CH_3CN produced solutions suitable for UV measurement. A blank sample was similarly prepared with 0.4 mL of host solution and 0.5 mL of demineralized water.

UV measurements were made on a Uvikon 930 spectrophotometer. The same cell was used as reference on each occasion and the pair of cells were always oriented in the same way inside the spectrophotometer. The cells were "zeroed" in the instrument at 380 nm. The extraction constants (K_{ex}) were calculated using equilibrium equation (2) in ref 28b from the concentration of picrate salt measured in the original $CDCl_3$ layer. Correction for the water solubility of hosts was made by measurement of K_d for hosts ($CHCl_3/H_2O$) according to the literature method.[28b] The following K_d values were determined: 15-crown-5, 0.17; 12-crown-4, 0.20; **9**, 0.05; **11**, 0.05; **10**, 0.06; **7**, 0.03.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-8703091) and the National Institutes of Health (Grant GM-28468) for the financial support of this work, to the Fulbright Commission for a travel grant (to J.T.N.), to Dr. Charles Cottrell for the 2-D NMR experiments, and to David E. Lawhorn for some preliminary experiments.

Registry No. **7**, 141411-92-9; Na^+ Pic^- **7**, 141412-06-8; K^+ Pic^- **7**, 141412-08-0; **8**, 141436-74-0; **9**, 134178-97-5; Na^+ Pic^- **9**, 141412-10-4; K^+ Pic^- **9**, 141412-12-6; **10**, 134236-71-8; Na^+ Pic^- **10**, 141507-83-7; K^+ Pic^- **10**, 141507-87-1; **11**, 134236-72-9; Na^+ Pic^- **11**, 141507-81-5; K^+ Pic^- **11**, 141507-85-9; **13**, 129529-77-7; **14**, 141411-93-0; **15**, 141411-94-1; **16**, 141436-75-1; **17**, 141411-95-2; **18**, 141411-96-3; **19**, 134179-00-3; **20**, 141411-97-4; *trans*-**21**, 141411-98-5; *cis*-**21**, 141411-99-6; **22**, 141412-00-2; **23**, 141412-01-3; **24**, 141412-02-4; **25**, 141412-03-5; **26**, 141412-04-6; **27**, 141505-51-3; **28**, 141505-52-4; **29**, 141505-53-5; cyclopentanone, 120-92-3; 2,3-dihydrofuran, 1191-99-7; cyclobutanone, 1191-95-3.

Supplementary Material Available: ^1H NMR spectra of **19**, **21**, **24**, and **28** together with X-ray experimental procedures, tables of bond distances and angles, final fractional coordinates, thermal parameters for **9**, **11**, **22**, and **24**, and ORTEP diagram of **24** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Regio- and Stereochemical Course of the Ring Expansion of Bridged Bicyclic Ketones to Spirocyclic α-Keto Tetrahydrofurans

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The regio- and stereochemical aspects of oxonium-promoted pinacol-like rearrangements have been investigated starting from the bridged bicyclic ketones (±)-norcamphor, (1*R*)-(−)-fenchone, and (1*R*)-(−)-3,3-dimethyl-1-vinyl-2-norbornanone. 1,2-Addition of 5-lithio-2,3-dihydrofuran to these substrates provided alcohols that smoothly underwent acid-catalyzed ring expansion. Whereas bridgehead carbon migration was observed in the first and third examples, the alternative available 1,2 Wagner–Meerwein shift operated in the fenchone series. In every instance, a substantial kinetic preference for formation of the O-exo spirotetrahydrofuranyl ketone was noted. Positioning of the dihydrofuranyl unit in sterically congested endo environments as accomplished by condensation of the α-lithio vinyl ether with (1*R*)-(+)-camphor, (1*S*)-(+)-7,7-dimethyl-1-vinyl-2-norbornanone, and (1*S*)-(−)-apocamphor was accompanied by increased hydrolytic sensitivity. Second-stage ring expansion of two of the spirocyclic ketones was characterized by continued adherence to anticipated migratory aptitudes. However, loss of stereochemistry occurred both at the original α carbon and at the newly introduced stereogenic center. These observations and relevant control experiments are most consistent with a push–pull fragmentation scheme leading to a ring-opened oxonium ion–enol pair that, because they are tethered, find it possible to cyclize. Prior to final bonding, either terminus may rotate relative to the other. The kinetic and thermodynamic interrelationships of these phenomena are discussed.

The ability of 4,5-dihydrofurans bearing a carbinol substituent at C-2 to function as oxonium ion initiators of pinacol-like rearrangements has come to light recently.[4] Even in its simplest form, this transformation affords spirotetrahydrofuranyl ketones holding considerable synthetic potential as precursors to ionophores.[5] More widespread utilization of the reaction in organic synthesis would appear dependent on elucidation of its intrinsic characteristics. One of these is regiochemistry. Since ring expansion of the alcohols proceeds under acid catalysis, the expectation is that the migrating center most able to bring electron density to the neighboring cationic carbon will be transferred preferentially. However, should the flanking groups be closely balanced in their electronic make-up, will secondary factors such as the relative spatial orientation of the dihydrofuran ring hold relevance? Questions of this ilk can best be answered by suitable examination of topologically well-defined substrates.

Another key feature of these processes is their stereochemical course. Once again, an attractive way of systematically investigating stereoselectivity is to construct a series of molecules in which conformational variables are constrained.

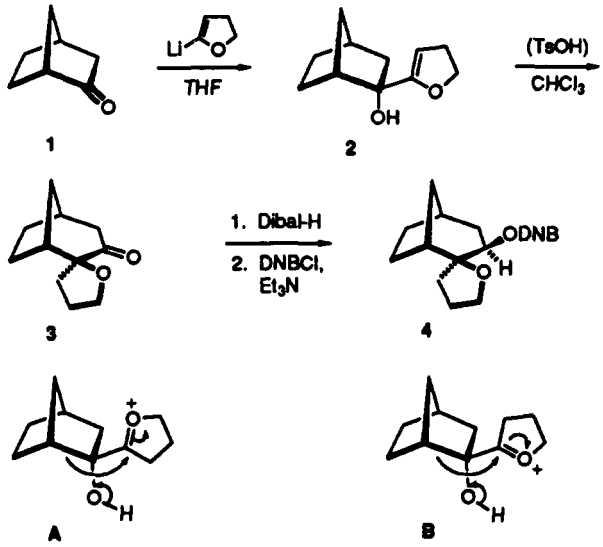
(1) Recipient of a "Bourse Lavoisier" postdoctoral fellowship awarded by the Ministère des Affaires Etrangères, Paris, France.
(2) Undergraduate Research Scholar, Summer 1988.
(3) Author to whom inquiries regarding the X-ray crystallographic analyses should be made.
(4) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765.
(5) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.*, preceding article in this issue.

0022-3263/92/1957-3956$03.00/0

Consequently, we have proceeded to prepare carbinols derived from a select group of bicyclo[2.2.1]heptan-2-ones, the substitution patterns in which have been varied to a level that provides a reasonably global view of the impact of molecular environment on reaction pathway.

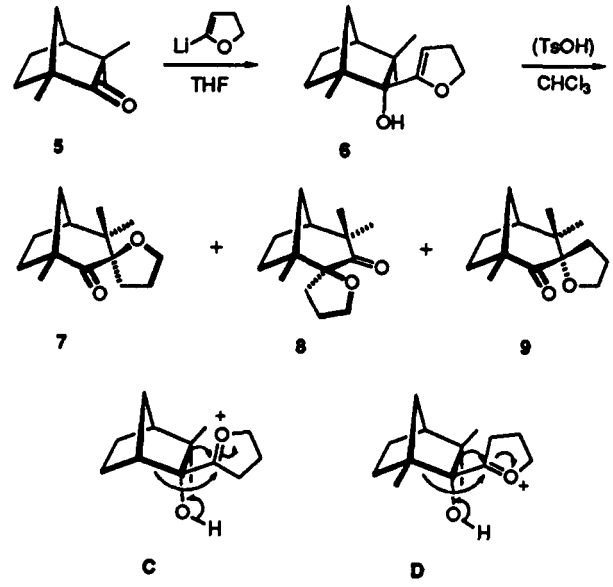
Results

Response of *endo*-Bicyclo[2.2.1]heptan-2-ols to Acid-Catalyzed Isomerization. Deprotonation of 4,5-dihydrofuran with *tert*-butyllithium[6] and condensation of the resultant organometallic with (±)-norcamphor (1) gave 2 in 99% yield. The exo trajectory of nucleophilic attack is well established in this system,[7] this precedent forming the basis of our stereochemical assignment. When 2 was isomerized by overnight stirring with a catalytic quantity of *p*-toluenesulfonic acid in $CHCl_3$ at room temperature, exclusive conversion to 3 (83% isolated) was observed. Although the presence in 3 of a pair of α-carbonyl protons provided documentation of bridgehead carbon migration, the stereoalignment of the tetrahydrofuran ring could not be unambiguously ascertained by ^1H NMR spectroscopy. Oily 3 was reduced with Dibal-H and the less prevalent alcohol so produced was converted into its suitably crystalline 3,5-dinitrobenzoate ester 4 to resolve this important issue. By means of X-ray diffraction, 4 was shown to possess an exo-directed C–O bond at its spirocyclic carbon. Accordingly, the reactivity of 2, once transformed to its oxonium ion, can be characterized in terms of a substantial kinetic preference for structural reorganization via A, with no detectable involvement of B.



(1*R*)-(–)-Fenchone (5) was next studied in order to gauge if this stereochemical course is "normal". In this series, carbinol 6 underwent acid-catalyzed ring expansion in good yield to afford the isomeric spiro ketones 7, 8, and 9, with 7 heavily dominating the mixture (17:1:1). Following chromatographic separation, the three-dimensional structural features of the two highly crystalline compounds 7 and 8 were established directly by X-ray crystallographic analysis. Oily 9 was reluctant to undergo conversion to its semicarbazone. Steric hindrance did not comparably deter reduction to a 1:1 mixture of diastereomeric alcohols. However, these and their 3,5-dinitrobenzoate esters proved to be inadequately crystalline low-melting solids. For these reasons, the indicated assignment has been made on the strength of comparative ^{13}C NMR analysis. Thus, the pairs of quatenary carbons in 7–9 give rise to chemical shift patterns that appear to be characteristic of their respective frameworks. In 7, these two carbons resonate at 52.3 and 42.2 ppm, with $\Delta\delta$ approximating 10 ppm. While the equivalent carbons in 9 appear at 52.5 and 41.5 ppm, those in 8 are much more closely spaced (48.4 and 47.0 ppm). It is therefore likely that 7 and 9 constitute a diastereomeric pair of the same regioisomer and that 8 is the sole representative of the other possible series.

Since the α and α′ positions adjacent to the carbonyl group in fenchone are both quaternary, a more competitive partitioning of migratory aptitudes was anticipated from the outset. The almost complete dominance by the adjacent *gem*-dimethyl-substituted center is consequently noteworthy. More striking still is the finding that both 7 and 8 share in common with 3 an O-exo spirotetrahydrofuranyl part structure. Therefore 1,2 Wagner–Meerwein shift via C (both options) must surmount an energy barrier significantly lower than the alternatives depicted in D.



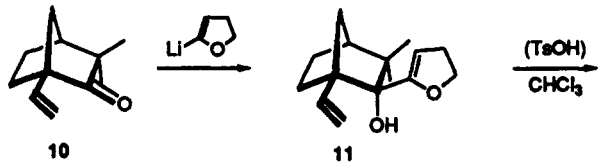
A second example of minor divergence from the emerging stereochemical trend surfaced during examination of (1*R*)-(–)-3,3-dimethyl-1-vinyl-2-norbornanone (10), prepared as previously described.[8] In fact, alcohol 11 proved to be the source of some interesting rearrangement data. Ring expansion proceeded smoothly to deliver 12 and 13 in a ratio of 21:1. Ketone 12 was inadequately crystalline for X-ray analysis and was therefore reduced to 14 for this purpose. Slow crystallization of 13 eventually provided material of adequate quality for diffraction measurements. Exclusive migration of the bridgehead carbon atom was thereby confirmed. This course of events contrasts in a striking way with that observed in the fenchone series. The impact of vinyl substitution on the enhancement of migratory capability in carbocationic processes is therefore substantial. The advantages that accrue from the introduction of this double bond do not lead to a crossover in product stereochemistry but do allow for modest operation of the alternative option. Thus, we find that passage through E is strongly favored. The low-level utilization by 11 of transition state F likely stems

(6) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107 and relevant references cited therein.

(7) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York and London, 1990; Part A, p 171, 438.

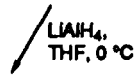
(8) Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 265.

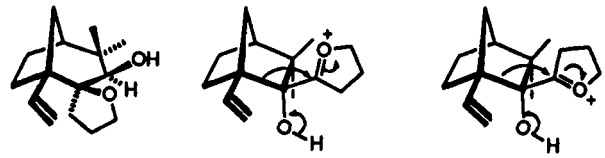
from accelerated, less discriminatory bridgehead bond migration.



10 11

12 13

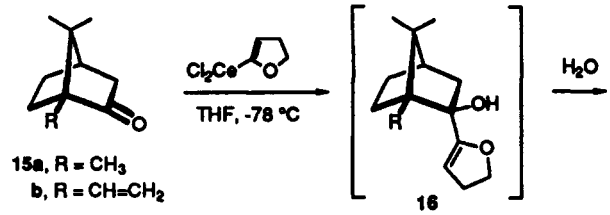




14 E F

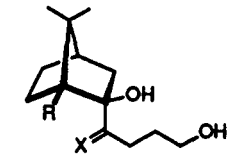
Hydrolytic Sensitivity of *exo*-Bicyclo[2.2.1]heptan-2-ols. As part of our survey of the scope of this reaction, experiments were also conducted on (1*R*)-(+)-camphor (**15a**), (1*S*)-(+)-7,7-dimethyl-1-vinyl-2-norbornanone (**15b**),[9] and (1*S*)-(−)-apocamphor (**18**).[10] Since the C-7 substitution plan in these ketones directs nucleophilic attack to the endo surface, use of the dichlorocerate[11] was mandated in order to curtail simple deprotonation that is often rampant with vinyllithium derivatives.[12] In all three examples, the condensations to produce the exo norbornanols proceeded slowly and inefficiently. Furthermore, alcohols such as **16a** and **16b** could not be isolated because of an unexpectedly high tendency to undergo hydrolysis of the vinyl ether moiety. Placement of the dihydrofuran ring in the rather crowded endo environment of these molecules may be responsible for this behavior.[13] With acquisition of the X-ray crystal structure of **17c** to confirm the indicated structural assignments, it became clear that these substrates were not to be useful in the context of this study.

Second-Stage Ring Expansions. The preceding developments did not restrict further practical evaluation of the title reaction. Two of the monoexpanded spirocyclic ketones were resubmitted to the identical two-step reaction sequence to widen the body of empirical observations. This phase of our investigation led to the resolution of some relevant mechanistic issues.



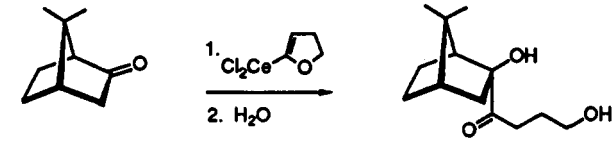
15a, R = CH3
b, R = CH=CH2

16



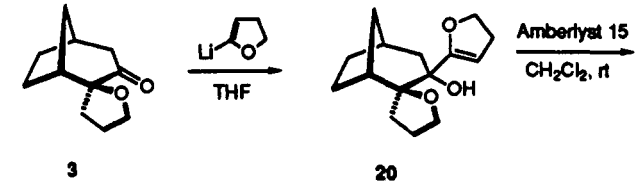
17a, R = CH3, X = O
b, R = CH=CH2, X = O
c, R = CH3, X = H, OH

LiAlH4

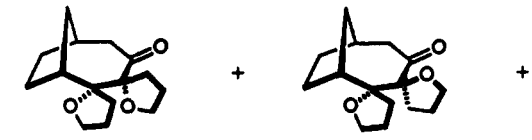


18 19

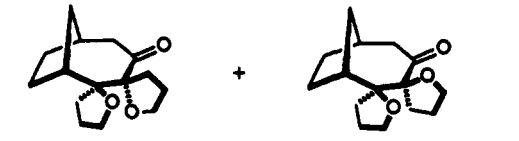
Following the conversion of **3** to **20**, stirring with Amberlyst 15 in CH_2Cl_2 at room temperature led to the isolation of four ketones (**21**–**24**) having a relative distribution of 1:1:4:1 (HPLC analysis). Once again, recourse was made to X-ray crystallography in order to permit rigorous assignment of stereochemistry to these structurally related products. While **22** was sufficiently crystalline for direct examination, it was necessary to transform **21** and **23** into **25** and **26**, respectively, to obtain derivatives with comparable physical characteristics. Once accomplished, the structure of **24** was arrived at by deduction and NMR correlation.



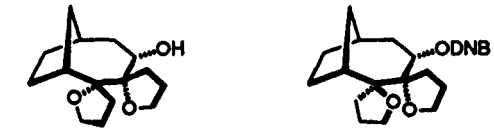
3 20



21 22



23 24



25 26

These data provide a firm basis for the conclusion that the spirocyclic carbon in **20** migrates to the exclusion of

(9) Fischer, N.; Opitz, G. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 877.

(10) The synthesis of (1*S*)-(−)-apocamphor (**18**) was accomplished by permanganate oxidation of *d*-10-camphorsulfonyl chloride to the carboxylic acid [Kuusinen, T.; Lampinen, M. *Suom. Kemist.* **1958**, *31B*, 381], conversion to the acid chloride with oxalyl chloride [Brown, F. C.; Morris, D. G. *J. Chem. Soc., Perkin Trans. II* **1977**, 125], reduction to the aldehyde with $(Ph_3P)_2CuBH_4$, and decarbonylation [Polónski, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 305].

(11) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392 and earlier relevant references cited therein.

(12) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873 (1986). (b) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31. (c) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879. (d) Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. *Tetrahedron* **1988**, *44*, 3139.

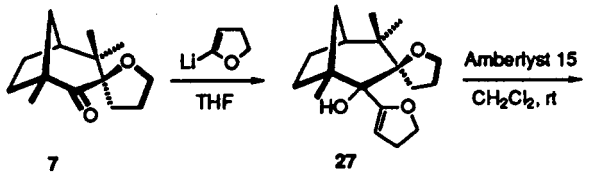
(13) Evidence has been presented for kinetic acceleration in *endo*-norbornylcarbinyl systems as a direct consequence of steric strain: Brown, H. C.; Ravindranathan, M. *J. Am. Chem. Soc.* **1978**, *100*, 1865.

Table I. Computed Energies of the Lowest Energy Conformers of Doubly Ring Expanded Ketones

structure	ΔE_{strain} (kcal/mol)	ΔE_{total} (kcal/mol)
	A. Norcamphor Series	
21	28.7	48.0
22	28.1	47.3
23	28.7	47.9
24	29.4	48.7
	B. Fenchone Series	
28	46.5	68.6
29	45.3	67.5
30	42.8	64.9
31	41.8	63.9

other possibilities. The stereochemical course of this 1,2-shift does not, however, conform to the configurational retention pattern so often observed for related cationically-induced processes such as the Beckmann, Hofmann, Curtius, Schmidt, Lossen, and Baeyer–Villiger reactions.[14] Indeed, the many examples of these transformations that have been reported require as a fundamental constitutional feature that no change in configuration occur in the migrating group. Circumvention of the long-standing Wagner–Meerwein mechanistic model can be rationalized in terms of a fragmentation–cyclization alternative. In fact, this pathway is made obligatory if the individual products are shown not to be interconvertible under the reaction conditions (see below).

Are γ-oxido oxonium ions generally prone to retrograde fragmentation? To gain a different perspective on this question, **7** was likewise treated with 5-lithio-2,3-dihydrofuran to give carbinol **27**, which was isomerized in the presence of Amberlyst 15 as before. Under these acidic conditions, the ring-expanded ketones **28** and **29** were formed in a 2.6:1 ratio. These were distinguished by X-ray



7 **27**

28 **29**

diffraction. In this instance, inversion of configuration in the migrating carbon materializes to a higher degree. This unconventional stereochemical behavior signifies that the mechanism of these ring expansions is characterized by a degree of latitude not available to the more classical 1,2 Wagner–Meerwein shifts.

Control Experiments. Computational assessments of the global minimum energy conformations of **21–24** by combined use of existing MM2 (Model KS 2.96)[15] and MMX software packages afforded the strain energy and total energy values compiled in Table I. Comparison of the computer-generated three-dimensional features of **22** (Figure 1) with those obtained by crystallographic means shows the level of correspondence to be very good. The important aspect of the data contained in Table I is the approximate equivalence of the E_T content of the four isomers. No member of this subset enjoys a thermodynamic advantage not also present in the others. Consequently, the 1:1:4:1 distribution of these ketones realized upon isomerization of **20** appears to reflect a kinetic preference for the formation of **23**.

Table II. Acid-Catalyzed Equilibration Experiments Involving 21–24[a]

	product distribution, %			
starting ketone	21	22	23	24
21	>99	<0.5	<0.5	
22	5	95		
23	2	7	91	
24	3		13	84

[a] Reactions were conducted in refluxing $CHCl_3$ containing a catalytic quantity of camphorsulfonic acid for a period of 1 week.

The next logical step was to examine the possible equilibration of each diastereomerically pure ketone under conditions equivalent to, and even more forcing than, those under which they have been formed. At the upper limit, each isomer was refluxed in chloroform for 1 week in the presence of a catalytic quantity of camphorsulfonic acid. The product ratios from duplicate experiments, determined by means of analytical HPLC, are given in Table II. These studies illustrate a general reluctance on the part of any of the four isomers to undergo sweeping equilibration. Ketone **24** proved most amenable to isomerization at these elevated temperatures. Notwithstanding, the product distribution originally derived from **20** is now clearly recognized as being of kinetic origin.

Molecular modeling studies similar to those described above were also performed on **28**, **29**, and the remaining two possible diastereomers **30** and **31**.[16] The results collected in Table I suggest that **30** and **31** might well be the products most heavily favored if the ring expansion were thermodynamically controlled, since **28** and **29** are intrinsically more highly strained compounds. Our inability to detect the formation of either **30** or **31** provides added confirmation of the kinetic basis underlying the product distributions from **20** and **27**.

30 **31**

Equilibration experiments identical to those carried out in the norcamphor series were also undertaken with ketones **28** and **29**. These compounds responded quite differently to the action of *p*-toluenesulfonic acid in refluxing chloroform. Anti stereoisomer **29** was completely destroyed when heated overnight. Careful monitoring of the process as a function of time determined the maximum useful reaction period to be 4–6 h. At this point, capillary GC analysis showed a 23:1 mixture of **29** and **28** to be present. In contrast, syn isomer **28** easily survived reflux periods of 2 weeks. After this elapsed time, the product

(14) Bethell, D.; Gold, V. *Carbonium Ions*; Academic Press: London and New York, 1969; p 208.

(15) (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washingtoin, D.C., 1982; Monograph 177. (b) Still, W. C.; Steliou, K. Private communication.

(16) In contrast to the situation with **22**, the computationally derived global energy minima for **28** and **29** do not correspond closely to the conformations observed in the solid state. The more noticeable differences are seen in the vicinity of the carbonyl groups and spirocyclic tetrahydrofuran rings (Figure 1). Interestingly, the spatial arrangements found in the calculated structures conform better to the minimization of electrostatic interactions involving the carbonyl functionality and adjacent (axial) polar bond as well as a gauche relationship (where possible) between the pair of C–O bonds to the quaternary carbons.

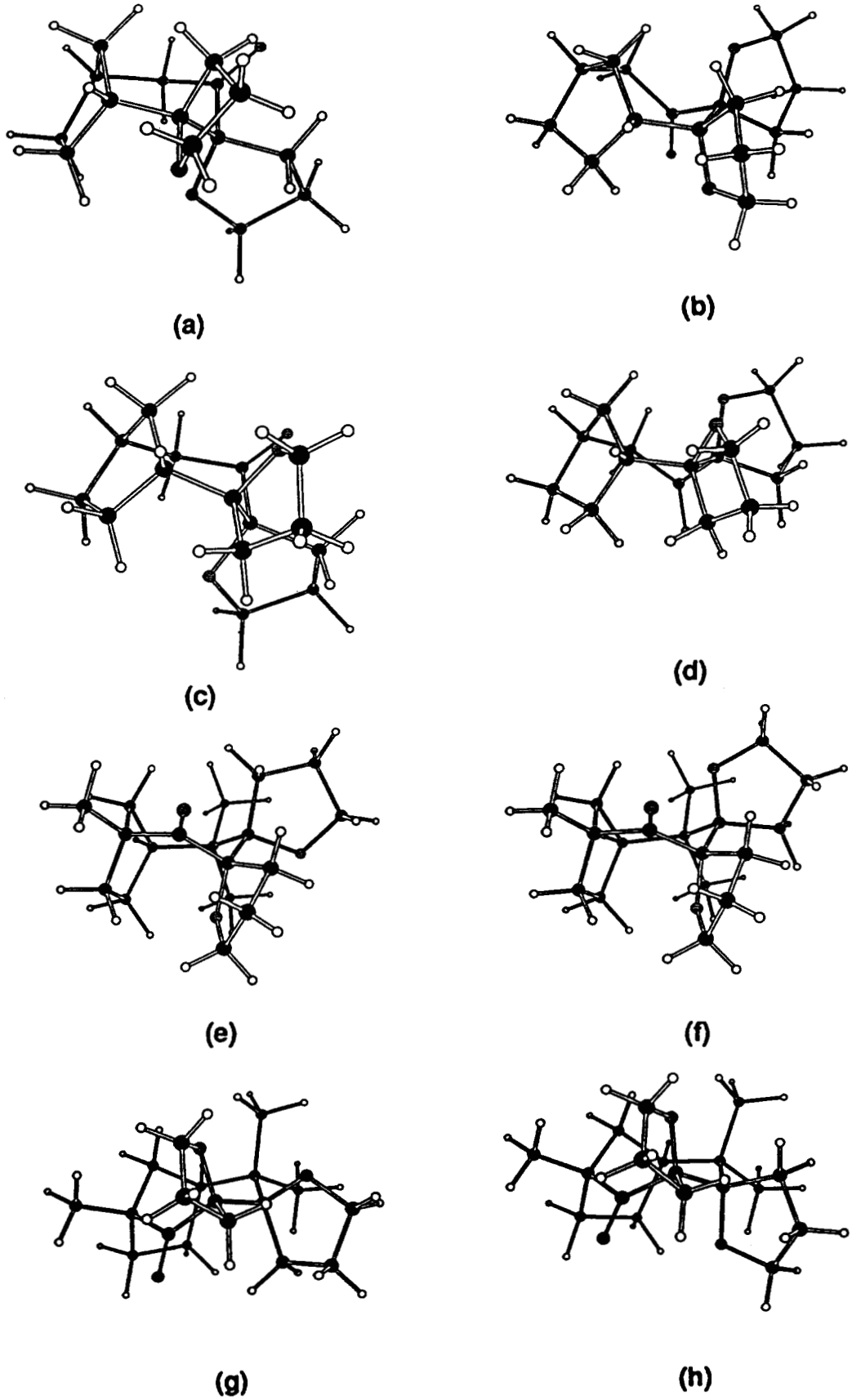
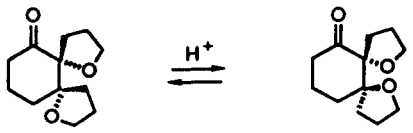


Figure 1. Global minimum energy conformations of (a) **21**, (b) **22**, (c) **23**, (d) **24**, (e) **28**, (f) **29**, (g) **30**, and (h) **31** as determined by molecular mechanics calculations (Chem 3-D output).

ratio was determined to be 60:1 in favor of the starting material. Clearly, both **28** and **29** are recalcitrant to equilibration.

We suspected that the bicyclic nature of **20–24** and **28–29** might be contributory to their reluctance to epimerize via a ring opening–cyclization sequence. Consequently, the less structurally constrained cyclohexanones **32** and **33**[5] were studied under a variety of conditions (Table III). Dowex-50X resin was found to act on **32** in CH_2Cl_2 at room temperature so as to cause 7% conversion

to **33** after 16 h. Under otherwise identical conditions,



32 **33**

p-toluenesulfonic acid promoted 25% conversion to the trans isomer. An increase in temperature facilitated the buildup of **33** to the point where it was the dominant constituent (1:1.6–1.8). Similar treatment of **33** showed analogous results, thereby confirming that true equilibrium was indeed being realized.

These observations demonstrate the feasibility of effecting the remarkable epimerization of neighboring quaternary carbon centers provided that an ether oxygen is suitably positioned to drive the initial fragmentation.

Discussion

In a formal sense, the "first-stage" rearrangements of **2**, **6**, and **11** correspond to pinacol-like 1,2-shifts promoted by an adjacent oxonium ion center and bear a modest resemblance to Berson's fundamental studies on the fate of *endo*- and *exo*-2-norbornylcarbinyl cations.[17] The major ring-expanded ketone in each instance correlates well with the usual cogent explanation advanced for generic cationic processes of this type in that the group that is more electron-rich in character migrates faster. The formation of **3** is the result of the enhanced electron density resident in a tertiary relative to a secondary carbon atom. Since the α and α′ carbons are both quaternary in **6**, the magnitude to which the *gem*-dimethyl-substituted carbon (C-3) becomes involved in the Wagner–Meerwein shift clearly stems from more subtle effects. Of the factors involved, stereoelectronic effects and product stability control must be accorded consideration. The balance of effects must be reasonably delicate in these systems since **11**, which is substituted by vinyl instead of methyl at the bridgehead site, isomerizes totally by migration of C-1. This observation has a parallel in thermal sigmatropic processes where attachment of an sp^2-hybridized carbon (usually in the form of a vinyl, carbomethoxy, etc., group) at the migrating center is recognized to greatly reduce the energy barrier to its migration.[18]

The high diastereoselectivity observed during installation of the spirocyclic carbon is of both mechanistic and preparative significance. The obviously high kinetic preference for migration to "exo" oxonium ions in **A**, **C**, and **E** is striking. To our knowledge, no precedence exists for comparably stereocontrolled cationic rearrangements. Usually, inversion at the migrating terminus occurs in pinacol and related processes because covalent bonding to the carbocationic center normally develops before the leaving group has completely departed.[19] However, the carbinols in the present study are bonded to a digonal center that is planar and consequently lacking a pre-existing configurational bias.

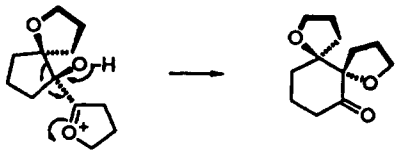
It is therefore relevant to ask whether a stereoelectronic effect might be responsible for the observed results. One possible consideration is that the "endo" conformations

Table III. Acid-Catalyzed Equilibration of 32 and 33

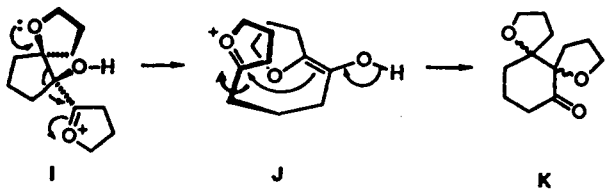
starting ketone	conditions	time, h	ratio of 32:33
32	Dowex-50X, CH_2Cl_2, rt	16	97:3
	(TsOH), CH_2Cl_2, rt	16	75:25
	(TsOH), $CHCl_3$, reflux	7	2:1
		24	1:1.6
		31	1:1.8
		48	1:1.8
33	(TsOH), $CHCl_3$, reflux	21	1:1.9

labeled as **B**, **D**, and **F** are destabilized relative to their "exo" counterparts. For steric reasons, the endo hydroxyl group would likely be turned outward and away from the congested underside of the bicyclic framework (see structures). As oxonium ion formation develops and proton loss from the hydroxyl group commences, the "endo" species find it necessary to place two positively charged centers in relatively close proximity. The solvation required to dampen these charges could also prove somewhat sterically obtrusive. These factors do not surface in **A**, **C**, and **E**. Dipole–dipole interactions may also play a role, but these are rather less obvious. In any event, exploitation of this phenomenon for diastereoselective synthesis looms as an attractive possibility.

Turning to the "second-stage" ring expansions, we must emphasize that a comparable mechanistic profile does not apply. As seen in the simple prototype **G**, adoption by these oxonium ions of a stereodirected pinacol-like pathway should result in migration of the spirocyclic carbon with retention of configuration[14,19] to give trans ketone **H**.



G **H**



I **J** **K**

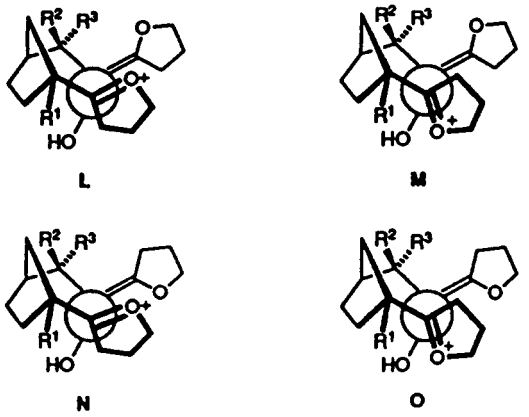
In the cases studied presently, loss of stereochemistry is seen at the β-oxido center. Furthermore, the configuration of the resulting α-oxido carbon is mixed. This behavior can be understood if ring expansion is triggered by a push–pull fragmentation resulting in the conversion of **I** to **J**. Once the ring is cleaved, either terminus of the chain may rotate relative to the other prior to capture of the oxonium ion by the tethered nucleophilic enol. In this way, stereochemical "memory" is lost.

In the present scenario, the interconnective bond would actually be part of a cis-1,3-disubstituted cyclopentane unit as in **L**–**O**. The effects of substitution on the five-membered ring and on the carbon atom of the chain are noteworthy. When R^1, R^2, and R^3 are hydrogen, closure occurs somewhat faster via **M**, but the other three options defined by **L**, **N**, and **O** operate as well. The positioning of methyl groups at R^1, R^2, and R^3 as in **27** gives evidence of altering the product-forming steps such that only **N** and **O** operate. The space demands on these substituents could modify the conformational features sufficiently to disfavor rebonding along pathways **L** and **M**. The emergence of **O** as the intermediate of greatest kinetic consequence eventuates in predominant inversion of configuration in

(17) (a) Berson, J. A.; Reynolds-Warnoff, P. *J. Am. Chem. Soc.* **1964**, *86*, 595. (b) Berson, J. A.; Willner, D. *J. Am. Chem. Soc.* **1964**, *86*, 609 and previous communications from this group.

(18) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981.

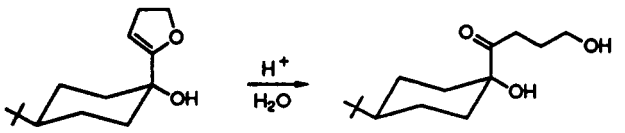
(19) Pocker, Y. In *Molecular Rearrangements, Part One*; de Mayo, P., Ed.; Interscience Publishers: New York, 1963; Chapter 1.



the neighboring spirocyclic carbon.

The reluctance of **21–24** and **28–29** to undergo interconversion could arise from one or both of two factors, one kinetic and the other thermodynamic. Thus, for ring opening to materialize *after ring expansion is complete*, the system must be capable of suitably aligning the carbonyl π-cloud and a nonbonded electron pair on the β-oxygen across the interconnective C_α–C_β bond. Since models indicate that this stereoelectronic requirement cannot be met in most cases without some buildup of nonbonded steric strain, this could well be a deterrent to ring cleavage in several of the samples. A more serious limitation is considered to be thermodynamic in origin. The facility with which these cationic rearrangements occur attests to their exothermicity. Should the spirocyclic α-keto tetrahydrofuran products be *significantly* more stable than the starting alcohols, then return to the ring-opened intermediate would rendered difficult. A hypothetical reaction diagram is given in Figure 2. Since the ring enlargement of bicyclic systems is accompanied by strain release appreciably in excess of that encountered in going from more conventional five- to six-membered rings, the sensitivity of **32** and **33** to acid-catalyzed interconversion is entirely comprehensible.

Finally, it should be mentioned that the hydrolytic sensitivity of *exo*-bicyclo[2.2.1]heptan-2-ols related to **16** is not restricted to this class of compounds. Rapid conversion to ring-opened keto diols has been noted whenever the dihydrofuran ring is placed in a congested environment as it is in **34**.[20]



34 **35**

Conclusions. With the exception of sterically crowded examples, the oxonium-promoted pinacol rearrangement can be implemented to produce spirocyclic α-keto tetrahydrofurans selectively. The ring expansion occurs with predictable regiochemistry and with stereoselectivity consistent with a charge repulsion model. When the ketone substrate already carries an α-oxido substituent, its subjection to this chemistry likewise gives rise to a ring-enlarged product. However, loss of stereochemistry can now materialize as a direct consequence of a kinetic preference for a fragmentation–recyclization pathway. Our current efforts are focused on the application of this chemistry in new contexts and on the stereocontrolled preparation of polyspirotetrahydrofurans and -pyrans.

(20) Vanucci, C. Unpublished results.

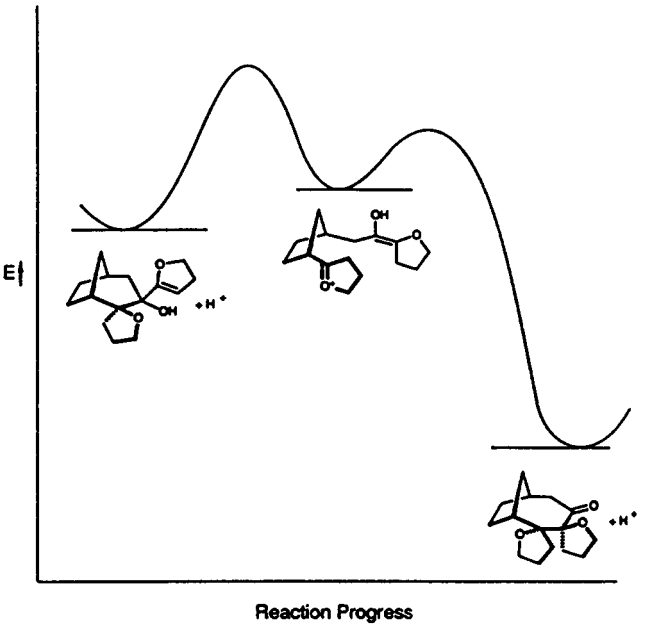


Figure 2. Hypothetical reaction coordinate for "second stage" ring expansion.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz and the ^{13}C NMR data obtained at 75 MHz. Mass spectra were measured on a Kratos MS-30 instrument at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All flash chromatographic separations were carried out on Merck silica 60 (60–200 mesh). MPLC purifications were accomplished on Merck Lichroprep Si 60 columns. All reactions were routinely performed under a nitrogen atmosphere. Solvents were reagent grade and dried prior to use.

General Procedure for the Addition of 5-Lithio-2,3-dihydrofuran to Ketones. An oven-dried, round-bottomed flask was flushed with nitrogen, charged with dry THF and 2,3-dihydrofuran, and cooled to −78 °C. To the magnetically stirred solution was added *tert*-butyllithium (1.7 M in pentane, 1.2 equiv) at −78 °C. The dry ice bath was replaced by an ice bath for 30 min, at which time the contents were recooled to −78 °C. A solution of the ketone (1 equiv) in dry THF was added dropwise at −78 °C and the reaction mixture was allowed to warm to room temperature overnight, recooled to −78 °C, quenched with saturated NH_4Cl solution, and allowed to return to ambient temperature with stirring. The separated aqueous layer was extracted three times with ether and the combined organic phases were washed with brine, dried, and concentrated in vacuo to give the tertiary alcohol.

(±)-(1*R,2*S**,4*S**)-2-(4,5-Dihydro-2-furyl)-2-norbornanol (2):** produced as a single diastereoisomer in quantitative yield (8.44 g, >99%) from 5.0 g (45.4 mmol) of norcamphor (Aldrich); colorless oil; IR (neat, cm^{-1}) 3500; ^{1}H NMR ($CDCl_3$) δ 4.74 (t, J = 2.5 Hz, 1 H), 4.33 (dt, J = 1.0, 9.4 Hz, 2 H), 2.62 (dt, J = 2.5, 9.4 Hz, 2 H), 2.3 (m, 1 H), 2.25 (m, 2 H), 1.98 (m, 3 H), 1.53 (m, 2 H), 1.27 (m, 3 H); ^{13}C NMR ($CDCl_3$) ppm 162.1, 94.3, 76.8, 70.2, 45.7, 43.3, 38.6, 36.5, 30.1, 28.7, 21.4; MS m/z (M^+) calcd 180.1150, obsd 180.1150.

General Procedure for *p*-Toluenesulfonic Acid-Catalyzed Rearrangement of Tertiary Alcohols. A solution of the tertiary alcohol in chloroform was treated with a catalytic quantity of *p*-toluenesulfonic acid, stirred overnight at room temperature, and poured into saturated $NaHCO_3$ solution. The separated organic phase was washed with saturated brine, dried, and concentrated in vacuo to give the ring-expanded ketone(s) which was (were) purified by column chromatography.

(±)-(1*R,2*S**,5*S**)-Dihydrospiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan]-3-one (3):** obtained in good yield (7.32 g, 83%) from **2** (8.44 g, 46.9 mmol) after flash chromatography (silica gel,

elution with 10% ethyl acetate in petroleum ether); colorless oil; IR (neat, cm^{-1}) 1745; ^1H NMR ($CDCl_3$) δ 3.78 (dt, J = 7.8, 4.8 Hz, 1 H), 3.46 (q, J = 8.0 Hz, 1 H), 2.67 (ddd, J = 6.0, 1.8, 1.6 Hz, 1 H), 2.47 (m, 1 H), 2.35 (m, 1 H), 2.34 (m, 2 H), 2.09 (dt, J = 3.0, 15.0 Hz, 1 H), 1.87–1.54 (m, 4 H), 1.42–1.13 (m, 4 H); ^{13}C NMR ($CDCl_3$) ppm 209.1, 89.4, 68.1, 47.2, 46.2, 35.4, 34.1, 29.3, 28.2, 26.0, 24.3; MS m/z calcd 180.1150, obsd 180.1174.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 73.35; H, 8.95.

General Procedure for the Preparation of 3,5-Dinitrobenzoate Esters. The alcohol (1 equiv) in dry CH_2Cl_2 was treated with triethylamine (1.5 equiv) or DMAP (1.5 equiv) under nitrogen at 0 °C. Once a CH_2Cl_2 solution of 3,5-dinitrobenzoyl chloride (1.1 equiv) was added, the reaction mixture was gradually warmed to room temperature and stirred until esterification was complete (TLC analysis).

(±)-(1*R,2*S**,3*R**,5*S**)-Dihydrospiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan]-3-ol 3,5-Dinitrobenzoate (4).** To a magnetically stirred solution of **3** (199.5 mg, 1.11 mmol) in dry THF (3 mL) at 0 °C under nitrogen was added a solution of Dibal-H (1.11 mL of 1 M in hexane, 1.11 mmol). The reaction took 2 h to proceed to completion (TLC analysis), after which 0.16 mL of methanol and 5.5 mL of unsaturated sodium potassium tartrate solution were sequentially introduced. The separated organic phase was washed with brine, dried, and concentrated to yield a 5:1 mixture (GC analysis) of diastereoisomeric alcohols (145 mg, 72%). This mixture was directly esterified according to the general procedure and the dinitrobenzoates were separated by MPLC (silica gel, elution with 10% ethyl acetate in petroleum ether). The major diastereomer (33.4 mg) was less crystalline than the minor component (9.2 mg). Therefore, the latter was recrystallized for the X-ray studies: colorless crystals, mp 172–173 °C; ^1H NMR ($CDCl_3$) δ 9.20 (t, J = 2.1 Hz, 1 H), 9.14 (d, J = 2.1 Hz, 2 H), 5.16 (dd, J = 6.2, 11.4 Hz, 1 H), 4.05 (m, 1 H), 3.90 (m, 1 H), 2.31 (m, 1 H), 2.16 (m, 1 H), 2.07 (d, J = 11.5 Hz, 1 H), 1.99–1.45 (series of m, 10 H), 1.32–1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) ppm 162.3, 148.7, 134.3, 129.4, 122.3, 85.7, 76.7, 69.3, 46.3, 35.6, 33.8, 33.6, 33.2, 27.7, 26.2, 25.8.

(1*R*,2*R*,4*S*)-2-(4,5-Dihydro-2-furyl)-1,3,3-trimethyl-2-norbornanol (6): produced as a single diastereomer in quantitative yield (8.33, >99%) from **5** (5.0 g, 32.8 mmol); colorless oil; IR (neat, cm^{-1}) 3600, 3520; ^1H NMR ($CDCl_3$) δ 4.87 (t, J = 2.5 Hz, 1 H), 4.28 (dt, J = 4.4, 9.3 Hz, 2 H), 2.55 (dt, J = 2.5, 9.1 Hz, 2 H), 2.15 (m, 1 H), 1.95 (m, 1 H), 1.65 (m, 2 H), 1.35 (m, 1 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.90 (s, 3 H), 1.14–0.04 (series of m, 3 H); ^{13}C NMR ($CDCl_3$) ppm 161.8, 95.9, 82.3, 69.5, 51.9, 48.5, 44.8, 40.9, 30.3, 29.4, 27.3, 25.1, 21.8, 17.0; MS m/z (M^+) calcd 222.1620, obsd 222.1598; $[\alpha]^{23}_D$ +51.5° (c 1.90, $CHCl_3$).

Acid-Catalyzed Rearrangement of 6. Ring expansion of **6** (7.79 g) according to the general procedure followed by flash chromatography (silica gel, elution with 2–20% ethyl acetate in petroleum ether) afforded 5.37 g (69%) of pure **7** and 700 mg (9%) of a 1:1 mixture of **8** and **9**. The last two isomers were separated by MPLC (silica gel, elution with 2% ethyl acetate in petroleum ether).

For **7**: white solid, mp 39–40 °C; IR (neat, cm^{-1}) 1715; ^1H NMR ($CDCl_3$) δ 3.68 (m, 2 H), 1.95 (m, 3 H), 1.68 (m, 6 H), 1.38 (m, 1 H), 1.29 (dd, J = 12.3, 4.2 Hz, 1 H), 0.98 (s, 3 H), 0.80 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 214.7, 91.1, 67.5, 52.3, 47.9, 42.2, 40.9, 34.6, 31.9, 26.1, 25.6, 25.3, 22.0, 20.1; MS m/z (M^+) calcd 222.1620, obsd 222.1606; $[\alpha]^{20}_D$ +2.9° (c 0.91, $CHCl_3$).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98. Found: C, 75.37; H, 9.98.

For **8**: white solid, mp 34–35 °C; IR (neat, cm^{-1}) 1705; ^1H NMR ($CDCl_3$) δ 3.86 (dt, J = 7.9, 3.8 Hz, 1 H), 3.49 (dq, J = 8.6, 2.0 Hz, 1 H), 2.54 (d, J = 12.3 Hz), 2.45 (m, 1 H), 1.98–1.87 (m, 2 H), 1.80–1.49 (m, 5 H), 1.44–1.20 (m, 2 H), 1.30 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 213.9, 92.4, 68.7, 48.3, 47.3, 47.0, 38.5, 32.5, 26.92, 26.86, 26.75, 26.0, 24.2, 20.6; MS m/z (M^+) calcd 222.1620, obsd 222.1660.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98. Found: C, 75.60; H, 9.98.

For **9**: colorless oil; IR (neat, cm^{-1}) 1705; ^1H NMR ($CDCl_3$) δ 3.73 (dd, J = 7.8, 7.6 Hz, 1 H), 3.61 (dt, J = 8.2, 4.7 Hz, 1 H), 2.32–2.19 (m, 3 H), 1.94–1.67 (m, 5 H), 1.53–1.38 (m, 3 H), 1.11 (s, 3 H), 1.00 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 211.6, 91.8, 68.9, 52.5, 48.8, 42.6, 41.5, 35.2, 28.0, 26.7, 25.7, 25.5, 21.0, 20.8; MS m/z (M^+) calcd 222.1620, obsd 222.1622.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98. Found: C, 75.60; H, 10.02.

(1*R*,2*S*,4*S*)-2-(4,5-Dihydro-2-furyl)-3,3-dimethyl-1-vinyl-2-norbornanol (11): produced as a single diastereomer in high yield (1.39 g, 98%) from **10** (1.0 g, 6.09 mmol); colorless oil; IR (neat, cm^{-1}) 3560; ^1H NMR ($CDCl_3$) δ 6.05 (dd, J = 17, 11 Hz, 1 H), 5.66 (m, 3 H), 5.02 (dd, J = 17, 2.2 Hz, 1 H), 4.96 (dd, J = 12, 1.9 Hz, 1 H), 2.65–2.15 (m, 5 H), 2.10–2.00 (m, 1 H), 1.60–1.30 (m, 3 H), 1.16 (dt, J = 12, 4.2 Hz, 1 H), 0.99 (s, 3 H), 0.92 (s, 3 H).

As with **2** and **6**, this alcohol slowly isomerized upon standing at room temperature, a process that was accelerated in $CDCl_3$.

Acid-Catalyzed Rearrangement of 11. Ring expansion of **11** (1.39 g) as described above required 1.5 h to go to completion. Silica gel chromatography (elution with 3% ethyl acetate in petroleum ether) afforded 905 mg (64%) of **12** and 41 mg (3%) of **13**.

For **12**: colorless oil; IR (neat, cm^{-1}) 1705; ^1H NMR ($CDCl_3$) δ 6.13 (dd, J = 17, 10 Hz, 1 H), 5.10 (dd, J = 10, 2 Hz, 1 H), 5.08 (dd, J = 17, 2 Hz, 1 H), 3.83 (m, 1 H), 3.50 (m, 1 H), 2.71 (d, J = 12 Hz, 1 H), 2.43 (m, 1 H), 1.98–1.63 (m, 5 H), 1.57–1.36 (m, 2 H), 1.35 (s, 3 H), 1.26–1.10 (m, 2 H), 1.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 212.6, 140.5, 113.9, 91.8, 68.9, 53.8, 48.6, 46.8, 36.6, 28.3, 26.8, 26.72, 26.68, 26.1, 24.1; MS m/z (M^+) calcd 234.1620, obsd 234.1623; $[\alpha]^{23}_D$ −90.5° (c 2.8, $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.65; H, 9.45.

For **13**: colorless, crystalline solid, mp 59–60 °C; IR (film, cm^{-1}) 1700; ^1H NMR ($CDCl_3$) δ 6.06 (m, 1 H), 5.08 (d, J = 1.8 Hz, 1 H), 5.03 (dd, J = 4.1, 1.5 Hz, 1 H), 3.98 (m, 2 H), 2.07 (m, 3 H), 1.79 (m, 7 H), 1.42 (m, 1 H), 1.19 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 217.9, 140.8, 113.0, 92.5, 70.1, 54.6, 48.8, 46.7, 34.7, 33.5, 31.0, 26.9, 26.3, 26.0, 23.8; MS m/z (M^+) calcd 234.1620, obsd 234.1624; $[\alpha]^{23}_D$ +44.5° (c 1.41, $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.52; H, 9.50.

(1*R*,2*S*,3*R*,5*S*)-Dihydro-4,4-dimethyl-1-vinylspiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan-3-ol (14). An ice-cold, magnetically stirred suspension of lithium aluminum hydride (51 mg, 1.34 mmol) in dry THF (6 mL) was treated with **12** (365 mg, 1.56 mmol) dissolved in THF (2 mL), stirred at 0 °C for 2 h, and carefully quenched with saturated Na_2SO_4 solution (2 mL). The mixture was filtered and the aluminum salts were thoroughly washed with ether. The combined organic layers were dried and concentrated, and the residue was subjected to MPLC (silica gel, elution with 3% ethyl acetate in petroleum ether). The less polar endo alcohol was obtained as a colorless oil (141 mg), while **14** proved to be a colorless solid, mp 86–88 °C (145 mg, total yield 78%).

For the endo alcohol: IR (neat, cm^{-1}) 3510; ^1H NMR ($CDCl_3$) δ 6.16–6.06 (m, 1 H), 5.03–5.01 (m, 1 H), 4.98–4.96 (m, 1 H), 3.90–3.83 (m, 1 H), 3.66–3.58 (m, 1 H), 3.08 (d, J = 0.8 Hz, 1 H), 2.32–2.28 (m, 1 H), 2.15–2.08 (m, 1 H), 2.00–1.94 (m, 1 H), 1.85–1.55 (series of m, 8 H), 1.34 (s, 3 H), 1.12–1.08 (m, 1 H), 1.01 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 143.2, 112.6, 89.7, 79.1, 68.4, 52.8, 45.2, 37.8, 36.3, 30.9, 28.1, 27.7, 26.5, 26.2, 25.7; MS m/z (M^+) calcd 236.1776, obsd 236.1762.

For **14**: IR (KBr, cm^{-1}) 3490; ^1H NMR ($CDCl_3$) δ 6.10–6.01 (m, 1 H), 5.03 (s, 1 H), 4.98 (dd, J = 8.6, 1.6 Hz, 1 H), 3.94–3.91 (m, 2 H), 3.13 (s, 1 H), 2.24 (d, J = 11.9 Hz, 1 H), 1.96–1.86 (m, 2 H), 1.84–1.55 (series of m, 7 H), 1.44–1.35 (m, 1 H), 1.09 (dd, J = 11.9, 4.9 Hz, 1 H), 0.99 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 142.6, 113.3, 90.8, 78.3, 71.7, 54.4, 46.2, 39.3, 35.3, 32.3, 29.9, 26.8, 26.5, 25.1, 20.7; MS m/z (M^+) calcd 236.1776, obsd 236.1799.

4-Hydroxy-1-[(1*R*,2*R*,4*R*)-2-hydroxy-2-bornyl]-1-butanone (17a). Cerium trichloride heptahydrate (16.32 g, 43.74 mmol) was dried overnight at 140 °C under high vacuum. The flask was cooled and flushed with nitrogen. Dry THF (120 mL) was added and the resulting suspension was stirred magnetically for 24 h. Meanwhile, a cold (−78 °C), magnetically stirred, and nitrogen-blanketed solution of 2,3-dihydrofuran (3.15 mL, 41.6 mmol) in 125 mL of THF was treated dropwise with *tert*-butyllithium (1.7 M in pentane, 24.47 mL, 41.60 mmol). After completion of the addition, the reaction mixture was allowed to warm to 0 °C for

30 min, recooled to −78 °C, and transferred via cannula to the $CeCl_3$ slurry. After 30 min, a solution of **15a** (5.0 g, 32.8 mmol) in THF (25 mL) was introduced dropwise. The mixture was stirred for 2 h at −78 °C, quenched with anhydrous methanol (1.68 mL, 41.6 mmol), stirred for 10 min, and resubjected twice more to the cerate reagent. Finally, saturated $NaHCO_3$ solution (20 mL) was added, and the solution was warmed to room temperature, filtered through a Celite pad, and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (75 mL), dried, and concentrated. The residue, which consisted chiefly of unreacted **15a**, was subjected to flash chromatography (silica gel, elution with 40% ethyl acetate in petroleum ether) to give **17a** (541 mg, 8%) as a colorless solid: mp 83.5–84.5 °C; IR ($CHCl_3$, cm^{-1}) 3620, 3450, 1700; ^1H NMR ($CDCl_3$) δ 3.67 (m, 2 H), 2.99 (m, 1 H), 2.46–2.29 (m, 2 H), 1.99–1.80 (m, 4 H), 1.70 (m, 1 H), 1.40 (m, 1 H), 1.22 (m, 1 H), 1.13 (s, 3 H), 0.98 (s, 3 H), 0.92 (m, 1 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 214.4, 87.9, 62.1, 51.8, 50.6, 45.0, 41.1, 35.8, 30.3, 27.7, 26.3, 20.8, 20.5, 10.8; MS m/z ($M^+ - H_2O + 1$) calcd 223.28, obsd 223.22; $[\alpha]^{27}_D$ −31.6° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.95; H, 10.07. Found: C, 69.86; H, 10.01.

4-Hydroxy-1-[(1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethyl-1-vinyl-2-norbornyl]-1-butanone (17b). The procedure used was the same as for **17a**. From $CeCl_3 \cdot 7H_2O$ (14.77 g, 0.04 mol, 1.3 equiv), THF (120 plus 100 × 3 mL), 2,3-dihydrofuran (3 mL × 3, 0.039 mmol × 3, 1.26 eq × 3), **15b** (5.0 g, 0.03 mol, 1 equiv), *tert*-butyllithium (1.5 M in pentane, 26 mL × 3, 0.–39 mol × 3, 1.26 equiv × 3), and methanol (1.56 mL, 0.039 mol × 3, 1.26 equiv × 3), there was isolated after flash chromatography (silica gel, elution with 25% ethyl acetate in petroleum ether) 235 mg (3%) of **17b** as a colorless oil: IR (neat, cm^{-1}) 3650–3100, 1700; ^1H NMR ($CDCl_3$) δ 6.25 (dd, *J* = 17.7, 11.0 Hz, 1 H), 5.30 (dd, *J* = 1.8, 11.04 Hz, 1 H), 5.03 (dd, *J* = 1.8, 7.8 Hz, 1 H), 3.65 (m, 1 H), 3.54 (m, 1 H), 3.3 (br s, 1 H), 2.91 (m, 1 H), 2.45 (d, *J* = 12.7 Hz, 1 H), 2.27 (m, 1 H), 2.18–1.61 (series of m, 6 H), 1.28–1.16 (m, 2 H), 1.23 (s, 3 H), 0.84–0.79 (m, 1 H), 0.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 212.5, 135.6, 117.1, 89.5, 62.4, 57.4, 52.2, 45.8, 40.9, 35.4, 27.5, 25.6, 25.1, 21.2, 20.4; MS FAB m/z (M^+) calcd 252.19, obsd 252.20; $[\alpha]^{27}_D$ +0.7° (*c* 1.5, $CHCl_3$).

Hydride Reduction of 17a. Ketone **17a** (195 mg, 0.8 mmol) in THF (2 mL) was added in a dropwise manner at 0 °C to a slurry of lithium aluminum hydride (27 mg, 0.7 mmol) in THF (1.5 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated Na_2SO_3 solution, filtered, separated, dried, and concentrated. The residue was subjected to flash chromatography on silica gel (elution with 40% ethyl acetate in petroleum ether) to yield **17c** as a colorless crystalline solid; mp 105–110 °C (106 mg, 54%); ^1H NMR ($CDCl_3$) δ 3.64 (m, 1 H), 3.53 (m, 2 H), 3.21 (br s, 3 H), 1.79 (m, 1 H), 1.72–1.54 (series of m, 6 H), 1.51–1.27 (series of m, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H), 0.89 (m, 1 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) 82.4, 77.7, 62.6, 52.4, 49.5, 44.3, 43.0, 30.0, 29.7, 27.4, 21.1, 20.6, 12.0 (2 C).

4-Hydroxy-1-[(1*S*,2*S*,4*S*)-2-hydroxy-7,7-dimethyl-2-norbornyl]-1-butanone (19). In like fashion, the above procedure was adopted for **18** (152 mg, 1.09 mmol). After 3 exposures to the dichlorocerate derived from 5-lithio-2,3-dihydrofuran and flash chromatography (silica gel, elution with 15% ethyl acetate in petroleum ether), there was isolated **19** as a colorless oil (52 mg, 21%); IR (neat, cm^{-1}) 3650–3000, 1700; ^1H NMR ($CDCl_3$) δ 3.66 (m, 2 H), 3.03 (m, 1 H), 2.78–2.55 (br s, 2 H), 2.37 (m, 2 H), 1.94 (m, 1 H), 1.79 (m, 4 H), 1.64 (m, 2 H), 1.35 (s, 3 H), 1.08 (m, 1 H), 0.98 (s, 3 H), 0.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) ppm 211.5, 87.9, 62.3, 52.5, 49.2, 45.0, 40.1, 34.2, 27.3, 26.1, 22.9 (2C), 22.4; MS FAB m/z (M^+) calcd 226.17, obsd 226.19.

(±)-(1*R,2*S**,3*R**,5*S**)-3-(4,5-Dihydro-2-furyl)dihydrospiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan]-3-ol (20):** produced according to the general procedure from **3** (5.82 g, 32.3 mmol) and isolated after flash chromatography (silica gel, elution with 12% ethyl acetate in petroleum ether) as a colorless oil (3.56 g, 44%); IR (neat, cm^{-1}) 3470, 1710; ^1H NMR ($CDCl_3$) δ 5.06 (t, *J* = 2.6 Hz, 1 H), 4.30 (dt, *J* = 3.0, 9.5 Hz, 2 H), 3.90 (m, 1 H), 3.75 (q, *J* = 7.8 Hz, 1 H), 3.44 (s, 1 H), 2.59 (dt, *J* = 2.5, 9.5 Hz, 2 H), 2.25 (m, 2 H), 2.09 (m, 2 H), 1.99 (m, 1 H), 1.91 (m, 2 H), 1.78–1.39 (m, 6 H), 1.25–1.07 (m, 1 H); ^{13}C NMR ($CDCl_3$) ppm 160.5, 97.4, 89.5, 72.2, 69.5, 67.5, 44.4, 43.4, 33.9, 33.8, 31.8, 29.8, 28.1, 25.5, 24.9; MS m/z (M^+) calcd 250.1569, obsd 250.1560.

Acid-Catalyzed Rearrangement of 20. Ring expansion of **20** (1.5 equiv) according to the general procedure followed by MPLC (silica gel, elution with 10% ethyl acetate in petroleum ether) gave a mixture of **21** and **22** (247 mg), pure **23** (430 mg, 29%), and pure **24** (122 mg, 8%). The first two stereoisomers were mutually separated by repeat MPLC (elution with 3% ethyl acetate in petroleum ether) and gave pure **21** (123 mg, 8%) and pure **22** (123 mg, 8%).

For **21**: colorless oil; IR (neat, cm^{-1}) 1705; ^1H NMR ($CDCl_3$) δ 3.89 (m, 3 H), 3.65 (dt, *J* = 5.0, 8.0 Hz, 1 H), 2.8 (m, 1 H), 2.45 (m, 4 H), 2.23 (t, *J* = 8.4 Hz, 1 H), 2.12 (m, 4 H), 2.10–1.63 (series of m, 5 H), 1.61–1.44 (m, 3 H); ^{13}C NMR ($CDCl_3$) ppm 216.5, 98.0, 86.6, 68.7, 68.6, 49.4, 48.8, 34.6, 34.3, 34.0, 32.8, 29.4, 26.2, 26.0, 24.2; MS m/z (M^+) calcd 250.1569, obsd 250.1563.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.80; H, 8.78.

For **22**: colorless crystals, mp 80–81 °C; IR (neat, cm^{-1}) 1705; ^1H NMR ($CDCl_3$) δ 3.80 (m, 4 H), 3.16 (dd, *J* = 5.2, 10.8 Hz, 1 H), 2.6 (m, 1 H), 2.4 (d, *J* = 13.2 Hz, 1 H), 2.28 (m, 2 H), 2.13 (s, 1 H), 2.01–1.45 (series of m, 12 H); ^{13}C NMR ($CDCl_3$) ppm 216.8, 96.9, 88.1, 69.23; 69.21; 46.1, 45.1, 37.2, 34.7, 32.3 (2C), 29.6, 24.5 (2 C), 24.3; MS m/z calcd 250.1569, obsd 140.1557.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.70; H, 8.82.

For **23**: colorless oil; IR (neat, cm^{-1}) 1705; ^1H NMR ($CDCl_3$) δ 3.8 (m, 3 H), 3.60 (dq, *J* = 1.4, 6.4 Hz, 1 H), 2.67 (dt, *J* = 12.6, 1.2 Hz, 1 H), 2.5 (m, 2 H), 2.3 (m, 2 H), 2.1–1.4 (series of m, 13 H); ^{13}C NMR ($CDCl_3$) ppm 214.0, 96.3, 88.1, 68.7, 68.4, 48.3, 46.5, 34.4, 32.91, 32.86, 32.5, 30.5, 26.4, 25.7, 24.8; MS m/z (M^+) calcd 250.1569, obsd 250.1568.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.66; H, 8.84.

For **24**: colorless oil; IR (neat, cm^{-1}) 1710; ^1H NMR ($CDCl_3$) δ 3.85 (m, 2 H), 3.76 (m, 1 H), 3.59 (m, 1 H), 2.69 (dt, *J* = 1.3, 12.6 Hz, 1 H), 2.51 (m, 2 H), 2.33 (m, 2 H), 2.09–1.47 (series of m, 13 H); ^{13}C NMR ($CDCl_3$) ppm 214.1, 96.4, 88.2, 68.7, 68.4, 48.3, 46.5, 34.4, 33.0, 32.9, 32.5, 30.6, 26.4, 25.7, 24.9; MS m/z (M^+) calcd 250.1569, obsd 250.1571.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.67; H, 8.90.

(±)-(1′*R,2′*R**,3′*S**,4′*S**,6′*S**)-Tetrahydrodispiro[furan-2(3*H*),2′-bicyclo[4.2.1]nonane-3′,2″(3″*H*)-furan]-4′-ol (25).** Ketone **21** (85.9 mg, 0.34 mmol) as a solution in THF (1 mL) was added to a cold (0 °C) suspension of lithium aluminum hydride (11.2 mg, 0.3 mmol) in THF (1.5 mL) under nitrogen with stirring overnight and gradual warming to room temperature. After the addition of saturated Na_2SO_3 solution, the reaction mixture was filtered and the solid rinsed with ether. The combined organic phases were dried and concentrated in vacuo to leave a residue (89 mg, 100%) that was purified by MPLC on silica gel (elution with 30% ethyl acetate in petroleum ether). Two diastereomeric alcohols were isolated in a 1:1 ratio, the least polar of which (15 mg, 17%) was obtained as a high quality crystalline solid: mp 120–122 6C; ^1H NMR ($CDCl_3$) δ 3.87 (m, 4 H), 3.61 (br m, 1 H), 2.40 (m, 1 H), 2.35–1.17 (series of m, 18 H); ^{13}C NMR ($CDCl_3$) ppm 93.9, 90.5, 73.1, 69.6, 67.8, 48.0, 41.4, 35.1, 34.5, 33.4, 33.0, 31.5, 27.4, 26.2, 25.2.

(±)-(1′*R,2′*S**,3′*S**,4′*S**,6′*S**)-Tetrahydrodispiro[furan-2(3*H*),2′-bicyclo[4.2.1]nonane-3′,2″(3″*H*)-furan]-4′-ol 3,5-Dinitrobenzoate (26).** Ketone **23** (52.2 mg, 0.21 mmol) in THF (0.5 mL) was added in a dropwise manner at 0 °C to a stirred slurry of lithium aluminum hydride (6.8 mg, 0.18 mmol) in THF (1 mL). After 3 h, the reaction mixture was quenched with saturated Na_2SO_3 solution, filtered, separated, dried, and concentrated. Two diastereoisomeric alcohols were obtained in a 1:1 ratio, the more polar of which (19.7 mg, 37%) was dissolved in CH_2Cl_2 (0.5 mL) and treated sequentially with 4-(dimethylamino)pyridine (14.3 mg, 0.12 mmol) and 3,5-dinitrobenzoyl chloride (21.5 mg, 0.09 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. After being warmed to room temperature overnight, the reaction mixture was quenched with 0.5 mL of water and diluted with ether (5 mL). The organic phase was washed with 5% HCl, saturated $NaHCO_3$ solution, and brine, dried, concentrated, and subjected to MPLC (elution with 20% ethyl acetate in petroleum ether). The desired

denitrobenzoate was isolated as yellow crystals (17 mg, 51%): mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 9.21 (t, J = 2.1 Hz, 1 H), 9.1 (d, J = 2.1 Hz, 2 H), 5.67 (dd, J = 10.9, 4.9 Hz, 1 H), 4.08 (m, 2 H), 3.89 (m, 2 H), 2.36 (m, 2 H), 2.17–1.58 (series of m, 15 H), 1.40 (m, 1 H).

(1*R*,3*R*,5*S*)-2-(4,5-Dihydro-2-furyl)dihydro-1,4,4-trimethylspiro[bicyclo[3.2.1]octane-3,2′(3′*H*)-furan]-2-ol (27). Alcohol **27** was produced as a single diastereomer according to the general procedure (3.14 g, 46%) from 5.22 g of **7** after flash chromatography (silica gel, elution with 12% ethyl acetate in petroleum ether): colorless oil; IR (neat, cm^{-1}) 3500; ^{1}H NMR ($CDCl_3$) δ 4.93 (t, J = 2.5 Hz, 1 H), 4.30 (m, 2 H), 3.79 (s, 1 H), 3.72 (m, 2 H), 2.47 (m, 5 H), 2.03 (m, 1 H), 1.85 (m, 2 H), 1.60 (m, 3 H), 1.20 (m, 2 H), 1.17 (s, 3 H), 1.02 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 163.0, 99.7, 90.1, 81.5, 70.5, 68.5, 48.1, 46.7, 42.6, 38.1, 32.9, 29.33, 29.30, 27.7, 27.0, 26.3, 25.8, 22.8; MS m/z (M^+) calcd 292.2038, obsd 292.2046; $[\alpha]^{20}_D$ +3.4° (c 2.5, $CHCl_3$).

Acid-Catalyzed Rearrangement of 27. Isomerization of **27** (3.38 g, 15.2 mmol) according to the general procedure gave 325 mg (31%) of **28** and 136 mg (12%) of **29** after MPLC (silica gel, elution with 10% ethyl acetate in petroleum ether).

For **28**: colorless crystals, mp 67.5–68.5 °C; IR ($CHCl_3$, cm^{-1}) 1700; ^{1}H NMR ($CDCl_3$) δ 4.04 (dt, J = 4.6, 7.8 Hz, 1 H), 3.94 (dt, J = 4.0, 8.0 Hz, 1 H), 3.70 (dq, J = 6.0, 7.4 Hz, 2 H), 2.46 (d, J = 14.1 Hz, 1 H), 2.35 (m, 1 H), 2.25 (m, 1 H), 2.14–1.80 (series of m, 7 H), 1.75–1.55 (m, 3 H), 1.50–1.35 (m, 2 H), 1.23 (s, 3 H), 1.12 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) pm 214.7, 99.4, 95.4, 71.2, 66.6, 53.4, 51.7, 43.9, 40.9, 39.0, 32.8, 31.8, 27.5, 26.69, 26.67, 26.3, 25.8, 25.5; MS m/z (M^+) calcd 292.2038, obsd 292.2020; $[\alpha]^{27}_D$ −89.8° (c 2.2, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.92; H, 9.66. Found: C, 73.94; H, 9.63.

For **29**: colorless crystals, mp 40–41 °C; IR ($CHCl_3$, cm^{-1}) 1690; ^{1}H NMR ($CDCl_3$) δ 3.89–3.70 (m, 3 H), 3.58 (dt, J = 9.5, 6.7 Hz, 1 H), 2.55 (d, J = 1.37 Hz, 1 H), 2.50 (m, 1 H), 2.11–1.41 (series of m, 13 H), 1.21 (s, 3 H), 1.20 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 215.9, 100.2, 91.0, 69.3, 66.2, 53.3, 50.6, 44.0, 49.8, 39.8, 38.8, 32.0, 31.4, 27.9, 27.3, 26.6, 26.5, 26.3, 25.5; MS m/z (M^+) calcd 292.2038, obsd 292.2063; $[\alpha]^{23}_D$ −54.7° (c 1.2, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.92; H, 9.66. Found: C, 73.90; H, 9.70.

Prototypical Control Experiment. Pure **32** (93 mg, 0.44 mmol) in $CHCl_3$ (45 mL) containing 8 mg of p-toluenesulfonic acid was heated at reflux under nitrogen for 19 h. After cooling, the solvent was carefully evaporated and the residue chromatographed (silica gel, elution with 15–30% ether in petroleum ether) to give 48.8 mg (54%) of **33** and return 24.2 mg (26%) of **32**.

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Supplementary Material Available: ^{1}H NMR spectra of **2**, **4**, **6**, **14**, **17b**, **17c**, **19**, **20**, **25**, **26**, and **27** as well as ORTEP diagrams of all 11 compounds studied, figure of the second molecule of **25**, figure of the unit cell of **25**, crystallographic experimental and tables of X-ray crystal data, bond lengths and angles, final fractional parameters, thermal parameters **4**, **7**, **8**, **13**, **14**, **17c**, **22**, **25**, **26**, **28**, and **29**, and final computed atomic coordinates for **21**, **22**, **23**, **24**, **28**, **29**, **30**, and **31** (85 pages); observed and calculated structure factors (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Approaches to the Synthesis of Heptitol Derivatives via Iron-Mediated Stereocontrolled Functionalization of Cycloheptatrienone

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Stereocontrolled reduction of tropone–$Fe(CO)_3$ (**9**) followed by alcohol protection gives the [(trialkylsilyl)oxy]cycloheptatriene complex **11**. Osmylation of **11** proceeds with complete stereoselectivity to give the protected trihydroxycycloheptadiene complex **12**, treatment of which with acid in the presence of methanol (generated in situ) gives the symmetrically trioxygenated diene complex **15**. Decomplexation of these complexes, followed by stereocontrolled diene oxygenation and ring cleavage, provides methodology for the construction of heptitol derivatives. Conversion of complex **15** to ether-substituted dienyl–$Fe(CO)_3$ cationic complexes was studied. These complexes react with nucleophiles to give diene-, dienyl-, or enediyl–$Fe(CO)_2L$ complexes, depending on the nature of the nucleophile and the spectator ligand.

Introduction

Previous studies in our laboratories have led to the development of methods for the stereocontrolled functionalization of cycloheptadienes via nucleophile additions to the derived diene–$Mo(CO)_2Cp$[1] and dienyl–$Fe(CO)_2L$[2] cationic complexes (L = CO, triphenylphosphine, or triphenyl phosphite). This methodology has led to efficient synthetic routes to the (+)-Prelog–Djerassi lactone[3] and subunits of the macrolide antibiotics carbomycin[4] and tylosin.[5] Recent work has also indicated potential approaches to building blocks for FK-506 and the macbecins.[6] The latter studies have revealed that the introduction of one alkyl group and one heteroatom substituent onto the cycloheptadiene ring with complete stereocontrol, as shown for the conversion of **1** to **5** or **6**, is very straightforward, but the introduction of *two* heteroatom substituents is not possible using this chemistry. This is due to the fact that

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