(15% inhibition) at 10^{-5} M concentration; under the same conditions the known asterosaponins thornasteroside A[21] and marthasteroside B[23a] and C[23a] were active (ca. 50% inhibition) at 10^{-7} M.

Acknowledgment. Work supported by CNR (P.F. Chimica Fine II). The sea urchin eggs assays were done in the Laboratory of Dr. Cariello (Stazione Zoologica, Napoli) to whom we express our gratitude. We are grateful to Professor William Fenical, Scripps Institution of Oceanography, La Jolla, CA, for collecting and identifying the organism. FAB MS spectra were provided by the "Servizio di Spettrometria di massa del CNR e dell'-Università di Napoli". The assistance of the staff is gratefully acknowledged.

Registry No. 1, 130799-35-8; 2, 130799-36-9; 3, 130829-31-1; 4, 130799-37-0; 5, 130799-38-1; 6, 130829-32-2; 7, 130829-33-3; 8, 130829-34-4; 9, 129725-35-5; 10, 130856-16-5; 11, 82485-96-9; 12a, 81477-23-8; 12b, 81477-24-9; 13a, 81477-27-2; 13b, 81502-57-2; 14a, 130829-35-5; 14b, 130930-22-2.

Supplementary Material Available: NMR spectra for compounds 1-8 (20 pages). Ordering information is given on any current masthead page.

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1,4-Dioxaspiro[2.2]pentanes. Synthesis, Spectroscopic Properties, and Reactions with Nucleophiles

Jack K. Crandall,* David J. Batal, David P. Sebesta, and Feng Lin

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

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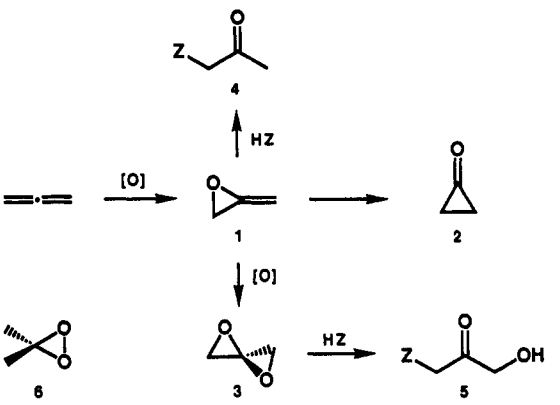
A number of simple allenes have been converted cleanly to the corresponding 1,4-dioxaspiro[2.2]pentanes in good yields by oxidation with dimethyldioxirane. Mono- and trisubstituted allenes give the anti diastereomers with good stereoselectivity, whereas 1,3-disubstituted allenes show only a slight preference for the anti,anti isomers, unless steric effects are extreme. Stereochemical assignments are based on steric considerations and a consistent set of NMR characteristics that permit structural attributions. The addition of a range of nucleophiles (water, alcohols, amines, thiophenol, acetate, chloride, and fluoride) to these intermediates proceeded smoothly under buffered conditions to give highly functionalized products of general type **5**. These reactions were shown to take place with the appropriate selectivities for S_N2 substitutions in instances where these features were observable, namely, regioselective attack at the less-substituted epoxide carbon and inversion of configuration at the site of substitution. Under acidic conditions dioxaspiropentanes gave mixtures of other types of products, which appear to arise from carbocationic processes.

Earlier studies on the epoxidation of allenes have revealed a rich chemistry that has been established to involve reactive intermediates (Scheme I) such as allene oxides (**1**), cyclopropanones (**2**), and 1,4-dioxaspiro[2.2]pentanes (spirodioxides **3**).[1-3] Although these species have been isolated and characterized on occasion, they are usually transformed further under the reaction conditions to a variety of stable products including nucleophilic adducts **4** and **5**.[4,5] The overall transformation of allenes, via the corresponding spirodioxides **3**, to products of type **5** constitutes a potentially efficient protocol for the introduction of different functionality at each of the three allenic carbons. Such a conversion should prove to be of considerable utility in the synthesis of densely functionalized molecules of the type that abound in nature. However, prior to the present study only three relatively hindered examples of spirodioxides had been described adequately in the literature.[2,6] Furthermore, the nucleophilic adducts **5** were not normally major products of the oxidation processes, especially when peracids were used as the oxidizing agents. In this case, the carboxylic acids formed as byproducts in the epoxidations promote acid-catalyzed transformation to other products. In addition, these acids are necessarily among the nucleophilic species that add to any spirodioxides that might be generated, thus limiting the nature of adducts **5**.

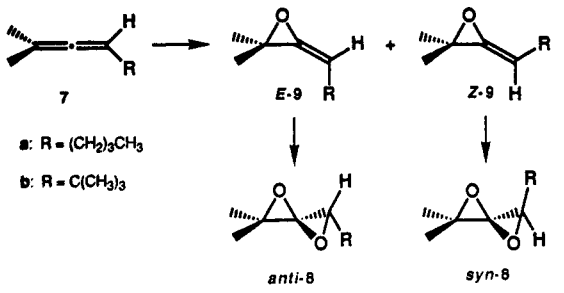
Scheme I



(1) Greene, F. D.; Camp, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 7349.
(2) (a) Crandall, J. K.; Conover, W. W.; Komin, J. B.; Machleder, W. H. *J. Org. Chem.* **1974**, *39*, 1723. (b) Crandall, J. K.; Machleder, W. H. *J. Heterocycl. Chem.* **1969**, *6*, 777. (c) Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7347. (d) Crandall, J. K.; Machleder, W. H.; Thomas, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 7346.
(3) For reviews of allene oxide chemistry, see: (a) Stang, P. J. The Chemistry of Functional Groups, Supplement E: *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Analogs*; Patai, S., Ed.; Wiley: New York, 1983; pp 859-879. (b) L'Abbe, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 276. (c) Smadja, W. *Chem. Rev.* **1983**, *83*, 263.
(4) (a) Crandall, J. K.; Machleder, W. H.; Sojka, S. A. *J. Org. Chem.* **1973**, *38*, 1149. (b) Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7292.
(5) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269.
(6) Wolff, S.; Agosta, W. C. *Can. J. Chem.* **1984**, *62*, 2429.

0022-3263/91/1956-1153$02.50/0

Scheme II



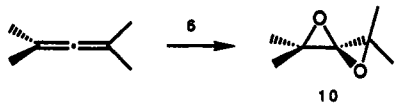
In this report we demonstrate that the use of dimethyldioxirane (**6**) in acetone as an epoxidizing reagent under the neutral, nonnucleophilic conditions permitted by the Murray methodology[7,8] allows for the facile isolation of variously substituted spirodioxides. Subsequent reaction of these versatile intermediates with a variety of nucleophiles under the appropriate conditions results in smooth conversion to adducts of type **5**.[9]

Synthesis of 1,4-Dioxaspiro[2.2]pentanes. Allenes were combined with dilute acetone solutions of dimethyldioxirane (**6**), prepared by a simplified version of the published procedure,[7] usually in the presence of solid potassium carbonate as a buffering agent. Reactions were allowed to proceed until the allene had disappeared, ordinarily in a matter of minutes. Removal of the acetone, drying, and concentration normally gave the spirodioxides in a high state of purity as evidenced by detailed spectroscopic analysis. These materials are surprisingly stable in the pure state, although traces of acid can provoke decomposition.

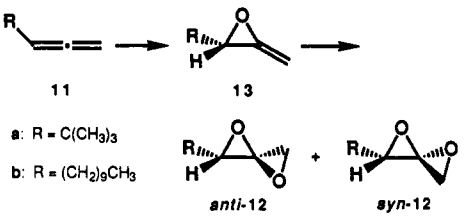
In this manner, the trisubstituted allene **7a** was converted in 95% yield to a 9:1 mixture of diastereomeric allene dioxides **8a** (Scheme II). These are assigned as *anti*- and *syn*-5-butyl-2,2-dimethyl-1,4-dioxaspiro[2.2]pentane (*anti*- and *syn*-**8a**), respectively, on the basis of steric arguments.[10] Thus, if the substituent effects for allenes are similar to those for the epoxidation of olefins by dimethyldioxirane,[11] the initial oxidation should proceed largely at the disubstituted double bond of **7a**. Furthermore, reaction should also be biased in favor of approach of the oxidant at the π face of this double bond away from the butyl group of the second double bond (this substituent projects over the opposite π surface owing to the special allene geometry). This would explain the preferential formation of the *E* allene oxide (*E*)-**9a** over its *Z* isomer (*Z*)-**9a**. The mixture of dioxides **8a** formed by subsequent epoxidation is, of course, predetermined by the ratio of these allene oxide isomers. The absence of products derived from **9a** in this and similar transformations to be discussed below, suggests that the second oxidation is more rapid than the first one, in accord with earlier deductions.[2] This situation is attributed to the electronic influence of the oxygen atom that is introduced at the vinyl position in the initial epoxidation step.

Oxidation of the *tert*-butyl analogue **7b** with **6** proceeded cleanly to give the known dioxide **8b** (84% yield), which was confirmed to be a single diastereomer assigned as *anti*-**8b**.[2] In this case, the sterically more demanding *tert*-butyl substituent results in a very high degree of stereoselectivity for formation of the *E* isomer of the putative allene oxide intermediate **9b** in the initial oxidation and, consequently, for the anti spirodioxide.

Tetramethylallene was likewise converted to the corresponding dioxide **10**, a species originally proposed as a reactive intermediate in our first study of allene epoxidation using peracids.[12] This compound is a white crystalline solid (mp 52–52.5°C), whose high volatility explains its mediocre yield (44%), since significant amounts of other products were not observed.



An efficient epoxidation of *tert*-butylallene (**11a**) was fortuitously found to take place with an acetone solution of **6** that had not been subjected to the usual drying procedure. In this manner a 78% yield of a monosubstituted spirodioxide, assigned as *anti*-**12a**, was obtained. The



presence of ^{1}H NMR signals reasonably consistent with structure *syn*-**12a** suggests that as much as 2% of this minor isomer may be present. Initial reaction in this case seems more likely to proceed preferentially at the substituted double bond, leading to allene oxide **13a** as the major intermediate. The steric influence of the bulky *tert*-butyl group directs subsequent oxidation of **12a** to the opposite side to give *anti*-**11a** highly selectively.[13] The use of wet oxidant solutions in this reaction was adopted after observing that the poor conversion of **11a** to **12a** using rigorously dried oxidant was improved by the addition of water to the reaction. The unusual hydrolytic stability of *anti*-**12a** permitted its isolation in this experiment, which was originally designed to perform a sequential oxidation and hydrolysis. These observations suggest that the presence of water can promote the oxidation process probably by hydrogen bonding with dioxirane **6**.[11b,14] This may be a useful ploy with unreactive substrates such as **11a**.

However, this approach was not successful with 1,2-tridecadiene (**11b**), owing to the rapid hydrolysis of spirodioxide **12b**. Partial conversion of **11b** was effected with rigorously dried oxidant solutions to give a 9:1 diastereomeric ratio of *anti*- and *syn*-**12b**. Thus, the sterically smaller straight-chain substituent was also less effective

(7) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699.

(8) For reviews on dioxiranes, see: (a) Curci, R. *Advances In Oxygenated Procedures*; Baumstark, A. L., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 2, Chapter 1. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.

(9) For a preliminary communication describing part of this work, see: Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1338.

(10) The designation anti and syn refer to the relative geometry of the highest priority group at one of the ring carbons with respect to the oxygen of the second ring.

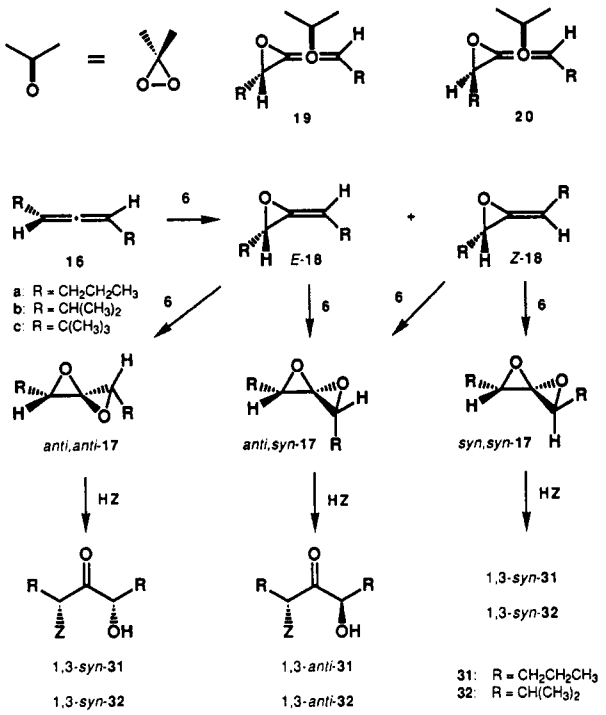
(11) For relative rates of epoxidation of variously substituted olefins by **6**, see: (a) Baumstark, A. L.; McClosky, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. (b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437.

(12) Crandall, J. K.; Machleder, W. H. *Tetrahedron Lett.* **1966**, 6037.

(13) The reversed oxidation sequence would also be expected to give a similar result.

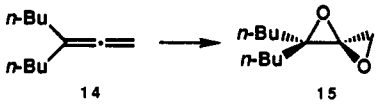
(14) Mono- and disubstituted allenic alcohols are oxidized significantly more rapidly than the corresponding hydrocarbons, indicating an accelerating influence of a hydroxyl group, which may be an intra- or intermolecular effect: Crandall, J. K.; Batal, D. J. *Tetrahedron Lett.* **1988**, *29*, 4791.

Scheme III



than the *tert*-butyl group in controlling the stereoselectivity of the conversion to spirodioxide **12b**. This reaction was difficult to reproduce, owing to facile hydration of the intermediate dioxide.

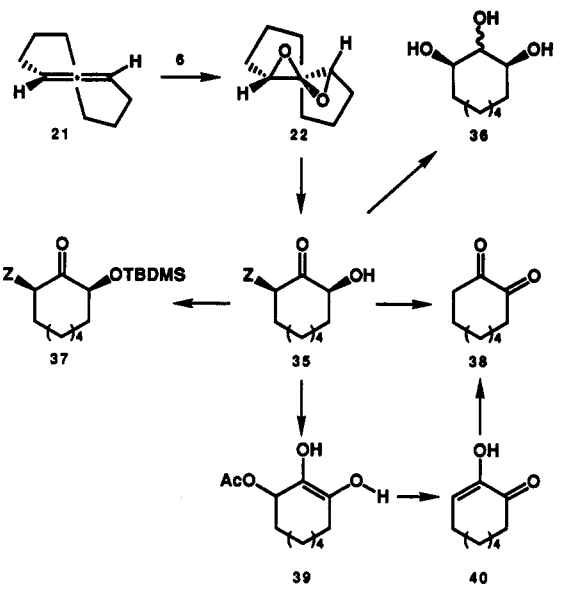
The 1,1-disubstituted allene **14** reacted with **6** at −40 °C to give the corresponding dioxide **15** (83% yield). Reactions run at room temperature generated additional, uncharacterized polar products.



Given the significant stereoselectivities found above for mono- and trisubstituted allenes, it was anticipated that 1,3-disubstituted allenes would also epoxidize in a stereoselective manner. However, this proved not to be the case, as was shown by the oxidation of the series of allenes **16a–c**, which are symmetrically disubstituted with increasingly bulky alkyl groups (Scheme III). Di-*n*-propylallene **16a** gave a 1:1:0.15 mixture of the three possible diastereomeric spirodioxides, namely, the symmetrical anti,anti, unsymmetrical anti,syn, and symmetrical syn,syn isomers of **17a**, respectively. The symmetry of these species is quite useful in structure assignments. The corresponding diisopropylallene **16b** was oxidized to a 2:1 mixture of symmetrical *anti,anti*- and unsymmetrical *anti,syn*-**17b**; observable amounts of *syn,syn*-**17b** were not present in this product mixture. Finally, the di-*tert*-butyl homologue **16c** gave a single symmetrical dioxide, assigned as *anti,anti*-**17c**. Thus, increasing the steric bulk of the substituent once again improves stereoselectivity in the formation of the allene dioxide. However, with the exception of the di-*tert*-butyl-substituted allene **16c**, the oxidations of these 1,3-disubstituted allenes are not very selective.

The first epoxidation step of these disubstituted allenes is probably similar to that of the trisubstituted allene **7a**, namely, with a clear preference for the *E* over the *Z* isomer of allene oxide **18**. It seems likely that it is the second oxidation step that displays a lower level of discrimination. Baumstark has proposed that transfer of an oxygen from

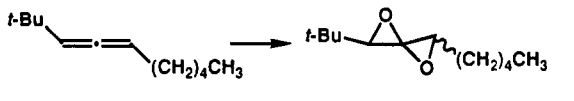
Scheme IV



dimethyldioxirane to a double bond involves a "spiro" transition state in which steric interactions between the substituents on the double bond and the methyl groups of the reagent are important.[11] Assuming this model, there are two reasonable modes of attack of the reagent on the major *E* allene oxide **18** that avoid these destabilizing interactions. These can be roughly represented by **19** and **20**. The steric interactions in **19** and **20** are not very different as long as the substituent on the epoxide moiety is not particularly sterically demanding. Of course, increasing the size of this group will disfavor syn epoxidation (**20**) and result in more anti epoxidation (**19**), consistent with experiment. Similar considerations apply to the minor *Z* allene oxide, which will supplement *anti,syn*-**17** as its major epoxidation product and permit the formation of some *syn,syn*-**17** when steric effects are relatively unimportant.

The cyclic allene **21** is converted by **6** to a single symmetrical dioxide assigned as the anti,anti isomer **22** (Scheme IV). The relatively rigid ring residue of **21** effectively shields one face of the double bonds and also the double bond in the corresponding allene oxide intermediate, thereby enforcing anti epoxidation in both steps.

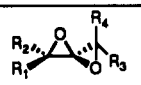
Finally, a brief study of the differentially 1,3-disubstituted allene **23** indicated that only two of the four possible dioxaspiropentane isomers (2.4:1 ratio) were generated in observable quantities upon oxidation with **6**.[15] These are assigned as *anti,anti*-**24** and *anti,syn*-**24**, respectively, assuming that the bulky *tert*-butyl group enforces strict anti attack in either oxidation step as observed for this substituent in several cases described above. The spectroscopic data (vide infra) support this interpretation.



Spectroscopic Properties of 1,4-Dioxaspiro[2.2]pentanes. Table I lists some of the pertinent spectral data obtained for the various allene dioxides prepared in this study. A number of interesting correlations can be extracted from this information, and these provide strong

(15) A sample of allene **23** was kindly furnished by Alex Alexakis, whom we gratefully thank.

Table I. Spectroscopic Data for 1,4-Dioxaspiro[2.2]pentanes



	R_1	R_2	R_3	R_4	IR (cm^{-1})	^1H NMR: δ (J in Hz)[a]	^{13}C NMR: δ (J in Hz)[b]
10	Me	Me	Me	Me	1629		93.6, 64.5
a-**8a**[c]	Me	Me	*n*-Bu	H	1643	3.73 (dd, 6, 5)	89.4, 63.3, 61.7 (174)
s-**8a**[c]	Me	Me	H	*n*-Bu		3.55 (dd, 6, 5)	
8b	Me	Me	*t*-Bu	H	1635	3.52 (s)	88.3, 69.4 (171), 63.4
15	*n*-Bu	*n*-Bu	H	H	1619	3.46 (d, 3), 3.28 (d, 3)	85.6, 68.8, 48.8 (175)
17c	H	*t*-Bu	*t*-Bu	H	1600	3.47 (s)	84.0, 68.7 (170)
aa-**24**	H	*t*-Bu	*n*-C_5H_{11}	H	1620	3.68 (ddd, 8, 3, 1), 3.47 (d, 1)	84.36, 67.8, 60.6
as-**24**	H	*t*-Bu	H	*n*-C_5H_{11}		3.51 (dd, 6.4, 5.7), 3.50 (s)	84.43, 68.3, 59.9
aa-**17b**	H	*i*-Pr	*i*-Pr	H	1619[d]	3.48 (d, 8)	85.0, 65.1 (173)
as-**17b**	H	*i*-Pr	H	*i*-Pr		3.53 (d, 6), 3.27 (d, 9)	85.0, 65.0, 64.1
aa-**17a**	H	*n*-Pr	*n*-Pr	H	1625[d]	3.71 (dd, 7, 5)	85.3, 60.1 (174)
as-**17a**	H	*n*-Pr	H	*n*-Pr		3.74 (t, 6), 3.54 (t, 6)	85.7, 61.0 (174), 59.3 (171)
ss-**17a**	*n*-Pr	H	H	*n*-Pr		3.58 (dd, 7, 5)	
aa-**22**	H	$-(CH_2)_6-$		H	1626, 1605	3.75 (dd, 6, 4)	84.3, 60.1 (170)
12a	H	*t*-Bu	H	H	1615	3.53 (d, 1), 3.52 (dd, 3, 1), 3.30 (d, 3)	80.8, 67.3 (172), 48.3 (177, 178)
a-**12b**	H	*n*-$C_{10}H_{21}$	H	H	1616	3.75 (td, 6, 1), 3.47 (dd, 3, 1), 3.30 (d, 3)	82.3, 60.5, 47.8
s-**12b**	*n*-$C_{10}H_{21}$	H	H	H		3.60 (dd, 7, 6), 3.51 (d, 3), 3.34 (d, 3)	

[a] Directly attached protons only. [b] Spirodioxide carbons only. [c] *a* = anti; *s* = syn. [d] Data obtained from a mixture of diastereomers.

support for the structural assignments given above.

The curious band previously noted[2] in the infrared spectrum of **8b** is a uniform feature of allene dioxides that is observed as a medium intensity signal in the range of 1600–1640 cm^{-1}. Although the vibrational origin of this band remains a mystery, it appears to be a dependable characteristic of this spiro-fused heterocyclic system.

The ^1H NMR chemical shifts of hydrogens attached to the basic ring system prove to be excellent stereochemical indicators. Thus, an epoxide proton syn to the oxygen atom of the second epoxide ring is shifted downfield by about 0.2 ppm relative to an anti proton in a similar local environment. This situation is observed with stereoisomers and with unsubstituted epoxide moieties, where the two hydrogens necessarily have a different relationship with the other epoxide ring. The examples for which measurements were made include a number of monoalkyl-substituted ring carbons bearing primary alkyl groups, which show syn hydrogens in the range of 3.7–3.8 ppm and anti ones at 3.5–3.6 ppm. The bulkier *tert*-butyl and isopropyl substituents cause a slightly shielding of the syn protons to 3.5 ppm and anti protons to 3.3 ppm. In instances with an unsubstituted ring carbon, the syn signals are found at 3.5, and anti at 3.3 ppm.

Vicinal coupling of the ring protons of alkyl-substituted carbons with side-chain protons fall in the expected range of J = 4–9 Hz, usually with different values for the two diastereotopic hydrogens of side-chain methylene groups. Coupling between geminal protons on an unsubstituted ring carbon show J = 3 Hz. Interestingly, there is a long-range, four-bond coupling of about 1 Hz between nonidentical syn hydrogens at the two epoxide moieties, which is clearly evident in monosubstituted spirodioxides. Protons in an anti,syn arrangement do not show this coupling; no example with the anti,anti disposition of nonidentical protons has been measured.

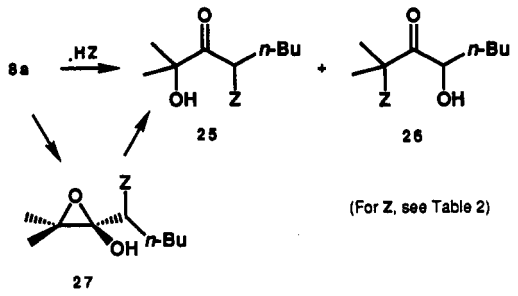
The assignment of structures *anti,anti*-**24** and *anti,syn*-**24** to the two spirodioxide diastereomers from the oxidation of allene **23** is fully consistent with these proton chemical shift correlations; the experimental data do not fit expectations for the two remaining diastereomers. Furthermore, the major isomer shows the long-range coupling expected for an anti,anti compound.

The ^{13}C NMR chemical shifts of the spiro carbon of the dioxides fall into a range of about 80–95 ppm, with further grouping according to the number of alkyl substituents on the dioxaspiropentane unit. Thus, each additional substituent causes a 3–4 ppm deshielding (β-effect), although this is modified somewhat by branching at the directly attached substituent carbon that introduces additional γ interactions, resulting in a small opposing effect (<1 ppm shielding per γ carbon). Unsubstituted peripheral ring carbons are found at about 48 ppm. Monosubstituted examples show their ring carbons in the range of 60–70 ppm with subgroups for *n*-propyl or longer straight-chain groups at about 60 ppm, isopropyl at about 65 ppm, and *tert*-butyl at about 68 ppm. All but one of the disubstituted ring carbons bear geminal dimethyl substitution and appear at about 64 ppm; the dibutyl derivative **15** shows this carbon shifted downfield to 69 ppm. In the *gem*-dimethyl compounds there is a consistent pattern with one of the methyl carbons 1–2 ppm downfield from the other probably owing to its syn disposition with respect to the oxygen of the spiro ring. (A similar splitting is observed for the proton chemical shifts of these methyls, although the difference here is only about 0.05 ppm.) Finally, the measured C–H coupling constants for the ring carbons are all within a few hertz of the value for ethylene oxide ($^1J_{CH}$ = 176 Hz).[16]

Nucleophilic Additions to 1,4-Dioxaspiro[2.2]pentanes. In the absence of acids, the various spirodioxides are subject to clean, efficient nucleophilic additions to form products of general type **5**. Table II summarizes a number of the unoptimized reactions that have been performed. In favorable circumstances these reactions occur with good regio- and stereoselectivities. Furthermore, an impressive range of nucleophiles can be employed.

Much of the initial exploratory work was carried out on the trisubstituted spirodioxide **8a**. Aqueous THF smoothly converts **8a** to dihydroxy ketone **25a**. Interestingly, the use of tetrabutylammonium acetate in the presence of acetic acid provokes a highly regioselective addition at the secondary epoxide center to give **25b**. The reaction with 1-propanol in the presence of K_2CO_3 was less regioselective in the generation of a 4.9:1 mixture of **25c** and its regioisomer **26c**. However, this ratio could be improved to 32:1 by the use of 1-propanol, which had been pretreated with a small amount (0.15 equiv) of NaH. The bulkier 2-propanol gave a reasonably selective reaction in the

(16) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; Ebel, H. F., Ed.; VCH: New York, 1987; p 288.

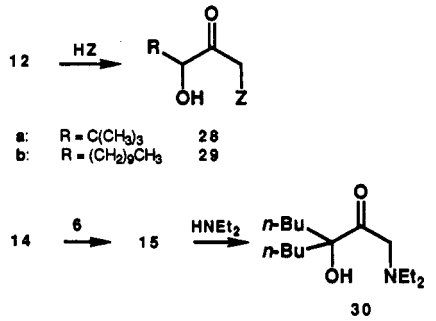


presence of K_2CO_3 (16:1 ratio of **25d:26d**). The regioisomers of the alcohol adducts could be assigned on the basis of the characteristic fragmentations observed in their mass spectra.

Nitrogen nucleophiles also add readily to **8a**. Thus, ammonia adds regioselectively to give the unstable amino ketone **25e** by at least a 10:1 ratio over **26e**. Adduct **25e** could be characterized by ^1H NMR, but had to be acetylated to permit isolation as **25f**. Benzylamine, *n*-propylamine, and imidazole all gave isolable adducts of structures **25**, **25h**, and **25i** with at least a 10:1 selectivity. Thiophenol likewise generates adduct **25j**. Finally, a modest yield of the α-fluoro ketone **25K** was obtained upon treatment of **8a** with tetrabutylammonium fluoride.

The observed pattern of reactivity of **8a** is consistent with S_N2-like openings of the spirodioxide, which display the anticipated preference for attack at the less-substituted carbon center. This sort of ring opening leads to the α hemiacetal **27** (or its anion) as an initial intermediate, but this strained species would certainly unravel rapidly to give the more stable acyclic ketone isomer **25**.

The behavior of the diepoxides from terminal allenes is also in accord with the proposed S_N2 attack. Thus, nucleophilic addition of acetate and diethylamine occurs exclusively at the unsubstituted site of the *tert*-butyl-substituted spirodioxide **12a** to give **28a** and **28b**, respectively. Diepoxide **12a** also hydrolyzes cleanly to **28c**. Alternatively, dihydroxy ketone **28c** can be formed directly from allene **11a** by performing the dioxirane oxidation in the presence of a large excess of water. The more fragile decyl-substituted spirodioxide **12b** is best generated and hydrolyzed to **29** in situ by oxidation of allene **11b** in aqueous acetone. In a similar manner, the 1,1-disubsti-



tuted allene **14** was converted to **30**, the diethylamine adduct of spirodioxide **15**, by a sequence involving low-temperature dioxirane oxidation, quenching of excess oxidant with tetramethylethylene, and subsequent addition of diethylamine. Thus, the predicted regioselective attack at the unsubstituted center of **15** was also confirmed.

The proposed S_N2-like nature of the nucleophilic additions to spirodioxides further implies inversion of stereochemistry at the carbon center undergoing reaction, whereas the stereocenter at the hydroxy-bearing carbon of the final product should retain its configuration. Information concerning stereochemistry was obtained from

Table II. Nucleophilic Additions to 1,4-Dioxaspiro[2.2]pentanes

startg matls	nucleophiles	conditions	products	yield (%)
8a	OH	H_2O	**25a**	80
	OAc	Bu_4NOAc, HOAc	**25b**	93
	$OCH_2CH_2CH_3$	*n*-PrOH, K_2CO_3	**25c**, **26c** (4.9:1)[b]	95
	$OCH_2CH_2CH_3$	*n*-PrOH, NaH	**25c**, **26c** (32:1)	78
	$OCH(CH_3)_2$	*i*-PrOH, K_2CO_3	**25d**, **26d** (16:1)	44
	NH_2	NH_3	**25e**, **26e** (10:1)	
	NHAc	NH_3; Ac_2O, pyridine	**25f**	33
	$NHCH_2C_6H_5$	$C_6H_5CH_2NH_2$	**25g**	61
	$NHCH_2CH_2CH_3$	*n*-$PrNH_2$	**25h**, **26h** (10:1)	83
	1-imidazolyl	imidazole	**25i**	48
	SC_6H_5	C_6H_5SH	**25j**	55
	F	Bu_4NF	**25k**	35
12a	OAc	Et_3NHOAc	**28a**	68
	$N(CH_2CH_3)_2$	Et_2NH	**28b**	66
	OH	H_2O	**28c**	88
11a (12a)[a]	OH	**6**, H_2O	**28c**	79
11b (12b)[a]	OH	**6**, H_2O	**29**	97
14 (15)[a]	$N(CH_2CH_3)_2$	**6**, Et_2NH	**30**	76
17a	OH	H_2O	**31a** (1.1:1)[c]	78
	OAc	Bu_4NOAc, HOAc	**31b** (1.4:1)	85
	$OCH_2CH_2CH_3$	*n*-PrOH, K_2CO_3	**31c** (1.3:1)	53
	$NHCH_2C_6H_5$	$C_6H_5CH_2NH_2$	**31d** (1.1:1)	
	$NHCH_2CH_2CH_3$	*n*-$PrNH_2$	**31e** (1.1:1)	
	$N(CH_2CH_3)_2$	Et_2NH	**31f** (1.2:1)	85
	F	Et_3NHF, CH_3CN	**31g**[d]	54
17b	OH	H_2O	**32a** (2:1)	62
	OAc	Bu_4NOAc, HOAc	**32b** (2:1)	75
	Cl	KCl, $KHSO_4$	**32c** (2:1)	93
22	OH	H_2O	**35a**	98
	OAc	Bu_4NOAc, HOAc	**35b**	76
	$N(CH_2CH_3)_2$	Et_2NH	**35c**	

[a] Spirodioxide generated in situ. [b] Ratio of regioisomers. [c] Ratio of the 1,3-syn isomer to the 1,3-anti isomer. [d] Ratio of diastereomers was not determined.

a study of nucleophilic additions to the spirodioxides derived from 1,3-disubstituted allenes. As illustrated in Scheme III, the anti,anti diastereomer of dioxide **17** should lead to nucleophilic adduct **31** with the 1,3-syn stereochemistry,[17] whereas the anti,syn isomer should give the 1,3-anti stereoisomer of **31**. The syn,syn spirodioxide would also yield 1,3-*syn*-**31** by the suggested process.

The di-*n*-propylspirodioxide **17a** smoothly added water, acetate, 1-propanol, and several amines to give, in each case, a mixture of adducts **31** in which one diastereomer predominated by about 1.1:1 over the other. In view of the fact that the spirodioxide was a 1:1:0.15 mixture of anti,anti, anti,syn, and syn,syn isomers, the observed product mixture is consistent with expectations for S_N2 attack, provided that the major product is the 1,3-syn isomer derived from both *anti,anti*- and *syn,syn*-**17a** and the less abundant adduct is the 1,3-anti isomer formed from the anti,syn spirodioxide.

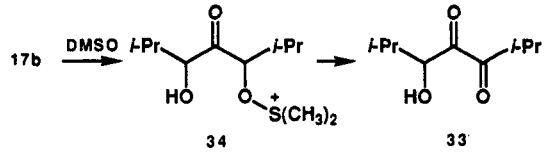
The primary amine adducts **31d** and **31e** were rather unstable, especially to chromatography (vide infra), whereas **31f**, the adduct from diethylamine, survived this type of purification. The diastereomeric fluoro ketones **31g**, obtained by treatment of **17a** with triethylammonium fluoride in acetonitrile, could be separated by preparative TLC.

The diisopropyl analogues **17b** undergo nucleophilic additions in an analogous manner. Thus, the 2:1 mixture of *anti,anti*- and *anti,syn*-**17b** gave a 2:1 mixture of ad-

(17) (a) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (b) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

ducts assigned as 1,3-*syn*- and 1,3-*anti*-**32**. In this case, water, acetate, and chloride were employed as nucleophiles; chloride **32c** was obtained from a reaction using potassium chloride, potassium bisulfate, and 18-crown-6 in THF.

A rather interesting reaction of spirodioxide **17b** was first discovered in an attempt to utilize DMSO as a solvent for nucleophilic additions. It was subsequently demonstrated that reaction with DMSO alone oxidized **17b** to the bright yellow hydroxy dione **33**. This reaction undoubtedly proceeds by way of the DMSO adduct **34**, which spontaneously decomposes to **33**. Simple epoxides are known to behave in an analogous manner to give ketols.[18]



34 33

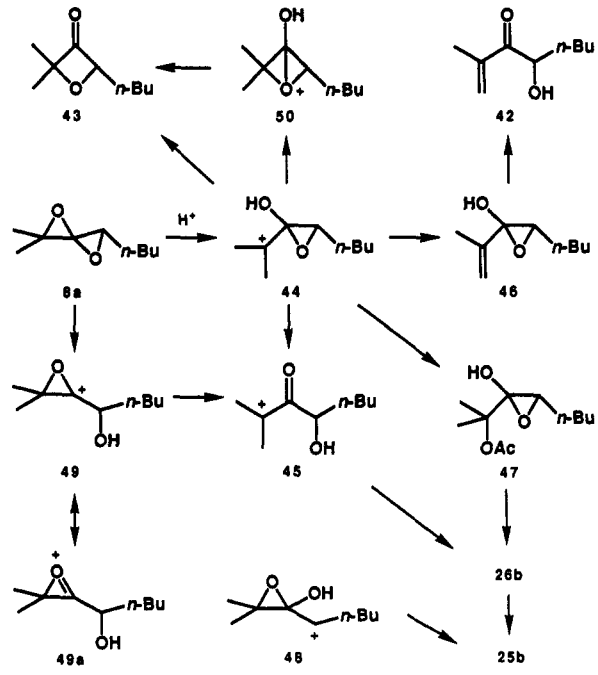
The di-*tert*-butyl spirodioxide **17c** was particularly unreactive to nucleophilic attack owing, no doubt, to steric shielding by the bulky alkyl substituents. Unreacted starting material was recovered even after prolonged exposure to water, tetrabutylammonium acetate, or diethylamine under conditions where other spirodioxides were smoothly converted to adducts. Unfortunately, this prevented stereochemical correlations in this system where a single diastereomer of the spirodioxide was available.

The stereochemical course of nucleophilic addition could be clearly demonstrated with the cyclic spirodioxide **22**, which was generated as a single symmetrical diastereomer assigned the anti,anti structure (Scheme IV). The chemical shift of the spirodioxide protons (3.75 ppm) supports this assignment. (Furthermore, it seems highly improbable that the symmetrical syn,syn isomer would be formed exclusively in view of the need for both of the epoxidation steps to occur from the more hindered face of the reacting double bond.) Hydrolysis of **22** gave a single dihydroxy ketone (**35a**), which was symmetrical by ^{13}C NMR. (On a time-averaged basis the cis dihydroxy ketone has a symmetry plane, whereas the trans isomer possesses a C_2 axis.) Reduction of this ketone by lithium aluminum hydride generated two triols, which were shown by ^{13}C NMR to be the symmetrical meso compounds corresponding to structure **36**. This observation unequivocally establishes the stereochemistry of dihydroxy ketone **35a** as cis, since the trans isomer would have been reduced to a single unsymmetrical triol. Thus, clean inversion of configuration at one of the peripheral epoxide carbons of **22** during hydration is established. Only an S_N2 displacement in the initial step of nucleophilic addition would appear to provide a reasonable accounting for this observation. All the available evidence suggests that the same is true for the other nucleophilic additions described above.

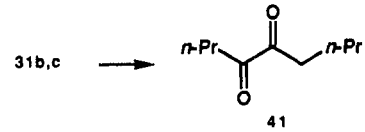
The two triols corresponding to structure **36** are formed in a 7:1 ratio from the hydride reduction of **35a** as ascertained by ^1H NMR of the corresponding triacetates. The major isomer is assigned as the cis,cis triol on the basis of a small coupling constant (J = 2 Hz) of the proton of the central oxygenated carbon with its neighboring protons. The minor trans,trans isomer has a much larger value (J = 8 Hz) for this interaction. These coupling constants appear to be compatible only with the indicated structures, when reasonable conformations of the cyclic triols are examined.

(18) (a) Cohen, T.; Tsuji, T. *J. Org. Chem.* **1961**, *26*, 1681. (b) Khuddus, M. A.; Swern, D. *J. Am. Chem. Soc.* **1973**, *95*, 8393. (c) Santosusso, T. M.; Swern, D. *J. Org. Chem.* **1975**, *40*, 2764. (d) Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1988**, *29*, 2163.

Scheme V



Spirodioxide **22** was also converted to acetate **35b** and diethylamino ketone **35c** under the usual conditions. Both of these materials decomposed extensively upon chromatography, although conversion of the latter to its *tert*-butyldimethylsilyl ether **37** did permit purification. When acetate **35b** was stirred overnight with a slurry of silica gel in CH_2Cl_2, it was efficiently transformed into a bright yellow oil easily identified as cyclononane-1,2-dione (**38**). It was also evident that this process was occurring during the chromatography of **35b** and **35c**. This interesting transformation, which we have previously encountered during preparative GC of a related compound,[4] is thought to involve tautomerization of **35** to enediol **39**, followed by the elimination of acetic acid to give enol **40** and, finally, isomerization of **40** to its more stable tautomer **38**. Both acetate **31b** and amino ketone **31f** could be converted to nonane-4,5-dione (**41**) in an analogous manner. The formation of **41** was also apparent during the attempted chromatography of primary amino adducts **31d** and **31e**.

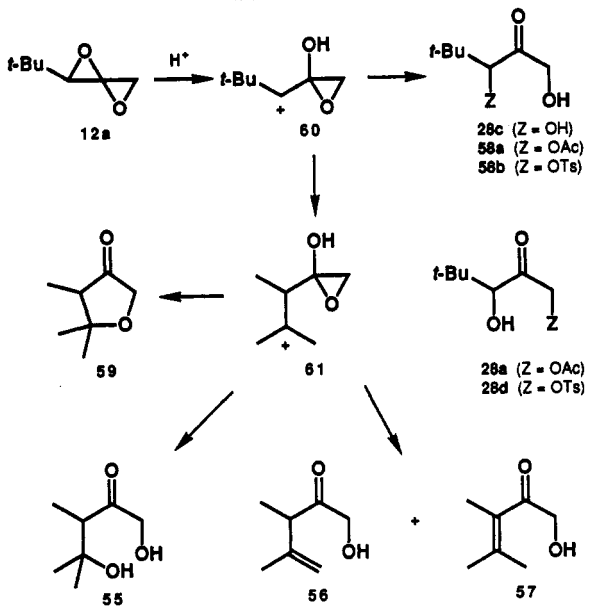


41

Acid-Catalyzed Transformations of 1,4-Dioxaspiro[2.2]pentanes. Unlike the controlled nucleophilic additions described above, reactions of spirodioxides performed under acidic conditions generally lead to different types of products that appear to be formed by carbocationic processes. Related conversions are also found upon chromatography on silica gel, where active sites are apparently capable of inducing analogous transformations.

This type of reaction was first noted during attempted preparative TLC of spirodioxide **8a**, which was observed to give spots corresponding to three new compounds in roughly comparable quantities (Scheme V). These were identified as the isomeric enone **42** and oxetanone **43** and the hydration product **25a**. This chemistry is reminiscent of that observed in our earlier studies on peracid oxidations of allenes.[2] A similar process was observed upon treatment with acetic acid. This transformation was conveniently followed by ^1H NMR using acetic acid-d_4 in $CDCl_3$ as the

Scheme VI



reaction medium. Under these circumstances **8a** reacted rapidly to give a complex product mixture. About half of the product consisted of a 1:3 mixture of enone **42** and oxetanone **43** that was invariant with time, whereas the remainder of the product was a mixture of acetate adduct **25b** and a second compound assigned as the regioisomeric acetate **26b**. The relative amounts of these acetates changed over time from a 1:5.6 ratio of **25b**:**26b** after a few minutes to a 34:1 ratio after equilibration for 4 days. The complication introduced by acetate migration from the tertiary to the secondary site, however, does not obscure the very substantial change in regiochemistry relative to that found under buffered conditions where only **25b** was found.

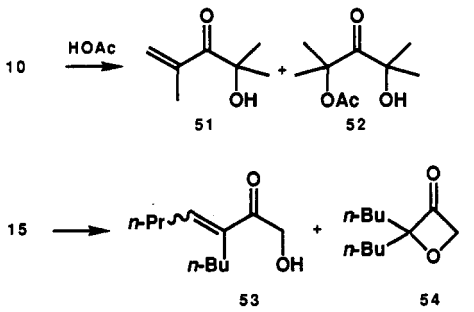
These transformation under acidic conditions are best understood in terms of ring-opening processes leading to carbocation intermediates (Scheme V). Thus, protonation at the appropriate oxygen followed by C–O bond rupture would preferentially lead to the tertiary cation **44**. Elimination of a proton or attack of acetate probably occurs from **44**, since these processes are likely to be faster than unraveling of the hemiacetal moiety to give the isomeric carbocation **45**. The opening of the hemiacetal should, however, proceed readily subsequent to disposition of the carbocationic site, leading to the expression of products **42** and **26b** via intermediates **46** and **47**, respectively.

The facile conversion of acetate **26b** to its more stable isomer **25b** makes it difficult to determine how much, if any, of the latter is formed directly from spirodioxide **8a**. However, either a competing carbocationic route proceeding via the analogous secondary species **47** or an S_N2 process provides a feasible pathway to **25b**.

An interesting feature of the acid-catalyzed reactions of spirodioxide **8a** is the lack of evidence requiring ketal-type reactivity that involves an intermediate such as **49**. It may be that this pathway is rendered unimportant by the strain and stereoelectronic features that inhibit the stabilization of this cation by the adjacent oxygen (i.e., resonance contributor **49a** is less effective than usual). It cannot be excluded, however, that this species is formed, but leads only to the observed products owing to further reactions under the reaction conditions. For example, cation **49** could isomerize to the α-keto cation **45**, which is a reasonable precursor of **42** and **43**. Further experimentation is required to assess the importance of **49** in the acid-catalyzed reactions of spirodioxides.

The interesting oxetanone product **43** could, in principle, be formed by direct rearrangement of **44** or by cyclization or cation **45**, although four-membered ring formation of this type is rare. A more likely alternative, in our view, involves participation of the epoxide oxygen to close **44** to the bicyclic species **50**, which should experience little trouble in proceeding on to oxetanone **43**. A similar involvement of the epoxide ring with cationic centers has been previously suggested.[19]

Other spirodioxide reactions generalize the types of transformations observed with **8a**. Thus, the tetramethyl compound **10** is converted by acetic acid into a 1:1 mixture of enone **51** and acetoxy ketone **52**. On the other hand, preparative TLC of the dibutyl derivative **15** leads to the isomeric *E* and *Z* enones of structure **53** as well as oxetanone **54**.



Convincing evidence for the intervention of carbocations is provided by the reactions of *tert*-butylspirodioxide **12a** (Scheme VI). Preparative TLC of **12a** (after waiting half an hour between application and development of the plate) gave a significant amount of rearranged diol **55** in addition to the normal hydration product **28c**. A mixture of two unsaturated ketols were also formed in this process, whose formulation as the rearranged structures **56** and **57** is assigned on the basis of spectral data on the mixture (see Experimental Section). These unsaturated ketols were also observed as minor products in the reaction of acetic acid with **12a** in $CDCl_3$, which gave acetates **58a** and **28a** as the major products. The ratio of these acetates decreased with time, indicating the isomerization of **58a** to **28a**. (Triethylammonium acetate in a mixture of $CDCl_3$ and acetone-d_6 also promoted this interconversion, but too slowly to be of importance in the buffered acetate additions discussed earlier.) Finally, reaction of *p*-toluenesulfonic acid with **12a** gave the secondary tosylate **58b** as the major product along with the rearranged enones **56** and **57** and a new product whose spectral data allows assignment of cyclic structure **59**. It is noteworthy here that none of primary tosylate **28d** was observed, which suggests that direct attack of nucleophile at the unsubstituted carbon of **12a** is not important. The structurally rearranged compounds are reminiscent of transformations of *tert*-butyl-substituted spirodioxides described in earlier studies of peracid oxidations of allenes.[2] These reactions all appear to require a 1,2-methyl migration to a carbocationic center adjacent to a *tert*-butyl group. In this case, the rearrangement of **60** to **61** provides a reasonable key intermediate on the way to all of the structurally rearranged products.

Conclusions. Allenes with a variety of alkyl substitution patterns react with dimethyldioxirane (**6**) to give the corresponding spirodioxide compounds, normally in good

(19) (a) Morita, H.; Oae, S. *Tetrahedron Lett.* **1969**, 1347. (b) Richey, H. G.; Kinsman, D. V. *Tetrahedron Lett.* **1969**, 2505.

yields and purities. In instances where diastereomeric spirodioxides are possible, there is usually a reasonable stereochemical preference for epoxidation to occur anti to alkyl substituents. These reactive spirodioxides undergo typical S_N2 substitutions with an assortment of nucleophiles under controlled conditions to give, after unraveling of the second oxirane ring, α'-substituted α-hydroxy ketones **5**. These materials, which bear different functional groups at each of the three carbons of the original allene unit, are thus readily available in two simple steps from the allenes. They constitute potentially valuable intermediates for the synthesis of highly functionalized molecules. Applications of this type are currently underway.

Experimental Section

General. Infrared (IR) spectra were determined as thin film between NaCl disks or as solutions in $CDCl_3$ on a Perkin-Elmer Model 298 grating spectrometer or a Mattson Galaxy 4020 FT-IR instrument. ^1H Nuclear magnetic resonance (NMR) spectra were recorded on $CDCl_3$ solutions, unless otherwise specified, on a Varian XL-300 instrument at 300 MHz or a Bruker AM-500 instruments at 500 MHz where specified. ^{13}C NMR were normally recorded on $CDCl_3$ solutions on the Varian XL-300 spectrometer at 75 MHz or the Bruker AM-500 instrument at 125 MHz. The multiplicities of ^{13}C signals were determined by APT or DEPT techniques or by recording fully coupled spectra (gated decoupling).[20] Coupling constants from the latter are given only when they deviate significantly from simple aliphatic hydrocarbon values. Mass spectra (MS) were obtained on a Kratos MS 80 RFAQQ spectrometer using chemical (CI) or electron-impact (EI) ionization. Exact-mass measurements are reported for the (M + 1) or (M) peak unless otherwise specified. Melting points were determined on a Thomas-Hoover Unimelt apparatus. Analytical gas chromatography (GC) was performed on a Varian 3700 instrument fitted with a 50 m × 0.25 mm DB-5 fused silica capillary column, a flame-ionization detector, and a Hewlett-Packard Model 3390-A integrator. Preparative GC was performed on an Aerograph A700 instrument. Preparative thin-layer chromatography (TLC) was performed on kieselgel 60 F-254 silica gel on 10 × 20 cm plates of 0.25 mm thickness unless otherwise indicated. Anhydrous diethyl ether was used directly from Mallinkrodt anhydrous ether cans. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Reagent grade acetone was used in the preparation of solutions of **6**.

Preparation of Dimethyldioxirane Solutions (6). A simplified version of the procedure described by Murray[7] was used. A 1-L, three-necked, round-bottomed flask was equipped with a solid addition funnel, a magnetic stirring bar, and a 20-cm air-cooled condenser. The top of the condenser was connected to a large vacuum trap cooled to −78 °C. In a typical experiment, the flask was charged with 80 g of $NaHCO_3$, 130 mL of H_2O, and 90 mL of acetone, and 160 g of Oxone ($2KHSO_5$, $KHSO_4$, K_2SO_4) was added in approximately 15-g increments. The total addition time was about 10 min. Vigorous stirring was continued an additional 20 min, during which time a pink color usually appeared in the reaction pot. Vacuum was applied to the system (10 Torr maximum) until most of the acetone had been collected in the cold trap. The cold trap was removed and the yellow solution was allowed to warm to ca. 0 °C. The oxidant solution was usually successively dried over $MgSO_4$, freshly ground $CaSO_4$, and stored over $CaSO_4$ at −20 °C. Solutions were used within 1 week; a concentration of 0.1 M was generally assumed.

5-Butyl-2,2-dimethyl-1,4-dioxaspiro[2.2]pentane (8a). To a stirred solution of 56 mL (3.5 equiv) of **6** containing 5 g of K_2CO_3 was added 200 mg (1.6 mmol) of 2-methyl-2,3-octadiene (**7a**).[21] After 10 min, the reaction was concentrated. The residue was diluted with ether, filtered, dried (K_2CO_3), and concentrated to provide 235 mg (95%) of a 9:1 mixture of *anti*- and *syn*-**8a** as a colorless liquid as determined by ^1H NMR integration. The major product *anti*-**8a** showed the following: IR 2931, 2880, 1643, 1459, 1383, 1029 cm^{-1}; ^1H NMR δ 3.73 (dd, 1 J = 6, 5 Hz), 1.9–1.7 (m, 2), 1.55 (s, 3), 1.49 (s, 3), 1.4–1.3 (m, 4), 0.91 (t, 3, J = 7 Hz); ^{13}C NMR δ 89.4 (s), 63.3 (septet, J = 4 Hz), 61.7 (d, J = 174 Hz), 29.6 (t), 27.3 (t), 22.4 (q), 21.5 (t), 20.5 (q), 13.8 (q); MS (CI) m/z (rel intensity) 157 (3), 139 (6), 125 (5), 86 (70), 85 (58), 84 (100), 69 (25); exact mass 157.125, calcd for $C_9H_{17}O_2$ 157.1229. The presence of *syn*-**8a** was indicated by the following ^1H NMR resonances: δ 3.55 (dd, J = 6, 5 Hz), 1.53 (s), 1.47 (s).

Attempted purification of a 51-mg sample of **8a** by preparative TLC on two plates using 1% MeOH/$CHCl_3$ as the eluent gave 17 mg (34%) of 4-hydroxy-2-methyloct-1-en-3-one (**42**), 17 mg (34%) of 2,4-dihydroxy-2-methyl-3-octanone (**25a**), and 15 mg (30%) of 4-butyl-2,2-dimethyl-3-oxacyclobutanone (**43**). Compound **42**: IR 3480, 3103, 2960, 2862, 1674, 1632, 1054 cm^{-1}; ^1H NMR δ 5.89 (q, 2, J = 1 Hz), 4.81 (dd, 1, J = 9, 5 Hz), 3.6–3.3 (br s, 1), 1.93 (t, 3, J = 1 Hz), 1.9–1.2 (m, 6), 0.88 (t, 3, J = 7 Hz); MS (CI) m/z (rel intensity) 157 (32), 139 (13), 85 (64), 70 (100), 69 (81); exact mass 157.122, calcd for $C_9H_{17}O_2$ 157.1229. Compound **25a**: IR 3420, 2961, 2865, 1711, 1183, 1042 cm^{-1}; ^1H NMR δ 4.63 (dd, 1, J = 8, 6 Hz), 3.1–2.5 (br s, 2), 2.0–1.8 (m, 2), 1.6–1.2 (m, 10, including singlets at 1.43 and 1.42), 0.91 (t, 3, J = 7 Hz); MS (CI) m/z (rel intensity) 175 (12), 157 (35), 139 (17), 117 (36), 98 (99), 89 (35), 85 (100), 69 (78); exact mass 175.133, calcd for $C_9H_{19}O_3$ 175.1334. Compound **43**: IR 2962, 2864, 1820, 1022 cm^{-1}; ^1H NMR δ 5.30 (t, 1, J = 7 Hz), 1.81 (q, 2, J = 7 Hz), 1.5–1.3 (m, 10, including singlets at 1.47 and 1.46), 0.91 (t, 3, J = 7 Hz); MS (CI) m/z (rel intensity) 157 (10), 128 (7), 113 (25), 98 (25), 85 (64), 70 (100); exact mass 157.121, calcd for $C_9H_{17}O_2$ 157.1229.

2,4-Dihydroxy-2-methyl-3-octanone (25a). To a 10.7-mg (0.07 mmol) sample of **8a** in 1 mL of THF was added 1 mL of water. After being stirred for 2 h at room temperature, the reaction mixture was concentrated. The residue was diluted with ether, dried (K_2CO_3), and concentrated to give 9.5 mg (80%) of **25a** as a colorless liquid.

4-Acetoxy-2-hydroxy-2-methyl-3-octanone (25b). To a stirred mixture consisting of 92 mg (2 equiv) of Bu_4NOAc, 11 mg (1.3 equiv) of acetic acid, and 0.5 g of 4-Å molecular sieves in 2 mL of THF under nitrogen at 0 °C was added 23 mg (0.15 mmol) of **8a** in 1.5 mL of THF. The reaction was stirred at 0 °C for 15 min and allowed to warm to room temperature overnight. Ether was added and the mixture was washed with water, saturated $NaHCO_3$ solution, and dried (K_2CO_3). Concentration gave 27 mg (93%) of **25b** as a colorless liquid: IR 3490, 2972, 2941, 2878, 1751, 1729, 1465, 1378, 1252, 1049 cm^{-1}; ^1H NMR δ 5.51 (dd, 1, J = 9, 3 Hz), 3.0 (br s, 1), 2.10 (s, 3), 1.9–1.7 (m, 2), 1.5–1.3 (m, 10, including singlets at 1.42 and 1.38), 0.91 (t, 3, J = 7 Hz); MS (CI) m/z (rel intensity) 217 (9), 199 (10), 157 (10), 98 (86), 85 (100), 69 (45); exact mass 217.142, calcd for $C_{11}H_{21}O_4$ 217.1434.

Reaction of 8a with Acetic Acid. A solution of 44 mg of **8a** in 0.5 mL of acetic acid was stirred at room temperature for 0.5 h. The mixture was diluted with ether, washed with saturated $NaHCO_3$ solution, dried (K_2CO_3), and concentrated to give 42 mg of a colorless liquid. This was shown by ^1H NMR to be a mixture of **42**, **43**, **26a**, and **25a** in the proportions of 1:2.7:2.2:0.9. After standing for 20 h at room temperature, ^1H NMR analysis of the $CDCl_3$ solution indicated a 1:3.1:2.1:1.4 mixture. The assignment of structure **26a** is based on a partial ^1H NMR spectrum obtained on this mixture: δ 4.48 (dd, 1, J = 8, 3 Hz), 2.07 (s, 3), 1.58 (s, 3), 1.57 (s, 3). The facile isomerization of **26a** to **25a** precluded its isolation in pure form.

To an NMR tube containing 100 μL of $CDCl_3$ and 400 μL of acetic acid-d_4 was added 15 mg of **8a**. ^1H NMR data after 5 min showed a 1.6:5.1:5.6:1 ratio of **42**, **43**, **26b**, and **25b**, respectively. After standing at room temperature for 4 days, ^1H NMR analysis showed no change in the relative amounts of **42** and **43**, but the ratio of **26b** to **25b** had changed to 1:34.

Reaction of 8a with 1-Propanol. A solution of 14 mg (0.09 mmol) of **8a** and 20 mg of K_2CO_3 in 4 mL of dry 1-propanol was stirred overnight at room temperature. After concentration, the residue was diluted with ether, dried (K_2CO_3), and concentrated to give 19 mg (95%) of an 83:17 mixture (as assessed by GLPC analysis) of 2-methyl-2-hydroxy-4-(propyloxy)-3-octanone (**25c**) and 2-methyl-4-hydroxy-2-(propyloxy)-3-octanone (**26c**) as a colorless liquid. The mixture showed the following: IR 3490, 2963, 2940, 2891, 1718, 1464, 1362, 1182, 1090 cm^{-1}; ^1H NMR **25c**, δ 4.10 (dd, 1, J = 7, 6 Hz), 3.96 (s, 1), 3.41 (m, 2), 1.8–1.2 (m, 14, including

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singlets at 1.40 and 1.38), 0.95 (m, 6); **26c**, δ 4.63 (dd, J = 7, 6 Hz), 3.61 (t, J = 7 Hz), 1.35 (s), 1.34 (s) (plus additional signals overlapping with those of **25e**). GC-MS (CI) analysis showed the following: **25c**, m/z (rel intensity) 217 (8), 199 (2), 173 (12), 159 (13), 129 (96), 87 (44), 69 (100), 59 (39); exact mass 217.184, calcd for $C_{12}H_{25}O_3$ 217.1804; **26c**, m/z (rel intensity) 217 (3), 199 (0.3), 101 (100), 85 (33), 59 (95); exact mass 217.184, calcd for $C_{12}H_{25}O_3$ 217.1804.

Reaction of 8a with 1-Propanol Containing NaH. To a stirred mixture of 10 mg (0.02 mmol) of 56.8% NaH in oil (washed with pentane) in 1.5 mL of dry 1-propanol over 4-Å molecular sieves was added 20 mg (0.13 mmol) of **8a** in 0.75 mL of THF. Stirring was continued overnight at room temperature. Ether was added and the mixture was washed with a saturated NH_4Cl solution and water and dried (K_2CO_3). Concentration gave 21 mg (78%) of a 97:3 mixture of **25c** and **26c** as shown by GC.

Reaction of 8a with 2-Propanol. A mixture of 18 mg (0.11 mmol) of **8a** and 50 mg of K_2CO_3 in 3 mL of 2-propanol was stirred for 17 h at room temperature and concentrated. Purification by preparative TLC on a 0.25-mm plate using ether–hexane (65:35) gave 11 mg (44%) of a 16:1 mixture of 2-hydroxy-2-methyl-4-(isopropyloxy)-3-octanone (**25d**) and 4-hydroxy-2-methyl-2-(isopropyloxy)-3-octanone (**26d**) as assessed by GC analysis. Compound **25d**: ^{1}H NMR δ 4.16 (dd, 1, J = 7, 6 Hz), 4.13 (s, 1), 3.61 (septet, 1, J = 7 Hz), 1.9–1.7 (m, 2), 1.5–1.2 (m, 10, including singlets at 1.39 and 1.36), 1.21 (d, 3, J = 7 Hz), 1.19 (d, 3, J = 7 Hz), 0.89 (t, 3, J = 7 Hz). The presence of **26d** was indicated by a septet at δ 3.88 (J = 7 Hz) in the ^{1}H NMR spectrum of the product mixture. GC/MS (CI) showed the following: **25d**, m/z (rel intensity) 217 (1), 173 (3), 157 (4), 131 (17), 129 (53), 128 (33), 98 (6), 87 (100), 86 (66); **26d**, 217 (1), 155 (3), 101 (50), 100 (11), 85 (100), 83 (24); exact mass on the mixture gave 217.180, calcd for $C_{12}H_{25}O_3$, 217.1804.

4-Amino-2-hydroxy-2-methyl-3-octanone (25e). A slow stream of anhydrous ammonia gas was passed through a solution of 18 mg (0.11 mmol) of **8a** in 1.5 mL of $CDCl_3$ for 1.5 h. Nitrogen was bubbled through the reaction until the volume was reduced to 0.5 mL. Analysis of this solution showed **25e** to be the major product: IR 3500, 3460, 3320, 2989, 2942, 2891, 1716 cm^{-1}; ^{1}H NMR δ 3.82 (dd, 1, J = 8, 5 Hz), 3.0–2.0 (br s, 2), 1.8–1.2 (m, 13, including singlets at 1.38 and 1.37), 0.89 (t, 3, J = 7 Hz). Also observed in the ^{1}H NMR was 3% of **25a** and 9% of another compound showing δ 4.50 (dd, J = 8, 4 Hz), which is tentatively assigned as 2-amino-4-hydroxy-2-methyl-3-octanone (**26e**).

4-Acetamido-2-hydroxy-2-methyl-3-octanone (25f). A 19-mg (0.12 mmol) sample of **8a** in 2.5 mL of THF was treated with ammonia as described above. To this mixture were added 16 mg (1.6 eq) of dry pyridine and 17 mg (1.4 equiv) of acetic anhydride. After 30 min, the reaction mixture was hydrolyzed and ether was added. The organic layer was washed with saturated $CuSO_4$ solution and water and dried (K_2CO_3). Concentration followed by preparative TLC using ethyl acetate as eluent gave 9 mg (33%) of **25f** as a colorless liquid: IR 3320, 2963, 2934, 2862, 1714, 1652, 1530, 1375, 789 cm^{-1}; ^{1}H NMR δ 5.96 (br d, 1, J = 6 Hz), 5.18 (td, 1, J = 8, 5 Hz), 3.91 (s, 1), 2.00 (s, 3), 1.9–1.2 (m, 12, including singlets at 1.40 and 1.36), 0.89 (t, 3, J = 7 Hz); MS (EI) (rel intensity) m/z 216 (1), 156 (2), 129 (43), 128 (23), 86 (100); exact mass 216.159, calcd for $C_{11}H_{22}O_3N$ 216.1600.

4-(Benzylamino)-2-hydroxy-2-methyloctan-3-one (25g). To a stirred solution of 26 mg (0.16 mmol) of **8a** in 0.1 mL of $CDCl_3$ was added 21 mg (1.2 equiv) of benzylamine. After stirring 2 h at room temperature, ^{1}H NMR analysis showed **25g** and benzylamine. The mixture was concentrated and purified by TLC on two plates using 60% ether–hexane to give 27 mg (61%) of **25g** as a light yellow liquid: IR 3430, 3320, 3059, 3014, 2959, 2865, 1710, 1454, 1189, 762, 697 cm^{-1}; ^{1}H NMR δ 7.4–7.2 (m, 5), 3.72 (dd, 1, J = 7, 6 Hz), 3.69 (AB, 2, J_{AB} = 13 Hz, $\Delta\nu$ = 47 Hz), 3.7–2.6 (br s, 2), 1.8–1.5 (m, 2), 1.4–1.2 (m, 10, including singlets at 1.37 and 1.35), 0.90 (t, 3, J = 7 Hz); MS (EI) m/z (rel intensity) 264 (1), 176 (41), 133 (6), 91 (100), 68 (5); exact mass 264.195, calcd for $C_{16}H_{26}O_2N$ 264.1964.

2-Hydroxy-2-methyl-4-(propylamino)-3-octanone (25h). To a stirred solution of 29 mg (0.2 mmol) of **8a** in 2 mL of $CDCl_3$ was added 55 mg (5 equiv) of n-propylamine. After being stirred for 0.5 h at room temperature, the reaction mixture was concentrated to give a colorless liquid. Preparative TLC on two plates using 2.5% MeOH in $CHCl_3$ containing 1% NH_4OH provided 33 mg (83%) of **25h** as a colorless liquid: IR 3410, 3320, 1705, 1462, 1371, 1189 cm^{-1}; ^{1}H NMR δ 5.0–3.0 (br s, 2), 3.58 (t, 1, J = 7 Hz), 2.46 (t, 2, J = 7 Hz), 1.8–1.2 (m, 14, including singlets at 1.34 and 1.32), 0.90 (t, 3, J = 7 Hz), 0.88 (t, 3, J = 7 Hz); MS (CI) m/z (rel intensity) 216 (13), 198 (1), 129 (8), 128 (100), 100 (7), 98 (3), 86 (6), 70 (3); exact mass 216.196, calcd for $C_{13}H_{26}O_2N$ 216.1965. The ^{1}H NMR spectrum also showed <10% of a second component with a signal at δ 4.33 (dd, J = 8, 3 Hz) tentatively assigned as 4-hydroxy-2-methyl-2-(propylamino)octan-3-one (**26h**).

2-Hydroxy-4-(1-imidazolyl)-2-methyloctan-3-one (25i). To a stirred solution of 20 mg (0.13 mmol) of **8a** in 0.35 mL of $CDCl_3$ was added 26 mg (3 equiv) of imidazole. After stirring for 2.5 h at room temperature, ^{1}H NMR analysis showed **25i** and imidazole. The reaction mixture was concentrated and the product was purified by TLC on two plates using 10% MeOH and 1% Et_2NH in $CHCl_3$ to provide 14 mg (48%) of **25i** as a colorless liquid: IR 3120, 2959, 2928, 2857, 1726, 1499, 1466, 1371, 1195, 912, 762 cm^{-1}; ^{1}H NMR δ 7.59 (s, 1), 7.02 (s, 1), 6.94 (s, 1), 5.54 (dd, 1, J = 8, 6 Hz), 3.8 (br s, 1), 2.1–1.8 (m, 2), 1.39 (s, 3), 1.37 (s, 3), 1.4–1.0 (m, 4), 0.85 (t, 3, J = 7 Hz); MS (EI) m/z (rel intensity) 225 (8), 181 (7), 137 (100), 109 (25), 96 (22), 95 (87), 81 (38); exact mass 225.159, calcd for $C_{12}H_{21}O_2N_2$ 225.1604.

2-Hydroxy-2-methyl-4-(phenylthio)octan-3-one (25j). To a stirred solution of 42 mg (0.27 mmol) of **8a** in 0.5 mL of $CDCl_3$ was added 31 mg (1.1 equiv) of benzenethiol. After being stirred for 21 h at room temperature, the reaction mixture was concentrated and purified by TLC on two plates using 40% ether–hexane to provide 39 mg (55%) of **25j** as a colorless liquid: IR 3480, 3061, 2962, 2863, 1701, 1463, 911, 732, 691 cm^{-1}; ^{1}H NMR δ 7.4–7.3 (m, 5), 4.11 (dd, 1, J = 8, 7 Hz), 3.2 (br s, 1), 1.9–1.6 (m, 2), 1.5–1.2 (m, 10, including singlets at 1.45 and 1.37), 0.87 (t, 3, J = 7 Hz); MS (EI) m/z (rel intensity) 266 (42), 249 (51), 218 (4), 208 (15), 180 (21), 179 (55), 168 (20), 151 (20), 123 (50), 110 (100), 85 (39), 59 (69); exact mass 266.132, calcd for $C_{15}H_{22}O_2S$ 266.1341.

4-Fluoro-2-hydroxy-2-methyloctan-3-one (25k). To a stirred solution of 26 mg (0.16 mmol) of **8a** in 0.5 mL of THF was added 0.20 mL (1.2 equiv) of 1.0 M n-Bu_4NF in THF all at once. The resulting solution was yellow in color. After being stirred for 5 min, the reaction mixture was hydrolyzed with water and ether was added. The organic phase was separated and washed with water, dried (K_2CO_3), and concentrated to give a brown liquid. Preparative TLC using 50% ether–hexane gave 10 mg (35%) of **25k** as a colorless liquid: IR 3480, 2960, 2864, 1723, 1462, 1176 cm^{-1}; ^{1}H NMR δ 5.16 (ddd, 1, J = 50, 8, 4 Hz), 3.4 (br s, 1), 2.1–1.8 (m, 2), 1.7–1.3 (m, 10, including singlets at 1.47 and 1.46), 0.92 (t, 3, J = 7 Hz); MS (EI) m/z (rel intensity) 177 (4), 159 (16), 142 (9), 125 (37), 103 (5), 98 (100), 85 (30), 83 (13), 71 (22); exact mass 177.129, calcd for $C_9H_{18}O_2F$ 177.1291.

5-*tert*-Butyl-2,2-dimethyl-1,4-dioxaspiro[2.2]pentane (8b).[2] To a 40-mg (0.32 mmol) sample of 2,2,5-trimethyl-3,4-hexadiene (**7b**) was added 16 mL (5 equiv) of a solution of **6**. After 10 min, the solvent was removed and the residue was diluted with ether, dried (K_2CO_3), and concentrated to give 42 mg (84%) of **8b** as a colorless liquid: IR 1635, 949, 807 cm^{-1}; ^{1}H NMR δ 3.52 (s, 1), 1.53 (s, 3), 1.50 (s, 3), 0.97 (s, 9); ^{13}C NMR δ 88.3 (s), 69.4 (dm, J = 171, 5 Hz), 63.4 (m, J = 5 Hz), 31.1 (m, J = 4 Hz), 25.6 (qm, J = 125, 4 Hz), 22.4 (qd, J = 128, 4 Hz), 20.2 (qd, J = 128, 4 Hz).

2,2,5,5-Tetramethyl-1,4-dioxaspiro[2.2]pentane (10). A mixture of 25 mL (4 equiv) of **6** containing 4 g of K_2CO_3 was stirred under nitrogen at room temperature for 5 min. The solution was cooled to −50 °C and 60 mg (0.63 mmol) of tetramethylallene[4] was added. Stirring was continued at −50 °C for 0.5 h. The reaction mixture was concentrated to dryness and the salts were washed with ether. The ether extract was dried (K_2CO_3) and concentrated on the rotary evaporator with the bath temperature below 20 °C, to give 35 mg (44%) of **10** as a white, crystalline solid: mp (sealed cap) 52–53.5 °C; IR (Nujol) 1629 cm^{-1}; ^{1}H NMR δ 1.54 (s, 6), 1.47 (s, 6); ^{13}C NMR δ 93.6 (s), 64.5 (m, J = 5 Hz), 21.3 (qm, J = 128, 3 Hz), 20.1 (qm, J = 128, 3 Hz); MS (CI) m/z (rel intensity) 129 (9), 111 (19), 100 (5), 83 (15), 71 (13), 70 (100), 69 (31); exact mass 129.091, calcd for $C_7H_{13}O_2$ 129.0916.

Reaction of 10 with Acetic Acid. To a stirred solution of 7 mg (0.05 mmol) of **10** in 0.4 mL of $CDCl_3$ was added 31 mg (10 equiv) of acetic acid. The reaction was stirred at room temperature for 3.5 h. Excess K_2CO_3 was added, and after being stirred for

15 min, the reaction mixture was filtered and concentrated. ^1H NMR analysis showed a 1:1 ratio of 2-acetoxy-4-hydroxy-2,4-dimethylpentan-3-one (**52**) and 4-hydroxy-2,4-dimethyl-1-penten-3-one (**51**), respectively. Compound **52**: ^1H NMR δ 2.08 (s, 3), 1.65 (s, 6), 1.48 (s, 6). Compound **51**: δ 5.94 (s, 1), 5.84 (q, 1, J = 1 Hz), 1.96 (t, 3, J = 1 Hz), 1.52 (s, 6). These data are in good agreement with those reported earlier.[4]

2,2-Dibutyl-1,4-dioxaspiro[2.2]pentane (15). To a stirred solution of 12 mL (7 equiv) of **6** containing 2 g of K_2CO_3 at −40 °C under nitrogen was added 25 mg (0.16 mmol) of 3-butyl-1,2-heptadiene (**14**). The reaction mixture was stirred at −40 °C for 1.5 h and allowed to warm to ca. −5 °C over a 40-min period. The reaction was concentrated to dryness and the salts were washed with ether. Filtration and concentration gave 25 mg (83%) of **15** as a colorless liquid: IR 1619 cm^{-1}; ^1H NMR δ 3.46 (d, 1, J = 3 Hz), 3.28 (d, 1, J = 3 Hz), 2.0–1.7 (m, 4), 1.5–1.2 (m, 8), 0.91 (t, 3, J = 7 Hz), 0.89 (t, 3, J = 7 Hz); ^{13}C NMR δ 85.6 (s), 68.8 (s), 48.8 (t, J = 175 Hz), 32.3 (t), 31.9 (t), 26.5 (t), 26.2 (t), 22.7 (t), 13.9 (q).

Attempted purification of a 43-mg sample of **15** by preparative TLC using 50% ether–hexane gave 11 mg (26%) of (*Z*)-3-butyl-1-hydroxy-3-hepten-2-one ((*Z*)-**53**), 7 mg (16%) of (*E*)-3-butyl-1-hydroxy-3-hepten-2-one ((*E*)-**53**), and 7 mg (16%) of (*E*)-3-butyl-1-hydroxy-3-hepten-2-one ((*E*)-**53**), and 7 mg (16%) of 2,2-dibutyl-3-oxacyclobutanone (**54**). A small amount (4 mg) of an unidentified polar compound was also isolated. Compound (*Z*)-**53**: IR 3460, 2962, 2937, 2866, 1690, 1620, 1054 cm^{-1}; ^1H NMR δ 5.84 (t, 1, J = 6 Hz), 4.36 (d, 2, J = 4 Hz), 3.45 (t, 1, J = 4 Hz), 2.3–2.2 (m, 4), 1.5–1.2 (m, 6), 1.0–0.9 (m, 6); MS (CI) m/z (rel intensity) 185 (4), 153 (93), 143 (31), 137 (10), 111 (11), 98 (13), 85 (83), 69 (100); exact mass 185.154, calcd for $C_{11}H_{21}O_2$ 185.1542. Compound (*E*)-**53**: IR 3480, 2961, 2939, 2864, 1675, 1641, 1071 cm^{-1}; ^1H NMR δ 6.51 (t, 1, J = 7 Hz), 4.52 (d, 2, J = 5 Hz), 3.45 (t, 1, J = 5 Hz), 2.4–2.2 (m, 4), 1.6–1.2 (m, 6), 0.97 (t, 3, J = 7 Hz), 0.92 (t, 3, J = 7 Hz); MS (CI) m/z (rel intensity) 185 (3), 159 (13), 153 (87), 131 (63), 119 (20), 85 (100), 69 (66); exact mass 185.151, calcd for $C_{11}H_{21}O_2$ 185.1542. Compound **54**: IR 2961, 2940, 2863, 1820, 1461, 962 cm^{-1}; ^1H NMR δ 5.09 (s, 2), 1.8–1.2 (m, 12), 0.92 (t, 6, J = 7 Hz); MS (CI) m/z (rel intensity) 185 (3), 169 (11), 155 (22), 153 (44), 143 (36), 141 (100), 127 (18), 85 (50), 71 (75); exact mass 185.152, calcd for $C_{11}H_{21}O_2$ 185.1542.

3-Butyl-1-(diethylamino)-3-hydroxyheptan-2-one (30). To a stirred solution of 20 mL (12 equiv) of **6** (stirred over K_2CO_3 at room temperature for 10 min, then filtered) at −50 °C under nitrogen was added 25 mg (0.16 mmol) of 3-butyl-1,2-heptadiene (**14**). The reaction mixture was stirred at −40 °C for 1 h and allowed to warm to 10 °C over a period of 1 h. The mixture was cooled to −40 °C and 166 mg (12 equiv) of tetramethylethylene was added. After stirring for 5 min, 96 mg (8 equiv) of diethylamine was added, and the cooling bath was removed. The mixture was allowed to warm to room temperature and stirred an additional 0.5 h. The reaction volume was reduced to 1 mL and ether was added. The solution was dried (K_2CO_3), concentrated, and purified by preparative TLC on two plates using 2.5% MeOH in $CHCl_3$ containing 1% NH_4OH to provide 32 mg (76%) of **30** as a colorless liquid: IR 3490, 2962, 2871, 1710, 1455, 1379, 1163, 1045 cm^{-1}; ^1H NMR δ 3.67 (s, 2), 2.57 (q, 4, J = 7 Hz), 1.7–1.6 (m, 4), 1.5–1.2 (m, 8), 1.06 (t, 6, J = 7 Hz), 0.87 (t, 6, J = 7 Hz); MS (CI) m/z 258 (10), 200 (2), 143 (2), 116 (1), 100 (1), 86 (100); exact mass 258.242, calcd for $C_{15}H_{32}O_2N$ 258.2435.

2-*tert*-Butyl-1,4-dioxaspiro[2.2]pentane (12a). To a stirred mixture of 15 mL of a solution of **6** and 2 g of K_2CO_3 was added 22 mg (0.23 mmol) of **11a**. This oxidant solution had only been treated with K_2CO_3 prior to use. After 1 h at room temperature, the mixture was concentrated and the solid residue was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 23 mg (78%) of *anti*-**12a** as a clear liquid: IR 1615 cm^{-1}; ^1H NMR δ 3.53 (d, 1, J = 1 Hz), 3.52 (dd, 1, J = 3, 1 Hz), 3.30 (d, 1, J = 3 Hz), 0.99 (s, 9); ^{13}C NMR δ 80.8 (td, J = 5, 2 Hz), 67.3 (dm, J = 172, 5 Hz), 48.3 (dd, J = 178, 177 Hz), 31.1 (dm, J = 8, 4 Hz), 25.7 (q); MS (CI) m/z (rel intensity) 129 (18), 128 (20), 113 (8), 99 (33), 97 (43), 87 (100), 69 (99); exact mass 128.084, calcd for $C_7H_{12}O_2$ 128.0837.

The presence of ca. 2% of *syn*-**12a** was suggested by weak ^1H NMR signals at δ 3.35 (s, 1), 3.34 (d, 1, J = 3 Hz), 3.20 (d, 1, J = 3 Hz), and 1.05 (s, 9). The same ^1H NMR sample after standing 12 h showed 97% of *anti*-**12a** and 3% of **28c** with no *syn*-**12a** evident.

Repeated oxidations of **11a** with carefully dried dioxirane solutions afforded **12a** cleanly, but in only 10–15% yields. A reaction of 97 mg (1 mmol) of **11a** with 25 mL of a solution of **6** containing 2.5 mL of added water gave a mixture of **12a** (25%) and **28c** (10%).

1,3-Dihydroxy-4,4-dimethyl-2-pentanone (28c). A solution of 16 mg (0.125 mmol) of **12a** in 1 mL of H_2O and 1 mL of THF was stirred at room temperature for 2 h. The reaction mixture was concentrated, diluted with ether, dried ($MgSO_4$), and concentrated to give 16 mg (88%) of **28c** as a colorless liquid, which subsequently crystallized: mp 46–48 °C; IR 3500 (br), 1712, 1470, 1400, 1362, 1276, 1072, 1014 cm^{-1}; ^1H NMR δ 4.50 (dd, 1, J = 20, 5 Hz), 4.34 (dd, 1, J = 20, 5 Hz), 3.90 (d, 1, J = 6.5 Hz), 3.02 (t, 1, J = 5 Hz), 2.50 (d, 1, J = 6.5 Hz), 0.98 (s, 9); ^{13}C NMR δ 208.8 (s), 82.5 (d), 68.1 (t), 35.6 (s), 25.8 (q); MS (CI) m/z (rel intensity) 147 (9), 129 (18), 87 (100), 69 (56); exact mass 147.098, calcd for $C_7H_{15}O_3$ 147.1021.

Preparation of 28c from 11a. A mixture of 15 mg (0.16 mmol) of **11a** in 10 mL of a solution of **6** and 5 mL of water was stirred for 1 h. The mixture was concentrated, diluted with ether, dried ($MgSO_4$), and concentrated to give 18 mg (79%) of **28c**.

1-(Diethylamino)-3-hydroxy-4,4-dimethyl-2-pentanone (28b). To a solution of 10 mg (0.1 mmol) of **12a** in $CDCl_3$ in an NMR tube was added 15 μL (0.15 mmol) of diethylamine. After 24 h at room temperature, NMR indicated clean conversion to **28b**. Concentration gave 13 mg (83%) of **28b** as a yellow liquid: IR 1710 cm^{-1}; ^1H NMR δ 4.8 (br s, 1), 3.90 (s, 1), 3.48 (d, 1, J = 15 Hz), 3.12 (d, 1, J = 15 Hz); 2.60 (dq, 2, J = 13, 7 Hz), 2.50 (dq, 2, J = 13, 7 Hz), 1.04 (t, 6, J = 7 Hz), 0.96 (s, 9); ^{13}C NMR δ 211.9 (s), 84.8 (d), 64.5 (t), 47.9 (t), 36.0 (s), 26.1 (q), 11.5 (q); MS (CI) m/z (rel intensity) 202 (6), 144 (4), 121 (100), 102 (2), 86 (84); exact mass 202.181, calcd for $C_{11}H_{24}NO_2$ 202.1808.

1-Acetoxy-3-hydroxy-4,4-dimethyl-2-pentanone (28a). To a solution of 15 μL (0.1 mmol) of **12a** and 600 μL of $CDCl_3$ in a NMR tube was added 100 μL of triethylammonium acetate (prepared by mixing 100 μL of glacial acetic acid with 240 μL of triethylamine). After 18 h, **12a** was converted into **28a** as the only product by ^1H NMR. The reaction mixture was diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and concentrated to give 15 mg (68%) of **28a** as a yellow liquid: IR 3450, 1742, 1725 cm^{-1}; ^1H NMR δ 4.97 (d, 1, J = 18 Hz), 4.73 (d, 1, J = 18 Hz), 3.88 (s, 1), 2.80 (br s, 1), 2.15 (s, 3), 0.99 (s, 9); ^{13}C NMR δ 205.8 (s), 170.4 (s), 82.8 (d), 68.1 (t), 35.5 (s), 25.8 (q), 20.4 (q); MS (CI) m/z (rel intensity) 189 (11), 171 (10), 129 (40), 99 (34), 87 (100), 69 (71); exact mass 189.113, calcd for $C_9H_{17}O_4$ 189.1127.

Reaction of 12a with Acetic Acid. To a solution of 15 μL of **12a** and 600 μL of $CDCl_3$ in a NMR tube was added 100 μL of glacial acetic acid. The progress of the reaction was monitored by ^1H NMR. After 1 min, the proportions of **12a**, **58a**, **28a** was 1.9:4.5:1. After 15 min, **12a** had reacted completely, and the ratio of **58a** to **28a** was 2.5:1; after 30 min, the ratio was 1.9:1. After 20 h, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to give 15 mg of a colorless liquid, which consisted of **58a**, **28a**, **56**, and **57** in the proportions of 1.8:1.0:0.2:0.1, along with two unidentified products in smaller amounts. Compound **58a** shows the following ^1H NMR spectrum: δ 4.80 (s, 1), 4.38 (dd, 1, J = 19, 5 Hz), 4.25 (dd, 1, J = 19, 5 Hz), 2.97 (t, 1, J = 5 Hz), 2.13 (s, 3), 1.00 (s, 9). Its facile isomerization to **28a** prevented isolation of **58a** in pure form.

Rearrangement of 58a to 28a by Triethylammonium Acetate. To a 1.8:1 mixture of **58a** and **28a** in 500 μL of $CDCl_3$ in an NMR tube was added 50 μL of triethylammonium acetate in 250 μL of acetone-d_6. After 1.5 h, the ratio of **58a** to **28a** as determined by ^1H NMR had changed to 1.5:1; after 21 h, it was 1:2.

Decomposition of 12a on Silica Gel. A sample of **12a** was applied to a preparative TLC plate. After standing for 0.5 h, it was developed with ether to give three bands. The low R_f band was identified as **55**: IR 3400 (br), 1710, 1160, 1080, 1000, 940, 875 cm^{-1}; ^1H NMR δ 4.30 (d, 2, J = 5 Hz), 3.10 (t, 1, J = 5 Hz), 2.64 (q, 1, J = 7 Hz), 2.45 (s, 1), 1.24 (s, 3), 1.19 (s, 3), 1.15 (d, 3, J = 7 Hz); ^{13}C NMR δ 214.9 (s), 72.0 (s), 69.0 (t), 51.1 (d), 29.3 (q), 26.1 (q), 12.4 (q); MS (CI) m/z (rel intensity) 147 (59), 129

(100), 115 (26), 97 (46), 91 (31); exact mass 147.103, calcd for $C_7H_{15}O_3$ 147.1021. The middle band was identified as **28c**. The high R_f band was a mixture of two compounds assigned as **56** and **57**: IR 3484, 1716, 1677, 1644, 1614, 1291, 1096, 1007 cm^{-1}; exact mass 128.084, calcd for $C_7H_{12}O$ 128.0837. Compound **56**: ^1H NMR δ 4.93 (m, 1), 4.89 (m, 1), 4.36 (dd, 1, J = 19, 5 Hz), 4.19 (dd, 1, J = 19, 5 Hz), 3.24 (q, 1, J = 7 Hz), 2.99 (t, 1, J = 5 Hz); 1.67 (m, 3), 1.23 (d, 3, J = 7 Hz); ^{13}C NMR δ 210.3 (s), 143.3 (s), 114.4 (t), 66.5 (t), 50.8 (d), 23.1 (q), 14.3 (q). Compound **57**: ^1H NMR δ 4.33 (d, 2, J = 5 Hz), 3.52 (t, 1, J = 5 Hz), 2.03 (m, 3), 1.84 (m, 3), 1.83 (m, 3); ^{13}C NMR δ 202.6 (s), 146.5 (s), 126.4 (s), 67.3 (t), 23.3 (q), 19.9 (q), 14.2 (q). GC-MS showed characteristic fragmentation for **56** at m/z (rel intensity) 128 (0.4), 113 (3), 97 (44), 69 (100) and **57** at m/z 128 (2), 97 (100), 69 (69). Compounds **58a**, **28c**, **56**, and **57** were obtained in the proportions of 1.9:3.3:1.5:1 as determined by ^1H NMR analysis of a sample obtained by extracting all organic material from a vertical section of the TLC plate.

Reaction of 12a with *p*-Toluenesulfonic Acid. To a solution of 8 mg (0.06 mmol) of **12a** and 500 μL of $CDCl_3$ in an NMR tube was added 20 mg (0.1 mmol) of *p*-toluenesulfonic acid hydrate. About 150 μL of acetone-d_6 was added to dissolve the acid. After 0.5 h, **12a** had completely reacted as indicated by ^1H NMR. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to give 15 mg of a colorless liquid which consisted of **58b**, **56**, **57**, and **59** in the proportions of 11:2:1:3. Compound **58b** was isolated by column chromatography on silica gel with ether as eluant: mp 83–84 °C; IR 3520 (br), 1730, 1601, 1374, 1198, 964, 790 cm^{-1}; ^1H NMR δ 7.77 (m, 2), 7.35 (m, 2), 4.51 (s, 1), 4.41 (dd, 1, J = 20, 4 Hz), 4.32 (dd, 1, J = 20, 6 Hz), 2.83 (dd, 1, J = 6, 4 Hz), 2.45 (s, 3), 0.88 (s, 9); ^{13}C NMR δ 206.8 (s), 145.7 (s), 132.4 (s), 130.1 (d), 128.1 (d), 88.8 (d), 67.7 (t), 35.3 (s), 25.9 (q), 21.7 (q); MS (CI) m/z (rel intensity) 301 (0.5), 283 (4), 241 (10), 155 (100), 129 (16), 91 (81); exact mass 301.111, calcd for $C_{14}H_{21}O_5S$ 301.1110. Assignment of 4,4,5-trimethyl-3-oxacyclopentanone (**59**) rests on its spectral data: IR 1759, 1456, 1441, 1389, 1373, 1310, 1292, 1182, 1054, 841, 787, 774, 760, 745, 731; ^1H NMR δ 4.09 (dd, 1, J = 17, 1 Hz), 3.86 (d, 1, J = 17 Hz); 2.25 (qd, 1, J = 7, 1 Hz); 1.43 (s, 3); 1.07 (s, 3), 1.00 (d, 3, J = 7 Hz); ^{13}C NMR δ 217.7 (s), 82.6 (s), 68.9 (t), 52.4 (d), 27.5 (q), 20.9 (q), 8.6 (q); MS (EI) m/z (rel intensity) 128 (21), 113 (14), 85 (89), 70 (100).

2-Decyl-1,4-dioxaspiro[2.2]pentane (12b). To a stirred solution of 10 mL (5 equiv) of **6** containing 2 g of K_2CO_3 and 2 g of 4-Å molecular sieves was added 40 mg (0.2 mmol) of 1,2-tridecadiene (**11b**). After 1.6 h, the reaction mixture was concentrated, and the residue was extracted with ether. The extract was filtered, dried ($MgSO_4$), and concentrated to give 17 mg of a yellow liquid, which consisted of **11b**, *anti*-**12b**, *syn*-**12b**, and **29** in a ratio of 25:12:1:1. The yield of **12b** was ca. 15%. (In another experiment where no **29** was formed, the ratio of isomeric spirodioxides was 9:1). The IR spectrum of the mixture showed a band at 1616 cm^{-1}. The major isomer *anti*-**12b** showed the following characteristic spectral data: ^1H NMR δ 3.75 (td, 1, J = 6, 1 Hz), 3.47 (dd, 1, J = 3, 1 Hz), 3.30 (d, 1, J = 3 Hz); ^{13}C NMR δ 82.3, 60.5, 47.8. The following proton signals were characteristic of *syn*-**12b**: ^1H NMR δ 3.60 (dd, 1, J = 7, 6 Hz), 3.51 (d, 1, J = 3 Hz), 3.34 (d, 1, J = 3 Hz).

1,3-Dihydroxy-2-tridecanone (29). A mixture of 32 mg (0.18 mmol) of **11b** in 15 mL of a solution of **6** and 5 mL of water was stirred for 0.5 h. The mixture was concentrated, diluted with ether, dried ($MgSO_4$), and concentrated to give 36 mg (97%) of **29** as a colorless liquid: IR 3500, 1708, 1455, 1278, 1085, 1020 cm^{-1}; ^1H NMR δ 4.46 (dd, 1, J = 19, 4 Hz), 4.37 (dd, 1, J = 19, 4 Hz), 4.28 (dt, 1, J = 8, 4 Hz), 2.9 (m, 2), 1.75 (m, 1), 1.56 (m, 1), 1.23 (m, 16), 0.85 (t, 3, J = 7 Hz) (decoupling of the hydroxy protons at 2.9 ppm revealed a 1-Hz coupling between the proton at 4.46 and those at 4.37 and 4.28 ppm); ^{13}C NMR δ 209.0 (s), 74.9 (d), 65.5 (t), 34.2 (t), 31.9 (t), 29.54 (t), 29.50 (t), 29.4 (t), 29.30 (t), 29.28 (t), 24.6 (t), 22.7 (t), 14.1 (q); MS (CI) m/z (rel intensity) 231 (0.3), 169 (1), 137 (1), 133 (4), 121 (2), 119 (6), 83 (100); exact mass 231.202, calcd for $C_{13}H_{27}O_3$ 231.1961. On standing, **29** crystallized as a white solid (mp 115–118 °C), which is insoluble in hexane, dichloromethane, and DMSO.

2,5-Di-*n*-propyl-1,4-dioxaspiro[2.2]pentane (17a). To 35 mL of a stirred solution of **6** over 3 g of K_2CO_3 at room temperature was added 98 mg (0.8 mmol) of **16a**. After 20 min the reaction mixture was concentrated and the product was washed from the drying agent with ether. This solution was filtered, dried (K_2CO_3), and concentrated to give 125 mg (99%) of **17a** as a 1:1:0.15 mixture of diastereomers: IR 1625 cm^{-1}; MS (CI) m/z (rel intensity) 157 (19), 139 (12), 113 (23), 84 (47), 71 (100); exact mass 157.124, calcd for $C_9H_{17}O_2$ 157.1229. The ^1H NMR signal at δ 3.71 (dd, 1, J = 7, 5 Hz) is assigned to *anti,anti*-**17a**, those at δ 3.74 (t, J = 6 Hz) and 3.54 (t, J = 6) are assigned to *anti,syn*-**17a**, and the signal at δ 3.58 (dd, J = 7, 5 Hz) is assigned to *syn,syn*-**17a**. In addition, complex overlapping multiplets are observed at δ 1.95–1.65, 1.61–1.39, and 1.05–0.9 in a ratio of 3:5:6. The ^{13}C NMR signals at δ 85.3 (s), 60.1 (d, J = 174 Hz), 32.0 (t), 18.8 (t), and 13.8 (q) are assigned to *anti,anti*-**17a** and those at δ 85.7 (s), 61.0 (d, J = 174 Hz), 59.3 (d, J = 171 Hz), 32.0 (t), 31.0 (t), 18.9 (t), 18.5 (t), and 13.8 (t) are assigned to *anti,syn*-**17a**.

4,6-Dihydroxy-5-nonanone (31a). A solution of 100 mg (0.6 mmol) of **17a** in 2 mL of THF and 2 mL of water was stirred for 3.5 h. The mixture was diluted with ether and the extract was dried (K_2CO_3) and concentrated to give 87 mg (78%) of a 1.1 to 1 diastereomeric mixture of **31a** as a clear oil: ^1H NMR δ 4.42 (m, 2), 2.80 (br s, 2), 1.90–1.70 (m, 4), 1.65–1.25 (m, 4), 0.95 (t, 6, J = 7 Hz); IR 3440, 1710, 1250, 1060, 905, 730 cm^{-1}; MS (CI) m/z (rel intensity) 175 (4), 157 (15), 131 (9), 103 (26), 84 (100), 73 (100), 71 (62); exact mass 175.133, calcd for $C_9H_{19}O_3$ 175.1335. ^{13}C NMR signals at δ 214.6 (s), 74.6 (d, J = 147 Hz), 36.4 (t), 18.4 (t), and 13.8 (q) are assigned to 1,3-*syn*-**31a** and those at δ 214.2 (s), 73.5 (d, J = 143 Hz), 35.8 (t), 18.1 (t), and 13.8 (q) are assigned to 1,3-*anti*-**31a**.

4-Acetoxy-6-hydroxy-5-nonanone (31b). A mixture of 85 mg (0.3 mmol) of tetra-*n*-butylammonium acetate and 22 mg (0.1 mmol) of **17a** in 2 mL of THF containing 2 drops of glacial HOAc was stirred over 4-Å molecular sieves for 0.5 h at 0 °C and then at 2.5 h at ambient temperature. The reaction mixture was diluted with ether, washed with water, saturated $NaHCO_3$ solution, and brine, then dried ($MgSO_4$), and concentrated. Purification by flash chromatography through a column of silica gel using ether–hexane (1:2) gave 25 mg (85%) of a 1.4:1 diastereomeric mixture of **31b** as a clear oil: IR 3445, 1725 (br) cm^{-1}; MS (CI) m/z (rel intensity) 217 (60), 199 (50), 157 (100), 139 (30), 115 (15), 84 (59), 71 (64); exact mass 217.139, calcd for $C_{11}H_{20}O_4$ 217.1440. The ^1H NMR signals at δ 5.38 (dd, J = 8, 4 Hz), 4.42 (ddd, J = 8, 6, 3 Hz), 2.98 (d, J = 6 Hz), 2.11 (s) of relative intensity 1:1:1:3 are assigned to 1,3-*syn*-**31b**; signals at δ 5.30 (dd, J = 9, 5 Hz), 4.32 (ddd, J = 8, 6, 4 Hz), 3.15 (d, J = 6 Hz), 2.12 (s) of relative intensity 1:1:1:3 are assigned to 1,3-*anti*-**31b**. In addition there are complex overlapping multiplets at δ 1.90–1.65, 1.60–1.30, and 0.95 in a ratio of 4:4:6. The ^{13}C NMR signals at δ 210.5, 170.8, 75.4, 75.2, 35.9, 32.8, 20.9, 18.8, and 14.1 are assigned to 1,3-*anti*-**31b**. Those at δ 209.5, 170.9, 75.8, 74.6, 36.7, 33.4, 19.1, 18.8, and 14.1 are assigned to 1,3-*syn*-**31b**.

4-(Propyloxy)-6-hydroxy-5-nonanone (31c). A solution of 157 mg (1 mol) of **17a** in 3 mL of 1-propanol was stirred over K_2CO_3 for 2 h. The solution was diluted with ethyl acetate and washed with water and brine. The aqueous washings were extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated to give 159 mg of **31c** as a 1.3:1 diastereomeric mixture. Separation by elution through a column of silica gel using ether–hexane (1:5) gave 60 mg and 73 mg (53% combined yield) of compounds tentatively assigned as 1,3-*anti*- and 1,3-*syn*-**31c**, respectively. The mixture showed the following: IR 3460, 1717, 1100, 960 cm^{-1}; MS (CI) m/z (rel intensity) 217 (0.9), 199 (8), 157 (10), 115 (100), 73 (93), 69 (58); exact mass 217.182, calcd for $C_{12}H_{25}O_3$ 217.1805. The 1,3-syn isomer showed the following: ^1H NMR δ 4.42 (ddd, 1, J = 8, 7, 4 Hz), 3.91 (dd, 1, J = 7, 6 Hz), 3.50–3.29 (m, 2), 3.32 (d, 1, J = 7 Hz), 2.00–1.35 (m, 10), 1.02–0.95 (m, 9); ^{13}C NMR δ 214.9, 83.8, 74.4, 73.1, 35.8, 34.9, 23.1, 18.9, 18.6, 13.7 (2), 10.6. The 1,3-anti isomer showed the following: ^1H NMR δ 4.51 (ddd, 1, J = 7, 6, 2 Hz), 3.93 (t, 1, J = 5 Hz), 3.53–3.38 (m, 2), 3.30 (d, 1, J = 6 Hz), 1.90–1.30 (m, 10), 1.05–0.95 (m, 9); ^{13}C NMR δ 213.9, 82.8, 74.6, 71.8, 35.6, 32.7, 23.1, 18.6, 17.8, 14.0, 13.8, 10.6.

4-Hydroxy-6-(benzylamino)-5-nonanone (31a). A mixture of 26 mg (0.2 mmol) of **17a** and 21 μL (0.2 mmol) of benzylamine in 200 μL of $CDCl_3$ was stirred at room temperature. After 30 min, TLC and ^1H NMR analysis indicated complete transfor-

mation to **31d** as a 1.1:1 diastereomeric mixture. ^{1}H NMR signals at δ 4.31 (dd, 1, J = 8, 5 Hz), 3.68 (AB, J_{AB} = 13 Hz, $\Delta\nu$ = 31 Hz), and 3.54 (dd, J = 8, 5 Hz) are assigned to the 1,3-syn isomer; signals at δ 4.23 (dd, J = 8, 4 Hz), 3.72 (AB, J_{AB} = 12 Hz, $\Delta\nu$ = 14), and 3.48 (dd, J = 7, 5 Hz) are assigned to the 1,3-anti isomer. In addition complex overlapping multiplets are observed at δ 7.39–7.20, 2.55–1.90, 1.80–1.55, 1.55–1.23, 0.95, and 0.85. Attempted purification by preparative TLC resulted in decomposition.

4-Hydroxy-6-(propylamino)-5-nonanone (31e). A mixture of 28 mg (0.2 mmol) of **17a** and 18 μL (0.2 mmol) of n-propylamine in 200 μL of $CDCl_3$ was stirred at ambient temperature. After 1 h, TLC and ^{1}H NMR analysis indicated clean conversion to a product assigned as **31e** as a roughly 1.1:1 diastereomeric mixture. The ^{1}H NMR signals at δ 3.51 (dd, J = 7, 6 Hz) and 3.42 (dd, J = 7, 6 Hz) are assigned to the 1,3-syn and 1,3-anti isomers, respectively. In addition, complex multiplets and overlapping signals are observed at δ 4.34–4.24, 2.45–2.30, 2.30–1.85 (br), 2.48 (t, J = 7 Hz), 1.80–1.50, 1.50–1.20, and 0.98–0.85. Concentration resulted in decomposition.

6-(Diethylamino)-4-hydroxy-5-nonanone (31f). A mixture of 20 mg (0.1 mmol) of **17a** and 16 μL (0.2 mmol) of diethylamine in 200 μL of $CDCl_3$ was stirred at 0 °C for 1.5 h. TLC and ^{1}H NMR analysis indicated clean conversion to **31f**. The mixture was concentrated and the crude oil was purified by preparative TLC using ether–hexane (6:4) containing 1% NH_4OH to give 25 mg (85%) of **31f** as a 1.2:1 mixture of diastereomers: IR 3450, 1704, 1065, 730 cm^{-1}; MS (CI) (rel intensity) 230 (2), 128 (100), 112 (44), 98 (9), 84 (10), 71 (27); exact mass 230.212, calcd for $C_{13}H_{28}O_2N$ 230.2121; ^{1}H NMR signals at δ 4.18 (dd, 1, J = 8, 4 Hz) and 3.58 (dd, J = 10, 2 Hz) were assigned to the 1,3-syn isomer, those at δ 4.39 (dd, J = 8, 3 Hz) and 3.71 (dd, J = 10, 2 Hz) to the 1,3-anti isomer. Complex overlapping multiplets at δ 2.63–2.33, 1.83–1.20, 1.12–1.10, and 0.95–0.85 are common peaks.

6-Fluoro-4-hydroxy-5-nonanone (31g). A mixture of 42 mg (0.3 mmol) of **17a** and 155 mg (1.28 mmol) of triethylammonium fluoride in 0.8 mL of CH_3CN was stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with H_2O. The organic layer was dried ($MgSO_4$) and concentrated to give a light yellow oil. Purification by preparative TLC using 15% ether in hexane gave 12 mg (25%) of the high R_f diastereomer and 14 mg (29%) of the low R_f diastereomer. The mixture showed the following: IR 3510, 1720, 1465, 1073, 845 cm^{-1}; exact mass (CI) m/z 177.132, calcd for $C_9H_{18}O_2F$ 177.1291. The high R_f diastereomer showed the following: ^{1}H NMR δ 4.99 (ddd, 1, J = 49, 8, 4 Hz), 4.58 (m, 1), 3.06 (d, 1, J = 6 Hz), 1.95–1.70 (m, 3), 1.6–1.4 (m, 5), 0.94 (t, 6, J = 5.7 Hz); ^{13}C NMR δ 94.7 (d, J_{CF} = 181 Hz), 74.1, 35.8, 30.7 (d, J_{CF} = 21 Hz), 18.4, 17.7, 13.7, 13.6, (no carbonyl signal was observed for this diastereomer). The low R_f diastereomer showed the following: ^{1}H NMR δ 4.99 (ddd, 1, J = 49, 9, 4 Hz), 4.7 (m, 1), 3.11 (br s, 1), 1.93–1.70 (m, 3), 1.60–1.38 (m, 5), 1.00–0.88 (m, 6); ^{13}C NMR δ 211.3 (d, J_{CF} = 25 Hz), 95.2 (d, J_{CF} = 183 Hz), 74.2, 35.4, 34.4 (d, J_{CF} = 20 Hz), 18.5, 18.3, 13.7, 13.5. The available data does not permit assignment of stereochemistry in this case.

Nonane-4,5-dione (41). A slurry of 13 mg (0.06 mmol) of **31b** and 0.8 g of silica gel in 8 mL of CH_2Cl_2 was stirred for 3 h. The mixture was diluted with ether and filtered through Celite. The organic solution was dried (Na_2SO_4) and concentrated to give 9 mg (69%) of **41** as a bright yellow oil: ^{1}H NMR δ 2.73 (t, 2, J = 7 Hz), 2.71 (t, 2, J = 7 Hz), 1.7–1.5 (m, 6), 1.4–1.2 (m, 4), 0.9 (m, 6); ^{13}C NMR δ 200.4, 200.3, 38.3, 36.1, 25.5, 22.6, 16.9, 14.1, 14.0; IR 1710 cm^{-1}. This material was identical with an authentic sample.[22] In a similar manner **31c** was completely converted to **41** after 3 h.

2,5-Diisopropyl-1,4-dioxaspiro[2.2]pentane (17b). To 20 mL of a stirrred solution of **6** over 3 g of K_2CO_3 at room temperature was added 61 mg (0.5 mmol) of **16b**. After 20 min the reaction mixture was concentrated and the product was washed from the K_2CO_3 with ether. This solution was filtered, dried (K_2CO_3), and concentrated to give 60 mg (75%) of **17b** as a 2:1 mixture of diastereomers: IR 1619, 900, 775 cm^{-1}; MS (CI) m/z (rel intensity) 157 (18), 139 (10), 119 (21), 85 (17), 71 (100); exact mass 157.123, calcd for $C_9H_{17}O_2$ 157.1229. ^{1}H NMR resonances at δ 3.48 (d, J = 8 Hz), 1.90–1.73 (m), 1.07 (d, J = 7 Hz), and 1.04 (d, J = 7 Hz) with relative areas of 2:2:6 are assigned to the anti,anti isomer. Signals at δ 3.53 (d, J = 6 Hz), 3.27 (d, J = 9 Hz), 2.03–1.85 (m), 1.15 (d, J = 7 Hz), 1.03 (d, J = 7 Hz), 1.02 (d, J = 7 Hz), and 1.00 (d, J = 7 Hz) having relative areas of 1:1:2:3:3:3:3 are assigned to the anti,syn isomer. ^{13}C signals at δ 85.0 (s), 65.1 (d, J = 173 Hz), 29.3 (d), 18.4 (q), and 18.2 (q) are assigned to the anti,anti isomer, while signals at δ 85.0, 65.0, 64.1, 28.8, 28.7, 19.1, 18.2, 18.1, and 18.0 were assigned to the anti,syn isomer.

3,5-Dihydroxy-2,6-dimethyl-4-heptanone (32a). A solution of 62 mg (0.4 mmol) of **17b** in 2 mL of THF and 2 mL of water was stirred overnight. The reaction mixture was diluted with ether and washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated to give 42 mg (62%) of **32a** as a 2:1 mixture of diastereomers: IR 3620, 3500, 1703, 1009 cm^{-1}; MS (CI) m/z (rel intensity) 175 (21), 157 (41), 139 (8), 114 (9), 102 (11), 84 (40), 73 (100); exact mass 175.134, calcd for $C_9H_{19}O_3$ 175.1335. ^{1}H signals at δ 4.32–4.25 (m), 2.72 (d, J = 6 Hz), 2.31 (sept of d, J = 7, 3 Hz), 1.07 (d, J = 7 Hz), and 0.78 (d, J = 7 Hz) with relative areas of 2:2:2:6:6 are assigned to the 1,3-syn isomer, and signals at δ 4.32–4.25 (m), 3.22 (d, J = 6), 2.08 (sept of d, J = 7, 3 Hz), 1.13 (d, J = 7 Hz), and 0.74 (d, J = 7 Hz) having relative areas of 2:2:2:6:6 are assigned to the 1,3-anti isomer. ^{13}C NMR signals at δ 214.2 (s), 79.5 (d, J = 144 Hz), 30.9 (d), 19.7 (q), and 15.1 (q) are assigned to the 1,3-syn isomer, while signals at δ 213.7, 78.0, 32.4, 19.7, and 14.8 are assigned to the 1,3-anti isomer.

3-Acetoxy-2,6-dimethyl-5-hydroxy-4-heptanone (32b). A mixture of 230 mg (0.8 mmol) of tetra-n-butylammonium acetate and 60 mg (0.4 mmol) of **17b** in 1.5 mL of THF containing 1 drop of glacial acetic acid was stirred over 4-Å molecular sieves at 0 °C for 30 min. The mixture was warmed to room temperature and after 5 h was diluted with ether. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), and concentrated to give 62 mg (75%) of **32b** as a 2:1 mixture of diastereomers: IR 3450, 1735, 1715, 1630, 1390, 1370, 1235, 1025, 907 cm^{-1}; MS (CI) m/z (rel intensity) 217 (9), 199 (8), 157 (35), 143 (11), 115 (55), 84 (100), 71 (53); exact mass 217.145, calcd for $C_{11}H_{21}O_4$ 217.1440. ^{1}H NMR signals at δ 5.24 (d, J = 4 Hz), 4.19 (dd, J = 6, 3 Hz), 3.10 (d, J = 6 Hz), 2.32–2.15 (m), 2.15 (s), 1.10 (d, J = 7 Hz), 1.07 (d, J = 7 Hz), 0.90 (d, J = 7 Hz), and 0.79 (d, J = 7 Hz) with relative intensities of 1:1:2:2:3:3:3:3:3 are assigned to the 1,3-anti isomer; signals at δ 5.31 (d, J = 4 Hz), 4.26 (dd, J = 7, 3 Hz), 3.04 (d, J = 7 Hz), 2.36 (sept of d, J = 7, 4 Hz), 2.15 (s), 2.01 (sept of d, J = 7, 3 Hz), 1.09 (d, J = 7 Hz), 0.98 (d, J = 7 Hz), 0.89 (d, J = 7 Hz), and 0.72 (d, J = 7 Hz) with relative areas of 1:1:1:1:3:1:3:3:3:3 are assigned to the 1,3-syn isomer. ^{13}C signals at δ 209.6 (s), 170.4 (s), 79.5 (d, J = 147 Hz), 79.3 (d, J = 150 Hz), 30.3 (d), 29.9 (d), 20.6, 20.1, 19.2, 16.4, and 14.8 are assigned to the 1,3-syn isomer, while resonances at δ 207.8 (s), 170.6 (s), 79.6 (d, J = 150 Hz), 79.2 (d, J = 150 H), 32.0, 30.0, 20.4, 20.2, 19.7, 16.2, and 14.4 are assigned to the 1,3-anti diastereomer.

3-Chloro-2,6-dimethyl-5-hydroxy-4-heptanone (32c). A mixture of 34 mg (0.2 mmol) of **17b**, 30 mg (0.4 mmol) of KCl, 50 mg (0.4 mmol) of $KHSO_4$, and 2 mg of 18-crown-6 was stirred in 0.8 mL of THF for 5 h. The mixture was diluted with ethyl acetate and washed with water and brine. The organic extract was dried (Na_2SO_4) and concentrated to give 39 mg (93%) of a 2:1 diastereomeric mixture of **32c** as a clear oil: IR 3480, 1713, 1020, 937 cm^{-1}; MS (Cl) m/z (rel intensity) 195 (1), 193 (4), 163 (10), 157 (7), 91 (50), 84 (100), 74 (77), 69 (92); exact mass 193.099, calcd for $C_9H_{18}O_2Cl$ 193.1007. ^{1}H NMR signals at δ 4.57 (dd, J = 6, 3 Hz), 4.26 (d, J = 6 Hz), and 1.0 (d, J = 7 Hz) are assigned to the 1,3-syn isomer and signals at δ 4.32 (d, J = 6 Hz), 4.22 (dd, J = 6, 3 Hz), and 1.1 (d, J = 7 Hz) are assigned to the 1,3-anti isomer. Complex overlapping signals at δ 3.3–3.1 (br, s), 2.8–2.5 (m), 2.6–2.4 (m), and 1.6–1.2 (m) are not assigned to specific diastereomers. ^{13}C NMR signals at δ 207.0, 78.6, 65.7, 30.8, 30.5, 19.9, 17.8, and 14.7 are assigned to the 1,3-syn isomer, while signals at δ 206.9, 80.8, 65.3, 32.2, 31.3, 20.0, 18.1, and 15.1 are assigned to the 1,3-anti isomer.

2,6-Dimethyl-5-hydroxy-3,4-heptanedione (33). A solution of 40 mg (0.3 mmol) of **17b** in 1 mL of DMSO was stirred for 2

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h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried ($MgSO_4$) and concentrated to give 40 mg (90%) of **33** as a bright yellow oil: IR 3520, 1707, 1220, 1030, 760 cm^{-1}; ^1H NMR δ 4.73 (d, 1, J = 3 Hz); 3.34 (sept, 1, J = 7 Hz), 2.80 (br s, 1), 2.13 (sept of doublets, 1, J = 7, 3 Hz), 1,12 (d, 3, J = 7 Hz), 1.10 (d, 3, J = 7 Hz), 1.08 (d, 3, J = 7 Hz), 0.74 (d, 3, J = 7 Hz); ^{13}C NMR δ 202.6, 201.0, 77.3, 34.8, 30.9, 19.8, 17.4, 17.1, 15.3; MS (CI) m/z (rel intensity) 173 (4), 155 (4), 130 (8), 71 (100); exact mass (M - H_2O) found 155.108, calcd for $C_9H_{15}O_2$ 155.1073.

2,5-Di-*tert*-butyl-1,4-dioxaspiro[2.2]pentane (17c). To 9 mL (0.9 mmol) of a stirred solution of **6** over K_2CO_3 was added 19 mg (0.13 mmol) of **16c**.[1] After 25 min, the mixture was concentrated and the product was washed from the K_2CO_3 with ether. The solution was dried (K_2CO_3) and concentrated to give 24 mg (98%) of **17c** as a clear oil: IR 1600, 1479, 1107, 908 cm^{-1}; ^1H NMR δ 3.47 (s, 2), 1.01 (s, 18); ^{13}C NMR δ 84.0 (s), 68.7 (d, J = 170 Hz), 31.1 (s), 25.7 (q); MS (CI) m/z (rel intensity) 185 (2), 167 (2), 128 (1), 111 (3), 107 (10), 99 (8), 87 (51), 83 (99), 69 (100); exact mass 185.154, calcd for $C_{11}H_{21}O_2$ 185.1542.

2,5-Hexamethylene-1,4-dioxaspiro[2.2]pentane (22). To 40 mL of a stirred solution of **6** over K_2CO_3 was added 112 mg (0.9 mmol) of **21**.[23] After 20 min the reaction mixture was concentrated and the product was washed from the K_2CO_3 with ether. The extract was filtered, dried, and concentrated to give 135 mg (95%) of **22** as a clear oil: IR 1626, 1605 cm^{-1}; ^1H NMR δ 3.75 (dd, 2, J = 6, 4 Hz), 2.18–2.12 (m, 2), 1.74–1.69 (m, 2), 1.54–1.49 (m, 2), 1.42–1.35 (m, 6); ^{13}C NMR δ 84.3 (s), 60.1 (d, J = 170 Hz), 27.4 (t), 24.7 (t), 20.1 (t); MS (EI) m/z (rel intensity) 154 (8), 130 (29), 98 (100), 82 (83), 69 (65); exact mass 154.100, calcd for $C_9H_{14}O_2$ 154.0994.

***cis*-2,9-Dihydroxycyclononanone (35a).** A solution of 157 mg (1 mmol) of **22** in 2 mL of THF and 2 mL of water was stirred for 3 h. The reaction mixture was diluted with ethyl acetate and washed with H_2O and brine. The aqueous washings were extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated to give 170 mg (98%) of **35a** as a white, flaky solid, which was recrystallized from hexane–ethyl acetate: mp 79.5–82 °C; IR 3478, 1708, 1026 cm^{-1}; ^1H NMR δ 4.34 (dd, 2, J = 8, 2 Hz), 3.36 (br s, 2), 2.23 (ddt, 2, J = 15, 12, 3 Hz), 2.02 (dddd, 2, J = 15, 8, 7, 3 Hz), 1.83–1.75 (m, 2), 1.49–1.41 (m, 2), 1.23–1.17 (m, 2); ^{13}C NMR δ 217.6 (s), 74.8 (d, J = 142 Hz), 31.8 (t), 25.6 (t), 22.7 (t); MS (CI) m/z (rel intensity) 173 (18), 155 (68), 137 (52), 109 (39), 98 (100), 95 (71); exact mass 173.118, calcd for $C_9H_{17}O_3$ 173.1178.

***cis*-2-Acetoxy-9-hydroxycyclononanone (35b).** A mixture of 230 mg (0.8 mmol) of tetra-*n*-butylammonium acetate and 60 mg (0.4 mmol) of **22** in 1.5 mL of THF containing 3 drops of glacial acetic acid was stirred over 4-Å molecular sieves at 0 °C for 30 min and at room temperature for 5 h. The mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution, water, and brine. The organic extract was dried (Na_2SO_4) and concentrated to give 62 mg (76%) of **35b** as a clear oil: IR 3490, 1711, 1240 cm^{-1}; ^1H NMR δ 5.07 (dd, 1, J = 11, 3 Hz), 4.60 (dd, 1, J = 7, 2 Hz), 3.50 (s, 1), 2.25–2.10 (m, 2), 2.09 (s, 3), 2.0–1.8 (m, 2), 1.8–1.5 (m, 2), 1.5–1.2 (m, 6); ^{13}C NMR δ 213.3, 170.6, 75.8, 75.6, 30.4, 28.4, 23.7, 22.7, 22.1, 20.4; MS (CI) m/z (rel intensity) 215 (8), 197 (9), 155 (100), 141 (23), 125 (27), 107 (40), 98 (75), 81 (35), 69 (14); exact mass 215.127, calcd for $C_{11}H_{19}O_4$ 215.1284.

***cis*-9-(Diethylamino)-2-hydroxycyclononanone (35c).** A mixture of 60 mg (0.4 mmol) of **22** and 40 μL (0.8 mmol) of diethylamine in 75 μL of $CDCl_3$ was stirred for 5 h. The reaction mixture was diluted with $CDCl_3$. Spectral data were consistent with structure **35c**: IR 3400, 1700, 1450, 910, 824 cm^{-1}; ^1H NMR δ 4.29 (dd, 1, J = 6, 3 Hz), 3.68 (dd, 1, J = 11, 3 Hz), 2.72–2.63 (m, 2), 2.6–2.46 (m, 2), 2.24–1.96 (m, 2), 1.95–1.65 (m, 2), 1.65–1.15 (m, 8), 1.01 (t, 6, J = 8 Hz) (no OH signal could be assigned). Attempted purification by silica gel chromatography resulted in decomposition.

***cis*-2-((*tert*-Butyldimethylsilyl)oxy)-9-(diethylamino)-cyclononanone (37).** A mixture of 89 mg (0.6 mmol) of **22** and 45 μL (0.9 mmol) of diethylamine in 100 μL of $CDCl_3$ was stirred overnight. The mixture was diluted with 0.5 mL of $CHCl_3$ and 1.0 mL of DMF. To this solution were added 50 mg (0.7 mmol) of imidazole and 110 mg (0.7 mmol) of *tert*-butyldimethylsilyl chloride. After 4 h, 145 μL of triethylamine was added, and the mixture was diluted with ethyl acetate and washed with water and brine. The organic extract was dried (Na_2SO_4) and concentrated to give 100 mg of a bright yellow oil. Purification by silica gel chromatography using ether–hexane (1:4 containing 1% NH_4OH) gave 75 mg (41%) of **37** as a clear oil: IR 1720, 1465, 1250, 840, 730 cm^{-1}; ^1H NMR δ 4.37 (dd, 1, J = 9, 5 Hz), 3.61 (dd, 1, J = 10, 3 Hz), 2.71–2.63 (m, 2), 2.65–2.4 (m, 2), 2.22–2.1 (m, 2), 1.9–1.75 (m, 2), 1.70–1.10 (m, 8), 1.01 (t, 6, J = 7.5 Hz), 0.90 (s, 9), 0.11 (s, 3), 0.01 (s, 3); ^{13}C NMR δ 211.8, 78.3, 62.8, 44.4, 31.0, 26.2, 25.9, 25.8, 24.5, 23.9, 20.3, 18.5, 14.7, -4.3, -5.2; MS (CI) m/z (rel intensity) 342 (17), 313 (19), 284 (23), 255 (8), 112 (100), 99 (22), 86 (32), 73 (24); exact mass 342.284, calcd for $C_{19}H_{40}O_2NSi$ 342.2830.

1,2,3-Trihydroxycyclononane (36). To a stirred solution of 90 mg (0.5 mmol) of **35a** in 8 mL of ether at 0 °C was added 99 mg (2.6 mmol) of $LiAlH_4$ portionwise over a period of 5 min. After 40 min, 400 μL of water was added. The mixture was stirred at room temperature for 2 h and filtered. The filtrate was dried ($MgSO_4$) and concentrated to give 50 mg of a white solid, which consisted of two isomeric triols. These were separated by column chromatography on silica gel using MeOH–CH_2Cl_2 (1:9) as eluent. Triol *cis,cis*-**36** was obtained in pure form as a white solid: mp 88–91 °C; IR 3380, 1260, 1040, 1010, 790 cm^{-1}; ^1H NMR (acetone-d_6/benzene-d_6, 5:1) δ 4.41 (br d, 1, J = 4 Hz, exchangeable with D_2O), 4.09 (br s, 1), 4.01 (ddd, 2, J = 10, 4, 2 Hz after addition of D_2O), 2.24 (dtd, 2, J = 15, 10, 2 Hz; with decoupling at 4.05 ppm, becomes ddd, J = 15, 11, 2 Hz), 1.96 (dddd, 2, J = 15, 8, 4, 2 Hz; with decoupling at 4.05 ppm becomes ddd, J = 15, 8, 2 Hz), 1.86–1.77 (m, 2), 1.66–1.53 (m, 4), 1.51–1.43 (m, 2); ^{13}C NMR δ 78.0 (d), 72.6 (d), 32.9 (t), 27.6 (t), 25.1 (t); MS (CI) m/z (rel intensity) 175 (4), 157 (21), 139 (32), 121 (59), 111 (15), 109 (25), 95 (100); exact mass 175.136, calcd for $C_9H_{19}O_3$ 175.1335. Triol *Trans,trans*-**36** was contaminated with ca. 10% of the cis,cis isomer: ^1H NMR δ 3.70 (t, 1, J = 8 Hz), 3.61 (ddd, 2, J = 8, 6, 3 Hz), 3.20 (br s, 1), 2.57 (br s, 2), 1.86 (m, 2), 1.78 (m, 2), 1.70–1.42 (m, 8); ^{13}C NMR δ 75.5 (d), 72.5 (d), 32.4 (t), 27.1 (t), 22.5 (t).

To a mixture of 184 μL (2.0 mmol) of acetic anhydride, 197 μL (2.4 mmol) of pyridine, and 20 mg of (*N,N*-dimethylamino)-pyridine in 2 mL of CH_2Cl_2 at 0 °C was added 85 mg (0.5 mmol) of **36** in 3 mL of CH_2Cl_2. The mixture was stirred at room temperature for 20 min, diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and concentrated to give 53 mg (36%) of a viscous yellow liquid, which consisted of the cis,cis and trans,trans triacetates in a ratio of 7:1 by ^1H NMR: IR 1742, 1234, 1047, 1029, 956 cm^{-1}. The major cis,cis isomer shows the following: ^1H NMR δ 5.37 (br s, 1); 5.06 (ddd, 2, J = 9, 3, 2 Hz; decoupling at 5.37 gives dd, J = 9, 3 Hz), 2.18–2.08 (m, 2), 2.10 (s, 3), 2.03–1.96 (m, 2), 1.98 (s, 6), 1.76–1.67 (m, 2), 1.64–1.52 (m, 6); ^{13}C NMR δ 170.0 (s), 169.9 (s), 75.4 (d), 74.5 (d), 29.3 (t), 27.0 (t), 25.6 (t); MS (CI) m/z (rel intensity) 301 (3), 241 (90), 215 (20), 181 (100), 138 (100), 210 (60), 81 (20); exact mass (M - HOAc) 241.145, calcd for $C_{13}H_{21}O_4$ 241.1440. The trans,trans isomer shows the following partial spectra: ^1H NMR δ 5.32 (t, 1, J = 9 Hz), 5.0 (m, 2); ^{13}C NMR δ 169.8 (s), 71.9 (d), 29.1 (t), 25.5 (t), 20.5 (t).

1,2-Cyclononanedione (38).[4] A slurry of 108 mg (0.7 mmol) of **35b** and 3 g of silica gel in 5 mL of CH_2Cl_2 was stirred overnight. The mixture was diluted with ether and filtered through Celite. The filtrate was dried (Na_2SO_4), concentrated, and chromatographed (silica gel, 1:4 ether–hexanes) to give 40 mg (50%) of **38** as a yellow oil: IR 1700, 1116, 1195, 800 cm^{-1}; ^1H NMR δ 2.7 (m, 4), 1.9–1.8 (m, 4), 1.55–1.5 (m, 6); ^{13}C NMR δ 208.0, 37.2, 25.1, 24.8, 23.2.

2-*tert*-Butyl-5-pentyl-1,4-dioxaspiro[2.2]pentane (24). A solution of 67 mg (0.4 mmol) of **23**[15] in 20 mL of a solution of **6** over K_2CO_3 was stirred for 45 min at room temperature. The mixture was concentrated and the product was taken up in ether, dried, and concentrated to give 80 mg (100%) of **24** as a 2.4:1 mixture of isomers: IR 1620, 1083, 988, 735 cm^{-1}. ^1H NMR signals at δ 3.68 (ddd, 1, J = 8, 3, 1 Hz), 3.47 (d, 1, J = 1), and 0.97 (s, 9) are assigned to *anti,anti*-**24** and those at δ 3.51 (dd, 1, J = 6.4, 5.7 Hz), 3.50 (s, 1), and 0.96 (s, 9) to *anti,anti*-**24**; additional signals are observed at δ 1.98–1.90 (m), 1.89–1.83 (m), 1.81–1.74 (m), 1.60–1.40 (m), 1.38–1.20 (m), and 0.91–0.85 (m). ^{13}C NMR signals

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at δ 84.36 (s), 67.8 (d), 31.4 (t), 31.2 (s), 30.8 (t), 25.77 (q), 25.4 (t), 22.45 (t), and 13.9 (q) are assigned to *anti,anti*-**24**, those at δ 84.43 (s), 68.3 (d), 59.9 (d), 31.6 (t), 31.1 (s), 29.7 (t), 25.76 (q), 25.2 (t), 22.43 (t), and 13.9 (q) to *anti,anti*-**24**. This material was not further characterized.

Synthesis of Allenes. Applications of literature methods were used.

4,5-Nonadiene (16a).[24] A solution of *n*-propylmagnesium bromide was prepared from 11 g (89 mmol) of 1-bromopropane and 2.2 g (89 mmol) of Mg turnings in 80 mL of ether. This was added to a stirred mixture of 4.0 g (22 mmol) of the tetrapyranyl ether of 1-hexyn-3-ol (prepared from the commercially available alcohol)[25] and 1.7 g (5.6 mmol) of cuprous bromide in 30 mL of ether at −78 °C. The reaction mixture was allowed to warm to 0 °C over 3 h and hydrolyzed by the addition of NH_4Cl solution. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated by simple distillation of solvent, and eluted through a column of silica gel with pentane. The allene-containing fractions were concentrated and distilled to give 1.7 g (60%) of **16a** as a clear liquid: bp 52–55 °C (11 Torr); IR 1969, 880 cm^{-1}; ^1H NMR δ 5.09 (m, 2), 1.95 (m, 4), 1.43 (m, 4), 0.95 (t, 3, J = 7 Hz); ^{13}C NMR δ 204.0, 90.6, 31.1, 22.4, 13.6. The following allenes were prepared in a similar manner.

2,6-Dimethyl-3,4-heptadiene (16b):[26] bp 56–59 (38 Torr); IR 1965, 1385, 1368, 878, 740 cm^{-1}; ^1H NMR δ 5.16 (t, 2, J = 5 Hz), 2.34–2.2 (m, 2), 1.0 (d, 6, J = 7 Hz), 0.99 (d, 6, J = 7 Hz); ^{13}C NMR δ 200.8 (s), 99.7 (d, J = 150 Hz), 28.0 (d), 22.6 (q), 22.5 (q).

4,4-Dimethyl-1,2-pentadiene (11a).[27] A sample of **11a** was purified by preparative GC: IR 1965, 1352, 1260, 1198, 870, 840 cm^{-1}; ^1H NMR δ 5.09 (t, 1, J = 7 Hz), 4.06 (d, 2, J = 7 Hz), 1.02 (s, 9); ^{13}C NMR δ 205.9 (s), 102.0 (d), 76.3 (t), 31.2 (s), 30.1 (q).

1,2-Tridecadiene (11b).[28] A sample of **11b** was purified by preparative GC: IR 2940, 2860, 1964, 1460, 840 cm^{-1}; ^1H NMR δ 5.07 (quint, 1, J = 7 Hz), 4.62 (dt, 2, J = 7, 3 Hz), 1.97 (qt, 2, J = 7, 3 Hz), 1.38 (quint, 2, J = 7 Hz), 1.33–1.20 (m, 14), 0.86 (t, 3, J = 7 Hz); ^{13}C NMR δ 208.5 (s), 90.1 (d), 74.4 (t), 31.9 (t), 29.62 (t), 29.61 (t), 29.4 (t), 29.3 (t), 29.14 (t), 29.09 (t), 28.3 (t), 22.7 (t), 14.1 (q).

3-Butyl-1,2-heptadiene (14).[29] A solution of *n*-butylmagnesium bromide prepared from 27.4 g (0.2 mol) of *n*-butyl bromide and 4.8 g (0.2 mol) of magnesium turnings in 150 mL of THF was transferred over 15 min by cannula to a well-stirred slurry of 28 g (0.15 mol) of CuI and 13 g (0.15 mol) of LiBr in 120 mL of THF at −5 °C for 15 min before 10 g (0.07 mol) of 2-heptyn-1-yl acetate[30] in 40 mL of THF was added rapidly. The mixture was stirred at −5 °C for 2 h before hydrolysis by the addition of NH_4Cl solution. The organic layer was diluted with pentane, washed with NH_4Cl solution and brine, dried ($MgSO_4$), and concentrated to give a yellow liquid. Distillation gave a yellow liquid (bp 55–73 °C, 5 Torr). Column chromatography on silica gel using pentane provided 3.5 g (36%) of **14** as a colorless liquid: IR 3046, 2928, 2859, 1960, 1456, 841 cm^{-1}; ^1H NMR δ 4.63 (pentet, 2, J = 3 Hz), 1.94 (m, 4), 1.5–1.2 (m, 8), 0.91 (t, 6, J = 7 Hz).

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Supplementary Material Available: NMR spectra of new compounds (49 pages). Ordering information is given on any current masthead page.

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Synthesis of the Vinblastine-like Antitumor Bis-Indole Alkaloid Navelbine Analogue Desethyldihydronavelbine

Philip Magnus* and Lee S. Thurston

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712

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(*R*)-(−)-Ethyl nipecotate **6** was converted into the *N*-allyl bromide **10** whose derived Grignard reagent **11** was added to *N*-(phenylsulfonyl)-2-(methoxyoxalyl)indole **12** to give the diastereomeric alcohols **13**. Removal of the indole protecting group from **13** and coupling with vindoline gave the separable diastereomers **15**(*S*) and **17**(*R*). Deprotection of **15**/**17** and treatment with formaldehyde/acetic acid gave desethyldihydronavelbine **5**, and its 18′-epimer **19**. Only the natural 18′-epimer exhibited any antitumor activity.

The ring-contracted bis-indole alkaloid navelbine **4** (or 7′-noranhydrovinblastine) inhibits the in vitro assembly of the microtubule system and is currently in phase II clinical trials.[1] Navelbine is synthesized from anhydrovinblastine **1** by oxidation to the *N*-oxide **2** and Polonovski rearrangement, induced by trifluoroacetic anhydride to the putative bisiminium ion **3**, which upon hydration, loss of formaldehyde, and addition of the piperidine nitrogen to the gramine-type iminium ion results in **4** (27%)[2] (Scheme I). The excision of one carbon from the tryptamine bridge has precedent in the chemistry of vallesamine and apparicine.[3]

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