Definition of Several Control Elements Relevant to the Stereodefined Serial Elaboration of Belted Poly(spirotetrahydrofurans) Fitted with a Cyclohexane Core

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The stereochemistry of the condensations of 2-cyclohexenones, α-arylidenecyclohexanones, and α-(*tert*-butyldimethylsiloxy)cyclohexanones carrying one or two (both syn and anti) spirotetrahydrofuran units adjacent to the carbonyl with allyl organometallics (especially indium) and with the Normant reagent ($ClMgO(CH_2)_3MgCl$) is described. Good levels of anti stereoselection are observed in the α-arylidene series. Subsequent cyclization generates a second (or third) tetrahydrofuran ring possessing trans vicinal oxygens. Useful levels of matched and mismatched diastereoselection are also attainable by prior α-oxygenation. The intrinsic differences in diastereomer production between indium and magnesium organometallics are highlighted. A clear distinction regarding the anticipated direction of stereoselectivity is made on the grounds of chelation capabilities and the intra- or intermolecularity of carbon−carbon bond formation. Finally, the two protocols that are described in detail are shown to be iterative, a feature that augurs well for ultimately accessing the eight possible hexaspirocyclohexanes in an efficient and stereocontrolled manner.

The synthesis of structurally organized polyethers that have a preexisting disposition for strong metal ion binding continues to be the focus of much research.[1,2] Through reduction in the level of conformational freedom and proper spatial orientation of the several heteroatomic centers, efficient multipoint binding interactions can be gained. The better structurally disposed the ligand is for adopting the conformation favored for binding (both entropically and enthalpically), the better a receptor it will be.[1,3,4] Despite the vigor with which research in this area has been pursued, we are unaware of any report dealing with the question of possible *bifacial complexation*. This term is intended to encompass any ligand that finds it possible because of its unique structural features *to bind a metal ion (either the same or different) on both of its faces*.

These considerations have led us to accord attention to the elaboration of belted spirocyclic tetrahydrofurans.[5] The eight isomers possible when the central belt is six-membered are shown in Figure 1. To simplify reference to the individual isomers, they have been assigned simple numerical descriptors indicative of the locus of the

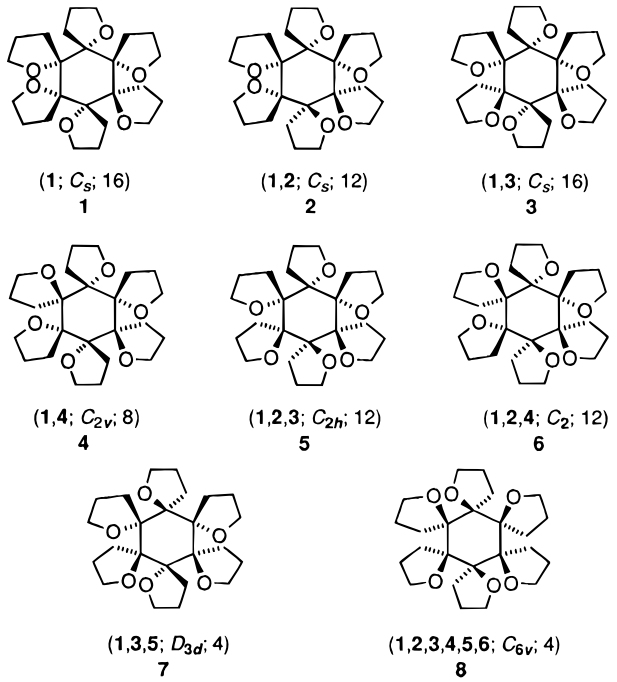

Figure 1. The eight possible stereoisomeric poly(spirotetrahydrofuranyl)cyclohexanes. The first (bold face) numerical designation specifies the unique locus of the β-oxygen atoms; the last digit delineates the number of ^{13}C signals each polyether will exhibit. The symmetry designations are for structures averaged over two chair conformations, equivalent to planar six-membered rings, having flexible spirocyclic side chains.

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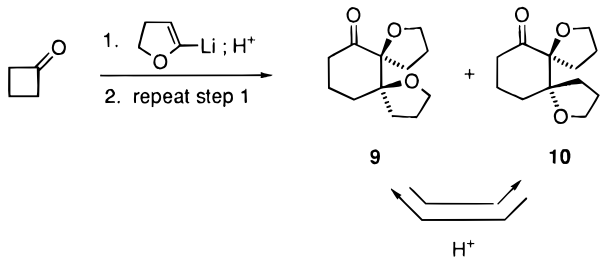
β-oriented C−O bonds.[6] The inherent time-averaged symmetry of each isomer is provided along with the number of ^{13}C NMR signals each will display. The all-anti and all-syn diastereomers, **7** and **8**, respectively, hold particular fascination since the degrees to which they exhibit cation coordination would likely constitute key points of reference for the others.

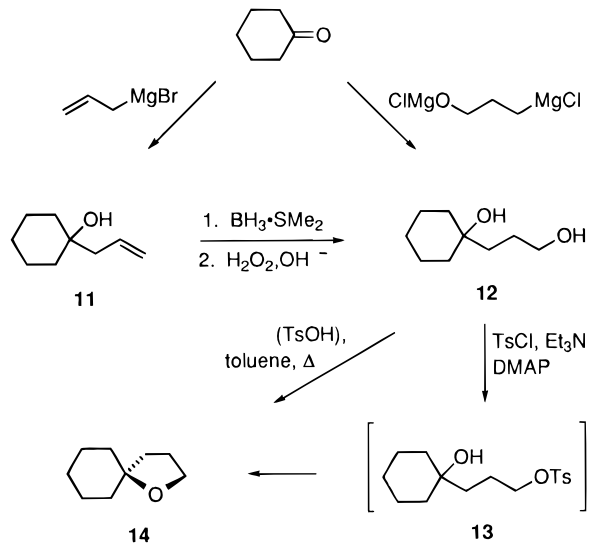
Retrosynthetic analysis associated with the preparation of **1**−**8** has been designed around the ready availability of the dispirocyclohexanones **9** and **10**, which are conveniently produced[5] by 2-fold ring expansion of cyclobutanone via oxonium ion-activated pinacol rearrangement.[7] Although **9** and **10** are produced in nearly equivalent amounts, each undergoes equilibration with the other when heated in chloroform solution containing a catalytic quantity of *p*-toluenesulfonic acid. At equilibrium, anti isomer **10** is slightly favored ($K_{eq} = 0.56$).[8] Since the remaining spirotetrahydrofuran subunits are to be introduced in turn around the perimeter of the cyclohexane core, protocols are needed that accomplish such transformations efficiently and with acceptably high levels of stereocontrol. This paper describes experiments addressed to these issues. These protocols have been developed to the point where their application in more advanced contexts has already proven feasible.[9−11]



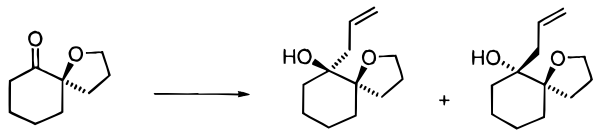
Discussion of Results

The reiterative capping model alluded to above must deal suitably not only with the diastereofacial control of nucleophilic 1,2-addition to the carbonyl group but also with substrate variations that will allow the condensation to be applied repetitively. Past experience has shown that two three-carbon organometallic reagents are utilitarian in elaborating spirotetrahydrofuran rings from carbonyl groups. The first utilizes allylmagnesium bromide and proceeds via **11** to diol **12** upon hydroboration−oxidation (Scheme 1).[5,12] The conversion of **12** to **14** can be accomplished under either basic or acidic conditions.[13] As will be shown herein, the Normant reagent, ClMgO-$(CH_2)_3$MgCl,[14] simplifies matters considerably by skirting the need for anti-Markovnikov hydration.

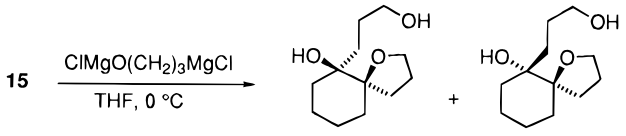
Scheme 1



Lobben demonstrated earlier with **15** that these two processes are not without their distinctive stereochemical nuances.[15] In tetrahydrofuran solution at 0 °C, allylmagnesium chloride gives little indication of being sensitive to chelation control. Quite strikingly, the Normant reagent elicits a very respectable chelate-controlled response from **15** (Scheme 2). Since **15** is conformationally flexible, it is legitimate to inquire whether this contrasting diastereoselectivity pattern will extend to less structurally dynamic cyclohexanones. Indeed, the 4-*tert*-



CH_2=$CHCH_2$MgCl, THF, 0 °C	1.2 : 1 (88%)
CH_2=$CHCH_2$MgCl, $CeCl_3$, THF, 0 °C	1 : 2.4 (96%)
CH_2=$CHCH_2$Br, $CrCl_2$ THF, 0 °C	1 : 2.6 (90%)
CH_2=$CHCH_2$Br, In, THF, 25 °C	5.6 :1 (82%)
CH_2=$CHCH_2$Br, In, H_2O, 25 °C	2.7 : 1 (81%)



butyl systems **16** and **17** have revealed the relevance of the conformational predisposition of the spirocyclic ether oxygen.[15] When chelation operates in **16** (equatorial oxy substituent), nucleophilic attack by the organomagnesium will be guided into addition from the axial surface. Indeed, both reagents favor kinetically controlled axial attack, the Normant reagent significantly more so. These results could reflect the overriding of steric effects by chelation. In the response of **17**, allylmagnesium bromide continues to undergo addition with a modest preference for anti attack while the Normant reagent

(6) This nomenclature was suggested to us by Dr. B. M. Branan.
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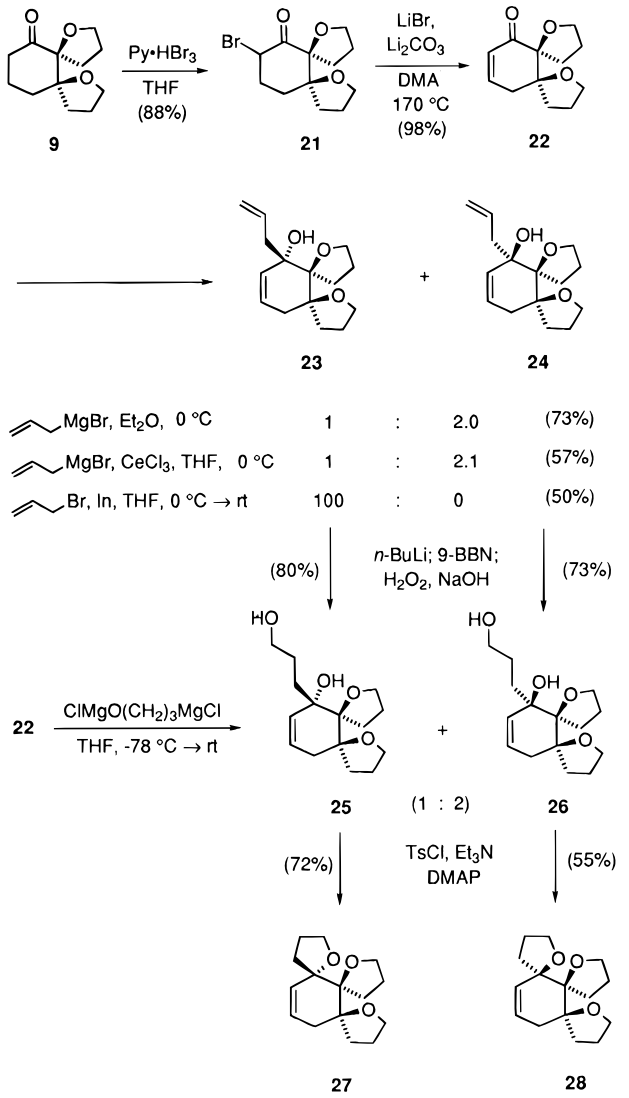
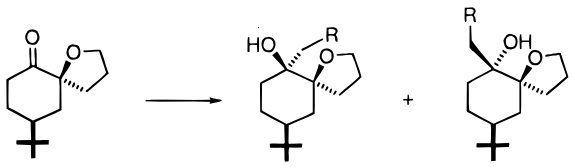
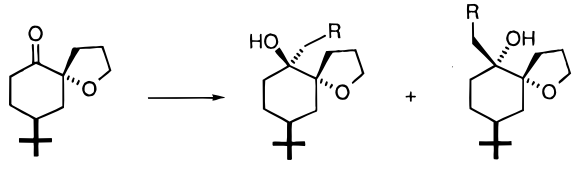
Scheme 2



prefers again to approach syn to the ether oxygen. Neither **16** nor **17** fares particularly well in competition experiments with its 2-methoxy analogue, thereby indicating that neither spirocyclic ketone engages in nucleophilic addition with *maximal* complexing capacity.

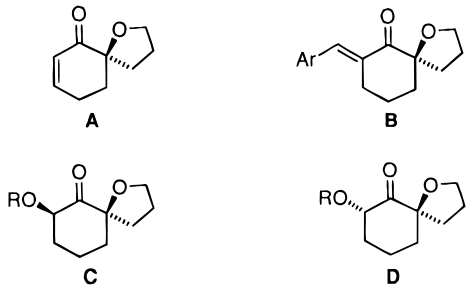


16 Grignard: 1 : 1.1 (R = CH =CH_2)
Normant: 1 : 14.2 (R = CH_2CH_2OH)



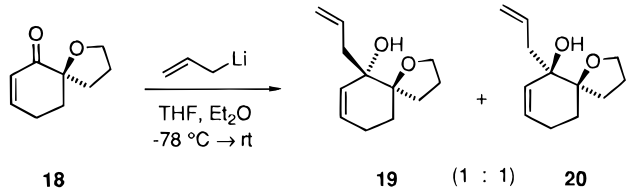
17 Grignard: 1 : 2.4 (R = CH =CH_2)
Normant: 7.6 : 1 (R = CH_2CH_2OH)

Consequently, application of this chemistry to the stereocontrolled synthesis of **1**−**8** appeared at the outset to be better served by the presence of other control elements. We reasoned that introduction of a double bond either internal to the cyclohexane ring as in **A** or external as in arylidene derivatives **B** would flatten the ring somewhat and render the carbonyl group more sterically accessible. Alternatively, an additional oxygen atom could be introduced at the α′-position (see **C** and **D**). Its role could be designed to induce enhanced



chelation or, contrastingly, to contribute added steric bulk on that molecular surface toward which it is projected. While the **A** and **B** options could open up the possibility for competing 1,4-addition,[16] all four motifs were presumed to provide the necessary latitude to continue spirocycle construction around the complete cyclohexane periphery. All four types of structural modification have been examined.

Unsaturation Internal to the Ring. The early precedent set by Klemeyer was not particularly encouraging.[16] Although the addition of allyllithium to **18** proceeded chemoselectively to deliver only 1,2-adducts, the ratio of **19** to **20** was 1:1 (56% yield). For allylmagnesium bromide, **19** (14%) and **20** (16%) were again formed, but the two stereoisomeric 1,4-adducts predominated (46% combined).



Consequently, when our attention became directed at enone **22**, it was already clear that alternative allylating reagents should also be examined (Scheme 2). The α-bromination of **9**, readily achieved with pyridinium hydrobromide perbromide in CH_2Cl_2 solution, furnished a 10:1 mixture of diastereomers **21** in a combined 88% yield. Upon heating this mixture with anhydrous lithium bromide and lithium carbonate in *N*,*N*-dimethylacetamide at 170 °C, dehydrobromination was complete in 2 h. Resulting enone **22** (98%) exhibited high-field ^1H and ^{13}C NMR spectra which were quite broad at 303 K as a result of slow conformational isomerizaton. Substantial improvement in resolution was observed at 373 K.

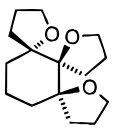
The response of **22** to the action of allylmagnesium bromide was closely comparable to that exhibited by **18**. Addition of anhydrous cerium trichloride did not significantly affect the syn/anti diastereoselectivity ratio of 1:2. Strikingly, however, treatment of **22** with allyl bromide and indium metal in THF afforded only alcohol **23**, the product of syn addition. The exclusive formation of **23** is consistent with superb chelation control in that

(16) Klemeyer, H. J.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 7924.

conformation of the ketone having the α-oxygen equatorially disposed.[15]

The next step toward the trispiro ethers involved hydroboration of the less sterically congested double bond. When either **23** or **24** was brought into reaction with 2 equiv of 9-BBN, complex product mixtures resulted. These undesirable reactions could, however, be suitably suppressed by deprotonating either alcohol with 1 equiv of *n*-butyllithium, followed by introduction of an equimolar quantity of 9-BBN. Subsequent oxidation with alkaline hydrogen peroxide or sodium perborate conveniently gave rise to the expected diols **25** (80%) and **26** (73%).

These advanced intermediates were individually cyclized via their primary tosylates to give **27** and **28**, respectively. The stereochemical assignments to these products were confirmed by catalytic hydrogenation to the dihydro derivatives. The plane of symmetry resident in the all-syn isomer **30** but not in the anti, syn product **29** was revealed by the anticipated simplification of the ^{1}H and ^{13}C NMR spectra of the former and by X-ray crystallographic analysis.[5b]



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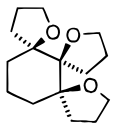

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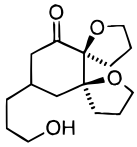

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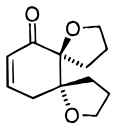
Although the allylation/hydroboration sequence proceeded adequately well, it was desirable to examine a more direct route to the 1,4-diols. Such a procedure, if adequately stereocontrolled, would reduce the number of steps and diminish the need for chromatographic purification. In his study of bifunctional Grignard reagents, Normant described the generation of $ClMgO(CH_2)_3MgCl$,[14] stock solutions of which can be stored for appreciable periods of time. When **22** was treated with a modest excess of this nucleophile in THF and the resulting products were directly tosylated, there was obtained a mixture of **27** (6%), **28** (13%), and **31** (22%). Although this finding was initially disconcerting, we soon came to realize that the response of **22** to the Normant reagent is aberrant. For example, the trans spiro enones **E** and **F** are attacked predominantly in syn-chelate 1,2-fashion to give adducts related to **25** in ≥75% yield.[9]



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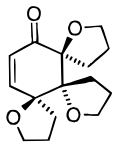
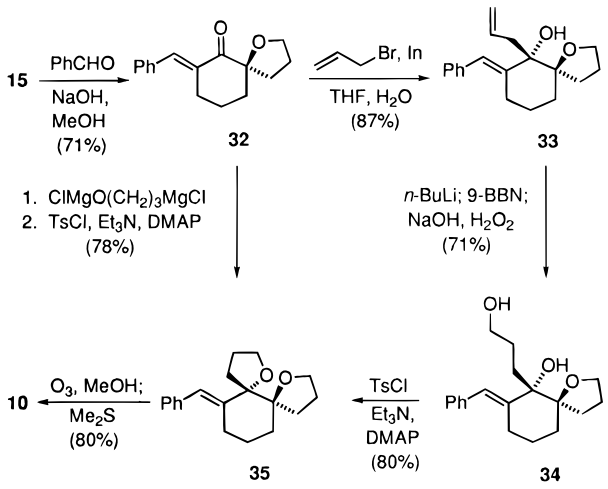


F

Notwithstanding, more extensive exploitation of the cyclohexenone approach to **1**−**8** was curtailed when regiocontrolled *monooxygenation* of the double bond in **27** and **28** could not be accomplished efficiently.[17]

The Repetitive Arylidene Option. The route followed in this instance began with the Claisen−Schmidt condensation of benzaldehyde with **15** (Scheme 3). Indium-promoted allylation of **32** proved to be a highly stereocontrolled syn-selective process, giving rise to **33** in 87% yield. X-ray crystallographic analysis of this

Scheme 3



alcohol revealed that both C−O bonds are projected equatorially in the solid state. Thus, incorporation of the benzylidene group in this fashion would appear to facilitate axial attack without promoting detectable levels of 1,4-addition.

When **33** was hydroborated with 9-BBN, a 71% yield of diol **34** was realized. In keeping with previous observations, **34** underwent ring closure to **35** in the presence of tosyl chloride, thereby permitting firm stereochemical assignment to this dispiro olefin. In further agreement with the trans arrangement of oxygenated centers, ozonolytic cleavage of **35** gave rise to the well-known ketone **10**.

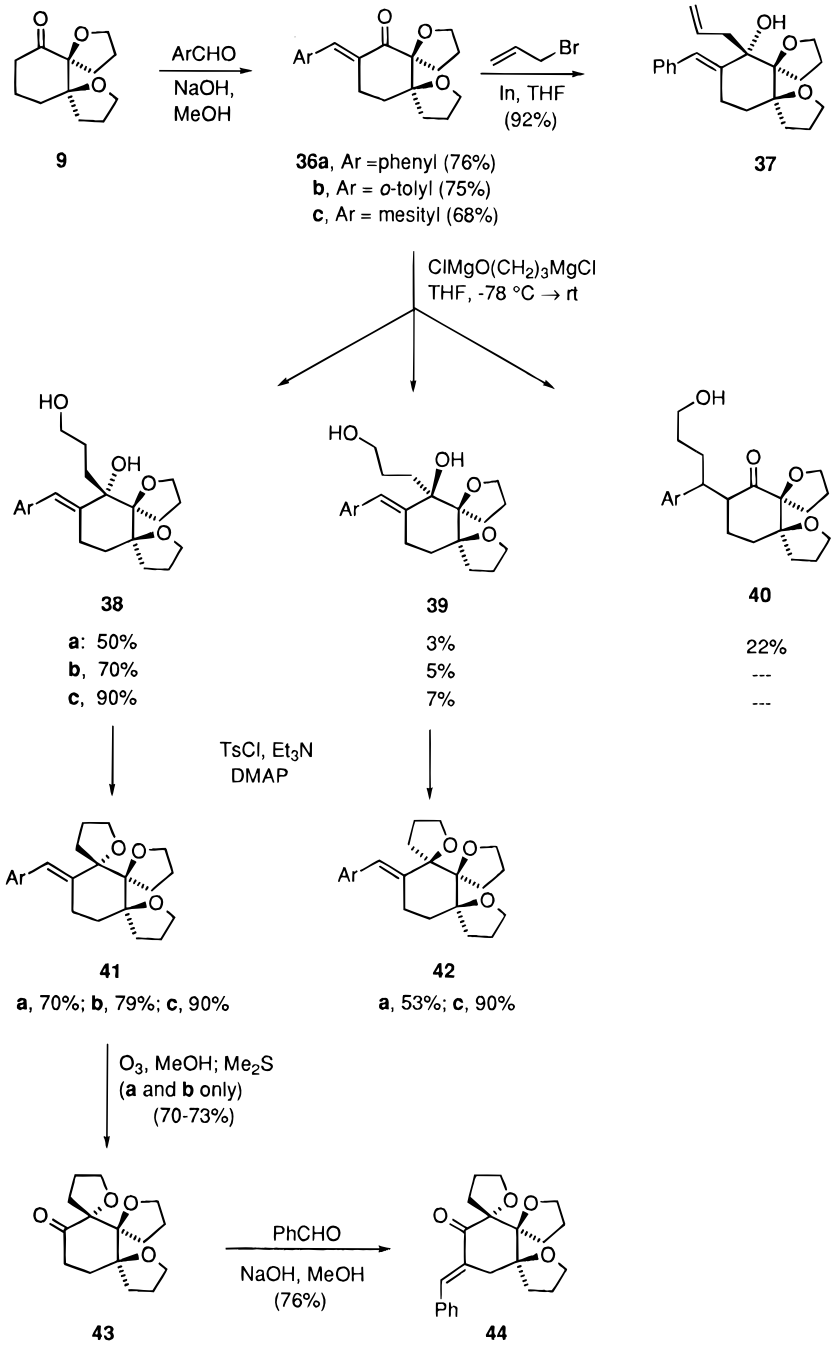
Since the cis dispiro series was earlier shown to be somewhat problematical in the extent and direction of diastereofacial selectivity, it was of interest to examine the discrimination that benzylidene derivative **36a** would exhibit. Our expectation of a dropoff in chelation control during reaction with the allylindium reagent was quickly dispelled by the isolation of **37** in 92% yield (Scheme 4). On the other hand, when **36a** was subjected to the bifunctional Grignard according to Normant, a three-component mixture was produced. The major and minor constituents were ultimately shown to be the diols **38a** (50%) and **39a** (3%), respectively. The third product **40a** was recognized to arise from competing conjugate addition. Substitution of *o*-tolualdehyde and mesitaldehyde for benzaldehyde afforded **36b** and **36c**. Neither of these ketones exhibited any evidence for entering into conjugate addition. Consequently, a single *o*-methyl group on the aryl ring provides adequate steric shielding to deter the unwanted formation of **40**.

Five of the six diols **38** and **39** were brought into ring closure. As usual, they were admirable precursors to **41a**−**c**, **42a**, and **42c**. Ozonolysis of trispiro olefins **41a**−**c** in methanol followed by treatment with dimethyl sulfide resulted in degradation to **43** in only two instances. The mesityl derivative **41c** was recovered unchanged, presumably as a result of substantive steric shielding in the area of the double bond. The subsequent conversion of **43** to **44** illustrates the reiterative potential of this sequence. The stereochemical assignments made to the more advanced intermediates in Scheme 4 are securely founded on the independent conversion of **43** to tetraspiro ketone **G** of established structure.[18]

(17) Lowinger, T. B. Unpublished observations in this laboratory.

(18) Paquette, L. A.; Stepanian, M. Manuscript in preparation.

Scheme 4



9

36a, Ar =phenyl (76%)
b, Ar = *o*-tolyl (75%)
c, Ar = mesityl (68%)

37

	38	**39**	**40**
a	50%	3%	22%
b	70%	5%	---
c	90%	7%	---

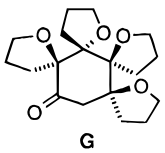
41
a, 70%; **b**, 79%; **c**, 90%

42
a, 53%; **c**, 90%

43

44

In view of the high selectivity encountered in the conversion of **36a** to **37**, the inefficient and uncontrolled response of **45** toward the allylindium reagent elicited

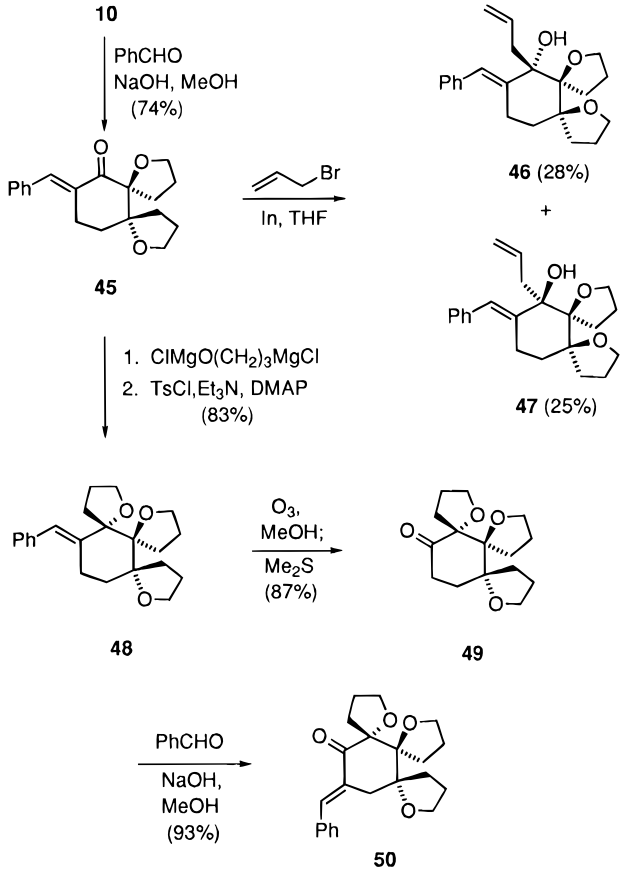


G

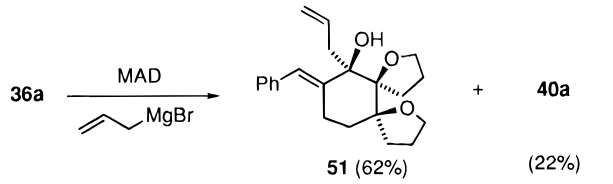
considerable consternation (Scheme 5). However, considerable improvement in stereocontrol and in conciseness was observed with the Normant reagent. In this instance, direct cyclization of the resulting diol furnished **48** in 83% yield. The efficiency of this transformation was parlayed into the preparation of ketone **49** and its benzylidene derivative **50**. The anti, anti arrangement of the spiro rings in **49**, which caused this ketone to be spectroscopically distinctive from **43**, was confirmed by an independent synthesis to be described (vide infra).

The findings summarized in Schemes 3−5 provide convincing evidence that introduction of a spirotetrahydrofuran ring immediately adjacent to a preexisting spirocyclic center of the same type is synthetically viable and suitably efficient when the disposition of the oxygen atoms is anti. In an attempt to redirect the facial selectivity of nucleophilic attack on those ketones presently of interest, the capability of the bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) reagent to function as an external controller was briefly examined. Yamamoto has demonstrated that prior formation of a complex between a 2-alkoxycyclohexanone and MAD so sterically encumbers the less congested equatorial surface of the carbonyl carbon that nucleophilic attack occurs from the axial direction.[19] In the

Scheme 5



Scheme 6

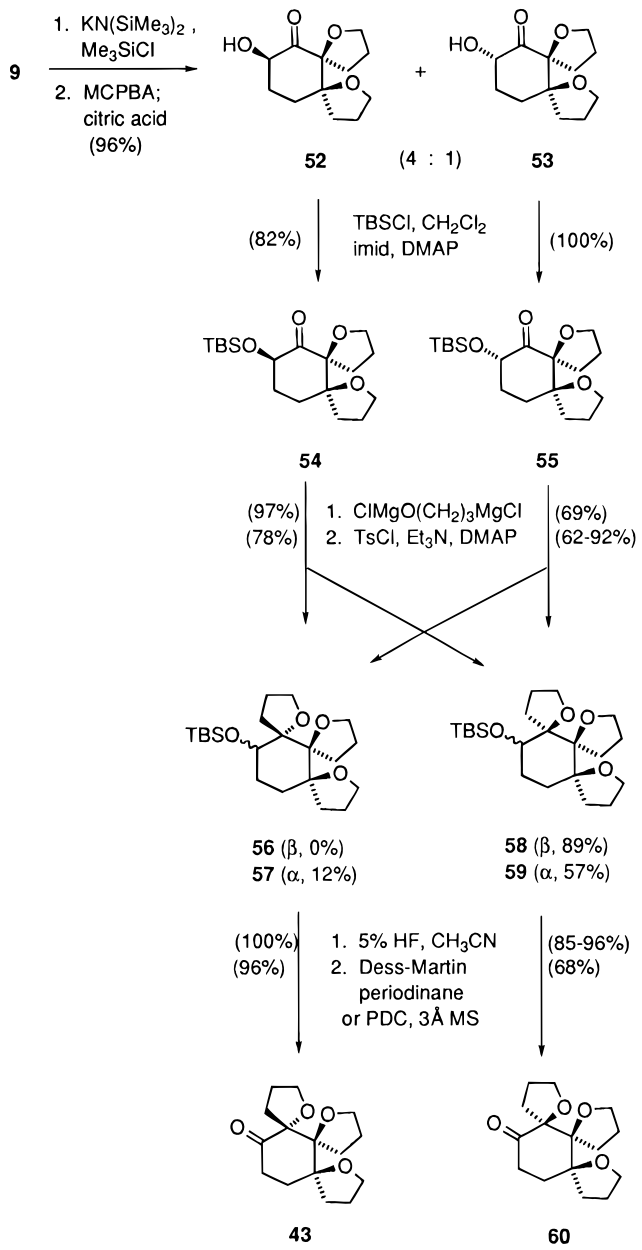


present context, **36a** was found to produce a mixture of **51** (62%) and **40a** (22%) following appropriate treatment with MAD and allylmagnesium bromide (Scheme 6). Thus, although the allyl substituent was indeed introduced from the face opposite that used by the allylindium reagent which delivers **37**, a significant level of competing 1,4-addition also materializes.

The advantages and disadvantages associated with the arylidene functionalization option were now quite apparent. Although certain facets of this chemistry are highly adaptable to selected synthetic goals, limitations do persist. Our quest for an enhanced range of options proved decisive in prompting examination of the consequences of preliminary α-oxygenation.

The Consequences of Preliminary α-Oxygenation. At the outset, the various means for the α-oxygenation of **9** and/or **10** were screened for their overall efficiency. On the strength of these experiments, it was determined that initial conversion to the silyl enol ethers[20] and subsequent oxidation with *m*-chloroperbenzoic acid[21] were especially suitable. Submission of **9** to this two-step sequence afforded a 4:1 mixture of **52** and **53** in 96% overall yield (Scheme 7). Without exception, separation of the stereoisomeric α-hydroxy ketones is readily accomplished via chromatography on silica gel. The stereochemistry of the individual epimers follows from the chemical shift of their carbinol proton. As illustrated in **H** and **I**, the appearance of the C*H*OH signal in **53** at a position significantly downfield of that in **52** convincingly points to its 1,3-diaxial relationship relative to the proximal ethereal oxygen.

Scheme 7

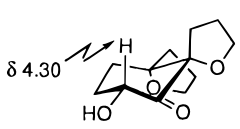


Individual silylation of **52** and **53** gave **54** and **55**, respectively, and led to an analysis of the stereochemical course of the addition of $ClMgO(CH_2)_3MgCl$. To facilitate product analysis, the resulting diols were directly cyclized as before. When the OTBS substituent was configured *β* as in **54**, the only product observed was **58** (89% for the two steps). Clearly, syn orientation of the α- and α′-

(19) (a) Maruoka, K.; Oishi, M.; Yamamoto, H. *Synlett* **1993**, 683. (b) Maruoka, K.; Oishi, M.; Shiohara, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 8983.

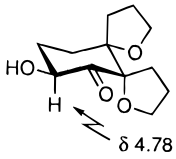
(20) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

(21) (a) Colvin, E. K. *Silicon in Organic Synthesis*; Butterworths: London, 1981; p 236 ff. (b) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.



(dd, J = 7.5, 11.3 Hz)

H

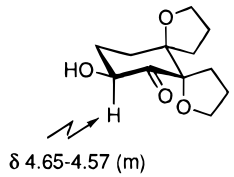


(dd, J = 7.7, 11.8 Hz)

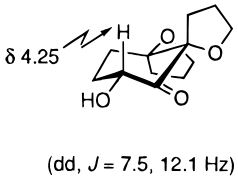
I

oxygen centers fosters exceptional levels of anti attack by the Normant reagent. When the same flanking oxygen substituents are disposed anti as in **55**, the combination is not equally synergistic. Despite the mismatch, anti attack continues to be favored, but **59** is formed only about 5 times faster than **57**. Unambiguous proof of the α-orientation of the third spiro oxygen atom in **57** followed from its conversion to **43**. Once this correlation was made, the assignment of stereochemistry to all of the intermediates in Scheme 7 was made possible. Thus, **60** became the third trispirocyclohexanone to be characterized in preparation for its utilization in more advanced functionalization protocols.

In order to establish if these results were general with respect to the stereoselectivity of the α-oxygenation and spiroalkylation steps, the Rubottom oxidation[21b] was applied to **10** (Scheme 8). This procedure led to the coformation of **61** and **62**, with the α-isomer now predominating by a factor of 2.6:1. This crossover in stereoselectivity, initially formulated by the strength of ^{1}H NMR chemical shift data (see **J** and **K**), was further



J



(dd, J = 7.5, 12.1 Hz)

K

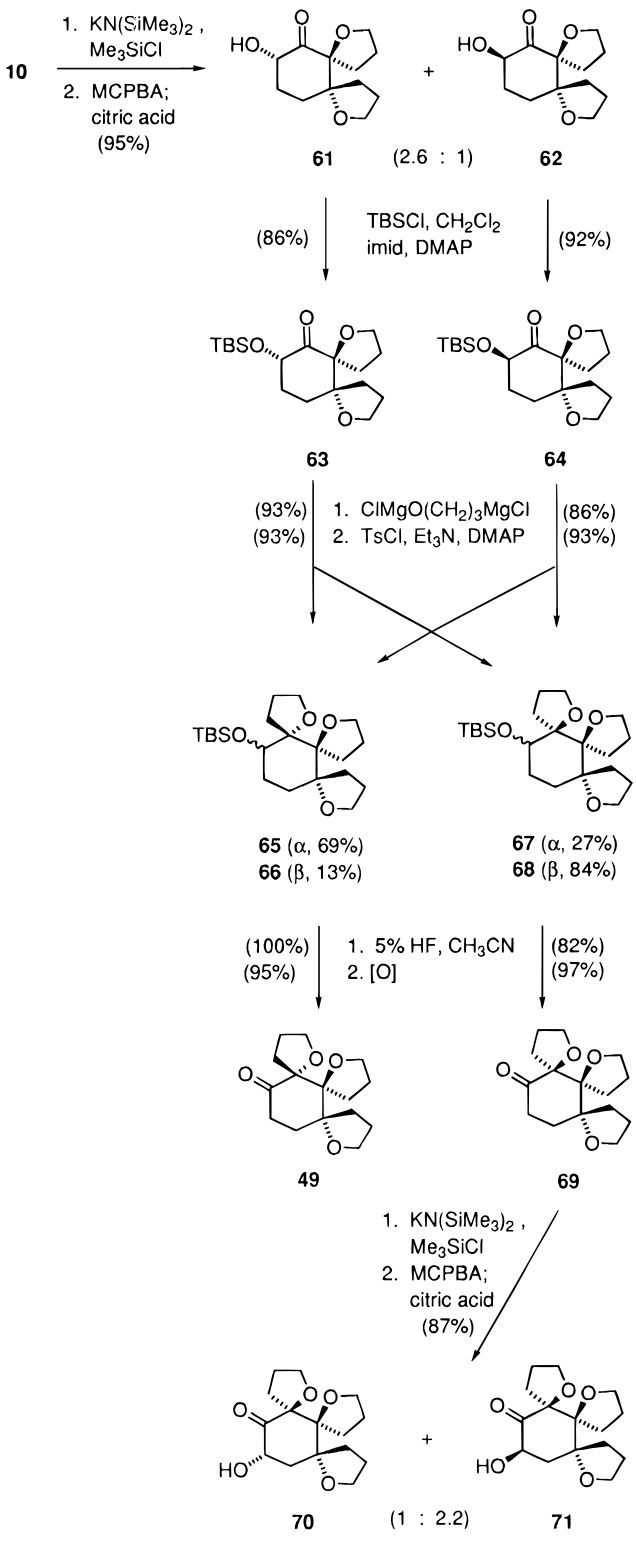
verified by single-crystal X-ray diffraction studies, which demonstrated that **61** does indeed adopt in the solid state that conformation in which the two spirotetrahydrofuran C−O bonds are projected axially as in **J**.

Another significant difference between Schemes 7 and 8 is the stereochemical outcome of the Normant additions. When the oxygen atoms flanking the carbonyl group are syn as in **64**, α-attack giving rise to **68** is no longer the exclusive reaction pathway. A 13% yield of **66** was also observed. Furthermore, **63** was converted into a 69:27 mixture of **65** and **67**. Since **54** and **55** differ from **63** and **64** only in the manner in which the "remote" spirotetrahydrofuran ring is attached (see **H**−**K**), it is appropriate to question its role in these nucleophilic additions (vide infra).

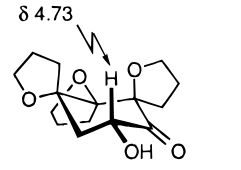
The trispiro ethers **65**−**68** were transformed conventionally into **49** and **69**. The latter ketone was α-oxygenated to produce **70** and **71** in a 1:2.2 ratio. X-ray crystallographic analysis of **70** indicated its solid state conformation to be as shown in **L**. It is noteworthy in this instance that the chemical shift of the axial α-carbinol proton again appears appreciably downfield. For **71**, adoption of conformer **M** prevails since the α-carbinol proton also finds itself shifted to below δ 4.5 and is clearly coupled in J_{ax-ax} and J_{ax-eq} fashion to the neighboring methylene protons.

The conversion of **69** to **70** and **71** illustrates the readiness with which the construction of multiply spiro

Scheme 8

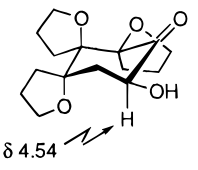


functionalized ethers, such as **1**−**8**, might be undertaken. These accomplishments shall be presented elsewhere.



(dd, J = 7.5, 12.7 Hz)

L



(dd, J = 7.1, 12.4 Hz)

M

Table 1. Facial Selectivity Observed in Allylindium Additions[a]

ketone	*T*, °C	attack anti to O:syn to O
15[b]	25	5.6:1
16[b]	25	11.8:1
17[b]	25	14.0:1
22	0	<3:>97
32	0	<3:>97
36a	0	<3:>97
45	0	1:1.1

[a] Solvent: THF. [b] Data derived from ref 15.

Table 2. Facial Selectivity Observed in Additions of the Normant Reagent[a]

ketone	*T*, °C	attack anti to O:syn to O
15[b]	0	1:8.8
16[b]	0	1:14.2
17[b]	0	7.6:1
22	−78 → rt	2:1
32	−78 → rt	<3:>97
36a	−78 → rt	1:16.7
45	−78 → rt	<3:>97
54	−78 → rt	>97:<3
55	−78 → rt	4.8:1
63	−78 → rt	1:2.6
64	−78 → rt	6.5:1

[a] Solvent: THF. [b] Data derived from ref 15.

Evaluation of the Stereochemical Events

A compilation of the facial selectivity exhibited for capture of the allylindium reagent is provided in Table 1. The analogous results for the Normant reagent are summarized in Table 2. At first glance, these data give the appearance of being very disparate. However, it is clear that different factors must play an important role in controlling the outcome of these sets of reactions. Indeed, our results show that indium and magnesium reagents exert rather different effects in a significant and previously unappreciated manner during addition to α-oxygenated cyclic ketones. The dissimilar roles played by these metals prove central to the ultimate determination of diastereofacial selection.

Consider first the properties of allylindium reagents that have been uncovered to the present time. One provocative aspect of their chemistry is a strong coordinating capability to neighboring free hydroxyl groups.[22] Comparably good attractive interactions persist when methoxyl substituents are in close proximity,[15] but a significant dropoff is seen when larger groups are present on the flanking oxygen (e.g., benzyl, trimethylsilyl) or when it is incorporated in a heterocyclic ring as in the present circumstances.[15] This is not to say that internal chelation will not materialize at all in the latter contexts. Rather, geometric considerations need to be properly preestablished for such to be operative. Added steric bulk sufficiently deters the ability of the indium to anchor onto the heteroatom so that conformational readjustments are not likely to be observed under these circumstances.

In contrast, Grignard reagents enter more vigorously into formation of preorganized complexes with α- and β-alkoxy carbonyl compounds.[23] For such reactions, adherence to Cram's chelate model is a consistent phenomenon provided that the chelating oxygen is adequately basic. The dominance of this reactivity pattern can be cited as strong evidence for Mg(II)-controlled conformational engineering prior to carbon−carbon bond formation. This key difference between magnesium and indium is considered to be one of the root causes of the diastereoselectivity differences observed in the present study.

The second important consideration is the fact that it is one single allylindium species which chelates and reacts.[15,22] This is quite distinct from other chelation control reactions where the reacting reagent is different from the chelating agent. Grignard reagents fall into the latter category.[24] This distinguishing feature for indium-mediated allylations may well be an argument that such reactions do indeed occur on the metal surface. However, this feature has not yet been established experimentally. Whatever the case, the reaction order can indeed impact impressively on the stereoselectivity of 1,2-addition to chiral ketones.

In order to facilitate visual analysis of the data in Tables 1 and 2, the contrasting transition states for the indium-promoted allylations and Normant additions have been grouped side-by-side in Table 3. The differing stereoinduction experienced by parent ketone **15** toward the two organometallic reagents is consistent with (a) axial delivery of an allyl group from indium in a complex, **N**, consisting of the thermodynamically more favored O-axial conformer,[5,15,25] and (b) utilization by the Grignard reagent of the ring-inverted O-equatorial option in order to allow for maximum chelation by magnesium ion as in **O**. Axial attack operates because less steric interference materializes along that trajectory.

Parallel thinking rationalizes the seemingly peculiar behavior of the conformationally more rigidified 4-*tert*-butyl substituted pair **16** and **17**. The highly preferred equatorial allylation of **16** can be envisioned as arising within complex **P**, where the enforced equatorial projection of the tetrahydrofuranyl oxygen invites suitable chelation to indium. Once this complex is formed, intramolecular delivery can materialize only on the equatorial face of the ketone carbonyl. The magnesium complex **Q** has the same fundamental structure. However, the subsequent attack by an independent nucleophilic entity has the freedom to approach axially as shown. Since **17** is so constructed as to disallow effective chelation of both oxygens simultaneously to either metal, **R** and **S** reflect contrasting access routes to the carbonyl carbon.

The advantages that can accrue to the intramolecular allylative option is clearly accentuated in those examples involving **22**. The placement of a double bond within the six-membered ring facilitates conformational flexing[26] to a degree such that the indium reagent can become coordinated as in **T**. This complex bears some similarity to **P** and can therefore be expected to proceed along a closely related trajectory to position the allyl substituent syn to the flanking oxygen atom. The magnesium complex **U** experiences a more equitable level of syn and anti nucleophile capture because the independent attacking Grignard reagent encounters steric congestion

(22) (a) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (b) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863.

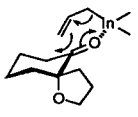
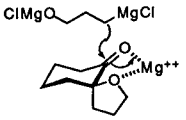
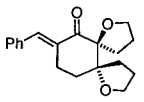
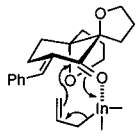
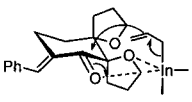
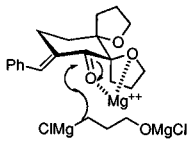
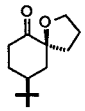
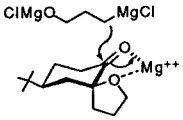
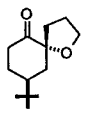
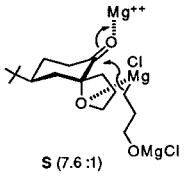
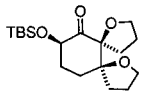
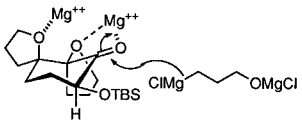
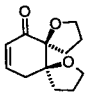
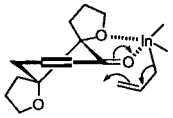
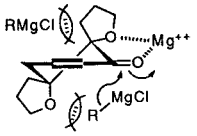
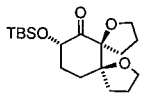
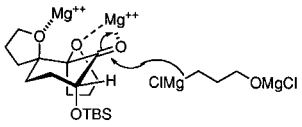
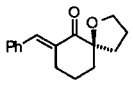
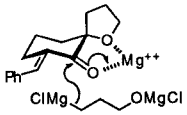
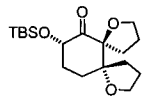
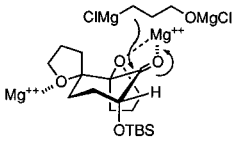
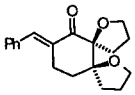
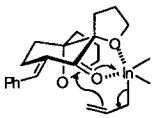
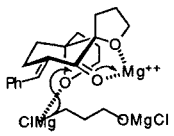
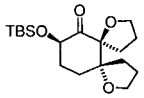
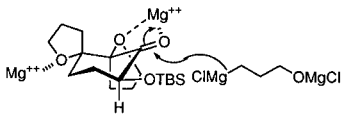
(23) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(24) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(25) (a) Fraser, R. R.; Faibish, N. C. *Can. J. Chem.* **1995**, *73*, 88. (b) Cantacuzene, D.; Tordeux, M. *Can. J. Chem.* **1976**, *54*, 2759. (c) Robinson, M. J. T. *Tetrahedron* **1974**, *30*, 1971.

(26) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Carbon Compounds*; John Wiley and Sons, Inc.: New York, 1994; p 726 ff.

Table 3. Compilation of the Assumed Reactive Transition States

ketone	indium-promoted	magnesium-promoted	ketone	indium-promoted	magnesium-promoted
 **15**	 **N** (5.6 :1)	 **O** (8.8 :1)	 **45**	 **Z** (1 : 1.1)  **AA**	 **AB** (>97 : <3)
 **16**	 **P** (11.8 :1)	 **Q** (14.2 :1)			
 **17**	 **R** (14.0 :1)	 **S** (7.6 :1)	 **54**		 **AC** (>97 : <3)
 **22**	 **T** (>97 : <3)	 **U** (a/s = 2:1)	 **55**		 **AD** (4.8 : 1)
 **32**	 **V** (>97 : <3)	 **W** (>97 : <3)	 **63**		 **AE** (2.6 : 1)
 **36a**	 **X** (>97 : <3)	 **Y** (16.7 : 1)	 **64**		 **AF** (6.5 : 1)

of near comparable magnitude along both available approaches to the carbonyl group.

The structural distortion and added flexibility resident in benzylidene derivative **32** allows for the intervention of complexes **V** and **W**. In this instance, axial delivery is more feasible irrespective of the reaction order. This state of affairs is not altered upon syn attachment of a second spiro ring as in **36a**. Of greater interest is the fact that the anti dispiro ketone **45** responds comparably to the Normant reagent, as clearly seen in **AB**. On the other hand, the considerably weaker chelating power of indium(III) is not capable of proceeding to product totally via **AA**. As a consequence, anti attack via **Z** competes effectively to give a 1:1.1 distribution of products.

Finally, the stereochemical outcome of Normant additions to **54**, **55**, **63**, and **64** can be concisely rationalized in terms of strongly chelated intermediates (see **AC**−**AF**). Once the intervention of these intermediates is accepted, their partitioning to the observed products is impacted directly by prevailing steric factors. All of the four α-oxygenated ketones undergo equatorial attack as expected from the model, although to quite differing degrees. In **AC** and **AD**, the remote axial ether oxygen, which is presumed to be coordinated to magnesium ion as well, exerts sufficiently large spatial demands to deter axial attack by the Normant reagent, even when this nucleophile has to contend with a large neighboring axial OTBS group as in **AD**. The inversion of stereochemistry that positions the distal ether oxygen equatorially in **AE** is accompanied by sufficient relief of nonbonded interaction that a modest level of axial entry by the Grignard species is operational.

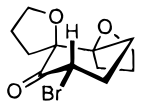
In summary, recourse either to α-arylidenation or to α-oxygenation offers an experimentally simple, highly attractive approach to repetitive introduction of spirotetrahydrofuran units around the perimeter of cyclohexane rings. Initial Claisen−Schmidt condensation with an aromatic aldehyde lends itself especially well to the introduction of the new C−O bond anti to a preexisiting one. Recourse to allylmagnesium bromide in the presence of the MAD reagent, a process not extensively screened here, merits further attention as a direct means for dictating a predominant syn-selective outcome. The presence of a stereodefined α′-OTBS substituent is also enabling of stereoselectivity control and constitutes a very competitive alternative approach to the same synthetic goals. Since the origins of asymmetry in the examples

surveyed appear to be primarily of steric origin, an important future consideration will be the impact of ever-increasing conventional nonbonded interactions on overall stereocontrol as the intermediates become increasingly functionalized. Extensions of these strategies to more extensively elaborated members of this class, including the development of efficient routes to **1**−**8**, are in progress and shall be reported in due course.

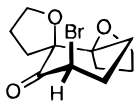
Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field strengths. High-resolution mass spectra were measured at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were carried out under a nitrogen atmosphere, and the ensuing separations were effected either with Merck Lobar columns (Lichroprep Si-60) fitted to a Fluid Metering INC pump (MPLC) or on Merck silica gel HF_{254} (flash chromatography). The organic extracts were dried over anhydrous magnesium sulfate or sodium sulfate. Solvents were reagent grade and in many cases dried prior to use.

(5*R,6*R**)-1,7-Dioxadispiro[4.0.4.4]tetradec-12-en-11-one (22).** To a magnetically stirred solution of **9** (400 mg, 1.89 mmol) in THF (5 mL) cooled to 0 °C was added dropwise a solution of pyridinium hydrobromide perbromide (612 mg, 2.0 mmol) in THF (7 mL). The reaction mixture was allowed to warm to rt for 15 min, diluted with ether, and washed sequentially with 10% sodium thiosulfate solution, water, and brine prior to drying and concentration. The residue was subjected to MPLC on silica gel (elution with 50% ether in petroleum ether) to give 433 mg (80%) of the major diastereomer, accompanied by 45 mg (8%) of the minor diastereomer. The spectral data which follow reveal these products to be **i** and **ii**, respectively.



i



ii

For **i**: colorless oil; IR (film, cm^{-1}) 1730, 1440, 1290, 1075; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (dd, J = 11.3, 6.7 Hz, 1 H), 3.87 (m, 3 H), 3.78 (m, 1 H), 2.52 (m, 2 H), 2.26 (m, 1 H), 1.91 (m, 3 H), 1.85−1.55 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.3, 94.5, 87.6, 69.4, 69.0, 52.7, 33.1, 32.3, 31.2, 26.1, 26.0, 25.9; MS m/z (M^+) calcd 290.0340, obsd 290.0370.

For **ii**: colorless oil; IR (film, cm^{-1}) 1730, 1700, 1440, 1300, 1220, 1100, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (dd, J = 11.3, 7.5 Hz, 1 H), 3.98−3.75 (m, 4 H), 2.53−2.31 (m, 2 H), 2.19−1.70 (series of m, 9 H), 1.54−1.41 (m, 1 H); MS m/z (M^+ − Br) calcd 209.1177, obsd 209.1174.

To a solution of the above mixture (830 mg, 2.87 mmol) in *N*,*N*-dimethylacetamide (17 mL) were added lithium carbonate (650 mg, 8.58 mmol) and anhydrous lithium bromide (640 mg, 7.33 mmol). The reaction temperature was maintained at 170 °C for 1.5 h. After cooling, the solvent was removed in vacuo at 30−40 °C and the residue was taken up in ether, filtered through a short pad of Celite, concentrated, and purified by flash chromatography on silica gel (elution with 40% ether in petroleum ether). There was isolated 585 mg (98%) of **22** as a colorless liquid: IR (neat, cm^{-1}) 1690, 1380, 1220, 1090, 1060; ^{1}H NMR (300 MHz, CCl_3) δ 6.74 (m, 1 H), 5.91 (m, 1 H), 4.04 (m, 1 H), 3.90−3.65 (m, 3 H), 2.57 (m, 1 H), 2.48−2.26 (m, 2 H), 2.13 (m, 1 H), 2.05−1.66 (series of m, 5 H), 1.54 (m, 1 H); MS m/z (M^+) calcd 208.1099, obsd 208.1105.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.97; H, 7.88.

Allylations of 22. A. Allylmagnesium Bromide. A solution of **22** (300 mg, 1.44 mmol) in anhydrous ether (3 mL) was cooled to 0 °C and treated dropwise with allylmagnesium bromide (1.73 mL of 1.0 M in ether, 1.73 mmol), stirred for 1 h, diluted with ether, and quenched by the addition of saturated NH_4Cl solution. The separated organic phase was dried and freed of solvent. Flash chromatography of the residue on silica gel (elution with 40% ether in petroleum ether) gave 97 mg of **23** and 165 mg of **24** (73% combined yield).

For **23**: colorless oil; IR (neat, cm^{-1}) 3600, 1205, 1050, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05−5.91 (m, 1 H), 5.79−5.57 (m, 2 H), 5.19−5.11 (m, 2 H), 4.10−3.65 (m, 4 H), 2.75−1.34 (series of m, 13 H); ^{13}C NMR (300 MHz, toluene-d_8, 353 K) ppm 135.8, 132.2, 126.4, 117.0, 91.2, 87.8, 76.5, 70.3, 67.8, 41.9, 37.1, 33.8, 29.0, 27.3, 26.1; MS m/z (M^+) calcd 250.1569, obsd 250.1574.

For **24**: colorless oil; IR (neat, cm^{-1}) 3640, 3440, 1520, 1430, 1230, 1060, 940, 770; ^{1}H NMR (300 MHz, toluene-d_8, 353 K) δ 6.27 (m, 1 H), 5.73 (dt, J = 10.2, 2.0 Hz, 1 H), 5.38 (dt, J = 10.2, 3.6 Hz, 1 H), 5.09 (m, 2 H), 3.85 (m, 3 H), 3.52 (m, 2 H), 2.49 (m, 1 H), 2.34 (d, J = 7.4 Hz, 1 H), 2.14 (m, 2 H), 1.92−1.50 (series of m, 7 H), 1.38 (m, 1 H); ^{13}C NMR (75 MHz, toluene-d_8, 353 K) ppm 135.7, 133.7, 124.2, 116.1, 91.0, 89.0, 75.5, 70.4, 67.9, 42.1, 37.2, 34.3, 28.7, 27.1, 25.9; MS m/z (M^+) calcd 250.1569, obsd 250.1559.

B. Organocerate Addition. A slurry of anhydrous cerium trichloride[27] (184 mg, 0.75 mmol) in dry THF (1 mL) cooled to 0 °C was treated dropwise with allylmagnesium bromide (0.75 mL of 1.0 M in ether, 0.75 mmol) via syringe. The resulting deep-orange-colored solution was stirred at 0 °C for 1.5 h, at which point **22** (104 mg, 0.50 mmol) dissolved in dry THF (1 mL) was introduced via cannula. An immediate color change from orange to white was noted. After 1 h of stirring, the reaction mixture was quenched with saturated NH_4Cl solution and filtered through a small pad of Celite. The organic phase was washed with saturated NH_4Cl solution and brine, dried, and evaporated. Chromatography as above gave 22 mg of **23** and 49 mg of **24** (57% combined yield).

C. Indium-Promoted Coupling. To a solution of **22** (500 mg, 2.4 mmol) in THF (5 mL) were added indium powder (820 mg, 7.2 mmol) and allyl bromide (0.62 mL, 7.2 mmol). The reaction mixture was stirred at rt overnight, quenched with 1 N HCl, diluted with ether, and filtered. The organic phase of the filtrate was washed with 1 N HCl and brine prior to drying. Purification of the residue by MPLC on silica gel (elution with 35% ether in petroleum ether) gave 306 mg (50%) of **23** as the only product.

(5*R,6*S**,11*R**)-11-Hydroxy-1,7-dioxadispiro[4.0.4.4]-tetradec-12-ene-11-propanol (25).** To a cold (0 °C) solution of **23** (126 mg, 0.50 mmol) in anhydrous THF (2 mL) was added *n*-butyllithium (0.39 mL of 1.3 M, 0.50 mmol) followed by 9-BBN (1.50 mL of 0.5 M in THF, 0.75 mmol). The reaction mixture was allowed to warm slowly to rt. After 10 h, sodium hydroxide (225 μL of 3.0 M, 0.675 mmol) was introduced, followed by 230 μL of 30% hydrogen peroxide. The resulting solution was stirred for 45 min and diluted with ether. The organic phase was washed with brine, dried, and evaporated. Purification of the residue by MPLC on silica gel (elution with 10% methanol in CH_2Cl_2) afforded 83 mg of **25** and 27 mg of recovered **23**. The corrected yield of diol is 80%: colorless oil; IR (neat, cm^{-1}) 3610, 3450, 1220, 1050, 870, 750; ^{1}H NMR (300 MHz, toluene-d_8, 353 K) δ 5.53 (m, 1 H), 5.47 (m, 1 H), 3.95 (m, 1 H), 3.86 (m, 1 H), 3.66 (m, 2 H), 3.41 (m, 2 H), 2.38 (br d, 1 H), 2.09 (m, 3 H), 2.00−1.26 (series of m, 12 H); ^{13}C NMR (75 MHz, toluene-d_8, 353 K) ppm 131.9, 126.5, 91.7, 87.8, 77.0, 70.3, 67.7, 63.7, 37.0, 33.9, 33.6, 29.2, 27.3, 26.1 (one C signal not observed); MS m/z (M^+) calcd 268.1675, obsd 268.1675.

(5*R,6*S**,11*S**)-11-Hydroxy-1,7-dioxadispiro[4.0.4.4]-tetradec-12-ene-11-propanol (26).** By means of the procedure detailed above, 261 mg (1.04 mmol) of **24** was transformed into 109 mg of **26** and 121 mg of unchanged starting material. The adjusted yield of **26** is 73%: colorless oil; IR (neat, cm^{-1}) 3400 (br), 1300, 1050, 930; ^{1}H NMR (300 MHz, toluene-d_8) δ 5.72 (dt, J = 10.3, 1.9 Hz, 1 H), 5.39 (dt, J = 7.4, 3.3 Hz, 1 H), 3.90 (m, 1 H), 3.78 (m, 1 H), 3.65−3.49 (m, 4 H), 2.32 (br s, 1 H), 2.19 (m, 1 H), 1.95−1.20 (series of m, 14 H); ^{13}C NMR (62.5

(27) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, 1995; pp 1031−4.

MHz, toluene-d_8, 373 K) ppm 133.4, 124.9, 91.7, 89.1, 75.8, 70.6, 67.9, 63.8, 37.3, 34.6, 34.2, 27.9, 27.4, 26.2 (1 C not observed); MS m/z (M^+) calcd 268.1675, obsd 268.1674.

(5*R,6*R**,11*R**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]octadec-16-ene (27).** A solution of **25** (163 mg, 0.61 mmol) in CH_2Cl_2 (4 mL) was treated with triethylamine (1 mL), *p*-toluenesulfonyl chloride (139 mg, 0.73 mmol), and 4-(dimethylamino)-pyridine (4 mg). The reaction mixture was stirred at 25 °C for 8 h, diluted with ether, washed with 1 N HCl and brine, dried, and concentrated. Purification of the residue by MPLC (silica gel, elution with 30% ether in petroleum ether) furnished 110 mg (72%) of **27** as a clear, colorless oil: ^{1}H NMR (250 MHz, toluene-d_8, 373 K) δ 5.53 (dt, J = 8.1, 1.8 Hz, 1 H), 5.34 (dt, J = 8.1, 3.1 Hz, 1 H), 3.91−3.55 (m, 6 H), 2.64 (m, 1 H), 2.26−1.51 (series of m, 13 H); ^{13}C NMR (62.5 MHz, toluene-d_8, 373 K) ppm 134.7, 123.3, 91.1, 88.4, 88.3, 70.5, 68.5, 67.7, 38.7, 34.3, 33.4, 31.8, 27.4, 27.3, 26.5; MS m/z (M^+) calcd 250.1569, obsd 250.1533.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.05; H, 8.90.

(5*R,6*R**,11*S**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]octadec-16-ene (28).** By means of the procedure detailed above, 185 mg (0.69 mmol) of **26** was transformed into **28** (94 mg, 55%), a colorless, crystalline solid: mp 75−77 °C; ^{1}H NMR (250 MHz, toluene-d_8, 373 K) δ 5.52 (m, 1 H), 5.33 (m, 1 H), 4.02 (m, 2 H), 3.75−3.45 (m, 4 H), 2.73 (s, 1 H), 2.64 (s, 1 H), 2.20−1.37 (series of m, 12 H); ^{13}C NMR (62.5 MHz, toluene-d_8, 373 K) ppm 132.8, 123.7, 91.2, 88.2, 87.8, 70.0, 67.4, 67.0, 36.9, 36.6, 34.5, 28.2, 27.2, 27.0, 26.3; MS m/z (M^+) calcd 250.1569, obsd 250.1572.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 9.06.

Hydrogenation of 27. To a solution of **27** (13 mg) in ethyl acetate (3 mL) was added 10 mg of 5% palladium on charcoal. This mixture was blanketed with hydrogen, stirred overnight, filtered through Celite, and evaporated to give 13 mg of **29** as a colorless oil spectroscopically identical to an authentic sample.[5b]

Normant Addition to 22. A cold (−78 °C), magnetically stirred solution of **22** (720 mg, 3.45 mmol) in dry THF (35 mL) was treated dropwise via syringe with a solution of the Normant reagent (8.68 mL of 0.40 N in THF, 3.45 mmol). The reaction mixture was allowed to warm to rt, where it was agitated for 5 h before being quenched with saturated NH_4Cl solution and diluted with ether. The separated aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were washed with brine, dried, and evaporated. Flash chromatography of the residue on silica gel (elution with 6% methanol in CH_2Cl_2) provided diols **25** (470 mg, 51%) and **26** (55 mg, 6%) alongside 1,4-adduct **31** (120 mg, 13%).

For **31**: colorless oil; IR (neat, cm^{-1}) 3417, 1715, 1453, 1308, 1055, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87−3.79 (m, 3 H), 3.66−3.53 (m, 3 H), 2.70−2.62 (m, 1 H), 2.38−2.30 (m, 1 H), 2.20−2.09 (m, 3 H), 1.99−1.35 (series of m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.0, 93.1, 86.8, 68.6, 68.5, 62.5, 42.8, 39.4, 32.7, 32.5, 31.6, 29.8, 26.2, 25.9, 23.3; MS m/z (M^+) calcd 268.1674, obsd 268.1674.

7-[(*E*)-Benzylidene]-1-oxaspiro[4.5]decan-6-one (32). A solution of **15** (3.08 g, 20.0 mmol) and sodium hydroxide (800 mg, 20.0 mmol) in methanol (80 mL) was stirred at 25 °C for 1 week, poured into 200 mL of iced 1 N H_2SO_4, extracted with ether (2×), dried, and concentrated. The residue was purified by column chromatography on silica gel (elution with 20% ether in petroleum ether) to give 3.01 g (70%) of **32** as colorless crystals: mp 56−58 °C; IR (film, cm^{-1}) 1688, 1601, 1572, 1490, 1442, 1139, 1091, 1043; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 6 H), 4.04−3.94 (m, 2 H), 2.91−2.84 (m, 1 H), 2.76−2.71 (m, 1 H), 2.29−2.21 (m, 1 H), 2.14−1.75 (m, 5 H), 1.73−1.55 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.5, 136.8, 135.7, 135.6, 130.0 (2 C), 128.3, 128.1 (2 C), 86.4, 69.0, 36.4, 34.6, 28.6, 25.5, 21.1; MS m/z (M^+) calcd 242.1307, obsd 242.1303.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.17; H, 7.49.

(5*R,6*S**)-6-Allyl-7-[(*E*)-benzylidene]-1-oxaspiro[4.5]-decan-6-ol (33).** A mixture of **32** (1.47 g, 6.0 mmol), indium powder (1.15 g, 10.0 mmol), and allyl bromide (0.9 mL, 10.0 mmol) in water (20 mL) and THF (50 mL) was stirred for 2 h, poured into 10% HCl, and extracted five times with ethyl acetate. The combined organic layers were washed with brine (2×), dried, and concentrated. Chromatography of the residue on silica gel (elution with 30% ether in petroleum ether) afforded 1.47 g (87%) of **33** as a colorless solid: mp 84−86 °C; IR (film, cm^{-1}) 3546, 1638, 1600, 1493, 1444, 1310, 1220, 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.30 (m, 2 H), 7.31−7.20 (m, 3 H), 6.73 (s, 1 H), 5.90−5.77 (m, 1 H), 5.20−5.13 (m, 2 H), 4.05−3.98 (m, 1 H), 3.89−3.82 (m, 1 H), 2.89−2.83 (m, 1 H), 2.67−2.59 (m, 1 H), 2.34−2.25 (m, 1 H), 2.04 (br s, 1 H), 2.00−1.65 (series of m, 7 H), 1.56−1.47 (m, 1 H), 1.40−1.20 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.8, 138.3, 133.3, 128.8, 127.9, 125.9, 123.5, 117.7, 88.5, 79.0, 68.5, 38.8, 34.5, 30.9, 26.9, 25.6, 23.21; MS m/z (M^+) calcd 284.1776, obsd 284.1775.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.01; H, 8.42.

This compound was subjected to X-ray crystallographic analysis.[28]

(5*R,6*S**)-7-[(*E*)-Benzylidene]-6-hydroxy-1-oxaspiro-[4.5]decane-6-propanol (34).** A cold (0 °C), magnetically stirred solution of **33** (1.14 g, 4.0 mmol) in anhydrous THF (12 mL) was treated sequentially with *n*-butyllithium (5.1 mL of 1.6 M, 8.1 mmol) and 9-BBN (17 mL of 0.5 M, 8.5 mmol), stirred overnight at 25 °C, and quenched with a solution of sodium hydroxide (200 mg) in 15% hydrogen peroxide (3 mL). After the predescribed workup and purification procedure, there was isolated 861 mg (71%) of **34** as a white solid: mp 114−116 °C; IR (film, cm^{-1}) 3358, 1446, 1374, 1301, 1057, 1006; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.14 (m, 5 H), 6.70 (s, 1 H), 4.05−3.93 (m, 1 H), 3.90−3.77 (m, 1 H), 3.75−3.50 (m, 2 H), 2.86−2.78 (m, 1 H), 2.40−2.05 (m, 2 H), 2.00−1.15 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.6, 138.3, 128.8, 127.9, 125.9, 123.5, 89.3, 79.5, 68.4, 62.9, 34.3, 31.0, 30.6, 26.9, 26.0, 25.6, 23.2; MS m/z (M^+) calcd 302.1882, obsd 302.1888.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.28; H, 8.90.

(5*R,6*S**)-11-[(*E*)-Benzylidene]-1,7-dioxadispiro[4.0.4.4]-tetradecane (35). A. Via Cyclization of 34.** A solution containing **34** (302 mg, 1.0 mmol), *p*-toluenesulfonyl chloride (343 g, 1.8 mmol), triethylamine (1 mL), and DMAP (5 mg) in CH_2Cl_2 (7 mL) was stirred overnight at 25 °C and processed in the usual manner to give 220 mg (78%) of **35** as a colorless oil: IR (film, cm^{-1}) 1495, 1445, 1309, 1188, 1070, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2 H), 7.20 (m, 3 H), 6.67 (s, 1 H), 3.80 (m, 4 H), 2.90−1.40 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.3, 138.5, 129.0, 128.0, 126.0, 121.5, 91.2, 88.0, 68.8, 68.3, 37.2, 31.8, 31.0, 27.0, 16.7, 26.4, 23.6; MS m/z (M^+) calcd 284.1776, obsd 284.1772.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.55; H, 8.32.

B. Normant Addition to 32 and Direct Cyclization. A 242 mg (1.0 mmol) sample of **32** dissolved in dry THF (10 mL) was treated dropwise with the Normant reagent (3.00 mL of 0.42 M in THF, 1.26 mmol) at −78 °C, allowed to warm slowly to 0 °C, and stirred for 1 h at this temperature prior to being quenched with saturated NH_4Cl solution. The normal workup afforded crude diol **34**, which was directly cyclized in the predescribed manner. There was obtained 272 mg (78%) of **35**, identical in all respects to the material obtained in part A.

Ozonolysis of 35. A solution of **35** (284 mg, 1.0 mmol) in methanol (10 mL) was ozonolyzed at −78 °C until a blue color appeared. Dimethyl sulfide (2 mL) was added, and the reaction mixture was allowed to warm to rt. After solvent evaporation, the residue was purified by chromatography on silica gel (elution with 30−40% ether in petroleum ether) to

(28) 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.

afford 170 mg (80%) of **10**, spectroscopically identical in all respects with authentic material.[5b]

(5*R,6*S**)-12-[(*E*)-Benzylidene]-1,7-dioxadispiro[4.0.4.4]-tetradecan-11-one (36a).** A mixture of **9** (4.27 g, 22.7 mmol), benzaldehyde (6.91 mL, 68.1 mmol), and sodium hydroxide (2.72 g, 68.1 mmol) in methanol (125 mL) was refluxed for 3 h under N_2. After cooling and the addition of cold 6 N HCl, the product was extracted into ethyl acetate (3 × 100 mL) and the organic phase was washed with base and brine prior to drying and solvent evaporation. Flash chromatography of the residue over silica gel (elution with 10% ether in petroleum ether) followed by recrystallization from petroleum ether−CH_2Cl_2 gave **36a** (5.08 g, 75%) as colorless crystals: mp 125−126 °C; IR (KBr, cm^{-1}) 1691, 1602, 1491, 1448, 1272, 1120, 1090, 1062, 911, 762; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 6 H), 4.28−4.20 (m, 1 H), 4.00−3.92 (m, 2 H), 3.89−3.81 (m, 1 H), 2.93−2.80 (m, 2 H), 2.09−1.57 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.5, 136.0, 135.7, 135.0, 130.1, 128.2, 128.1, 92.4, 87.7, 70.3, 68.9, 32.9, 32.8, 31.5, 25.9, 24.8, 24.0; MS *m*/*z* (M^+) calcd 298.1569, obsd 298.1565.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.46; H, 7.43. Found: C, 76.52; H, 7.48.

(5*R,6*S**)-12-[(*E*)-(*o*-Methylbenzylidene)]-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (36b).** A mixture of **9** (14.86 g, 70.76 mmol), *o*-tolualdehyde (24.56 mL, 212.28 mmol), and sodium hydroxide (8.49 g, 212 mmol) in methanol (300 mL) was refluxed for 3 h under N_2 and stirred at 25 °C overnight. Application of the predescribed workup followed by flash chromatography on silica gel (elution with 20% ethyl acetate in hexanes) and crystallization from hexane−CH_2Cl_2 gave pure **36b** (16.49 g, 75%) as shiny colorless crystals: mp 98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1 H), 7.20−7.12 (m, 4 H), 4.28−4.21 (m, 1 H), 4.01−3.92 (m, 2 H), 3.88−3.81 (m, 1 H), 2.85−2.75 (m, 1 H), 2.74−2.60 (m, 1 H), 2.25 (s, 3 H), 2.14 (s, 1 H), 2.10−1.57 (series of m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.3, 137.3, 136.8, 134.7, 133.2, 129.9, 129.1, 128.2, 125.2, 92.7, 88.0, 70.3, 68.9, 33.3, 33.2, 31.6, 25.9, 24.8, 23.9, 19.9; MS *m*/*z* (M^+) calcd 312.1725, obsd 312.1708.

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.88; H, 7.74. Found: C, 76.85; H, 7.82.

(5*R,6*S**)-12-[(*E*)-(2,4,6-Trimethylbenzylidene)]-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (36c).** A mixture of **9** (500 mg, 2.5 mmol), mesitaldehyde (1.84 mL, 12.5 mmol), and sodium hydroxide (1.2 g, 30 mmol) in methanol (25 mL) was refluxed for 12 h and stirred overnight at 25 °C. After the usual workup, flash chromatography (elution with 40% ethyl acetate in hexanes), and recrystallization from hexanes−CH_2Cl_2, there was obtained 555 mg (68%) of **36c** as fluffy white crystals: mp 122−123 °C; IR (KBr, cm^{-1}) 1691, 1617, 1092, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1 H), 6.86 (s, 2 H), 4.29−4.22 (m, 1 H), 4.03−3.93 (m, 2 H), 3.87−3.81 (m, 1 H), 2.55−2.43 (m, 1 H), 2.27 (s, 3 H), 2.13 (s, 6 H), 2.11−2.00 (m, 3 H), 1.98−1.86 (m, 3 H), 1.84−1.81 (m, 2 H), 1.80−1.56 (m, 3 H); ^{13}C NMR (75 MHz $CDCl_3$) ppm 202.6, 138.9, 136.9, 133.8, 132.1, 128.0, 99.7, 99.0, 92.8, 88.1, 70.3, 69.0, 33.2, 31.7, 25.9, 24.9, 23.5, 20.9, 20.0; MS *m*/*z* (M^+) calcd 340.2038, obsd 340.2035.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.60; H, 8.29. Found: C, 77.44; H, 8.26.

(5*R,6*S**,11*S**)-11-Allyl-12-[(*E*)-benzylidene]-1,7-dioxadispiro[4.0.4.4]tetradecan-11-ol (37).** A magnetically stirred mixture of allyl bromide (0.42 mL, 5.0 mmol) and indium powder (574 mg, 5.0 mmol) in dry THF (5 mL) was refluxed for 30 min, cooled to 25 °C, treated with **36a** (500 mg, 1.67 mmol), and agitated for 48 h. The predescribed workup was followed by flash chromatography on silica gel (elution with 10% ether in petroleum ether) to afford 520 mg (92%) of **37** as a colorless viscous oil: IR (neat, cm^{-1}) 3570, 1450, 1070, 1035, 1005, 910, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 6.66 (s, 1 H), 5.87−5.73 (m, 1 H), 5.28−5.09 (m, 2 H), 4.18−4.11 (m, 1 H), 4.06−3.96 (m, 2 H), 3.88−3.80 (m, 1 H), 3.45−3.38 (m, 1 H), 2.74−2.63 (m, 2 H), 2.36−1.26 (series of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.1, 138.4, 135.2, 128.9, 128.0, 126.0, 123.5, 118.2, 92.3, 88.6, 80.8, 71.6, 68.2, 40.3, 35.0, 33.5, 32.3, 26.9, 24.8, 22.5; MS *m*/*z* (M^+) calcd 340.2038, obsd 340.2047.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.60; H, 8.29. Found: C, 77.46, H, 8.32.

Normant Addition to 36a. To a solution of **36a** (500 mg, 1.67 mmol) in dry THF (25 mL) cooled to −78 °C was added a solution of the Normant reagent (4.21 mL of 0.40 M in THF, 1.68 mmol) dropwise during 10 min. The reaction mixture was allowed to warm to 25 °C and was stirred for 5 h at that temperature before being quenched with saturated NH_4Cl solution. The separated aqueous layers were extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 10% hexanes in ethyl acetate) gave **39a** (18.5 mg, 3%), **38a** (300 mg, 50%), and **40** (130 mg, 22%).

For **38a**: white solid: mp 49−50 °C; IR (KBr, cm^{-1}) 3414, 1654, 1598, 1492, 1443, 1069, 1003, 934, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.14 (m, 5 H), 6.71 (s, 1 H), 4.17−4.07 (m, 1 H), 4.02−3.93 (m, 2 H), 3.84−3.72 (m, 1 H), 3.70−3.56 (m, 2 H), 2.86−2.76 (m, 1 H), 2.70−2.63 (m, 1 H), 2.45−2.25 (m, 3 H), 2.15−1.44 (series of m, 11 H), 1.34−1.21 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.6, 138.5, 128.9, 128.0, 126.0, 123.6, 93.1, 88.7, 81.8, 71.8, 68.1, 63.4, 35.0, 33.8, 32.7, 31.5, 27.0, 26.5, 24.7, 22.4; MS *m*/*z* (M^+) calcd 358.2144, obsd 358.2166.

Diol **39a** was characterized as the trispiro ether **42a** (see below).

Hydroxy ketone **40a** was characterized as its tosylate: colorless oil; IR (neat, cm^{-1}) 1715, 1598, 1494, 1453, 1359, 1188, 1175, 1097, 1058, 927; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.25−7.06 (m, 5 H), 3.93−3.77 (m, 4 H), 3.47−3.36 (m, 2 H), 2.90−2.83 (m, 1 H), 2.40 (s, 3 H), 2.33−2.00 (m, 2 H), 1.99−1.33 (m, 14 H), 1.06−1.00 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.7, 144.6, 143.6, 133.2, 129.8, 128.2, 128.0, 127.8, 126.1, 94.4, 87.9, 70.7, 68.9, 68.4, 49.8, 43.1, 32.7, 31.0, 30.3, 27.3, 26.8, 26.1, 25.6, 24.0, 23.6, 21.6; MS *m*/*z* (M^+) calcd 512.2232, obsd 512.2245.

Normant Addition to 36b. Treatment of **36b** (774 mg, 2.3 mmol) in dry THF (30 mL) at −78 °C with the Normant reagent (6.06 mL of 0.33 M in THF, 2.0 mmol) was carried out as described above to give 614 mg (70%) of **38b** and 44 mg (5%) of **39b**.

For **38b**: colorless solid; mp 60−63 °C; IR (film, cm^{-1}) 3400, 1450, 1310, 1200, 1075, 945, 915; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.03 (m, 4 H), 6.66 (s, 1 H), 4.19−4.12 (m, 1 H), 4.10−3.96 (m, 2 H), 3.87−3.58 (m, 3 H), 2.85 (ddd, J = 7.5, 7.5, 14.8 Hz, 1 H), 2.45−1.40 (series of m, 19 H), 1.31−1.20 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.1, 137.9, 136.5, 129.6, 129.1, 126.4, 125.3, 123.1, 93.0, 88.7, 81.8, 71.9, 68.0, 63.5, 34.9, 33.8, 32.6, 31.5, 27.0, 26.6, 24.7, 22.7, 20.2; MS *m*/*z* (M^+) calcd 372.2292, obsd 372.2300.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.80; H, 8.41.

For **39b**: colorless solid; mp 56−58 °C; IR ($CHCl_3$, cm^{-1}) 3450 (br), 1470, 1380, 1040, 915, 740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.04 (m, 4 H), 6.49 (s, 1 H), 4.15−3.40 (m, 6 H), 2.65−1.25 (series of m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.7, 142.2, 137.5, 136.4, 130.4, 129.6, 129.1, 126.5, 125.3, 123.6, 71.0, 63.4, 33.4, 29.6, 27.2, 26.7, 24.03, 24.01, 20.1 (broadened signals not specified); MS *m*/*z* (M^+) calcd 372.2292, obsd 372.2293.

Normant Addition to 36c. Treatment of **36c** (340 mg, 1.0 mmol) in dry THF (15 mL) at −78 °C with the Normant reagent (2.51 mL of 0.40 M in THF, 1.0 mmol) was carried out as described above to give 360 mg (90%) of **38c** and 27 mg (7%) of **39c**.

For **38c**: colorless solid; mp 71−73 °C; IR (KBr, cm^{-1}) 3447, 1438, 1067; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2 H), 6.46 (s, 1 H), 4.19−4.11 (m, 1 H), 4.04−3.96 (m, 2 H), 3.82−3.63 (m, 3 H), 2.82−2.74 (m, 1 H), 2.49−2.40 (m, 3 H), 2.27 (s, 3 H), 2.17 (s, 3 H), 2.13 (s, 3 H), 2.10−2.02 (m, 2 H), 1.99−1.64 (m, 7 H), 1.62−1.41 (m, 4 H), 1.28−1.21 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.4, 136.3, 136.1, 135.5, 134.6, 127.8, 122.3, 93.3, 88.7, 81.9, 71.7, 68.0, 63.6, 34.5, 33.7, 32.7, 31.6, 27.0, 26.6, 24.7, 23.0, 20.91, 20.77; MS *m*/*z* (M^+) calcd 400.2613, obsd 400.2611.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.95; H, 9.06. Found: C, 74.40; H, 9.22.

For **39c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1 H), 6.83 (s, 1 H), 6.28 (s, 1 H), 4.07−4.02 (m, 2 H), 3.89−3.82 (m, 2 H), 3.70−3.65 (m, 2 H), 2.26 (s, 3H), 2.18 (s, 3 H), 2.12 (s, 3 H), 2.10−1.67 (series of m, 16 H), 1.35−1.25 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.4, 136.6, 135.8, 135.7, 128.0, 127.8, 127.6, 122.7, 70.9, 63.5, 33.3, 29.8, 27.2, 26.8, 26.0, 23.0, 20.9, 20.8, 20.3; MS *m*/*z* (M^+) calcd 400.2613, obsd 400.2625.

(5*R,6*S**,11*S**)-16-[(*E*)-Benzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane (41a).** Diol **38a** (275 mg, 0.768 mmol) was cyclized in the manner described above and purified by chromatography on silica gel (elution with 10% ethyl acetate in hexanes). There was obtained 145 mg (70%) of **41a**; colorless oil; IR (neat, cm^{-1}) 1444, 1099, 1062; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.21 (m, 2 H), 7.18−7.12 (m, 3 H), 6.56 (s, 1 H), 3.99−3.86 (m, 4 H), 3.83−3.72 (m, 1H), 3.70−3.64 (m, 1 H), 2.70−2.55 (m, 2 H), 2.31−1.22 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.6, 129.0, 128.0, 125.9, 122.0, 99.7, 92.3, 91.2, 88.4, 70.7, 68.2, 67.5, 35.2, 32.7, 32.3, 32.1, 26.9, 26.1, 25.3, 22.8; MS *m*/*z* (M^+) calcd 340.2038, obsd 340.2040.

(5*R,6*S**,11*S**)-16-[(*E*)-(*o*-Methylbenzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane (41b).** Diol **38b** (500 mg, 1.34 mmol) was cyclized as before and purified by chromatography on silica gel (elution with 6% ethyl acetate in hexanes) to give 375 mg (79%) of **41b** as a colorless oil: IR (neat, cm^{-1}) 1482, 1453, 1099, 1061; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.11 (m, 3 H), 7.06−7.02 (m, 1 H), 6.53 (s, 1 H), 4.02−3.90 (m, 4 H), 3.84−3.68 (m, 2 H), 2.66−2.55 (m, 1 H), 2.39−2.28 (m, 2 H), 2.23 (s, 3 H), 2.19−1.75 (m, 9H), 1.69−1.60 (m, 1 H), 1.59−1.45 (m, 2 H), 1.33−1.22 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.2, 138.0, 136.4, 129.1, 126.3, 125.2, 121.5, 92.2, 91.1, 88.4, 70.7, 68.1, 67.4, 35.2, 32.0, 26.9, 26.2, 25.2, 23.0, 20.0; MS *m*/*z* (M^+) calcd 354.2195, obsd 354.2194.

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.91; H, 8.53. Found: C, 77.78; H, 8.65.

(5*R,6*S**,11*S**)-16-[(*E*)-(2,4,6-Trimethylbenzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane (41c).** Cyclization of **38c** (342 mg, 0.85 mmol) in the usual way provided 295 mg (90%) of **41c** as a colorless oil: IR (neat, cm^{-1}) 1480, 1453, 1099, 1063; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2 H), 6.32 (s, 1 H), 4.03−3.91 (m, 4 H), 3.83−3.68 (m, 2 H), 2.61−2.34 (m, 2 H), 2.27 (s, 3 H), 2.16 (s, 3 H), 2.08 (s, 3 H), 2.06−1.77 (series of m, 10 H), 1.59−1.44 (m, 3 H), 1.30−1.19 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.2, 136.2, 135.4, 134.8, 127.7, 120.6, 92.2, 91.2, 88.5, 70.7, 68.2, 67.5, 34.8, 32.7, 32.1, 27.0, 26.2, 25.3, 23.3, 20.9, 20.6, 20.1; MS *m*/*z* (M^+) calcd 382.2508, obsd 382.2505.

(5*R,6*S**,11*R**)-16-[(*E*)-Benzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane (42a).** Cyclization of **39a** (740 mg, 2.07 mmol) in the usual way gave rise to **42a** (370 mg, 53%) as a white foam: mp 81−84 °C; IR (film, cm^{-1}) 1598, 1444, 1094, 1058; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.14 (m, 5 H), 6.55 (s, 1 H), 4.14−3.69 (m, 6 H), 2.90−2.85 (m, 1 H), 2.02−1.74 (series of m, 14 H), 1.50−1.43 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.0, 138.5, 129.2, 127.8 (2 C), 125.9 (2 C), 123.1, 93.2, 91.0, 88.4, 70.0, 68.4, 67.1, 33.5, 33.1, 31.7, 27.5, 27.4, 26.4, 25.2, 23.7; MS *m*/*z* (M^+) calcd 340.2038, obsd 340.2045.

(5*R,6*S**,11*R**)-16-[(*E*)-(2,4,6-Trimethylbenzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane (42c).** Cyclization of **39c** (25 mg, 0.06 mmol) in the manner described above afforded 21 mg (90%) of **42c**: colorless oil; IR (neat, cm^{-1}) 1485, 1440, 1100, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 2 H), 6.35 (s, 1 H), 4.08−3.94 (m, 4 H), 3.85−3.71 (m, 2 H), 2.67−2.57 (m, 1 H), 2.50−2.37 (m, 1 H), 2.29−1.70 (series of m, 19 H), 1.65−1.40 (m, 3 H), 1.27 (ddd, J = 4.5, 13.7, 13.7 Hz, 1 H); ^{13}H NMR (75 MHz, $CDCl_3$) ppm 144.1, 136.1, 135.3, 134.7, 127.8, 127.6, 120.5, 92.1, 91.0, 88.3, 70.6, 68.1, 67.4, 34.7, 32.6, 32.1, 26.9, 26.2, 25.2, 23.2, 20.9, 20.0; MS *m*/*z* (M^+) calcd 382.2499, obsd 382.2517.

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.34; H, 9.03.

(5*R,6*R**,11*S**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]-octadecan-16-one (43). A. Ozonolysis of 41a.** Ozonolysis of a solution of **41a** (248 mg, 0.72 mmol) in methanol (15 mL) at −78 °C as described above provided 130 mg (70%) of **43** as a colorless oil: IR (neat, cm^{-1}) 1720, 1445, 1117, 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97−3.80 (m, 4 H), 3.74−3.69 (m, 1 H), 2.89−2.77 (m, 1 H), 2.69−2.58 (m, 1 H), 2.24−1.45 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.0, 94.9, 91.4, 87.4, 70.8, 68.4, 68.2, 34.7, 32.6, 32.3, 31.8, 26.6, 26.0, 25.3; MS *m*/*z* (M^+) calcd 266.1518, obsd 266.1524.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.63; H, 8.33. Found: C, 67.51; H, 8.42.

B. Ozonolysis of 41b. Analogous exposure of **41b** (10.46 g, 29.5 mmol) dissolved in methanol (500 mL) at −78 °C to ozone gave 5.80 g (73%) of **43**.

(5*R,6*R**,11*S**)-[(*E*)-Benzylidene]-1,7,12-trioxatrispiro-[4.0.4.0.4.3]octadecan-16-one (44).** A mixture of **43** (5.80 g, 21.8 mmol), benzaldehyde (13.27 mL, 130.8 mmol), and sodium hydroxide (5.232 g, 130.8 mmol) in methanol (300 mL) was refluxed for 3 h under N_2 and stirred at 25 °C overnight. After the usual workup and chromatography on silica gel (elution with 10% ethyl acetate in hexanes), there was obtained 5.89 g (76%) of **44** as a faint yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.24 (m, 6 H), 4.12−3.72 (m, 6 H), 3.08 (dd, J = 16.1, 1.2 Hz, 1 H), 2.59 (dd, J = 16.1, 2.8 Hz, 1 H), 2.52−2.41 (m, 1 H), 2.25−1.62 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.0, 137.1, 135.6, 133.7, 130.1, 128.5, 128.3, 93.5, 90.0, 86.9, 70.7, 69.4, 68.7, 37.3, 32.4, 32.73, 32.67, 26.9, 26.1, 25.6; MS *m*/*z* (M^+) calcd 354.1831, obsd 354.1817.

(5*R,6*R**)-12-[(*E*)-Benzylidene]-1,7-dioxadispiro[4.0.4.4]-tetradecan-11-one (45).** A mixture of **10** (10.94 g, 52.0 mmol), benzaldehyde (15.87 mL, 1.56 mmol), and sodium hydroxide (6.25 g, 156 mmol) was refluxed under N_2 for 3 h and stirred overnight at 25 °C. The reaction mixture was cooled to 0 °C, and cold 6 N HCl was added dropwise until the pH was equal to 6. The product was extracted into ethyl acetate (3 × 250 mL) and processed as previously described to give, after chromatography on silica gel (elution with 10% ether in hexanes) and recrystallization from hexanes−CH_2Cl_2, 11.48 g (74%) of **45** as a colorless solid: mp 115−116 °C; IR (KBr, cm^{-1}) 1693, 1618, 1508, 1491, 1445, 1127, 1100, 1066; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 6 H), 4.11−4.02 (m, 1 H), 3.94−3.77 (m, 3 H), 3.03−2.94 (m, 1 H), 2.60−2.48 (m, 1 H), 2.30−2.17 (m, 1 H), 2.14−2.00 (m, 2H), 1.99−1.76 (m, 6H), 1.73−1.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.8, 135.9, 135.5, 135.2, 130.1, 128.5, 120.2, 93.3, 85.8, 69.9, 68.6, 33.3, 31.8, 30.9, 26.6, 25.9, 24.1; MS *m*/*z* (M^+) calcd 298.1569, obsd 298.1562.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.46; H, 7.43. Found: C, 76.44; H, 7.48.

(5*R,6*S**,11*R**)-11-Allyl-12-[(*E*)-benzylidene]-1,7-dioxadispiro-[4.0.4.4]tetradecan-11-ol (46) and (5*R**,6*S**,11*S**)-11-Allyl-12-[(*E*)-benzylidene]-1,7-dioxadispiro[4.0.4.4]-tetradecan-11-ol (47).** A mixture of **45** (300 mg, 1.46 mmol), allyl bromide (0.37 mL, 4.3 mmol), and indium powder (490 mg, 4.32 mmol) in dry THF (30 mL) was stirred at 25 °C for 48 h, treated with another 2.5 mmol of each reagent, and agitated for a final 2 h. The customary workup was followed by flash chromatography on silica gel (elution with 10% ether in petroleum ether). There were isolated 97 mg (28%) of **46** and 86 mg of **47** as viscous oils.

For **46**: IR (neat, cm^{-1}) 3570, 1450, 1070, 1035, 1005, 910; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 6.66 (s, 1 H), 5.87−5.73 (m, 1 H), 5.28−5.09 (m, 2 H), 4.18−4.11 (m, 1 H), 4.06−3.96 (m, 2 H), 3.88−3.80 (m, 1 H), 3.45−3.38 (m, 1 H), 2.74−2.63 (m, 2 H), 2.36−1.26 (series of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.1, 138.4, 135.2, 128.9, 128.0, 126.0, 123.5, 118.2, 92.3, 88.6, 80.8, 71.6, 68.2, 40.3, 33.5, 32.3, 26.9, 24.8, 22.7; MS *m*/*z* (M^+) calcd 340.2038, obsd 340.2048.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.60; H, 8.29. Found: C, 77.46; H, 8.32.

For **47**: colorless oil; IR (neat, cm^{-1}) 3570, 1635, 1600, 1495, 1450, 1330, 1200, 1070, 910; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 6.60 (s, 1 H), 5.91−5.77 (m, 1 H), 5.09−4.99 (m, 2 H), 4.06−3.82 (m, 4 H), 3.15−3.08 (m, 2 H), 2.68 (ddd, J = 3.9, 3.9, 13.9 Hz, 2 H), 2.38−1.57 (series of m, 11

H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.8, 138.3, 134.7, 129.0, 127.9, 125.9, 122.8, 114.0, 93.3, 87.4, 79.8, 70.5, 67.9, 38.7, 34.3, 33.9, 27.4, 27.1, 25.2, 22.4; MS *m*/*z* (M^+) calcd 340.2031, obsd 340.2040.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.59; H, 8.37.

(5*R,6*R**,11*R**)-16-[(*E*)-Benzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane (48).** Dropwise treatment of a solution of **45** (11.0 g, 37 mmol) in THF (550 mL) at −78 °C with the Normant reagent (115.3 mL of 0.32 M in THF) during 30 min, followed by stirring at 25 °C for 5 h, afforded a diol (16.76 g), which was immediately cyclized. Flash chromatography of the product on silica gel (elution with 6% ethyl acetate in hexanes) delivered 10.47 g (83%) of **48** as a colorless oil: IR (neat, cm^{-1}) 1650, 1088, 1057; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 6.62 (s, 1 H), 4.01−3.60 (m, 6 H), 2.86−2.79 (m, 1 H), 2.45−2.34 (m, 2 H), 2.12−1.27 (series of m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.9, 138.3, 129.0, 128.0, 126.1, 123.1, 91.3, 91.2, 88.0, 70.1, 67.6, 67.5, 35.9, 31.2, 30.1, 29.8, 27.7, 27.2, 26.0, 23.8; MS *m*/*z* (M^+) calcd 340.2038, obsd 340.2041.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.60; H, 8.29. Found: C, 77.23; H, 8.30.

(5*R,6*S**,11*R**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]-octadecan-16-one (49).** A solution of **48** (10.39 g, 30.5 mmol) in cold (−78 °C) methanol was ozonolyzed in the predescribed manner to give, after chromatography on silica gel (elution with 30% ethyl acetate in hexanes), 7.08 (87%) of **49** as a colorless oil; IR (neat, cm^{-1}) 1722, 1096, 1075, 1054, 1018, 997; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96−3.90 (m, 1 H), 3.85−3.75 (m, 3 H), 3.74−3.57 (m, 2 H), 2.49−2.27 (m, 4 H), 2.15−2.01 (m, 2 H), 2.04−1.53 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.7, 93.6, 90.7, 86.8, 70.1, 68.2, 67.6, 35.1, 32.3, 30.9, 30.8, 30.2, 27.7, 26.8, 25.7; MS *m*/*z* (M^+) calcd 266.1518, obsd 266.1521.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.63; H, 8.32.

(5*R,6*S**,11*R**)-17-[(*E*)-Benzylidene]-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecan-16-one (50).** A mixture of **49** (7.08 g, 26.6 mmol), benzaldehyde (10.8 mL, 106.4 mmol), and sodium hydroxide (4.256 g, 106.4 mmol) in methanol (300 mL) was refluxed under N_2 for 3 h, processed as before, and ultimately subjected to chromatography on silica gel (elution with 10% ethyl acetate in hexanes). There was obtained 8.85 g (93%) of **50** as an off-white solid: mp 99 °C; IR (neat, cm^{-1}) 1685, 1654, 1097, 1075, 1062, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 6 H), 4.20−4.14 (m, 2 H), 3.95−3.74 (m, 4 H), 3.65−3.57 (m, 2 H), 2.95 (d, J = 15.8 Hz, 1 H), 2.54 (dd, J = 15.7, 1.5 Hz, 1 H), 2.45−2.25 (m, 3 H), 2.15 (s, 1 H), 2.12−1.68 (m, 6 H), 1.69−1.47 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.7, 136.8, 135.2, 133.7, 130.0, 128.7, 128.4, 93.2, 89.1, 86.1, 70.1, 69.3, 68.0, 37.9, 32.0, 31.3, 30.5, 27.8, 26.9, 25.9; MS *m*/*z* (M^+) calcd 354.1831, obsd 354.1835.

MAD-Promoted Addition of Allylmagnesium Bromide to 36a. To a stirred solution of 2,6-di-*tert*-butyl-4-methylphenol (4.40 g, 19.96 mmol) in toluene (10 mL) was added trimethylaluminum (6.0 mL of 2.0 M in hexane, 10.0 mmol). After 1 h, the mixture was cooled to −78 °C and **36a** (2.0 g, 6.71 mmol) dissolved in toluene (15 mL) was added followed by allylmagnesium bromide (20 mL of 1.0 M in ether, 20 mmol). After 3 h, the mixture was poured into 1 M HCl (100 mL) and CH_2Cl_2 (50 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 20−50% ether in petroleum ether) to give **51** (1.41 g, 62%) as a clear foam in addition to a diastereomeric mixture of 1,4-addition products **40a** (0.56 g, 25%) as a waxy solid, mp 108−110 °C.

For **51**: IR (neat, cm^{-1}) 3534, 3421, 1636, 1600, 1492, 1445, 1337, 1301, 1058; ^{1}H NMR (300 Mz, $CDCl_3$) δ 7.37−7.14 (m, 5 H), 6.62 (s, 1 H), 6.04−5.91 (m, 1 H), 5.09−5.03 (m, 2 H), 4.18−3.80 (m, 4 H), 2.80−2.71 (m, 1 H), 2.49 (d, J = 6.7 Hz, 2 H), 2.21−1.75 (m, 9 H), 1.59 (s, 1 H), 1.49−1.41 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.6, 138.1, 134.4, 128.2, 128.1, 126.1, 125.9, 92.8, 89.5, 79.9, 70.9, 68.2, 38.0, 34.6, 33.2, 29.1, 27.1, 26.1, 22.6; MS *m*/*z* (M^+) calcd 340.2031, obsd 340.2041.

(5*R,6*R**,12*R**)-12-Hydroxy-1,7-dioxadispiro[4.0.4.4]-tetradecan-11-one (52) and (5*R**,6*R**,12*S**)-12-Hydroxy-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (53).** To a cold (−78 °C) magnetically stirred solution of **9** (3.15 g, 15.0 mmol) in dry THF (150 mL) was added potassium hexamethyldisilazide (33.0 mL of 0.5 M in toluene, 16.5 mmol) followed by chlorotrimethylsilane (2.82 g, 26.0 mmol) 1 h later. The reaction mixture was allowed to warm slowly to rt, stirred overnight, and partitioned between saturated $NaHCO_3$ solution (100 mL) and ether (100 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic solutions were dried, filtered, and concentrated.

An analytically pure sample of the silyl enol ether was obtained by chromatography on neutral alumina (elution with 10% ethyl acetate in petroleum ether) as a faint yellow oil: IR (neat, cm^{-1}) 1720, 1460, 1350, 1310, 1260, 1240, 1145, 1070, 970, 935, 920, 870; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (t, J = 3.5 Hz, 1 H), 3.99−3.77 (m, 4 H), 2.23−2.11 (m, 1 H), 2.03−1.48 (series of m, 11 H), 0.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 152.4, 103.6, 86.7, 86.6, 69.6, 67.9, 30.6, 29.39, 29.37, 28.0, 26.2, 21.1, 0.1; MS *m*/*z* (M^+ + H) calcd 283.1729, obsd 283.1724.

Anal. Calcd for $C_{15}H_{26}O_3Si$: C, 63.57; H, 9.61. Found: C, 63.19; H, 9.35.

The crude product from above was dissolved in CH_2Cl_2 (150 mL), then treated with $NaHCO_3$ (10.00 g, 11.90 mmol) and *m*-CPBA (5.0 g of 90% purity, 29.1 mmol) in several portions. The mixture was stirred for 20 h and quenched with Na_2SO_3 solution (50 mL). After 30 min, the separated aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), dried, and concentrated. The resulting residue was dissolved in methanolic citric acid (100 mL, 0.1 M), stirred for 1 h, and concentrated. Chromatography of the residue on silica gel (gradient elution, 50−95% ethyl acetate in petroleum ether) gave 630 mg (19%) of **53** and 2.57 g (76%) of **52**.

For **52**: white powder; mp 137.5−138.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (dd, J = 11.3, 7.5 Hz, 1 H), 4.10−3.75 (m, 4 H), 3.35 (br s, 1 H), 2.21−2.13 (m, 1 H), 2.07−1.73 (series of m, 10 H), 1.68−1.60 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.4, 92.3, 89.9, 72.4, 69.2, 69.1, 33.8, 31.8, 31.5, 30.1, 25.8, 25.4; MS *m*/*z* (M^+) calcd 226.1205, obsd 226.1203.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.82; H, 8.12.

For **53**: waxy white solid; mp 77−80 °C; IR (CCl_4, cm^{-1}) 3700, 3520, 1740, 1530, 1435, 1220, 1125, 1050, 930; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (dd, J = 7.7, 11.8 Hz, 1 H), 3.98−3.80 (m, 3 H), 3.72−3.65 (m, 1 H), 3.10 (br s, 1 H), 2.52−2.41 (m, 1 H), 2.35−2.20 (m, 2 H), 2.07−1.85 (m, 3 H), 1.83−1.70 (m, 2 H), 1.68−1.40 (m, 3 H), 1.19−1.04 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.3, 93.3, 87.8, 71.8, 69.1, 68.8, 31.1, 30.4, 30.0, 26.1, 26.0, 24.0; MS *m*/*z* (M^+) calcd 226.1205, obsd 226.1220.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.59; H, 7.94.

(5*R,6*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (54).** To a magnetically stirred solution of **52** (2.75 g, 12.17 mmol), imidazole (1.66 g, 24.4 mmol), and DMAP (420 mg, 3.44 mmol) in CH_2Cl_2 (250 mL) was added *tert*-butyldimethylsilyl chloride (2.75 g, 18.24 mmol). The reaction mixture was stirred for 24 h, and saturated $NaHCO_3$ solution (75 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were dried, filtered, and concentrated. Chromatography of the residue on silica gel (elution with 50% ether in petroleum ether) gave **54** (3.41 g, 82%) as a white powder: mp 93−95 °C; IR ($CHCl_3$, cm^{-1}) 1745, 1530, 1480, 1430, 1220, 1060, 1035, 935; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (dd, J = 11.4, 7.7 Hz, 1 H), 4.08−4.06 (m, 1 H), 3.97−3.85 (m, 2 H), 3.81−3.74 (m, 1 H), 2.10−1.58 (series of m, 12 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.7, 92.6, 89.3, 74.4, 69.1, 68.9, 34.1, 32.3, 31.4, 20.5, 15.8, 15.4, 18.5, −4.3, −5.3; MS *m*/*z* (M^+) calcd 340.2070, obsd 340.2052.

Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.48; H, 9.48. Found: C, 63.45; H, 9.39.

(5*R,6*R**,12*R**)-12-(*tert*-Butyldimethylsiloxy)-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (55).** Entirely parallel silylation of **53** (770 mg, 3.40 mmol) with *tert*-butyldimethylsilyl chloride (1.0 g, 6.63 mmol) afforded 1.18 g (100%) of **55** as a clear oil: IR (neat, cm^{-1}) 1745, 1465, 1450, 1260, 1155, 1085, 1065, 1040, 950; ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (dd, J = 11.2, 7.3 Hz, 1 H), 3.92−3.83 (m, 3 H), 3.70−3.63 (m, 1 H), 2.52−2.45 (m, 1 H), 2.23 (ddd, J = 13.4, 13,4, 4.5 Hz, 1 H), 2.11−2.01 (m, 1 H), 1.94−1.46 (series of m, 8 H), 1.40−1.26 (m, 1 H), 0.87 (s, 9 H), 0.08 (s, 3 H), −0.1 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 208.2, 94.2, 87.6, 73.6, 68.9, 68.8, 31.3, 30.9, 30.1, 26.1, 25.8, 25.7, 24.5, 18.4, −4.8, −5.4; MS m/z (M^+) calcd 340.2070, obsd 340.2073.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 63.48, H, 9.48. Found: C, 63.53; H, 9.38.

Capping of 54 with the Normant Reagent. A cold (−78 °C), magnetically stirred solution of **54** (3.02 g, 8.88 mmol) in THF (150 mL) was treated with the Normant reagent (85.0 mL of 0.15 M, 12.75 mmol) and processed in the usual way to give 3.80 g (97%) of diol. Without purification, this diol was cyclized in the presence of *p*-toluenesulfonyl chloride (2.82 g, 14.8 mmol) as previously detailed. Chromatography of the resulting material on silica gel (elution with 50−95% ethyl acetate in petroleum ether) afforded 2.85 g (78%) of **58** as the only product: colorless crystals; mp 84 °C; IR (film, cm^{-1}) 1465, 1240, 1165, 1110, 1080, 1010; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11−3.84 (m, 5 H), 3.82−3.65 (m, 1 H), 3.48−3.30 (m, 1 H), 2.14−1.55 (series of m, 15 H), 1.47−1.07 (m, 1 H), 0.82−0.78 (m, 9 H), 0.00 to −0.04 (m, 6 H); ^{13}H NMR (75 MHz, $CDCl_3$) ppm 91.8, 90.1, 87.5, 76.5, 70.8, 70.6, 67.4, 34.4, 33.1, 30.7, 30.3, 27.0, 26.2, 25.8, 25.6, 24.1, 17.8, −4.2, −5.1; MS m/z (M^+) calcd 382.2539, obsd 382.2537.

Capping of 55 with the Normant Reagent. Addition of the Normant reagent (10.0 mL of 0.60 M, 6.0 mmol) to a cold (−78 °C) solution of **55** (970 mg, 2.85 mmol) in anhydrous THF (75 mL) in the manner previously described gave rise to two diols following chromatography on silica gel (elution with ether followed by ethyl acetate). The minor diol (150 mg, 12%) was less polar than the major diol (740 mg, 59%).

Cyclization of the minor component (150 mg, 0.34 mmol) in conventional fashion furnished 90 mg (62%) of **57** as a clear oil: IR (neat, cm^{-1}) 1450, 1360, 1300, 1250, 1150, 1050, 950; ^1H NMR (300 MHz, $CDCl_3$) δ 4.14−4.01 (m, 1 H), 3.95−3.81 (m, 4 H), 3.70−3.54 (m, 2 H), 2.72−2.56 (m, 1 H), 2.24−1.29 (series of m, 15 H), 0.88 (s, 9 H), 0.08 (s, 6 H); MS m/z (M^+ − *t*-$BuMe_2SiO$) calcd 251.1651, obsd 251.1642.

Analogous cyclization of the major diol (740 mg, 1.67 mmol) provided **59** as a white powder (650 mg, 92%): mp 45 °C; IR ($CHCl_3$, cm^{-1}) 1530, 1480, 1440, 1400, 1370, 1345, 1310, 1230, 1120, 1075, 990, 970, 930; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07−3.80 (m, 4 H), 3.69−3.58 (m, 2 H), 2.20−1.45 (series of m, 15 H), 1.32 (ddd, J = 13.0, 3.6, 3.6 Hz, 1 H), 1.22−1.05 (m, 1 H), 0.83 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 93.3, 91.9, 88.0, 74.3, 69.8, 68.8, 66.9, 31.6, 30.4, 30.1, 28.0, 27.7, 27.0, 25.9, 25.8, 17.9, −4.7, −4.9; MS m/z (M^+) calcd 382.2539, obsd 382.2539.

Anal. Calcd for $C_{21}H_{38}O_4Si$: C, 65.92; H, 10.02. Found: C, 65.93; H, 9.97.

Deprotection−Oxidation of 57. To a magnetically stirred solution of **57** (9.17 g, 24.0 mmol) in acetonitrile (50 mL) was added a solution of 5% hydrofluoric acid in acetonitrile (100 mL). After 4 h, the mixture was treated with saturated $NaHCO_3$ solution (150 mL) and diluted with CH_2Cl_2 (150 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried and concentrated to give 6.57 g (100%) of the alcohol as a clear oil that solidified on standing.

To a stirred solution of this alcohol (2.54 g, 9.48 mmol) in CH_2Cl_2 (150 mL) was added the Dess−Martin periodinane reagent (10.35 g, 24.4 mmol). The mixture was stirred overnight, diluted with ether (400 mL), and poured into saturated $Na_2S_2O_3$ solution (150 mL). The separated organic phase was washed with saturated $NaHCO_3$ solution (150 mL), dried, and concentrated to leave a residue, which was purified by chromatography on silica gel. Elution with 50% ether in petroleum ether afforded **43** (2.40 g, 96%), identical in all respects with the material obtained above.

(5*R,6*R**,11*R**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]-octadecan-16-one (60). A. From 58.** A 2.85 g (6.72 mmol) sample of **58** was deprotected as described above to give 1.72 g (96%) of the alcohol, which was dissolved in CH_2Cl_2 (150 mL) and treated with pyridinium dichromate (10.2 g, 20.5 mmol) and powdered 3 Å molecular sieves (12.3 g). The mixture was stirred for 48 h, filtered through a pad of Celite, and concentrated. Chromatography of the residue on silica gel (elution with ethyl acetate) gave **60** (1.16 g, 68%) as a colorless solid: mp 68−70 °C; IR (film, cm^{-1}) 1730, 1455, 1310, 1100, 1000, 995; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11−3.73 (m, 4 H), 2.49−2.21 (m, 3 H), 2.08−1.64 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.6, 93.9, 93.2, 87.1, 77.4, 70.5, 68.3, 67.5, 34.5, 32.2, 31.7, 27.4, 27.3, 26.1, 25.1; MS m/z (M^+) calcd 266.1518, obsd 266.1521.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.63; H, 8.33. Found: C, 67.20; H, 8.34.

B. From 59. Deprotection of **59** (650 mg, 1.53 mmol) as before afforded 350 mg (85%) of the alcohol, which was oxidized with pyridinium dichromate in the manner detailed above. Chromatographic purification gave 240 mg (69%) of **60**, which was spectroscopically identical to the ketone obtained in part A.

(5*R,6*S**,12*S**)-12-Hydroxy-1,7-dioxadispiro[4.0.4.4]-tetradecan-11-one (61) and (5*R**,6*S**,12*R**)-12-Hydroxy-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (62).** To a cold (−78 °C), magnetically stirred solution of **10** (7.48 g, 35.6 mmol) in dry THF (250 mL) was added potassium hexamethyldisilazide (80.0 mL of 0.5 M in toluene, 40.0 mmol), followed by trimethylsilyl chloride (7.28 g, 67.0 mmol) 1 h later. Adaptation of the earlier procedure for purification of the silyl enol ether and for oxidation with *m*-CPBA (11.22 g of 90% purity, 58.7 mmol) delivered 5.54 g (69%) of **61** and 2.14 g (27%) of **62**.

For the silyl enol ether: colorless oil; IR (neat, cm^{-1}) 1660, 1245, 1195, 1170, 960, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (dd, J = 3.8, 3.8 Hz, 1 H), 3.89−3.74 (m, 4 H), 2.41−2.15 (m, 2 H), 2.06−1.71 (series of m, 8 H), 1.63−1.53 (m, 2 H), 0.19 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 153.4, 102.9, 87.2, 86.4, 70.0, 68.5, 32.9, 32.8, 31.2, 27.5, 26.5, 21.1, 0.4; MS m/z (M^+) calcd 283.1729, obsd 283.1741.

For **61**: colorless crystals; mp 90−91 °C; IR (CCl_4, cm^{-1}) 3710, 3520, 1730, 1525, 1435, 1220, 1130, 1050, 930; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65−4.57 (m, 1 H), 3.83−3.75 (m, 2 H), 3.68 (ddd, J = 8.6, 6.8, 6.7 Hz, 1 H), 3.54 (ddd, J = 8.3, 7.1, 7.0 Hz, 1 H), 3.32 (br s, 1 H), 2.60 (dt, J = 13.3, 6.8 Hz, 1 H), 2.13−1.48 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.1, 90.6, 89.1, 71.6, 68.8, 68.0, 32.8, 30.9, 30.8, 26.1, 25.7, 24.3; MS m/z (M^+) calcd 226.1205, obsd 226.1202.

Anal. Calcd For $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.78; H, 8.02.

This compound was subjected to X-ray crystallographic analysis.[28]

For **62**: white solid; mp 91−93 °C; IR (film, cm^{-1}) 3400, 1840, 1500, 1400, 1320, 1250, 1070, 990, 900; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, J = 12.1, 7.5 Hz, 1 H), 3.94−3.75 (m, 4 H), 3.50 (br s, 1 H), 2.55−2.42 (m, 1 H), 2.26 (dddd, J = 13.1, 7.4, 3.7, 3.7 Hz, 1 H), 2.11−1.65 (series of m, 8 H), 1.49−1.39 (m, 1 H), 1.32−1.18 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.1, 93.8, 88.6, 72.6, 69.1, 69.0, 32.6, 31.8, 31.7, 29.5, 26.7, 26.2; MS m/z (M^+) calcd 226.1205, obsd 226.1208.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.69; H, 8.00.

(5*R,6*S**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (63).** O-Silylation of **61** (5.54 g, 24.5 mmol) with *tert*-butyldimethylsilyl chloride (4.43 g, 2.05 mmol) in the predescribed manner afforded 7.13 g (86%) of **63** as a clear oil that solidified on standing: mp 65 °C; IR ($CHCl_3$, cm^{-1}) 1750, 1535, 1485, 1440, 1165, 1070, 1030, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (dd, J = 9.8, 7.3 Hz, 1 H), 3.88−3.80 (m, 2H), 3.79−3.70 (m, 2 H), 3.58 (dd, J = 15.4, 7.2 Hz, 1 H), 2.68−2.59 (m, 1 H), 2.01−1.56 (series of m, 10 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz,

$CDCl_3$) ppm 207.8, 92.1, 88.7, 73.7, 68.7, 68.1, 32.8, 31.7, 31.0, 26.3, 26.1, 25.8, 25.2, 18.4, −4.7, −5.4; MS *m/z* (M^+) calcd 340.2070, obsd 340.2086.

Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.48; H, 9.48. Found: C, 63.75; H, 9.53.

(5*R,6*S**,12*R**)-12-(*tert*-Butyldimethylsiloxy)-1,7-dioxadispiro[4.0.4.4]tetradecan-11-one (64).** From reaction of **62** (2.70 g, 12.0 mmol) with *tert*-butyldimethylsilyl chloride (4.0 g, 24.5 mmol) under the conditions detailed above, there was obtained 3.75 g (92%) of **64** as a white solid: mp 68 °C; IR ($CHCl_3$, cm^{-1}) 1750, 1480, 1400, 1265, 1155, 1110, 1000; ^1H NMR (300 MHz, $CDCl_3$) δ 4.34 (dd, J = 12.2, 7.1 Hz, 1 H), 3.93−3.75 (m, 4 H), 2.55−2.41 (m, 1 H), 2.15−1.65 (m, 9 H), 1.60−1.38 (m, 2 H), 0.87 (s, 9 H), 0.13 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.6, 94.0, 88.3, 74.7, 69.0, 68.9, 33.1, 31.9, 31.6, 29.9, 26.7, 26.3, 25.7, 18.5, −4.5, −5.5; MS *m/z* (M^+) calcd 340.2070, obsd 340.2081.

Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.48; H, 9.48. Found: C, 63.60; H, 9.45.

Capping of 63 with the Normant Reagent. Addition of the Normant reagent (78.0 mL of 0.60 M, 46.8 mmol) to a cold (−78 °C) solution of **63** (9.39 g, 27.6 mmol) in dry THF (200 mL) in the manner earlier described afforded 10.23 g (93%) of a mixture of diastereomeric diols, which was directly cyclized in the presence of *p*-toluenesulfonyl chloride (5.95 g, 31 mmol). After workup, the residue was subjected to chromatography on silica gel (elution with 20% ether in petroleum ether) to give 9.17 g (93%) of a diastereomeric mixture of **65** and **67**. This material was desilylated (6.57 g, 100%), and a portion of this alcohol (2.54 g, 9.48 mmol) was oxidized (Dess−Martin) as before to give, after chromatographic separation (silica gel, elution with 50% ether in petroleum ether), 670 mg (27%) of **69** and 1.73 g (69%) of **49**. The latter ketone proved spectroscopically identical to material prepared earlier.

For **69**: colorless oil; IR (neat, cm^{-1}) 1735, 1460, 1315, 1040, 970, 935, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98−3.71 (m, 6 H), 2.53−2.40 (m, 2 H), 2.29−2.14 (m, 2 H), 2.02−1.57 (series of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.7, 93.8, 92.0, 87.0, 70.3, 68.5, 67.7, 34.5, 32.9, 32.3, 29.1, 28.6, 27.1, 26.0, 25.0; MS *m/z* (M^+) calcd 266.1518, obsd 266.1516.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.63; H, 8.33. Found: C, 67.45; H, 8.43.

Capping of 64 with the Normant Reagent. Addition of the Normant reagent (30.0 mL of 0.60 M, 18.0 mmol) to a cold (−78 °C) solution of **64** (2.59 g, 7.62 mmol) in dry THF (200 mL) in the manner earlier described furnished 2.90 g (86%) of a mixture of diastereomeric diols. This mixture was cyclized as usual with *p*-toluenesulfonyl chloride (1.69 g, 8.86 mmol) to give after chromatography on silica gel (elution with 50% ether in petroleum ether) 2.60 g (93%) of a diastereomeric mixture of **66** and **68**. This material was sequentially desilylated (82%) and oxidized (PDC, 3 Å MS). Chromatographic separation was effected on silica gel (elution with 50% ether in petroleum ether) and provided 180 mg (13%) of **49** and 1.12 g (84%) of **69**.

(5*R,6*S**,11*S**,17*S**)-17-Hydroxy-1,7,12-trioxatrispiro-[4.0.4.0.4.3]octadecan-16-one (70) and (5*R**,6*S**,11*S**,-17*R**)-17-Hydroxy-1,7,12-trioxatrispiro[4.0.4.0.4.3]-octadecan-16-one (71).** To a cold (−78 °C), magnetically stirred solution of **69** (550 mg, 2.07 mmol) in dry THF (50 mL) was added potassium hexamethyldisilazide (4.8 mL of 0.5 M in toluene, 2.4 mmol) followed by trimethylsilyl chloride (4.30 g, 3.91 mmol) 3 h later. Adaptation of the earlier procedure and chromatographic separation afforded 160 mg (27%) of **70** and 350 mg (60%) of **71**.

For **70**: colorless solid; mp 98−100 °C; IR ($CHCl_3$, cm^{-1}) 3610, 3540, 1735, 1530, 1485, 1435, 1220, 1095, 1065, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (dd, J = 12.7, 7.5 Hz, 1 H), 4.20−3.45 (series of m, 6 H), 3.08 (br s, 1 H), 2.80−2.60 (m, 1 H), 2.57−2.40 (m, 1 H), 2.35−1.55 (series of m, 9 H), 1.50−1.25 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.1, 92.3, 90.3, 86.7, 70.9, 70.2, 69.3, 67.3, 42.6, 32.2, 30.3, 27.2, 27.0, 25.1, 25.0; MS *m/z* (M^+) calcd 282.1467, obsd 282.1468.

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.79; H, 7.82.

This compound was subjected to X-ray crystallographic analysis.[28]

For **71**: colorless oil; IR (neat, cm^{-1}) 3510, 1735, 1440, 1400, 1300, 1275, 1250, 1210, 1185, 1125, 1070, 985, 960, 935; ^1H NMR (300 MHz, $CDCl_3$) δ 4.54 (dd, J = 12.4, 7.1 Hz, 1 H), 4.10−3.75 (m, 6 H), 3.11 (br s, 1 H), 2.20 (dd, J = 13.0, 7.1 Hz, 1 H), 2.20−1.50 (series of m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.2, 94.0, 93.7, 85.4, 70.3, 69.3, 68.6, 68.4, 42.3, 33.7, 33.3, 27.42, 27.38, 25.4, 25.2; MS *m/z* (M^+) calcd 282.1467, obsd 282.1465.

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.72; H, 7.96.

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Supporting Information Available: Computer-generated perspective drawings of **33**, **61**, and **70**, as determined by X-ray crystallography (3 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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