Practical Synthesis of Spirocyclic Bis-C,C-glycosides. Mechanistic Models in Explanation of Rearrangement Stereoselectivity and the Bifurcation of Reaction Pathways

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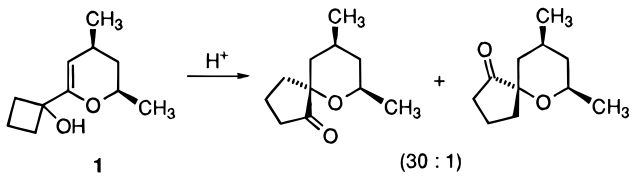
The susceptibility of glycal-derived carbinols to acid-catalyzed ring expansion is described. In the systems prepared from cyclopentanone, Ferrier ionization precedes the pinacol-like Wagner−Meerwein shift, thermodynamic control operates, and high stereoselectivity is seen if a C(6) substituent is present. In contrast, the adducts to cyclobutanone exhibit release of ring strain under kinetically controlled conditions and intercept the oxonium species reversibly formed via direct proton transfer. The results show that the substituents positioned on the glycal ring have a pronounced influence on whether a chair-like or twist-boat transition state geometry is adopted primarily. The composite reaction profiles reveal for the first time the fundamental importance of exothermicity and of substitution in these spiro glycosidation reactions. Since optical activity is preserved in all instances, the utility of this chemistry for the synthesis of bis-C,C-glycosides and more complex oxacyclics appears promising.

The field of carbohydrate chemistry has witnessed remarkable growth in recent times as a consequence of intense interest in the synthesis of C-glycosides. The discovery of biologically active members of this important class of sugars in nature has resulted in the development of many methods for their stereoselective construction.[1] Particularly noteworthy is the wide range of approaches which have proven serviceable. These extend from the utilization of both electrophilic and nucleophilic carbohydrates to the adoption of free radical techniques, Wittig olefinations, palladium-mediated couplings, and concerted processes. Notwithstanding these advances, spirocyclic bis-C,C-glycosides have not found similar favor. Only in connection with the recent independent discoveries by Descotes[2] and by Vasella[3] of the feasibility of preparing anomeric carbenes have reports of the capture of these reactive intermediates with olefins to give cyclopropanes made their appearance.

Recent work in these laboratories has illustrated that the acid-catalyzed rearrangement of dihydropyranylcarbinols such as **1** to spirocyclic ketones can be highly diastereoselective.[4] This efficient process results in the generation of a new stereogenic center by means of controlled pinacol-like 1,2-migration to a cyclic oxonium ion. Under conditions where the starting carbinols would



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be derived from glycals and would therefore be enantiomerically pure, this transformation would provide a convenient means for establishing the absolute configuration of a fully substituted carbon while delivering bis-C,C-glycosides. Presented here are the results of an extended study involving a variety of carbohydrate-based glycals substituted in diverse ways. A preliminary investigation[5] had previously uncovered divergent responses from systems amenable to operation of the Ferrier rearrangement.[6] These variances provided important insight with regard to the ranking of competing reactions available to six-membered oxonium ions and, accordingly, have been evaluated more extensively. The purpose of the present study was to develop an integrated mechanistic model for these utilitarian processes.

Discussion and Results

Scope of the Investigation. Glycal Synthesis and Coupling. The structural features of glycals **2**−**8** were considered to be sufficiently diverse for our purposes. The complications associated with the C-1 lithiation of 3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal[7] can be effectively skirted by making recourse instead to the TIPS derivative. Although the utilization of **2** is no longer accompanied by α-silyl deprotonation,[8] an excess of *tert*-butyllithium is still required[9] in order to realize efficient lithiation in advance of condensation with cyclobutanone and cyclopentanone to give **10** (78%) and **11** (96%), respectively. A comparable procedure could be easily applied to the acquisition of **12** and **13**.

The efficacy with which 3,4-di-*O*-acetyl-L-rhamnal responds to Ferrier rearrangement when treated with

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(3) (a) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1989**, *72*, 1371. (b) Vasella, A.; Uhlmann, P.; Waldraff, C. A. A.; Diederich, F.; Thilgen, C. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1388.

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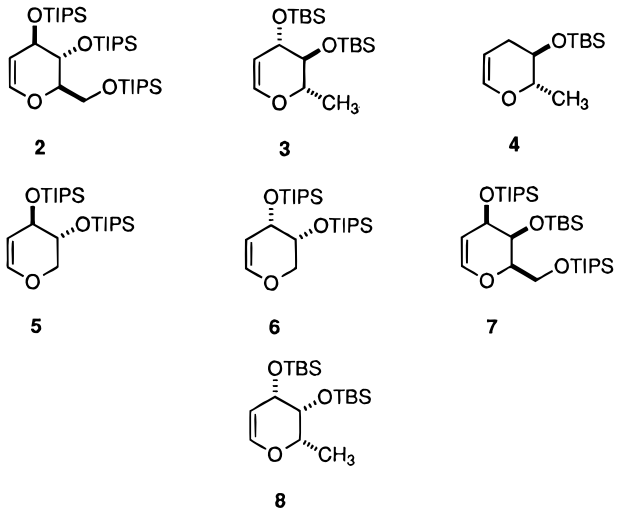
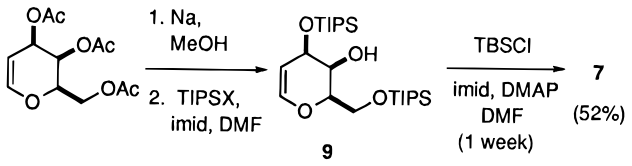


boron trifluoride etherate and methanol in acetonitrile, and the regioselectivity with which the resulting pseudoglycal undergoes hydride reduction,[10] proved highly attractive as a route to 3-deoxy-L-rhamnal, silylation of which gave **4** (94%). The subsequent conversion of **4** into **15** by means of *tert*-butyllithium in THF proceeded in 72% yield. The competing self-aldol condensation of cyclopentanone hampered purification, such that **15** could be isolated in a pure state only after several chromatographies. No such difficulties were encountered during the synthesis of **14**, which was available by analogous means in 65% yield.

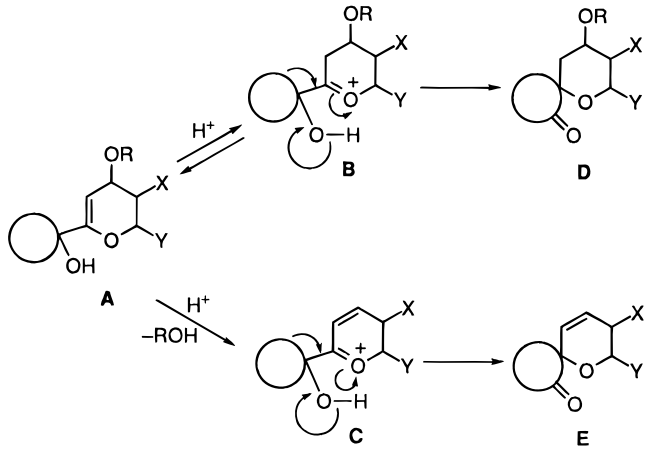
In our hands, the preferable route to the bissilylated D-xylal **5** consisted of the conversion of D-xylose into the triacetoxyglycosyl chloride by exposure to zinc chloride in acetyl chloride[11] followed by reductive elimination with chromium(II) acetate.[12] This route is less labor intensive than that involving the glycosyl bromide,[13] an intermediate much more prone to spontaneous hydrolysis and decomposition. With TIPS protection, the conversion of **5** to **16** (87%) and **17** (85%) proved uneventful. Entirely analogous considerations dictated our preparation of **6** from D-arabinose via the chloride[12] and not the bromide.[13]

When treated with excess TIPSCl or TIPSOTf, D-galactal[13] underwent silylation to give **9**. Further heating did not lead to protection of all three hydroxyl groups for steric reasons. A decrease in size to the TBS level did



permit advance to **7** to be made. However, the final capping proceeded very slowly and some intramolecular silyl transfer was noted. A related silyl group migration

Scheme 1



has been observed previously in the case of the bis-TBS ether of L-fucal.[14]

Glycal **8** was prepared comparably from L-fucal diacetate.[11,12] The presence of two TBS groups in **8** did not impede C-1 lithiation, as evidenced by the obtention of **22** and **23** in 77% and 83% yields, respectively.

Relevant Mechanistic Features. It has been known that glycals function well as glycosyl acceptors once activation has been accomplished with a suitable electrophilic reagent. We wished to exploit the use of a proton for this purpose. Since anhydrous conditions were mandated in order to circumvent simple hydration processes, recourse has been made throughout to the use of camphorsulfonic acid as a catalyst and dry dichloromethane as the solvent of choice. In those glycals substituted with a potential leaving group in the allylic C(4) position, there exists the possibility for operation of a process other than direct conversion to intermediate **B** (Scheme 1). The vulnerability of these systems for possible competing generation of more highly conjugated oxonium ions of type **C** could set the stage for the operation of a second rearrangement pathway.

It is well at this point to recognize that while the generation of **B** qualifies as a potentially reversible process, formation of **C** is essentially irreversible. Another distinction between these intermediates resides in their electrophilic character. In **B**, the positive charge is constrained to reside on two conjoined atoms and must

(10) Martin, A.; Pais, M.; Monneret, C. *Carbohydr. Res.* **1983**, *113*, 21.

(11) (a) Brauns, D. H. *J. Am. Chem. Soc.* **1924**, *46*, 1484. (b) Hudson, C. S.; Johnson, J. M. *J. Am. Chem. Soc.* **1915**, *37*, 2748. See also: (c) Vercellotti, J. R.; Egan, L. P.; Squires, T. G. *Carbohydrate Res.* **1970**, *14*, 263 and references cited therein.

(12) (a) Pollon, J. H. P.; Llewellyn, G.; Williams, J. M. *Synthesis* **1989**, 758. (b) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(13) (a) Weygand, F. *Methods Carbohydr. Chem. 1* **1962**, 182. (b) Humoller, F. L. *Methods Carbohydr. Chem.* **1962**, *1*, 83. (c) Pigman, W.; Roth, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405.

(14) Horton, D.; Priebe, W.; Varela, O. *Carbohydr. Res.* **1985**, *144*, 325 and references cited therein.

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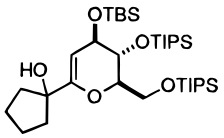
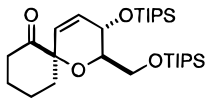
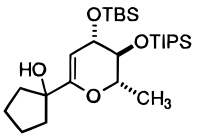
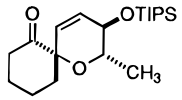
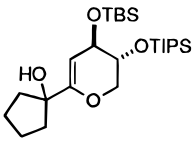
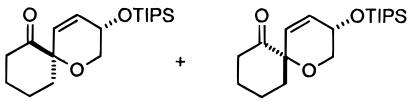
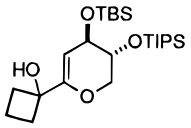
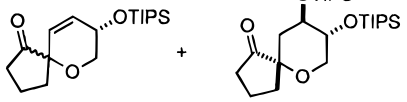
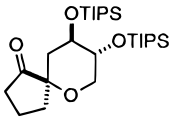
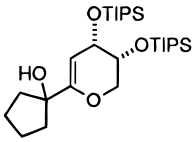
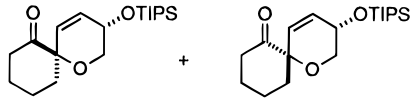
Table 1. Acid-Catalyzed Isomerization in Tandem with the Ferrier Rearrangement (CSA, CH_2Cl_2, rt)

expt	carbinol	reaction time, h	product(s) (% isolated yield)
1	 **11**	1	 **24** (53%)
2	 **13**	30	 **25** (81%)
3	 **17**	2	 **26** + **27** (1.1 : 1, 78%)
4	 **16**	0.5	 **28** + **29** (58%) (1.2 : 1; 38%)
			 **30** (2%)
5	 **19**	48	 **31** + **32** (1.1 : 1, 31%)

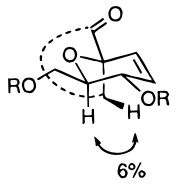
therefore be regarded as relatively dense. The greater degree of delocalization available to **C** can only serve to render its cationic character more diffuse.

The connectivity between the electrophilicity of the oxonium ion and ensuing pinacol-like rearrangement is multifaceted. Established elsewhere is the fact that simple substitution of the dihydropyran ring with one or two alkyl groups engenders sufficient inductive electron donation to reduce the potential for isomerization significantly.[4] Only cyclobutanol derivatives undergo ring expansion at a rate to be synthetically useful. We expected that the presence of electronegative oxygen substituents, so plentiful in carbohydrates of virtually all types, would reverse this effect and allow for the ring expansion of cyclopentanol derivatives as well. As will be seen, this has proven to be so.

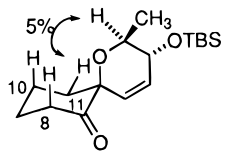
Beyond this, we became specifically interested in determining whether the Ferrier rearrangement option (viz. **A** → **C** → **E**), kinetically attractive in a great many circumstances because of the stabilization inherent to **C**,[15] might not be overridden in favor the **A** → **B** → **D** pathway by proper selection of the cyclic carbinol unit. Indeed, the longer lifetime enjoyed by **C** because of its enhanced thermodynamic stability allows such intermediates to be trapped by less strained neighboring cyclopentanol units.

Operation of the Ferrier Rearrangement. The first carbinol observed to follow the **A** → **C** → **E** reaction channel was **11** (Table 1). During the course of 1 h, its smooth conversion exclusively into the enantiopure ketone **24** could be conveniently monitored by TLC analysis. The stereochemistry assigned to this product followed straightforwardly from NOE measurements (see **F**). Comparable unidirectionality was exhibited by **13**, which was transformed rather more slowly (30 h) into **25** (81% isolated). The absolute configuration of the spirocyclic

carbon in **25** was unequivocally established on the basis of COSY and NOE experiments (see **G**). In addition, the



F



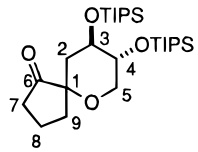
G

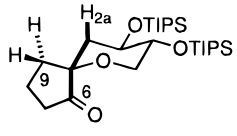
downfield shifting of $H(8)_{ax}$ and $H(10)_{ax}$ brought on by their 1,3-diaxial relationship to the ether oxygen allowed for the definition of $H(11)_{eq}$ and recognition of its proximity to the pyranyl proton shown. At this juncture, it was of more than passing interest that both **11** and **13** had responded to the intervention of **C** by migrating a methylene carbon to the axial surface of the pyran ring. A more detailed consideration of this significant issue is presented below.

By contrast, diastereofacial selectivity was almost totally eroded during the ring enlargement of **17**. Although the time required for complete consumption of this carbinol was short (2 h), irreversible conversion to a chromatographically inseparable 1.1:1 mixture of **26** and **27** materialized. Accordingly, an oxonium ion (**C**) carrying only the X substituent loses essentially all capability for controlling the stereoselectivity of the ring expansion. On this basis, the functional group Y, when present in tandem with and trans to X, is recognized to have broad impact on setting the configuration of the incipient spirocyclic center.

This conclusion receives additional support from **16**, the only cyclobutanol of the seven examined herein to be predisposed to the Ferrier process to some degree. In this instance, a 1.2:1 mixture of epimers **28** was produced in addition to **29** (58%) and **30** (2%). As in the preceding example, the Ferrier intermediate was inadequately substituted to engender desirable stereochemical control. The was not the case for direct ring expansion along the **A** → **B** → **D** reaction channel. The combined effect of the OR and X substituents resident in the intermediary oxonium species is to control migratory selectivity to the appealing extent of 30:1.

The stereochemical definition of **29** and **30** began by comparing the chemical shift data of several protons. The appearance of H(3) and $H(5)_{ax}$ in **29** at positions farther downfield than those in **30** is indicative of their spatial proximity to an axially disposed carbonyl group. Likewise



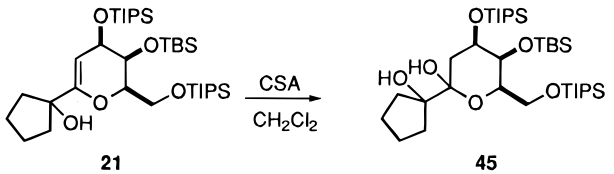


H

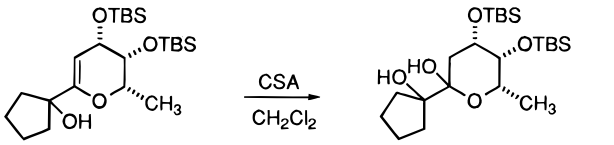
Proton	Chemical Shift	
	29	**30**
2_{ax}	1.46	2.06
2_{eq}	2.39	1.85
3	4.49	4.01
4	3.78	3.84
5_{ax}	3.65	3.45
5_{eq}	3.96	4.46

H(4), $H(5)_{eq}$, and $H(2)_{ax}$ in **30** are deshielded by an equatorially oriented carbonyl. This phenomenon has been widely observed in this study. Confirmation of the tentative assignments was derived from several 2-D NMR experiments. Following assignment of all ^1H and ^{13}C signals by means of $^1H-^1H$ COSY 90 and $^1H-^{13}C$ phase-sensitive correlation measurements, a long-range semiselective DEPT study in which $H(2)_{ax}$ was irradiated revealed strong enhancements of C(6), as well as C(1), C(3), and C(4) (see **H**). The intense response of C(6) is especially reinforcing of the earlier belief that the carbonyl center is oriented axially. Hence, the configuration of the spiro carbon (C(1)) in **29** is necessarily *S*.

Substrates **11** and **13**, which have their X and Y substituents trans-disposed at the Ferrier oxonium step (**C**), undergo ring expansion readily. Should **21** and **23** react similarly, the X/Y relationship in **C** would be cisoid.



21 **45**



23 **46**

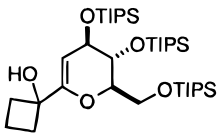
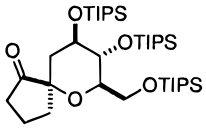
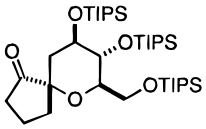
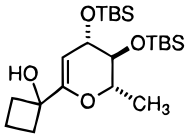
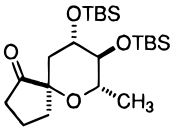
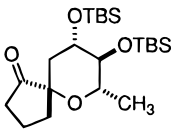
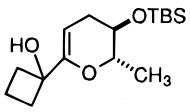
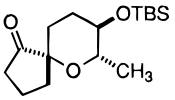
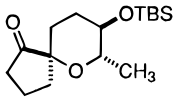
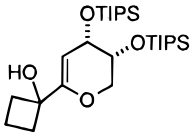
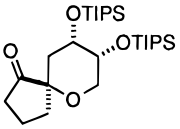
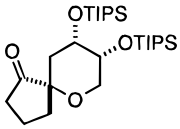
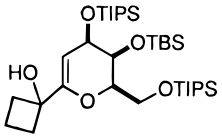
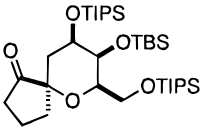
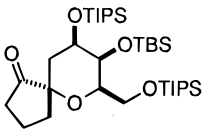
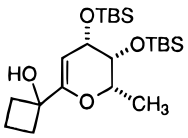
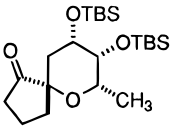
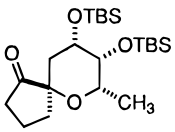
However, neither glycal experienced rearrangement over a prolonged period of time. Rather, adventitious moisture was incorporated to deliver the hydrated products **45** and **46**, respectively. An interesting reactivity profile had now been delineated.

Consequences of Ring Strain Relief. Of the several butanols prepared, only **14** is structurally unable to undergo the Ferrier rearrangement (Table 2, experiment 8). In the event, the response of **14** to acid-catalyzed isomerization was to deliver the (*S*)-configured spirocyclic ketone **37** four times more prevalently than the *R* diastereomer **38**. Only **16** (experiment 4) and **22** (experiment 11) subsequently proved stereoselective in the same direction. In the case of **16**, the bias for the *S* product proved to be the most accentuated (30:1). In the other four examples surveyed (**10**, **12**, **14**, and **18**), the dominant bicyclic ketone product was *R*-configured at the spirocyclic carbon atom. The detailed structural features of each bis-C,C-spiro glycoside were unequivocally established by spectroscopic methods of the type previously noted, with selected details provided in the Experimental Section. The highly crystalline nature of **37** allowed for its structural corroboration by crystallographic means (Figure 1).

No hint of even very modest operation of the Ferrier rearrangement could be uncovered in experiments 6, 7, and 9−11. These findings strongly implicate the operation of kinetic control during non-Ferrier ring expansion. According to this hypothesis, proton transfer to the dihydropyranyl carbinol **A** to generate the oxonium ion **B** in Scheme 1 occurs quite readily. The strain release associated with the ring expansion of a cyclobutanol causes **B** to be intercepted with only minimal energetic costs. The exothermicity associated with the conversion of **B** to **D** under these circumstances is likely mirrored to a large extent in the associated transition state.

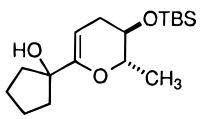
When less reactive cyclopentanol derivatives are involved, oxonium ions of type **B** are not comparably

Table 2. Spirocyclic Bis-C,C-glycoside Formation via Direct Ring Expansion (CSA, CH_2Cl_2, rt)

expt	carbinol	reaction time, h	product(s) (% isolated yield)	
6	 **10**	4	 **33** (50%)	 **34** (38%)
7	 **12**	3	 **35** (64%)	 **36** (14%)
8	 **14**	0.4	 **37** (80%)	 **38** (17%)
9	 **18**	0.5	 **39** (63%)	 **40** (22%)
10	 **20**	0.5	 **41** (70%)	 **42** (19%)
11	 **22**	1	 **43** (62%)	 **44** (30%)

consumed in the reaction manifold which results in the production of **D**. As a consequence, time is available for **B** to revert to **A**, which more slowly generates the more stable cationic intermediate **C**. Once formed, species **C** is much longer lived since it cannot return to **A** and ultimately proceeds forward to generate **E**. From this perspective, the Ferrier alternative is viewed to be the thermodynamic option. On the basis of the experimental data, we conclude that the rate of formation of **B** must be considerably faster than that of **C**. Beyond this, the Ferrier process is observed uniquely because little energy advantage accrues to the Wagner−Meerwein shift of a cyclopentanol in **B** to a cyclohexanone in **D**. Not only is ring strain presumed to be closely comparable in **B** and **D** but the trade-off of an oxonium ion for a carbonyl group may well be virtually isoenergetic.

A remaining consideration is the anomalous behavior of **15**. When exposed to camphorsulfonic acid under the standard conditions, this carbinol gave rise to a multi-

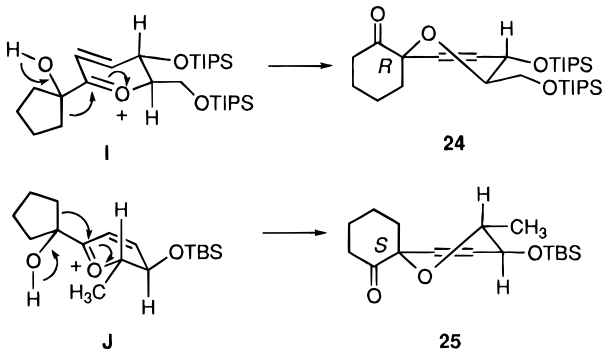


15

component product mixture reflected by at least seven different spots on TLC. The characterization of these substances was not pursued.

Stereochemical Considerations. The mechanistic model advanced to this point has not yet specifically addressed the very pertinent issue of stereochemistry. For the thermodynamic pathway which eventuates in the formation of Ferrier products, it is clear that a trans-disposed C-5/C-6 substituent pair is conducive to high-level control of π-facial stereoselectivity in the migratory

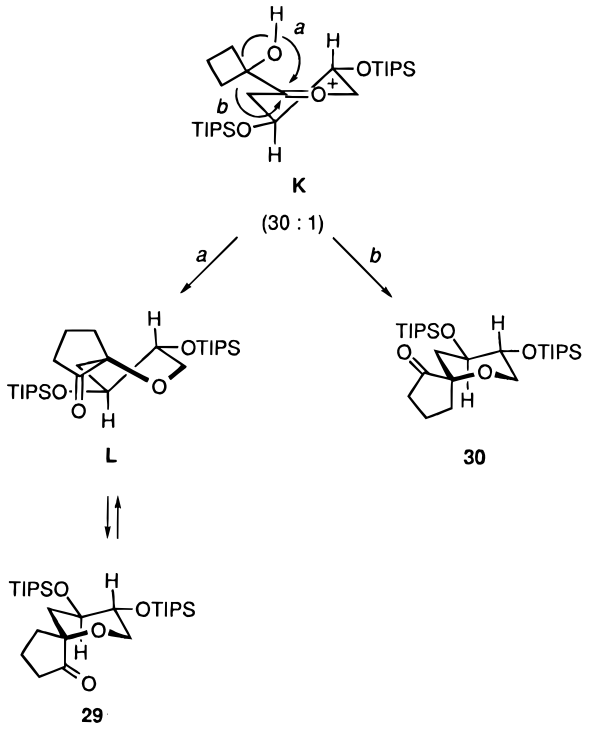
step. Upon inspection of conformations **I** and **J**, derived formally by appropriate ionization of **11** and **13**, respectively, the expectation is that the substituents positioned at C-5 and C-6 will act in tandem to demand concomitant projection into equatorial domains. The associated mini-



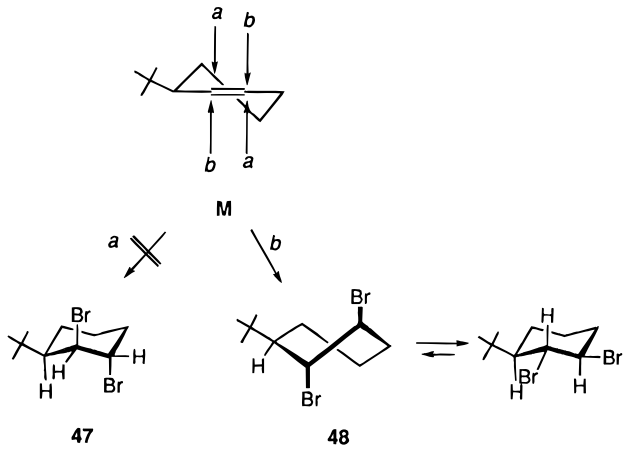
mization of nonbonded steric interactions will cause the illustrated, stereochemically enantiomeric conformations to be dominant. Stereoinduction will subsequently be manifested because of the advantages available to the development of chair-like (rather than twist-boat) characteristics in the transition state to product. For **I**, this guarantees that the spirocyclic carbon will eventuate as *S* in **24**. The change in configuration at the stereogenic centers in **J** will reverse the orientation of the pyran ring (as shown) and force a preference for gene—rating the spirocyclic carbon in the *R* series. The substantial dropoff in stereoselectivity exhibited by **16**, **17**, and **19** (Table 1) can be explained in terms of reduced rigidity within the relevant oxonium ion conformations.

To gain a comparable appreciation of the stereoselectivity of the direct ring expansion reactions requires a more detailed analysis of reaction exothermicity. It is reasonable to assume, since cyclobutanol **16** reacts in part via the Ferrier pathway, that it is the least reactive member of this subset of carbinols. A direct consequence of this scenario is the likelihood that the enhanced reaction enthalpy should be accompanied by heightened discrimination between the two diastereomeric transition states. Following the generation of the oxonium ion, conformation **K** will be adopted because of the diequatorial orientation of both pendant groups. Of the two stereocontrolled 1,2-shifts available to **K**, the experimental data reveal that pathway *a* leading via the twist-boat arrangement **L** to **29** dominates significantly (30:1) over the chair-like alternative which leads directly to **30** (Scheme 2). This ordering of events is viewed as plausible if the transition states are late and resemble the spirocyclic ketones. Under these circumstances, pathway *a* and the involvement of **L** serves to lessen the mutual repulsive interaction[16] of the very large OTIPS groups, a condition which persists in **30**. Our anticipation of a lower enthalpy content for **L** is supported by precedent. For example, *trans*-1,2-di-*tert*-butylcyclohexane prefers to exist in the boat form rather than either of the chair options because maximum relief from steric interactions is thereby realized.[17] Also, unlike the bromination of 4-*tert*-butylcyclohexene which proceeds with a greater than 94:6 preference for diaxial addition, the 3-*tert*-butyl isomer gives predominantly the diequatorial dibromide.[18]

Scheme 2



In the latter instance, the customarily preferred mode of addition, i.e., **M** → **47**, is impeded by the steric bulk of the neighboring substituent, such that antiperiplanar attack to give **48** operates instead.



A parallel situation, but with sterically less demanding substituents, is present in **12** as reflected in **N**. Although the level of nonbonded interaction between the groups is somewhat reduced, a kinetic predisposition for ring expansion via a twist-boat persists to the 4.6:1 level.

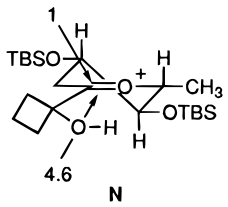
The energetics of two ring expansion pathways are seen to be capable of reversal with modest structural modifications. Removal of the 4-OTBS substituent in **N** (from **12**) as in **O** (from **14**) is a case in point. The response exhibited by **O** is to proceed to produce preferentially (4.7:1) via the chair-like transition state alternative. Evidently, the two diequatorial substituents resid-

(16) (a) Cieplak, P.; Howard, A. E.; Powers, J. P.; Rychnovsky, S. D.; Kollman, P. A. *J. Org. Chem.* **1996**, *61*, 3662. (b) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251. (c) Rychnovsky, S. D.; Skalitsky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

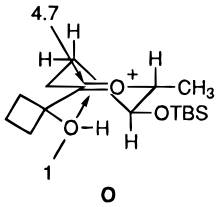
(17) (a) van de Graaf, G.; van Bekkum, H.; van Konigsveld, H.; Sinnema, A.; van Veen, A.; Wepster, B. M.; van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 135. (b) van de Graaf, B.; van Bekkum, H.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 268.

(18) Barili, P. L.; Bellucci, G.; Marioni, F.; Morelli, I.; Scartoni, V. *J. Org. Chem.* **1972**, *37*, 4353.

ing in **O** are insufficiently bulky to play a comparable controlling role.

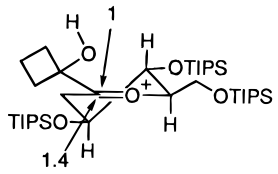


N

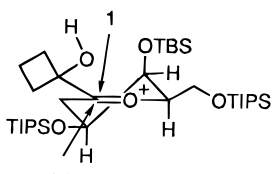


O

The definitive consequence of the extent of substitution and the stereochemical orientation of these groups on the favored reaction pathway is reflected also in the rearrangements of **10** and **20**. These isomeric glycals are almost identically substituted, but differ in the configuration of C(5). In the derived oxonium ions, this $OSiR_3$ is either equatorially disposed as in **P** or projected axially as in **Q**. Notwithstanding, both intermediates marginally favor isomerization by way of a chair-like geometry. The

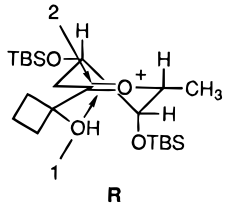


P

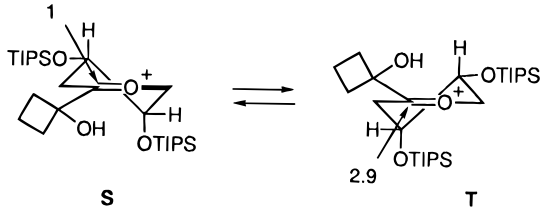


Q

bias exhibited by **P** is the opposite of that found in **K**, presumably because **P** (and **Q** as well) is more reactive and faces an earlier transition state. In addition, entry into the twist-boat manifold is met with the onset of 1,3-pseudodiaxial interaction involving the CH_2OTIPS group. When the C(5) substituent is positioned axially as it is for **20** (see **Q**) and **22** (see **R**), there exists an added steric deterrent to ring expansion via a twist-boat arrangement in the form of a developing 1,3-diaxial-like interaction. Since this pathway is not completely curtailed, it is entirely possible that our depictions of the oxonium ion intermediates are too chair-like. This issue is brought home in a more obvious manner when the stereoselection exhibited by **18** is scrutinized. The two axial/equatorial



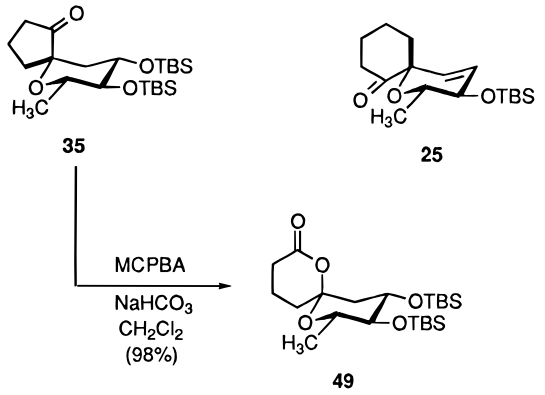
R



S **T**

disubstituted chair-like oxonium ion conformations theoretically available to this species are **S** and **T**. Although the formation of **39** is favored, there exists no clear indication whether this spiro glycoside arises by passage of **S** through a twist-boat geometry or by the direct advancement of **T** to a chair-like conformer. Note that the latter alternative must encounter a 1,3-diaxial interaction with an OTIPS group.

The fundamental importance of exothermicity in acid-catalyzed pinacol-like Wagner–Meerwein rearrangements of glycal-derived systems has been clearly demonstrated. The cyclobutanol systems rapidly isomerize directly in high yield under kinetically controlled conditions. When cyclopentanols are involved, the prior onset of the Ferrier rearrangement is necessary for ring expansion to occur. The stereoselectivity of these slower, thermodynamically controlled processes can be very high, particularly when the C(6) position is substituted. Interestingly, the direction of stereoinduction in the same carbohydrate series is sometimes reversed as the pendant ring is altered in size from 4- to 5-membered. The rhamnal derivatives **12** and **13** are exemplary. Whereas **12** isomerizes to give predominantly **35** in which the new bond is equatorial, **13** is transformed exclusively into **25** which has its new bond axially disposed.



The scope and mechanism of these reactions have been investigated in sufficient detail to provide clear guidance that nonbonded steric interactions between substituents on the pyran ring have considerable influence on the stereoselectivity of the Wagner–Meerwein shift. The formation of axially-substituted glycosides as the customary end products of Ferrier rearrangements is widely recognized.[6,15b] Similarly, the formation of α-glycosides is favored in nucleophilic additions to unsaturated sugar derivatives.[19] The dominance of axial attack has usually been attributed to the energy differences of the half-chair and half-boat transition states, but without serious consideration of global substitution.[7a] The kinetic anomeric effect has been noted to be overridden by steric effects in certain cases.[12,21] The accompanying paper[4] provides some indication of the impact of customary stereoelectronic control on the pinacol rearrangement in the absence of these secondary effects.

The current investigation makes apparent for the first time the potential of reaction sequences in which a glycal is deployed to serve as both the initiator and termination point of a pinacol rearrangement. Some indication of the richness of the chemistry made possible by these transformations is reflected in the Baeyer–Villiger oxidation of **35** to furnish the spiro acetal **49**. The development of further useful conversions founded on this concept is the object of ongoing studies.[22]

(19) Kennedy, J. F. *Carbohydrate Chemistry*; Oxford Science Publications: Clarendon Press: Oxford, England, 1988.
(20) Kaila, N.; Blumenstein, M.; Bielawska, H.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 4576.
(21) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer Verlag: New York, 1983.

Experimental Section

General Details. Consult ref 4.

3,4-Bis-*O*-(*tert*-butyldimethylsilyl)-L-rhamnal (3). 3,4-Di-*O*-acetyl-L-rhamnal (5.10 g, 23.8 mmol) was dissolved in methanol (55 mL), and a small piece of sodium wire was added. The mixture was stirred for 3 h and coconcentrated with benzene (50 mL) to afford a golden, crystalline material which was taken up in DMF (45 mL). Imidazole (7.81 g, 115 mmol) was introduced followed by TBSCl (8.78 g, 58.2 mmol). The mixture was stirred at rt for 27 h before being diluted with ether (200 mL) and washed with water (100 mL). The aqueous layer was extracted with ether (2 × 200 mL), and the combined organic solutions were washed with water (200 mL), dried, filtered, and concentrated. The residue was flash chromatographed (silica gel, elution with 5% ether in hexanes) to give 7.78 g (91%) of **3**: IR ($CHCl_3$, cm^{-1}) 1647, 1472, 1073; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, J = 6.2, 0.97 Hz, 1 H), 4.65 (dd, J = 6.2, 3.2 Hz, 1 H), 4.08−4.06 (m, 1 H), 3.93 (qd, J = 6.6, 6.6 Hz, 1 H), 3.56 (dd, J = 6.4, 5.0 Hz, 1 H), 1.31 (d, J = 6.7 Hz, 3 H), 0.91−0.90 (m, 18 H), 0.11−0.09 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.0, 102.8, 75.2, 74.7, 69.3, 26.0 (3 C), 25.9 (3 C), 18.1, 18.0, 17.2, −3.7, −3.9, −4.2, −4.3; MS *m/z* (M^+) calcd 358.2359, obsd 358.2357; $[\alpha]^{21}_D$ +42.3° (*c* 0.86, $CHCl_3$).

3-Deoxy-4-*O*-(*tert*-butyldimethylsilyl)-L-rhamnal (4). 3-Deoxy-L-rhamnal[10] (588 mg, 5.15 mmol) was analogously protected to yield 1.114 g (94%) of **4** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1655, 1257, 1237, 1124, 1048; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (dt, J = 6.0, 2.0 Hz, 1 H), 4.60 (td, J = 5.6, 2.4 Hz, 1 H), 3.67−3.54 (m, 2 H), 2.20 (dtd, J = 17.0, 5.6, 1.5 Hz, 1 H), 2.01 (ddt, J = 16.5, 9.0, 2.5 Hz, 1 H), 1.28 (d, J = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.2, 98.3, 75.7, 69.9, 30.9, 25.7 (3 C), 17.9, 17.9, −4.2, −4.8; MS *m/z* (M^+) calcd 228.1546, obsd 228.1533; $[\alpha]^{20.5}_D$ −91.5° (*c* 1.04, $CHCl_3$).

1,5-Anhydro-2-deoxy-1-*C*-(1-hydroxycyclobutyl)-3,4,6-tris-*O*-(triisopropylsilyl)-D-*arabino*-hex-1-enitol (10). A solution of **2** (264 mg, 0.44 mmol) in dry THF (2 mL) was cooled to −78 °C, treated with *tert*-butyllithium (1.54 mL of 1.7 M in pentane, 2.64 mmol), and stirred for 15 min at −78 °C before being warmed to 0 °C and stirred for an additional 60 min. After recooling to −78 °C, a solution of cyclobutanone (0.23 mL, 3.06 mmol) in dry THF (1 mL) was introduced via syringe. The reaction mixture was allowed to warm to rt and stirred for 2 h before being quenched with water and diluted with ether. The aqueous layer was extracted with ether, and the combined organic phases were dried and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 2% ethyl acetate in hexanes/1% triethylamine) gave **10** (176 mg, 81%) as a colorless oil: IR (C_6H_6, cm^{-1}) 3580; ^1H NMR (300 MHz, C_6D_6) δ 5.25 (dd, J = 5.2, 1.5 Hz, 1 H), 4.70−4.65 (m, 1 H), 4.37 (dd, J = 11.2, 8.2 Hz, 1 H), 4.33−4.27 (m, 2 H), 4.07 (dd, J = 11.2, 3.8 Hz, 1 H), 2.64−2.56 (m, 2 H), 2.43 (s, 1 H), 2.25−2.13 (m, 2 H), 1.82−1.70 (m, 2 H), 1.14 (s, 21 H), 1.13 (s, 21 H), 1.12 (s, 21 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 155.6, 93.8, 81.5, 75.2, 70.8, 67.0, 62.3, 35.2, 34.2, 18.43 (3 C), 18.39 (3 C), 18.32 (9 C), 18.26 (3 C), 13.4, 12.9 (3 C), 12.8 (3 C), 12.4 (3 C); MS *m/z* (M^+) calcd 684.5001, obsd 684.5024; $[\alpha]^{25}_D$ −14.3° (*c* 0.90, C_6H_6).

Anal. Calcd for $C_{37}H_{76}O_5Si_3$: C, 64.85; H, 11.18. Found: C, 65.20; H, 11.29.

1,5-Anhydro-2-deoxy-1-*C*-(1-hydroxycyclopentyl)-3,4,6-tris-*O*-(triisopropylsilyl)-D-*arabino*-hex-1-enitol (11). Reaction of **2** (229 mg, 0.38 mmol) with *tert*-butyllithium (1.16 mL of 1.7 M in pentane, 1.98 mmol) and then cyclopentanone (0.20 mL, 2.31 mmol) in the predescribed manner afforded 237 mg (94%) of **11** as a colorless oil: IR (C_6H_6, cm^{-1}) 3590; ^1H NMR (300 MHz, C_6D_6) δ 5.29 (dd, J = 5.2, 1.5 Hz, 1 H), 4.66−4.61 (m, 1 H), 4.39−4.27 (m, 3 H), 4.07 (dd, J = 11.1, 3.8 Hz, 1 H), 2.25−2.16 (m, 2 H), 1.90−1.76 (m, 3 H), 1.72−1.62 (m, 4 H), 1.15 (s, 42 H), 1.14 (s, 21 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.8, 93.8, 82.0, 81.5, 70.9, 67.1, 62.4, 39.6, 38.6, 24.6 (2 C), 18.47 (3 C), 18.43 (3 C), 18.35 (3 C), 18.28 (9 C), 12.9 (3 C), 12.8 (3 C), 12.4 (3 C); MS *m/z* (M^+ − OH) calcd 681.5129, obsd 681.5124; $[\alpha]^{25}_D$ −11.2° (*c* 0.69, C_6H_6).

Anal. Calcd for $C_{38}H_{78}O_5Si_3$: C, 65.27; H, 11.24. Found: C, 65.48; H, 11.32.

1,5-Anhydro-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-1-*C*-(1-hydroxycyclobutyl)-L-*arabino*-hex-1-enitol (12). A solution of **3**[7d] (1.047 g, 2.92 mmol) in dry THF (9 mL) was cooled to −78 °C, treated with *tert*-butyllithium (8.40 mL, 14.3 mmol, 1.7 M in pentane) via syringe, warmed to 0 °C, stirred for 45 min, recooled to −78 °C, treated with cyclobutanone (1.25 mL, 17.1 mmol) dissolved in THF (2.4 mL), warmed to rt for 2.5 h, quenched with water (10 mL), and diluted with ether (20 mL). The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic layers were dried, filtered, and concentrated. Flash chromatography of the residue (silica gel, 25% ether in hexanes/1% triethylamine) afforded 159 mg of unreacted **3** and 738 mg of **12** (70% based on recovered starting material) as a clear, colorless oil: IR (C_6H_6, cm^{-1}) 3581, 1107; ^1H NMR (300 MHz, C_6D_6) δ 5.04 (d, J = 3.4 Hz, 1 H), 4.26 (dd, J = 4.5, 4.4 Hz, 1 H), 3.94 (quint, J = 6.6 Hz, 1 H), 3.65 (dd, J = 6.4, 4.8 Hz, 1 H), 2.48−2.33 (m, 2 H), 2.14−2.04 (m, 3 H), 1.81−1.60 (m, 2H), 1.31 (d, J = 6.7 Hz, 3 H), 0.98 (s, 9 H), 0.97 (s, 9 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.13 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.3, 96.2, 75.7, 75.1, 74.8, 70.7, 34.8, 34.6, 26.3 (3 C), 26.1 (3 C), 18.4, 18.2, 17.3, 13.5, −3.5, −3.6, −3.8, −4.2; MS *m/z* (M^+) calcd 428.2778, obsd 428.2771; $[\alpha]^{20}_D$ +42.7° (*c* 0.965, C_6H_6).

Anal. Calcd for $C_{22}H_{44}O_4Si_2$: C, 61.63; H, 10.34. Found: C, 61.75; H, 10.36.

Prototypical Acid-Promoted Spirocyclization of the Carbinols. Experiment 1. A solution of **11** (61 mg, 0.09 mmol) in dry CH_2Cl_2 (40 mL) was stirred in the presence of a catalytic quantity of camphorsulfonic acid for 1 h. Following the addition of saturated $NaHCO_3$ solution (25 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried and evaporated. The crude product was purified by flash chromatography on silica gel (elution with 2% ethyl acetate in hexanes) to give **24** as a colorless oil (22 mg, 49%): IR (C_6H_6, cm^{-1}) 1735; ^1H NMR (300 MHz, C_6D_6) δ 6.02 (dd, J = 10.5, 1.6 Hz, 1 H), 5.86 (dd, J = 10.5, 1.9 Hz, 1 H), 4.28 (td, J = 8.0, 1.7 Hz, 1 H), 4.16 (dd, J = 10.4, 2.2 Hz, 1 H), 3.93 (dd, J = 10.4, 6.7 Hz, 1 H), 3.80 (ddd, J = 8.1, 6.6, 2.2 Hz, 1 H), 3.00 (ddd, J = 6.1, 13.0, 13.0 Hz, 1 H), 2.21 (td, J = 3.7, 12.5 Hz, 1 H), 2.12−1.85 (m, 2 H), 1.73−1.66 (m, 1 H), 1.37−0.83 (series of m, 45 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.0, 130.3, 130.1, 80.6, 76.8, 65.2, 64.5, 38.5, 36.2, 27.9, 20.7, 18.3 (6 C), 18.2 (6 C), 13.0 (3 C), 12.4 (3 C); MS *m/z* (M^+) calcd 524.3717, obsd 524.3748; $[\alpha]^{25}_D$ +76.5° (*c* 0.89, C_6H_6).

Anal. Calcd for $C_{29}H_{56}O_4Si_2$: C, 66.36; H, 10.75. Found: C, 66.12; H, 10.60.

Experiment 2. A solution of **13** (754 mg, 1.70 mmol) in dry CH_2Cl_2 (400 mL) containing a few milligrams of CSA was allowed to react for 30 h. Flash chromatographic purification (silica gel, elution with 2% ethyl acetate in hexanes/1% triethylamine) gave **25** as a colorless solid, mp 39−40 °C (426 mg, 81%): IR ($CHCl_3$, cm^{-1}) 1730; ^1H NMR (300 MHz, C_6D_6) δ 5.90 (dd, J = 10.5, 1.9 Hz, 1 H), 5.75 (dd, J = 10.5, 1.5 Hz, 1 H), 3.76 (td, J = 8.0, 1.7 Hz, 1 H), 3.57 (qd, J = 7.9, 6.1 Hz, 1 H), 2.80 (dt, J = 12.7, 5.9 Hz, 1 H), 2.13 (m, 1 H), 1.97−1.88 (m, 1 H), 1.69−1.51 (m, 2 H), 1.27 (d, J = 6.1 Hz, 3 H), 1.25−0.97 (m, 3 H), 0.93 (s, 9 H), −0.03 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.7, 131.0, 129.6, 80.9, 70.7, 70.4, 38.4, 36.0, 27.8, 25.9 (3 C), 20.9, 19.0, 18.1, −4.2, −4.7; MS *m/z* (M^+) calcd 310.1964, obsd 310.1942; $[\alpha]^{25}_D$ −105.3° (*c* 0.95, $CHCl_3$).

Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.92; H, 9.75.

Experiment 3. Stirring of **17** (228 mg, 0.443 mmol) in dry CH_2Cl_2 (50 mL) for 19 h followed by flash chromatography (silica gel, 10% ether in hexanes/1% triethylamine) yielded 117 mg (78%) of a mixture of **26** and **27** and a more polar

(22) Paquette, L. A.; Tae, J. *J. Org. Chem.* **1996**, *61*, 7860.

(23) The authors have deposited the atomic coordinates for the X-ray structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

unidentified material. The two major products were inseparable by column chromatography, but appeared as a 1.1:1 mixture on the basis of NMR integration: IR ($CHCl_3$, cm^{-1}) 1717, 1463, 1389, 1108, 1069, 882; ^1H NMR (300 MHz, C_6D_6, reported as a diastereomeric mixture) δ 5.95 (dt, J = 10.4, 1.5 Hz, 1 H), 5.90 (d, J = 10.5 Hz, 1 H), 5.81 (dd, J = 10.4, 1.0 Hz, 1 H), 5.72 (dd, J = 10.5, 2.0 Hz, 1 H), 4.35 (ddd, J = 8.9, 5.7, 1.8 Hz, 1 H), 4.04 (ddd, J = 10.7, 5.7, 1.3 Hz, 1 H), 3.97 (ddd, J = 4.5, 3.5, 1.0 Hz, 1 H), 3.77 (dd, J = 11.5, 3.9 Hz, 1 H), 3.71 (dd, J = 11.5, 4.3 Hz, 1 H), 3.63 (dd, J = 10.7, 8.9 Hz, 1 H), 2.65 (ddd, J = 12.8, 11.8, 5.9 Hz, 1 H), 2.53 (ddd, J = 13.0, 9.7, 5.6 Hz, 1 H), 2.14−1.90 (m, 3 H), 1.85−1.62 (m, 3 H), 1.59−1.41 (m, 3 H), 1.40−1.09 (m, 5H), 1.06−0.91 (m, 42 H); ^{13}C NMR (75 MHz, C_6D_6, reported as a diastereomeric mixture) ppm 208.13, 208.08, 132.5, 131.0, 129.2, 129.0, 80.5, 79.8, 67.7, 67.6, 64.1, 63.4, 40.6, 39.3, 38.9, 38.2, 27.8 (2 C), 20.9, 20.8, 18.2 (6 C), 18.1 (6 C), 12.5 (3 C), 12.4 (3 C); MS m/z (M^+) calcd 338.2277, obsd 338.2274.

Experiment 6. Submission of **10** (53 mg, 0.08 mmol) to reaction for 4 h and subsequent flash chromatography (silica gel, elution with 2% ethyl acetate in hexanes) gave 27 mg (50%) of **33** and 20 mg (38%) of **34**, both as colorless oils.

For **33**: IR ($CHCl_3$, cm^{-1}) 1740; ^1H NMR (300 MHz, C_6D_6) δ 4.33 (ddd, J = 8.0, 6.0, 4.0 Hz, 1 H), 3.94 (dd, J = 10.5, 3.5 Hz, 1 H), 3.78 (dd, J = 10.5, 5.5 Hz, 1 H), 3.69 (dd, J = 7.5, 6.0 Hz, 1 H), 3.52 (ddd, J = 7.5, 5.5, 3.5 Hz, 1 H), 2.46−2.32 (m, 1 H), 2.13 (dd, J = 13.5, 4.0 Hz, 1 H), 2.14−1.99 (m, 3 H), 1.87−1.71 (m, 2 H), 1.57 (dd, J = 13.5, 8.0 Hz, 1 H), 1.13−1.10 (m, 63 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.6, 78.1, 78.0, 72.6, 71.5, 64.0, 38.1, 35.3, 34.3, 18.42 (2 C), 18.35 (3 C), 18.31 (2 C), 18.29 (6 C), 17.94 (6 C), 17.8, 13.5 (3 C), 13.4 (3 C), 12.0 (3 C); MS m/z ($M^+ - C_3H_7$) calcd 641.4453, obsd 641.4452; $[\alpha]^{25}_D$ +17.7° (c 1.53, $CHCl_3$).

Anal. Calcd for $C_{37}H_{76}O_5Si_3$: C, 64.85; H, 11.18. Found: C, 63.51; H, 11.15.

For **34**: IR (C_6H_6, cm^{-1}) 1760; ^1H NMR (300 MHz, C_6D_6) δ 3.99 (dd, J = 10.5, 2.5 Hz, 1 H), 3.95 (ddd, J = 10.5, 7.5, 5.0 Hz, 1 H), 3.84 (dd, J = 10.5, 6.0 Hz, 1 H), 3.69 (dd, J = 8.0, 7.5 Hz, 1 H), 3.41 (ddd, J = 8.0, 6.0, 2.5 Hz, 1 H), 1.99 (dd, J = 13.0, 10.5 Hz, 1 H), 2.17−1.97 (m, 1 H), 1.90−1.65 (m, 1 H), 1.66 (dd, J = 13.0, 5.0 Hz, 1 H), 1.49−1.31 (m, 2 H), 1.28−1.15 (m, 2 H), 1.14−1.00 (m, 63 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.8, 79.3, 78.5, 74.2, 73.8, 64.7, 36.6, 35.1, 32.4, 18.8 (3 C), 18.7 (3 C), 18.59 (3 C), 18.56 (3 C), 18.2 (6 C), 18.1, 14.2 (3 C), 14.1 (3 C), 12.3 (3 C); MS m/z [$M^+ - (CO + 2CH_3)$] calcd 626.4583, obsd 626.4557; $[\alpha]^{25}_D$ −4.1 (c 1.39, C_6H_6).

Anal. Calcd for $C_{37}H_{76}O_5Si_3$: C, 64.85; H, 11.18. Found: C, 65.03; H, 11.40.

Experiment 7. Isomerization of **12** (206 mg, 0.480 mmol) in dry CH_2Cl_2 (40 mL) and subsequent flash chromatography (silica gel, elution with 10% ether in hexanes) yielded 131 mg (64%) of **35** and 29 mg (14%) of **36**.

For **35**: white solid, mp 55−56 °C; IR ($CHCl_3$, cm^{-1}) 1737, 1257, 1108, 1088, 837; ^1H NMR (300 MHz, C_6D_6) ppm 4.61 (ddd, J = 10.9, 8.4, 4.9 Hz, 1 H), 3.79 (dq, J = 8.9, 6.3 Hz, 1 H), 3.19 (t, J = 8.7 Hz, 1 H), 2.12−2.02 (m, 1 H), 1.91 (dd, J = 13.4, 5.0 Hz, 1 H), 1.86−1.61 (m, 3 H), 1.63 (dd, J = 13.4, 11.0 Hz, 1 H), 1.26 (d, J = 6.3 Hz, 3 H), 1.31−1.08 (m, 2 H), 1.03 (s, 9 H), 1.00 (s, 9 H), 0.24 (s, 3 H), 0.21 (s, 3 H), 0.18 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.5, 79.3, 78.9, 72.7, 70.9, 39.1, 38.0, 35.8, 26.5 (3 C), 26.4 (3 C), 19.4, 18.4, 18.3, 18.1, −2.3, −2.8, −3.6, −4.2; MS m/z (M^+) calcd 428.2778, obsd 428.2792; $[\alpha]^{20}_D$ −45.5° (c 0.95, $CHCl_3$).

Anal. Calcd for $C_{22}H_{44}O_4Si_2$: C, 61.63; H, 10.34. Found: C, 62.01; H, 10.37.

For **36**: white solid, mp 105−107 °C; IR ($CHCl_3$, cm^{-1}) 1749, 1472, 1257, 1215, 1109, 1066; ^1H NMR (300 MHz, C_6D_6) δ 3.71 (ddd, J = 11.8, 8.1, 4.6 Hz, 1 H), 3.32 (dq, J = 8.9, 6.1 Hz, 1 H), 3.20 (t, J = 8.5 Hz, 1 H), 2.10 (t, J = 12.8 Hz, 1 H), 2.04−1.90 (m, 1 H), 1.77−1.64 (m, 2 H), 1.59 (dd, J = 12.9, 4.6 Hz, 1 H), 1.47 (ddd, J = 12.5, 9.2, 6.5 Hz, 1 H), 1.43−1.33 (ddd, J = 13.1, 6.8, 6.4 Hz, 1 H), 1.27 (d, J = 6.1 Hz, 3H), 1.23−1.13 (m, 1 H), 1.01 (s, 9 H), 0.96 (s, 9 H), 0.19 (s, 3 H), 0.14 (s, 3 H), 0.05 (s, 3H), −0.00 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.0, 79.9, 78.9, 72.9, 72.8, 38.6, 35.3, 32.3, 26.5 (3 C), 26.4 (3 C), 19.4, 18.4 (2 C), 18.3, −2.5, −2.7, −3.8, −4.3; MS m/z (M^+) calcd 428.2778, obsd 428.2790; $[\alpha]^{22}_D$ +73.3° (c 0.24, $CHCl_3$).

Anal. Calcd for $C_{22}H_{44}O_4Si_2$: C, 61.63; H, 10.34. Found: C, 61.53; H, 10.44.

Experiment 8. Exposure of **14** (249 mg, 0.833 mmol) to CSA in dry CH_2Cl_2 (80 mL) for 1 h, and subsequent flash chromatography on silica gel (elution with 20% ether in hexanes) afforded 199 mg (80%) of **37** and 43 mg (17%) of **38**.

For **37**: white solid, mp 47−48 °C; IR ($CHCl_3$, cm^{-1}) 1747, 1256, 1105; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37−3.26 (m, 2 H), 2.38−2.21 (m, 3 H), 2.08−1.89 (m, 3 H), 1.76−1.47 (m, 4 H), 1.19 (d, J = 5.7 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.6, 80.7, 73.9, 72.5, 35.7, 31.7, 29.8, 28.4, 25.7 (3 C), 18.6, 17.9, 17.8, −4.1, −4.7; MS m/z (M^+) calcd 298.1964, obsd 298.1945; $[\alpha]^{22}_D$ −66.6° (c 0.38, $CHCl_3$).

Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.40; H, 10.11.

For **38**: white solid, mp 62−64 °C; IR ($CHCl_3$, cm^{-1}) 1710, 1362, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (dq, J = 8.8, 6.2 Hz, 1 H), 3.18 (td, J = 8.9, 4.2 Hz, 1 H), 2.46−2.35 (m, 1 H), 2.22−1.91 (m, 4 H), 1.82−1.59 (m, 5 H), 1.13 (d, J = 6.2 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$) ppm 216.7, 77.3, 73.3, 73.2, 38.3, 36.5, 28.9 (2 C), 25.7 (3 C), 18.7, 17.9, 17.5, −4.1, −4.7; MS m/z (M^+) calcd 298.1964, obsd 298.1957; $[\alpha]^{25}_D$ +93.4 (c 0.265, $CHCl_3$).

Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.26; H, 10.14.

Experiment 9. From the isomerization of **18** (223 mg, 0.447 mmol) during 30 min, there was isolated following flash chromatography (silica gel, elution with 10% ethyl acetate in hexanes/1% triethylamine) 140 mg (63%) of **39** and 50 mg (22%) of **40**. A small amount of **18** (9 mg, 4%) was also recovered.

For **39**: clear, colorless oil; IR ($CHCl_3$, cm^{-1}) 1734, 1464, 1030, 883; ^1H NMR (300 MHz, C_6D_6) δ 4.74 (ddd, J = 11.0, 4.5, 2.6 Hz, 1 H), 3.95 (br d, J = 2.0 Hz, 1 H), 3.73−3.72 (m, 2 H), 2.28 (dd, J = 12.9, 11.1 Hz, 1 H), 2.13−1.93 (m, 2 H), 1.83−1.65 (m, 2 H), 1.60 (dd, J = 12.9, 4.5 Hz, 1 H), 1.39−1.25 (m, 2 H), 1.17−1.16 (m, 42 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.6, 79.0, 71.2, 67.9, 67.7, 38.2, 36.1, 33.5, 18.5 (6 C), 18.4 (6 C), 18.3, 13.1 (3 C), 12.9 (3 C); MS m/z ($M^+ - C_3H_7$) calcd 455.3013, obsd 455.2963; $[\alpha]^{22}_D$ −55.2° (c 0.785, $CHCl_3$).

Anal. Calcd for $C_{27}H_{54}O_4Si_2$: C, 65.00; H, 10.91. Found: 65.28; H, 10.89.

For **40**: clear, colorless oil; IR ($CHCl_3$, cm^{-1}) 1752, 1464, 1062, 883; ^1H NMR (300 MHz, C_6D_6) ppm 3.89−3.81 (m, 3 H), 3.22 (dd, J = 12.2, 0.6 Hz, 1 H), 2.73 (dd, J = 12.2, 11.9 Hz, 1 H), 2.03−1.94 (m, 1 H), 1.85−1.71 (m, 2 H), 1.59−1.50 (m, 1 H), 1.41−1.25 (m, 3 H), 1.22−1.20 (m, 21 H), 1.12−1.10 (m, 21 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.1, 80.6, 71.2, 69.9, 67.6, 35.0, 32.9, 31.9, 18.5 (3 C), 18.4 (6 C), 18.3 (3 C), 18.1, 13.3 (3 C), 12.8 (3 C); MS m/z ($M^+ - C_3H_7$) calcd 455.3013, obsd 455.2938; $[\alpha]^{22}_D$ −2.81° (c 1.295, $CHCl_3$).

Anal. Calcd for $C_{27}H_{54}O_4Si_2$: C, 65.00; H, 10.91. Found: C, 64.90; H, 10.93.

Experiment 10. From the isomerization of **20** (179 mg, 0.278 mmol) in CH_2Cl_2 (20 mL) during 30 min, there was isolated following flash chromatography (silica gel, elution with 5% ethyl acetate in hexanes/1% triethylamine) 124 mg (70%) of **41** and 34 mg (19%) of **42**.

For **41**: colorless oil; IR ($CHCl_3$, cm^{-1}) 1751, 1463, 1110, 1063; ^1H NMR (300 MHz, C_6D_6) δ 4.06 (br s, 1 H), 4.00−3.86 (m, 3 H), 3.52 (t, J = 6.3 Hz, 1 H), 2.73 (t, J = 12.3 Hz, 1 H), 2.12−1.90 (m, 2 H), 1.82−1.62 (m, 2 H), 1.48−1.23 (m, 3H), 1.12−1.10 (m, 51 H), 0.33 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.8, 80.5, 77.0, 71.3, 70.7, 63.9, 35.0, 32.4, 32.3 (2 C), 26.4 (3 C), 18.9, 18.4 (3 C), 18.3 (3 C), 18.2 (6 C), 12.8 (3 C), 12.3 (3 C), −3.25, −4.3; MS m/z ($M^+ - C_3H_7$) calcd 599.3983, obsd 599.3957; $[\alpha]^{22}_D$ −5.13° (c 1.11, $CHCl_3$).

Anal. Calcd for $C_{34}H_{70}O_5Si_3$: C, 63.49; H, 10.97. Found: C, 63.76; H, 10.88.

For **42**: pale yellowish oil; IR ($CHCl_3$, cm^{-1}) 1735, 1463, 1110, 1057; ^1H NMR (300 MHz, C_6D_6) δ 4.82 (ddd, J = 11.5, 4.6, 2.2 Hz, 1 H), 4.19 (d, J = 0.7 Hz, 1 H), 4.04−3.88 (m, 3H), 2.30 (dd, J = 12.6, 11.8 Hz, 1 H), 2.20−2.09 (m, 1 H), 1.97−

1.67 (m, 3 H), 1.62 (ddd, J = 12.8, 4.6, 0.7 Hz, 1 H), 1.40−1.26 (m, 2 H), 1.20−1.01 (m, 51 H), 0.36 (s, 3 H), 0.28 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.6, 78.9, 76.3, 70.4, 68.6, 63.1, 38.0, 35.7, 33.0 (2 C), 26.2 (3 C), 18.7, 18.2 (3 C), 18.1 (3 C), 17.9 (6 C), 12.6 (3 C), 12.0 (3 C), −3.5, −4.6; MS m/z ($M^+ - C_3H_7$) calcd 599.3983, obsd 599.4031; $[\alpha]^{24}_D$ +26.8° (c 1.06, $CHCl_3$).

Anal. Calcd for $C_{34}H_{70}O_5Si_3$: C, 63.49; H, 10.97. Found: C, 63.22; H, 10.94.

Experiment 11. Stirring of **22** (239 mg, 0.557 mmol) in dry CH_2Cl_2 (45 mL) containing a catalytic quantity of CSA for 1 h with subsequent chromatography on silica gel (elution with 10% ethyl acetate in hexanes) provided 149 mg (62%) of **43** and 73 mg (30%) of **44**.

For **43**: white solid, mp 88−89 °C; IR ($CHCl_3$, cm^{-1}) 1751, 1471, 1372, 1255, 1109, 1069, 1031, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 3.68 (ddd, J = 12.2, 4.1, 2.4 Hz, 1 H), 3.41 (t, J = 1.0 Hz, 1 H), 3.22 (q, J = 6.2 Hz, 1 H), 2.58 (t, J = 12.3 Hz, 1 H), 2.05−1.95 (m, 1 H), 1.81−1.66 (m, 2 H), 1.60−1.48 (m, 1 H), 1.27 (dd, J = 12.2, 6.8 Hz, 1 H), 1.31−1.19 (m, 1 H), 1.17 (d, J = 6.3 Hz, 3 H), 1.08 (s, 9 H), 1.05 (ddd, J = 12.2, 4.2, 0.9 Hz, 1 H), 0.97 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.1, 80.2, 73.8, 71.4, 71.2, 35.1, 32.1, 32.0, 26.4 (6 C), 18.9 (2 C), 18.7, 18.3, −3.4, −4.2, −4.3, −4.5; MS m/z ($M^+ - C_4H_9$) calcd 371.2074, obsd 371.2067; $[\alpha]^{21}_D$ +7.96° (c 1.08, $CHCl_3$).

Anal. Calcd for $C_{22}H_{44}O_4Si_2$: C, 61.63; H, 10.34. Found: C, 61.74; H, 10.29.

For **44**: IR ($CHCl_3$, cm^{-1}) 1734, 1471, 1255, 1107, 1062, 1035, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 4.69 (ddd, J = 11.6, 4.6, 2.4 Hz, 1 H), 3.78 (q, J = 6.4 Hz, 1 H), 3.48 (d, J = 2.0 Hz, 1 H), 2.12 (t, J = 12.1 Hz, 1 H), 2.11−2.03 (m, 1 H), 1.92−1.77 (m, 2 H), 1.75−1.61 (m, 1 H), 1.42 (dd, J = 12.7, 4.6 Hz, 1 H), 1.30−1.20 (m, 2 H), 1.11 (d, J = 6.4 Hz, 3 H), 1.06 (s, 9 H), 1.02 (s, 9 H), 0.26 (s, 3 H), 0.19 (s, 3 H), 0.17 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.1, 78.9, 74.0, 71.3, 69.0, 38.4, 36.1, 32.5, 26.5 (3 C), 26.4 (3 C), 18.9 (2 C), 18.7, 18.2, −3.3, −4.0, −4.3, −4.4; MS m/z (M^+) calcd 371.2074, obsd 371.2071; $[\alpha]^{21}_D$ −55.6° (c 1.22, $CHCl_3$).

The stereochemistry of the spiro center of **44** was determined in a similar manner. A ^{1}H−^{1}H COSY 90 and a ^{1}H−^{13}C phase sensitive correlation experiment along with measurement of coupling constants enabled unambiguous assignment of all proton and carbon signals. Because the signals for H(2a) and H(8) were not completely resolved by ^{1}H NMR, clean irradiation of H(2a) could not be achieved. However, semiselective irradiation of the parent triplet representing H(2a) led to strong enhancement of the carbonyl carbon (C(7). Additionally, C(1), C(3), and C(10) were also enhanced, although the signal for C(10) was not as intense. Several NOE experiments were also performed to confirm the stereochemistry of the spiro center. A significant NOE enhancement (2.6%) was observed between H(2e) and H(10′) when H(2e) was irradiated. On this basis, the spirocyclic carbon must be of the *R* configuration.

Acid-Catalyzed Hydration of 21. A solution of **21** (82 mg, 0.125 mmol) in dry CH_2Cl_2 (17 mL) containing a catalytic quantity of CSA was stirred for 3 h and worked up in the usual way. Chromatography on silica gel (elution with 5% ethyl acetate in hexanes/1% triethylamine) provided 62 mg (73%) of **45** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3550, 1463, 1389, 1366, 1251, 1044; ^{1}H NMR (300 MHz, C_6D_6) δ 4.44 (ddd, J = 11.4, 4.4, 2.0 Hz, 1 H), 4.13−4.08 (m, 2 H), 3.99−3.86 (m, 2 H), 3.45 (d, J = 2.2 Hz, 1 H), 2.32 (ddd, J = 11.8, 11.4, 2.1 Hz, 1 H), 2.12−2.06 (m, 2 H), 1.98−1.93 (dd, J = 11.8, 4.2 Hz, 1 H), 1.83−1.71 (m, 3 H), 1.62−1.47 (m, 2 H), 1.29−1.03 (m, 53 H), 0.33 (s, 3 H), 0.26 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.6, 87.4, 74.4, 70.7, 70.4, 63.6, 36.2, 34.4, 33.0, 26.4 (3 C), 25.1, 25.0, 18.8, 18.5 (3 C), 18.4 (3 C), 18.2 (6 C), 12.8 (3 C), 12.4 (3 C), −3.2, −4.5; MS m/z ($M^+ - C_3H_7 - H_2O$) calcd 613.4140, obsd 613.4161; $[\alpha]^{21}_D$ +16.0° (c 0.95, $CHCl_3$).

Anal. Calcd for $C_{35}H_{74}O_6Si_3$: C, 62.26; H, 11.05. Found: C, 62.10; H, 11.13.

Acid-Catalyzed Hydration of 23. Analogous processing of **23** (176 mg, 0.398 mmol) provided 137 mg (75%) of **46** as a white solid, mp 74.5−76 °C: IR ($CHCl_3$, cm^{-1}) 3556, 1471, 1389, 1362, 1254, 1043, 837; ^{1}H NMR (300 MHz, C_6D_6) δ 4.27 (ddd, J = 11.5, 4.6, 2.3 Hz, 1 H), 3.86 (q, J = 6.4 Hz, 1 H), 3.50−3.49 (m, 1 H), 3.09 (d, J = 2.2 Hz, 1 H), 2.17 (ddd, J = 12.1, 11.5, 2.0 Hz, 1 H), 2.08−1.98 (m, 1 H), 1.89 (s, 1 H), 1.80 (dd, J = 12.1, 4.6 Hz, 1 H), 1.77−1.63 (m, 4 H), 1.56−1.43 (m, 3 H), 1.11 (d, J = 6.5 Hz, 3 H), 1.06 (s, 9 H), 0.99 (s, 9 H), 0.27 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 100.2, 87.2, 73.9, 70.5, 68.8, 36.0, 34.2, 32.3, 26.4 (3 C), 26.3 (3 C), 25.0, 24.9, 18.8, 18.7, 18.2, −3.2, −4.1, −4.4, −4.5; MS m/z ($M^+ - C_4H_9$) calcd 403.2336, obsd 403.2375; $[\alpha]^{21}_D$ −28.2° (c 0.97, $CHCl_3$).

Anal. Calcd for $C_{23}H_{48}O_5Si_2$: C, 59.95; H, 10.50. Found: C, 60.06; H, 10.58.

(6*S*,9*S*,9*S*,10*S*)-9,10-Bis(*tert*-butyldimethylsiloxy)-8-methyl-1,7-dioxaspiro[5.5]undecan-2-one (49). A cold (0 °C), magnetically stirred mixture of **35** (238 mg, 0.56 mmol) and sodium bicarbonate (252 mg, 3.00 mmol) in CH_2Cl_2 (10 mL) was treated with *m*-chloroperbenzoic acid (315 mg of 50−60% purity, ca. 1 mmol) and stirred for 30 min at 0 °C and 10 min at 25 °C. Following the addition of 10% Na_2SO_3 solution (15 mL) and a further 1 h of stirring, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 10% ethyl acetate in hexanes) furnished 237 mg (98% based on recovered **35**) of **49** as colorless crystals, mp 98 °C: IR ($CHCl_3$, cm^{-1}) 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (ddd, J = 4.9, 8.2, 10.9 Hz, 1 H), 3.81 (dq, J = 6.3, 9.1 Hz, 1 H), 3.17 (dd, J = 8.4, 8.8 Hz, 1 H), 2.67−2.57 (m, 1 H), 2.48−2.36 (m, 1 H), 2.19 (dd, J = 4.9, 13.4 Hz, 1 H), 2.15−2.05 (m, 1 H), 1.93−1.79 (m, 1 H), 1.78−1.69 (m, 2 H), 1.62 (dd, J = 10.9, 13.4 Hz, 1 H), 1.19 (d, J = 6.3 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 6 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.1, 103.7, 78.0, 71.1, 70.0, 44.3, 32.5, 29.3, 26.3 (3 C), 26.1 (3 C), 18.8, 18.2, 18.0, 15.5, −2.7, −3.2, −3.9, −4.3; MS m/z (M^+ − CO, $C(CH_3)_3$, − $2CH_3$) calcd 329.1604, obsd 329.1613; $[\alpha]^{25}_D$ −38.8° (c 0.96, $CHCl_3$).

Anal. Calcd for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97. Found: C, 59.56; H, 10.05.

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Supporting Information Available: A considerable portion of the Experimental Section, NOE and long-range DEPT data for **29**, **35**, **36**, **39**, **40**, **41**, and **43**, and an ORTEP drawing for **37** (13 pages). This material is contained in 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.

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