 1.02–1.05 (m, 1), 1.04 (s, 3), 1.14 (t, 1, J = 11.8), 1.32 (s, 3), 1.53 (ddd, 1, J = 2.1, 6.9, 12.0), 1.58 (bs, 2), 1.68 (ddd, 1, J = 2.1, 8.3, 12.7), 2.55 (d, 1, J = 19.0), 2.66–2.75 (m, 2), 2.90–2.97 (m, 1), 4.09 (d, 1, J = 3.3), 4.59 (dd, 1, J = 2.4, 17.3), 4.96 (dt, 1, J = 2.8, 17.3); ^{13}C NMR δ 26.41, 29.18, 31.56, 34.84, 36.88, 45.37, 45.57, 46.21, 49.02, 67.41, 71.75, 75.42, 123.16, 160.13, 175.591; M_r calcd for $C_{15}H_{23}O_4$ (MH+) 267.1597, found 267.1594.

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Registry No. (±)-**1a**, 143395-37-3; (±)-α-**1a**, 143395-38-4; (±)-**1b**, 143441-62-7; (±)-**2**, 126872-25-1; (±)-**5**, 143395-39-5; (±)-**6**, 143395-40-8; (*E*)-**7**, 104315-11-9; (*Z*)-**7**, 104315-12-0; (±)-*cis*-**8**, 126753-68-2; (±)-*trans*-**8**, 126753-70-6; (±)-*cis*-**9**, 126753-69-3; (±)-*trans*-**9**, 126788-28-1; (±)-*cis*-**10**, 126753-71-7; (±)-*trans*-**10**, 126753-77-3; (±)-**11**, 126753-72-8; (±)-*cis*-**12**, 143347-37-9; (±)-*trans*-**12**, 143347-38-0; **13**, 143347-39-1; (±)-**14**, 126753-73-9; (±)-**15**, 126753-74-0; (±)-**17**, 126753-75-1; (±)-**18**, 126753-76-2; (±)-**19**, 126872-26-2; (±)-**20**, 143347-40-4; (±)-**21**, 143347-41-5; (±)-**22**, 143395-41-9; (±)-**24**, 143347-42-6; (±)-**25**, 143347-43-7; (±)-α-**26**, 143395-43-1; (±)-β-**26**, 143395-42-0; (±)-**27**, 143395-44-2; (±)-**28**, 143395-45-3; (±)-**29**, 143395-46-4; (±)-α-**30**, 143395-48-6; (±)-β-**30**, 143395-47-5; (±)-α-**31**, 143395-50-0; (±)-β-**31**, 143395-49-7; (±)-α-**32**, 143441-69-4; (±)-β-**32**, 143395-51-1; (±)-α-**33**, 143395-53-3; (±)-β-**33**, 143395-52-2; (±)-α-**34**, 143395-55-5; (±)-β-**34**, 143395-54-4; (±)-α-**35**, 143395-57-7; (±)-β-**35**, 143395-56-6; (±)-**39**, 143395-58-8; (±)-**40**, 143347-44-8; (±)-*cis*-**S1**, 143347-45-9; (±)-*trans*-**S1**, 143347-46-0; (±)-*cis*-**S3**, 143347-47-1; (±)-*trans*-**S3**, 143347-48-2; (±)-(*E*)-**S4**, 143395-59-9; (±)-(*Z*)-**S4**, 143347-49-3; **S5**, 71203-75-3; **S6**, 143347-50-6; (±)-**S7**, 143347-51-7; (±)-**S8**, 143347-52-8; (±)-**S10**, 143347-53-9; (±)-**S12**, 143347-54-0; (±)-**S13**, 143347-55-1; (±)-**S14**, 143347-56-2; (±)-**S15**, 143347-57-3; (±)-**S16**, 143347-58-4; (±)-**S17**, 143347-59-5; (±)-**S18**, 143347-60-8; (±)-**S19**, 143347-61-9.

Supplementary Material Available: Discussion of model studies, 500-MHz 2D COSY and NOESY spectra of compounds **1a,b** and **7**, and 500-MHz ^1H NMR spectra of compounds **1a,b**, **2**, **5**, **6**, **22**, **26**, **28**, **29**, and **41** (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.