Chelation-Controlled Facially Selective Cyclocondensation Reactions of Chiral Alkoxy Aldehydes: Syntheses of a Mouse Androgen and of a Carbon-Linked Disaccharide

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Abstract: Magnesium bromide in tetrahydrofuran catalyzes the cycloaddition of a variety of chiral alkoxy aldehydes with activated butadienes. The stereochemistry of these products is such that they can be rationalized as arising from a reacting conformer in which the alkoxy group is syn to the carbonyl function. The C=O bond is attacked from its less hindered face. That chelation of the magnesium is involved in these reactions is indicated by a striking change from endo to exo topology as alkoxy functionality is introduced on the aldehyde. Titanium tetrachloride catalysis also provides excellent chelation-control stereoselectivity. The application of these findings to the synthesis of bridged ketals including the mouse androgen dehydrobrevicomin is described. Another application allows for the synthesis of carbon-linked disaccharides.

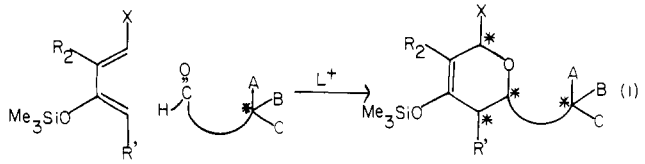
Background

The issue of diastereotopic preferences in the reactions of carbon nucleophiles with aldehydes or ketones has provoked considerable research[1] and interpretation.[2-6] Of course, nucleophilic addition to carbonyl groups is a central reaction type in organic chemistry. Thus, an insight into the relationship of chirality generated through such additions, with preexisting dissymmetry, is crucial to achieving stereochemical control in synthesis.

A major statement bearing on this problem was first provided by Cram and his associates.[2] Though the rationale of Cram's representations has been questioned and other formulations have been advanced,[4,5] these rules still provide a useful correlation of known information and constitute a convenient point of departure for predicting stereochemical results. In addition to addressing the situation where facial selectivity might arise from considerations of steric bulk, the Cram analysis also dealt with special cases in which the carbonyl group is flanked by a heteroatom.[2a,h,i] In this variation, it was recognized that the metal counterion associated with the carbon nucleophile could, due to chelation, impose a conformation with a defined syn relationship between the carbonyl group and the heteroatom. A proposal wherein the nucleophile attacks anti to the large (L) group in such a conformation was invoked to rationalize several stereochemical findings. The Cram chelation model, augmented and refined by more sophisticated allowances for the precise role of the metal, was a major bulwark in the Still synthesis of monensin.[7,8] Other workers have recently exploited this phenomenon.[9]

Our laboratory has been engaged in studying the Lewis acid catalyzed cycloaddition of aldehydes with activated dienes.[10,11] Variation of the catalyst can have profound consequences on the mechanism of the process and, accordingly, on the stereochemical relationship at the 2- and 3-positions of the resultant dihydropyrone.

If the aldehyde substrate contains preexisting chirality, the matter of diastereofacial preference presents itself. It is seen that, in the presence of a strong diastereofacial preference, the cycloaddition reaction shown in eq 1 has a potential to interrelate four chiral carbon centers. With facially selective operations around the resultant double bond, further possibilities for rapid stereochemical control can readily be anticipated. Given the enormous range of dienes and aldehydes that have been shown to participate in this chemistry,[12] significant advances in stereoselective synthesis can be contemplated if the diastereofacial issue would lend itself to control.



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Prior to the investigations described herein,[13] the selectivity characteristics of several chiral aldehydes had been studied in connection with cyclocondensation reactions. It had been demonstrated that, at least with certain dienes, 2-phenylpropanal[11,14] and glyceraldehyde[15] acetonide afforded essentially a single cycloadduct whose stereochemistry was in accord with that expected from the Cram[2] or Felkin[5] type of analysis. N-Cbz leucinal also gave substantially a single product, though the interpretation of this finding was left open.[15] On the other hand, the Prelog–Djerassi lactonic aldehyde gave a 4:2.7 mixture of two facial isomers.[11]

The hypothesis that underlays this research was that it might be possible to realize chelation control in the Lewis acid catalyzed cyclocondensations of activated dienes with aldehydes bearing heterofunctionality proximate to the carbonyl function. Facial selectivity with important classes of chiral aldehydes could be achieved.

The reduction of this concept to practice with a variety of α- and β-alkoxy aldehydes is described herein. The consequences of chelation control, not only on the diastereofacial outcome but also on the topology (endo vs. exo) of the cycloaddition, will be established. In fact, a remarkable degree of control can be exercised by the simple expedient of changing the Lewis acid catalyst.

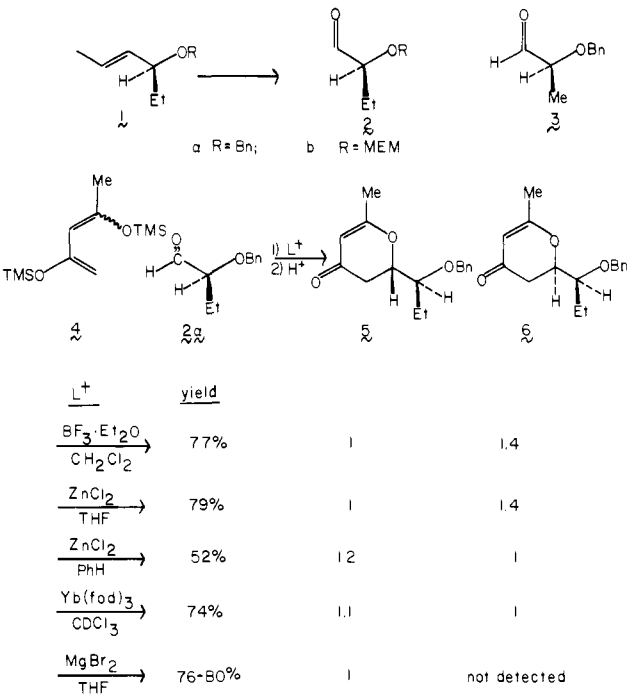
We first describe the application of magnesium bromide catalysis to the cyclocondensations of α-alkoxy aldehydes. We then report on the attempted application of the catalysis to β-alkoxy aldehydes. For this class of compounds, it was found that titanium tetrachloride provided strong diastereofacial control. We then reexamined the reactions of α-alkoxy aldehydes with titanium tetrachloride and discovered a remarkable difference in the topological outcome relative to that realized through the use of magnesium bromide. Notable applications of these findings to the synthesis of the mouse androgen, dehydrobrevicomin, and to the novel carbon-linked disaccharides will also be reported.

Results

α-Alkoxy Aldehydes. The alcohol function of hex-2-en-3-ol was protected as shown in formulas **1a** and **1b**. Ozonolysis of compounds **1** followed by reductive workup afforded compounds **2**. It subsequently emerged that the performances of these substrates vis-à-vis the chemistry to be described were similar. Most of our studies will be reported on the benzyl ether **2a**. In the lactaldehyde series, we examined only the benzyl ether **3**.

We first investigated the cyclocondensation of **4** with aldehyde **2a**. The successful utilization of 1-alkyl 1,3-dioxygenated butadienes in the cyclocondensation reaction has been recently reported.[12] Under Lewis acid catalysis by either $BF_3{\cdot}Et_2O$, $ZnCl_2$–THF, $ZnCl_2$–benzene, or $Yb(fod)_3$–$CDCl_3$, approximately 1:1 mixtures of the two cyclocondensation products were obtained. At the time we could not rigorously assign the stereochemistry of the individual pyrones. Subsequently (vide infra) the stereochemistry of **5** was proven by its conversion to *exo*-brevicomin **29**.

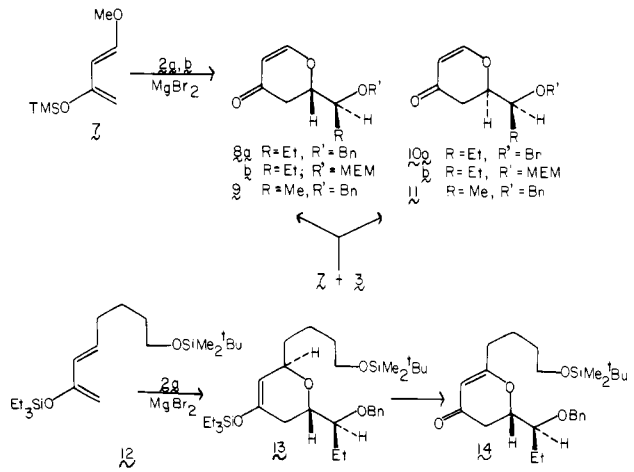
Mindful of the success enjoyed by Still and others in apparent chelation-controlled Grignard reactions, we turned to the use of magnesium bromide as the Lewis acid. When the reaction was conducted in THF, there was obtained a 76–80% yield of **5**. Since the spectral properties of **6** were very well-known to us, the lack of detection of this substance by GLC and NMR analyses of the crude reaction mixture was very significant. High stereoselectivity had been achieved.



The generality of this result with other dienes was tested. Reaction of aldehyde **2a** with diene **7** under the same conditions followed by acidic (AcOH) workup afforded dihydropyrone **8a** in 80% yield. Similarly, aldehyde **2b** afforded dihydropyrone **8b**. In each case, the corresponding stereoisomer **10** was not detected.

The applicability of the effect with substituted propionaldehydes was studied. This was a more critical test since, in the chelation model, the size differential between the large and small groups is reduced. Reaction of aldehyde **3** with diene **7** in the presence of $Yb(fod)_3$ afforded epimers **9** and **11** in a 1.6:1 ratio. As was the case with **2a** and **2b**, recourse to magnesium bromide in THF gave substantially a single compound. The ratio of **9**:**11** was minimally 40:1.

Stereoselectivity is also maintained in reaction of the previously described diene **12**, which lacks a 1-oxygen substituent. The ability of such dienes to function in the cyclocondensation chemistry has recently been reported.[12,16] In the case at hand, reaction of diene **12** with aldehyde **2a** under catalysis by magnesium bromide–THF afforded a single stereoisomer, shown as **13**. Reaction of **13** with palladium acetate gave rise to **14**. The similarity of the corresponding regions of the proton NMR spectra of **14** with those of **5** and **8a** (see Experimental Section), in contrast to those of **6**, serve to establish the same relative arrangement of chiral centers of these compounds. Since the stereochemistry of **5** was rigorously



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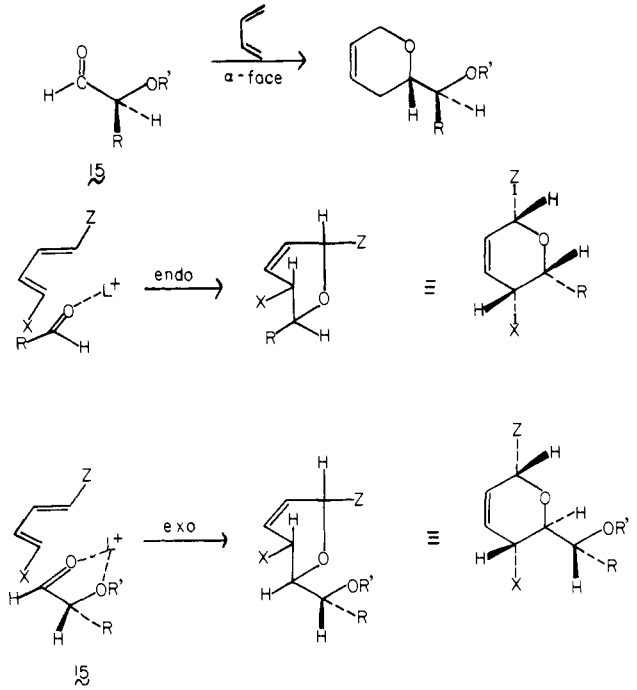
established (vide infra), dihydropyrone **14** is formulated as shown. The configuration drawn at the 2- and 6-positions in **13** is that arising from an "exo" disposition in the cycloaddition reaction. Such an orientation was rigorously established for the dienes bearing 1-alkoxy substitution (vide infra).

The relative configurations of the products (cf. **5**, **8**, **9**, and **13**) of the highly stereoselective magnesium bromide cycloadditions correspond to those expected if cycloaddition occurs from the less hindered α-face of syn conformer **15**. Presumably, chelation of the magnesium between the two oxygens is a dominant factor in directing reaction through this conformer.

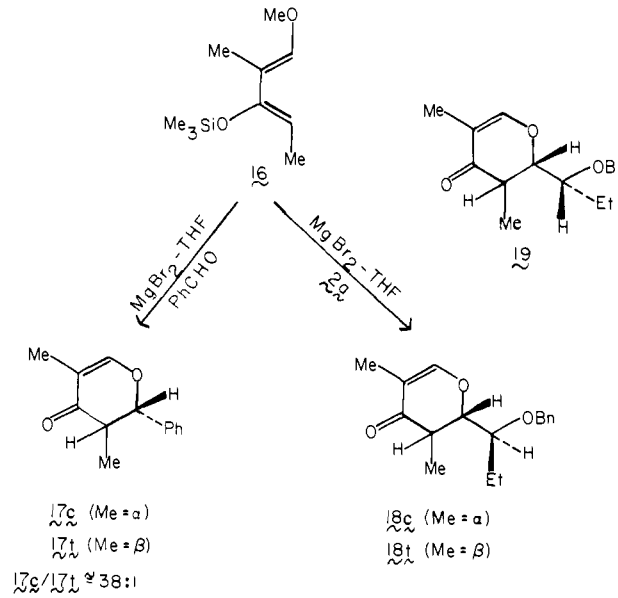
While chelation has previously been invoked as a determinative factor in diastereofacial selectivity in the reactions of nucleophiles with carbonyl linkages,[7-9] its actual involvement is not readily demonstrated experimentally. In the case at hand, a rare opportunity presented itself to probe the chelation hypothesis through a discriminating experiment. It will be recalled that, in the pericyclic variation of the cyclocondensation reaction,[10,11] endo addition prevails. An attractive explanation for this topology involved the reasonable presumption that the Lewis acid catalyst binds anti to the "R" group of the aldehyde. If it is further presumed that the catalyst–solvent ensemble is more sterically demanding than is the alkyl group of the aldehyde, an exo disposition of the catalyst, on purely steric grounds, would be anticipated. The alkyl function of the aldehyde thus, per force, emerges endo.

If, however, chelation via conformer ***15*** *is operative, it would be expected that both the catalyst and the alkyl group, which now encompasses C(H)(R)OR', are both disposed in an exo sense.* The seemingly strong connectivity between diastereofacial control through chelation and the expectation of exo topology allowed for a critical test.



15

An important control experiment was required. It was necessary to demonstrate that magnesium bromide in fact functioned as a "pericyclic catalyst" that promoted endo topology with aldehydes which lack the feature of potential chelation. In the event, reaction of benzaldehyde with diene **16** under magnesium bromide catalysis in THF afforded a 50% yield of a 38:1 mixture of **17c** and **17t**. This experiment identifies magnesium bromide (in THF) as an endo-directing catalyst much in the mold of zinc chloride[10,11] or lanthanides.[17] Reaction of the same diene with aldehyde **2a**, under magnesium bromide catalysis, afforded a 50% yield of **18t** in which the chelation model stereochemistry for facial selectivity and the exo topology are clearly expressed. None of **18c**, in which apparent chelation control would be accompanied by endo addition, could



16 **19**

17c (Me = α)
17t (Me = β)
17c/**17t** ≥ 38:1

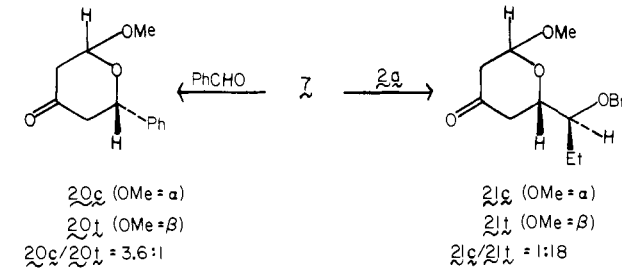
18c (Me = α)
18t (Me = β)

be detected. There was no indication of the formation of either isomer of **19**.

The stereochemical connectivity was further probed with diene **7**, which lacks a 4-substituent. Earlier studies[17] had indicated that with this parent diene, endo addition is the preferred process but that the selectivity is less pronounced than with dienes bearing a 4-substitutent. Of course, in order to ascertain the reaction topology with the parent diene, it is necessary to ensure survival of the anomeric methoxy group during reaction and workup.

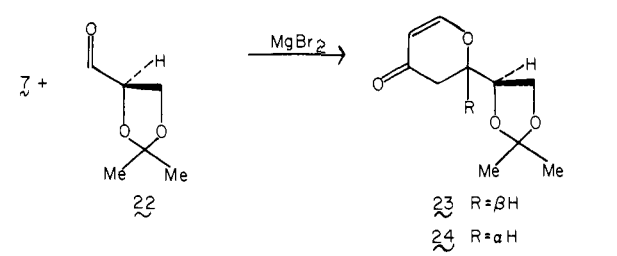
Again benzaldehyde was used as the reference heterodienophile. Reaction of **7** with benzaldehyde under magnesium bromide catalysis in THF followed by workup with triethylamine/methanol[17] afforded a 3.6:1 ratio of *endo*-**20c**/*exo*-**20t**. It was not ascertained whether, in the case at hand, this result is the consequence of some erosion of endo specificity or reflects Lewis acid catalyzed anomerization subsequent to cycloaddition. A dramatic change occurs in the cyclocondensation of aldehyde **2a** with diene **7**. Reaction was carried out as above with magnesium bromide in THF. In this case, compound **21t** is produced stereoselectively.

Finally, in this survey phase, it was of interest to test the behavior of aldehyde **22**. As noted above, in previously reported cyclocondensation processes, catalyzed by zinc chloride, aldehyde **22** reacted with diene **7** to afford dihydropyrone **23**. This result



20c (OMe = α)
20t (OMe = β)
20c/**20t** = 3.6:1

21c (OMe = α)
21t (OMe = β)
21c/**21t** = 1:18



22

23 R = βH
24 R = αH

is consistent with a Cram[2] (or Felkin)[5] formulation with no ap-

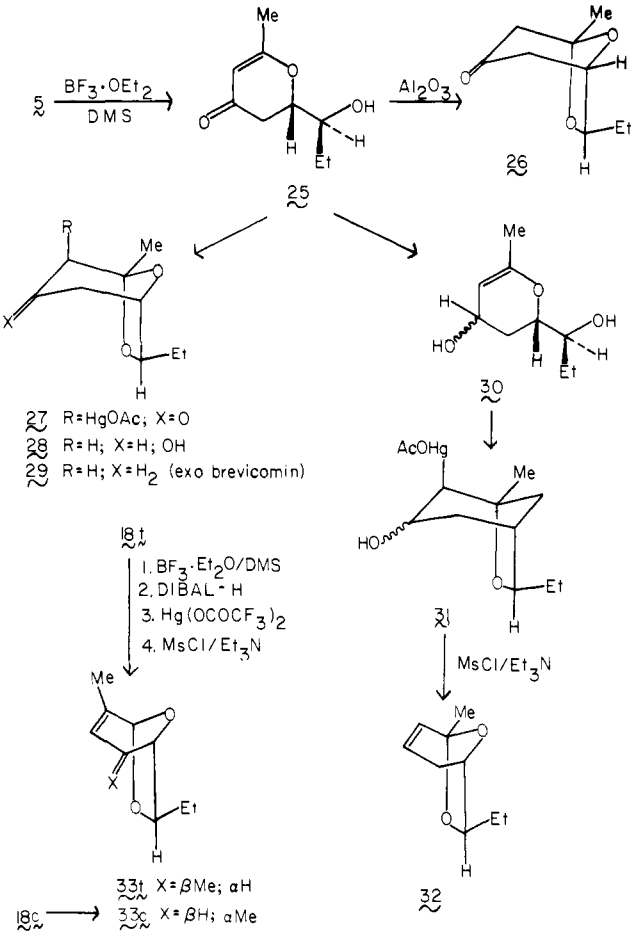
(17) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

parent indication of chelation control. It should also be noted that **22** had generally not exhibited chelation control with a variety of other organometallic nucleophiles.[18,21b,28e,g] Reaction of **22** with diene **7** in THF under magnesium bromide catalysis gave rise, as before,[15] to dihydropyrone **23**. In this reaction there was noted ca. 10% of epimer **24**. Thus, for reasons that are open to conjecture, aldehyde **22** had again demonstrated its resistance to reaction via a chelation-controlled conformer.

We now describe experiments that rigorously define the stereochemical assignments. In addition, these experiments serve to illustrate lines of application of this new capacity for stereocontrol. Reaction of compound **5** with boron trifluoride etherate/dimethyl sulfide[19] led to a high yield of debenzylated product **25**. Upon exposure to alumina,[16,20] **25** undergoes cyclization to **26**, though only in 56% yield. The conversion of **26** to *exo*-brevicomin **29**[21] was accomplished via Raney nickel desulfurization of its corresponding thioketal, though only in very low yield.

A more acceptable route to *exo*-brevicomin was achieved by treatment of **25** with mercuric acetate in THF. This intramolecular oxymercuration[16] gave rise to an α-mercurio ketone whose properties were not examined. Upon reduction with sodium borohydride in ethanol, the presumed **27** gave rise to alcohol epimers **28**. Reaction of **28** with bis(dimethylamino) phosphorochloridate followed by reduction of the resultant phosphoramide with lithium in ethylamine[22] gave *exo*-brevicomin **29** in 50% overall yield. This synthesis serves to define the stereochemistry of **5** and, therefore, that of **6**. With the structure of **5** and **6** established, it was possible to assign the stereochemistry in **8a**, **8b**, **9**, **11**, and **14** by the close similarity of their NMR spectra to either **5** or **6**.

A more significant target than *exo*-brevicomin is the recently identified mouse androgen **32**.[23,25] In contrast to the many



syntheses of *exo*-brevicomin, there had been only one report of the preparation of **32**.[24] The recent discovery of Carmack and Novotny,[23,25] wherein this compound was shown to play a central hormonal role in promoting libido in male mice, added a great deal of interest to its synthesis. Indeed, during the interim period, the Indiana workers described two syntheses of **32**.[23,25]

For the synthesis of this hormone, we sought a plan that would solve the issue of the double-bond placement in a regiodefined fashion. Fortunately, this objective could be accomplished in a pleasing way. Reduction of **25** with DIBAL-H afforded the somewhat unstable glycal **30**. Reaction of **30** with mercuric acetate in THF gave the α-mercuriocarbinol **31**. This compound undergoes very smooth retro-oxymercuration upon treatment with methanesulfonyl chloride.[26,27] There was thus obtained the volatile **32** in 50–70% yield from **30**.

With this chemistry developed, it was a relatively simple matter to carry out a parallel transformation starting with dihydropyrone **18t**. In this compound, the trans disposition of the C_2 and C_3

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(25) Wiesler, D. P.; Schwende, F. J.; Carmack, M.; Novotny, M. *J. Org. Chem.* **1984**, *49*, 882. We thank these authors for disclosure of their work prior to its publication.

(26) For a similar application in the synthesis of spiroketals, see ref 16. The use of organomercurials for the installation of functionality at fixed sites is a continuing interest in our laboratory. (a) Reference 16. (b) Danishefsky, S.; Taniyama, E. *Tetrahedron Lett.* **1983**, *24*, 15.

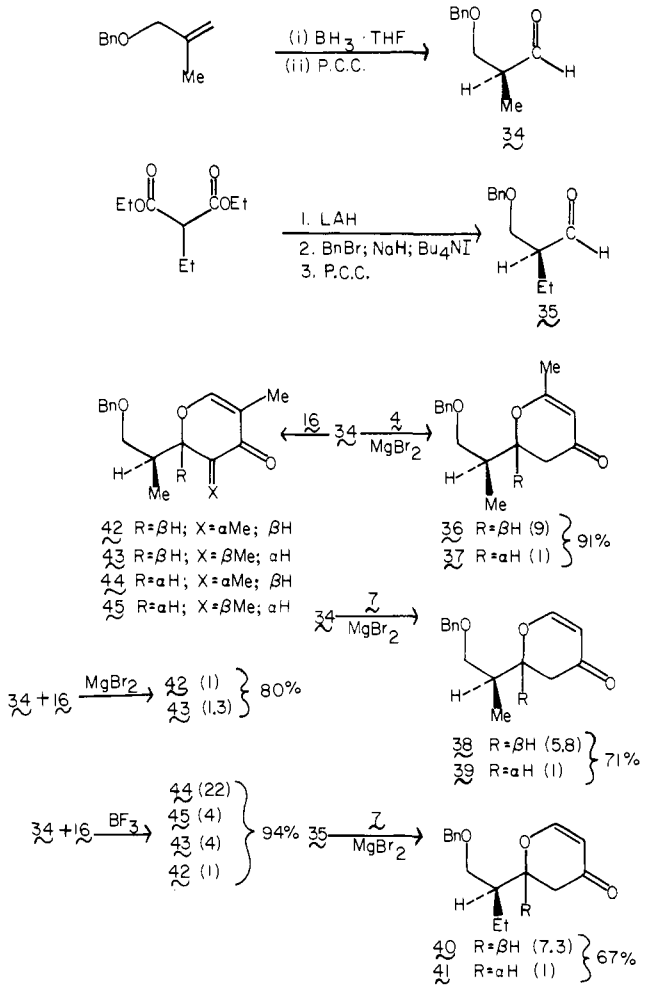
(27) For a related oxymercuration–demercuration, where the oxymercuration was carried out in the intermolecular mode, see: Remy, G.; Cottier, L.; Descotes, G. *Can. J. Chem.* **1983**, *61*, 434.

(28) Asymmetric syntheses: (a) See ref 9d–f. (b) Mukaiyama, T.; Sakito, Y.; Asami, M. *Chem. Lett.* **1979**, 705. (c) Mukaiyama, T., in ref 1c, Chapter 2, p 21. (d) Asami, M.; Mukaiyama, T. *Chem. Lett.* **1983**, 93. (e) Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021. (f) Columbo, L.; Gennari, C.; Scholastico, C.; Guanti, G.; Narisano, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1278. (g) Guanti, G.; Narisano, E.; Banfi, L.; Scholastico, C. *Tetrahedron Lett.* **1983**, *24*, 817. (h) Fuganti, C.; Grasselli, P.; Spreafico, F.; Zirotti, C. *J. Org. Chem.* **1984**, *49*, 543. (i) Ogura, K.; Fujita, M.; Inaba, T.; Takahashi, K.; Iida, H. *Tetrahedron Lett.* **1983**, *24*, 503. (j) See also ref 18k,l,o and reference therein. Protected lactaldehydes from lactic acid: (k) Reference 9i. (l) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. From carbohydrates: (m) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 999. Microbial reduction: (n) Takaishi, Y.; Yang, Y.; DiTullio, D.; Sih, C. J. *Ibid.* **1982**, *23*, 5489. For recent procedures producing optically active α-alkoxy acids, esters, amides, nitriles, or alcohols which may allow preparation of α-alkoxy aldehydes, see: (o) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704. (p) Whitesell, J. K.; Deya, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802. (q) Harada, K.; Munegumi, T. *Bull. Chem. Soc. Jpn.* **1983**, 2774. (r) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60. (s) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39. (t) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Ibid.* **1984**, *25*, 591 and reference therein.

substituents is clear from coupling constant (J = 12.7 Hz) of these protons. However, the stereochemistry at the side chain had only been surmised from the fact that the compound was produced via magnesium bromide catalysis. Rigorous evidence could now be obtained. Debenzylation[19] and reduction of **18t** with DIBAL-H gave a glycal which was not purified. Reaction of this glycal with mercuric trifluoroacetate in THF was followed by exposure of the resultant α-mercuriocarbinol to methanesulfonyl chloride in triethylamine. A 43% yield of **33t** (from **18t**) was thereby obtained. By an identical sequence the cis isomer **18c** was converted to **33c** in 65% yield. The NMR spectral properties (see Experimental Section) of **33c** and **33t** unambiguously define their stereochemistries and, hence, that of **18c** and **18t**.

Since aldehydes **2** are available in optically active form,[18l,28] and since this route appears to be quite general, it could well be of value in determining the effects of structural and stereochemical modifications on the biological profile in this interesting series.

β-Alkoxy Aldehydes. We next studied the magnesium bromide catalyzed cyclocondensation reactions of β-alkoxy aldehydes **34**[29,30] and **35** which were prepared as shown. Presumably because of



their vulnerability toward β-elimination, these compounds exhibited much greater lability than their α-oxygenated counterparts **2** and **3**. Therefore, it was necessary to accelerate the rate of reaction between these labile aldehydes and the silyloxy dienes to obtain reasonable yields. Toward this end, the solvent system was changed to 4:1 benzene/ether. Under these conditions, the reaction mechanism changed toward the Mukaiyama aldol type.[31] It was necessary to use trifluoroacetic acid (TFA) in methylene chloride to achieve complete cyclization. With dienes **4** and **7** (vide supra), good selectivities, in favor of the products of apparent chelation-controlled cyclocondensation, were obtained in the indicated yields. The basis for the stereochemical assignments involved cyclization to rigid structures whose configurations could be determined by NMR spectroscopy (vide infra).

Unfortunately, the solvent-induced change toward a Mukaiyama mechanism[11,31] had a damaging effect with respect to topological specificity. This is seen in the reaction of diene **16** with aldehyde **34**. Though diastereofacial selectivity is maintained in the apparent chelation mode, a ca. 1:1 ratio of cis (**42**):trans (**43**) isomers is isolated.

It was of interest to ascertain the effects of BF_3 catalysis. Hitherto, this catalyst had exhibited strong trans topological selectivity.[11] In its diastereofacial guidance, BF_3 had shown no proclivity for chelation control and had, in fact, exhibited strong apparent Cram–Felkin[2,5] preferences.[32] In practice, reaction of **34** and **16** with BF_3 in methylene chloride afforded an excellent yield (94%) of four products. The major product, **44** (66% yield), which was not previously encountered in the $MgBr_2$ reaction, was shown (vide infra) to contain the relative stereochemistry arising from apparent Cram–Felkin[2,5] facial selectivity coupled to an overall exo topology.

A small amount (12%) of the cis-Cram–Felkin product **45** was also obtained as was the previously seen trans-chelation-control product **43** (13%). Only a trace (3%) of the cis-chelation-control product **42** is produced. Looked at differently, the BF_3 process has afforded a 6 (**44** + **43**):1 (**42** + **45**) ratio of trans/cis products and a 5 (**44** + **45**):1 (**42** + **43**) ratio of Cram–Felkin[2,5]/anti Cram–Felkin products. Both specificities are typical of previous results with BF_3 catalysis.[11] However, the significant problem of attaining chelation-control facial specificity with cis topological specificity was, for the moment, unsolved.

Some very interesting recent results of Reetz and co-workers[9j-l] seemed to hold out promise for addressing the problem of concurrent chelation governed diastereofacial selectivity and topological control. The particularly crucial findings of Reetz were with titanium tetrachloride ($TiCl_4$) as the Lewis acid catalyst. High chelation control is evidenced by β-alkoxy aldehydes even when there is no chirality at the α-center (viz. **46**). This was an important advance since in the earlier Still methodology[8] guidance from the α-center was crucial for high induction. Furthermore, the nucleophile in the Reetz investigations[9j-l] could be a silyl enol ether (cf. **47**) wherein product **48**, which corresponds to erythro topology, was produced in high yield.

With the precedent from Reetz well in mind, we examined the $TiCl_4$-catalyzed reaction of aldehyde **34** with diene **16**. The resultant product was cyclized with TFA at room temperature in the usual way. It was interesting to find that the only dihydropyrone obtained was the previously encountered **42**, i.e., the product of apparent cis-chelation-control stereochemistry.

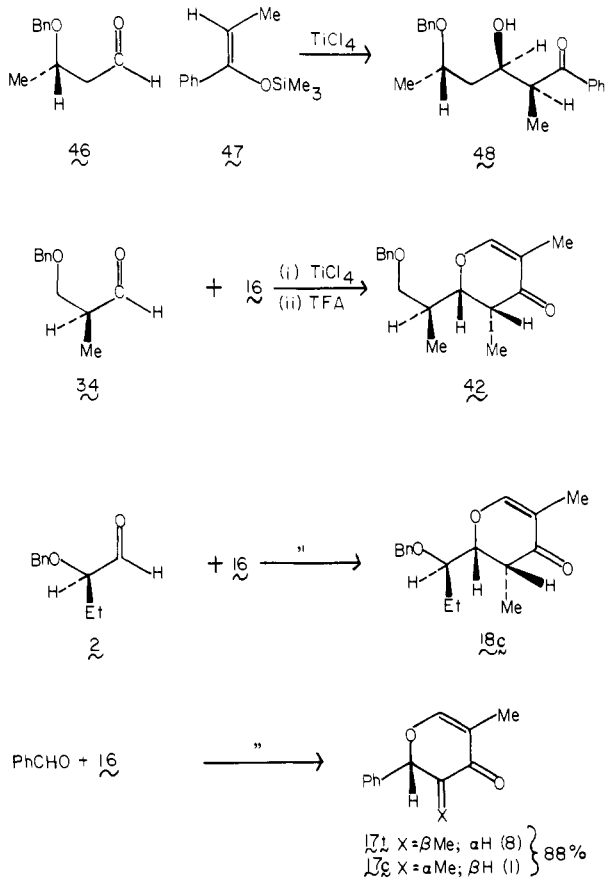
The feasibility of realizing chelation control during the synthesis of cis-2,3-dihydropyrones was tested with α-alkoxy aldehyde **2**. Indeed, reaction of this aldehyde with diene **16** under the influence of $TiCl_4$ followed by cyclization with TFA afforded a 93% yield of **18c**. Parenthetically we note that reaction of **16** with the nonchelatable benzaldehyde under catalysis by $TiCl_4$ followed by TFA cyclization affords an 8:1 ratio of the previously reported trans compound **17t**/cis product **17c**. Thus, the erythro specificity manifested by $TiCl_4$ seems to be limited to the important cases of chelatable aldehydes. In the absence of such chelation possibilities, strong trans selectivity with diene **16** pertains, much in the same fashion as BF_3.[11]

(29) For the preparation of racemic **34**, see: (a) Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357. (b) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 2643. (c) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347. (d) Paterson, I.; Patel, S. K.; Porter, J. R. *Tetrahedron Lett.* **1983**, *24*, 3395.

(30) For the preparation of (*S*)-**34**, see: (a) Reference 29c. (b) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377. For the preparation of (*R*)-**34**, see: (c) Meyers, A. I.; Hudspeth, J. P. *Ibid.* **1981**, *21*, 3925.

(31) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

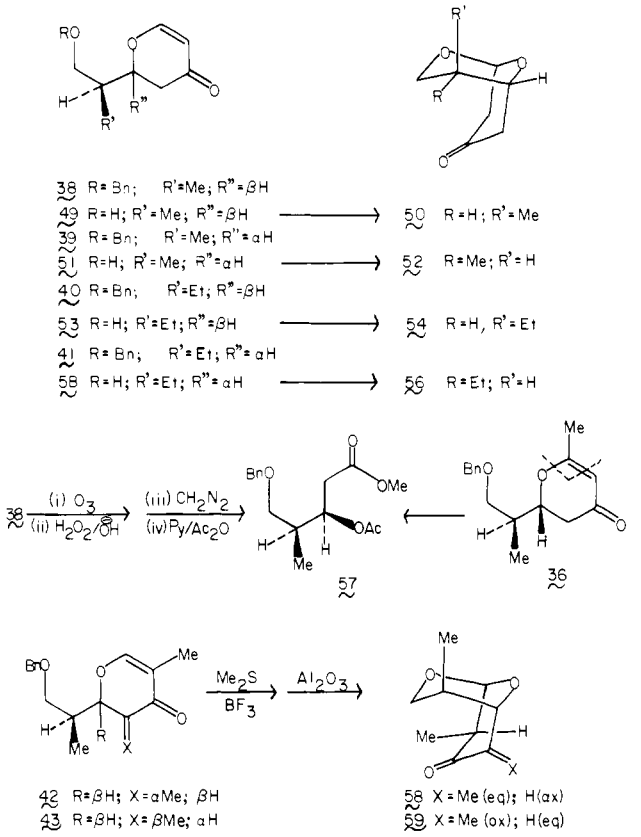
(32) (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (b) It has been observed by Reetz and co-workers that BF_3 catalysis favors the apparent chelation controlled product in additions to 3-(benzyloxy)butyraldehyde **46**. See ref 91.



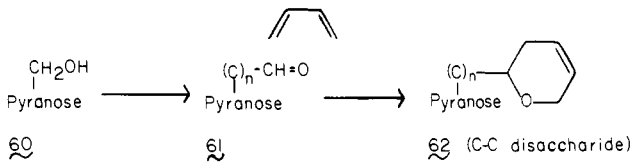
In summary, with chelatable aldehydes, a remarkable degree of differential selectivity is available by the simple expedient of changing the Lewis acid catalyst. With diene **16** and such aldehydes, under catalyst by magnesium bromide in THF, a pericyclic pathway pertains and trans-chelation-controlled products are produced with high selectivity. With BF_3–methylene chloride a Mukaiyama-like[31] mechanism pertains requiring treatment with TFA to complete the cyclization. Under these conditions, moderate trans selectivity in the nonchelated Cram–Felkin[2,5] sense pertains. With $TiCl_4$ and such aldehydes, a similar Mukaiyama-like[31] gross mechanism seems to pertain but a high erythro-chelation-control selectivity is observed. The fourth selectivity permutation, i.e., cis, classical Cram–Felkin control with chelatable aldehydes, is not yet available by any of the catalytic systems known to us.

As was the case with the products derived from the α-alkoxy aldehydes (cf. **5** and **18t**), stereochemical assignments of compounds **38–43** were possible through NMR analysis of their derived bridged ketals. For instance, debenzylation of compound **38** under the Fujita conditions[19] afforded hydroxy enone **49**, which was not characterized. Treatment of this compound with alumina[16] afforded bridged ketal **50** (43% yield). In a similar way, compounds **39**, **40**, **41**, **42**, and **43** were converted to the corresponding bridged ketals **52**, **54**, **56**, **58**, and **59**, respectively. Analysis of their high-field NMR spectra allowed for the determination of the stereochemistry of the secondary methyl (cf. **50** and **52**) and ethyl (cf. **54** and **56**) groups on the 1,3-dioxane rings. The alumina-induced cyclization of **42** and **43** appears to have occurred with apparent axial protonation, giving compounds **58** and **59**.[33]

Attempted cyclization of the debenzylated version of compound **36** was unsuccessful. Its structure was ascertained by its ozonolytic degradation[14] to compound **57**, which was also obtained by degradation of compound **38** of known (vide supra) configuration.



Synthesis of Carbon-Linked Disaccharides. The applicability of these findings to the synthesis of carbon-linked disaccharides was investigated. Given the significant biological role and activity of a variety of polysaccharides,[34] wherein the monosaccharides are linked through classical glycosidic bonds, there is a possibility that carbon-linked systems might perturb any of several enzymatically mediated processes. Furthermore, such systems could prove to be valuable intermediates in the total synthesis of complex monosaccharides such as hikosamine.[35] The general plan is envisioned in the schematic **60** → **61** → **62**. If the side chain,



$(C)_n$, contains asymmetry, problems could be encountered in achieving stereoselectivity in the synthesis of the required substrate, aldehyde **61**. However, the principal stereochemical issue to be addressed was the relationship of the newly created pyranose with that in its precursor.

Given the successes that were registered in achieving facial selectivity in the cyclocondensation process of α-alkoxy aldehydes via chelation-governed conformers, we turned to the use of a pyranose bearing an α-alkoxy aldehyde side chain. In this opening phase, we were primarily interested in probing the quality of the facial control in the cyclocondensation reaction and were less concerned with stereoselectivity in reaching the desired substrate.

The starting material was aldehyde **63** whose preparation from D-galactose had been well described.[36] There had also been

(33) In **58** the signals for the C_6 and C_8 methyls appear at δ 1.12 and 1.08. In **59** the now axial C_6 methyl has shifted downfield to δ 1.38–1.40 while the C_8 methyl remains at 1.08. Isomers corresponding to 8-epi-**58** and 8-epi-**59** were not seen. This leads us to believe that the intramolecular cyclization gave the stereochemistries indicated.

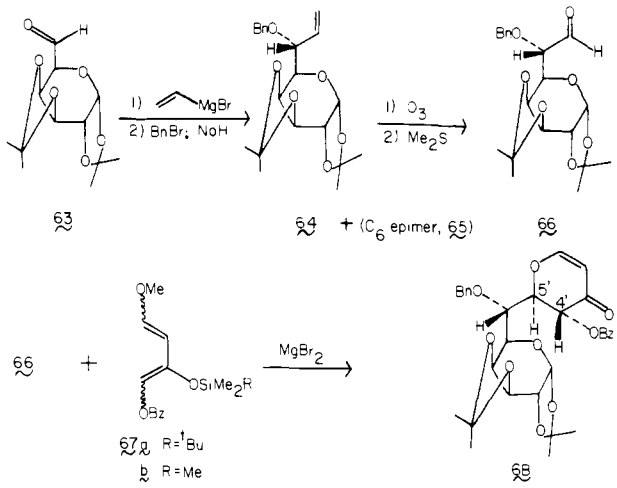
(34) (a) Kennedy, J. F.; White, C. A. "Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology"; Wiley: New York, 1983. (b) An approach to the synthesis of carbon-linked disaccharides has been described. Rouzand, D.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353.

(35) (a) Vuilhorgne, M.; Ennifar, S.; Das, B. C.; Paschal, J. W.; Nagarajan, R.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289. (b) The synthesis of a fully protected hikosamine derivative has been reported: Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4526.

considerable study of the consequences of reaction of the aldehyde function of **63** with organometallic reagents.[37,36b] The overall indication was that little in the way of stereoselectivity could be anticipated from such reactions.

Not surprisingly,[36b] reaction of **63** with vinylmagnesium bromide in THF at 0 °C gave a mixture of epimers, which was treated with sodium hydride–benzyl bromide. There was obtained a 52% yield of a mixture of benzyl ethers. Chromatographic separation afforded homogeneous **64** and **65** in a 2:1 ratio. At the time, the stereochemistry at C_6 in these epimers could not be rigorously assigned. This matter was clarified through subsequent reactions.

Ozonolysis of **64** in methylene chloride/methanol followed by reductive workup (dimethyl sulfide) afforded an 89% yield of aldehyde **66**. This compound reacted with diene mixture **67a**[38]



through catalysis by anhydrous magnesium bromide, under several conditions. In tetrahydrofuran a slow reaction leading to pyrone **68** was observed. After 5 days a 47% yield of a single pyrone was obtained. The stereochemistry of this compound need not be debated since an X-ray crystallographic determination[39,40] defined its structure to be that represented in **68**.

Most important for our concerns here, the cyclocondensation had occurred with apparent chelation control and had given a trans relationship at $C_{4'}$ and $C_{5'}$ within the newly formed hexose ring. We also learn from the crystallographic determination that the major product from the addition of vinyl magnesium bromide to aldehyde **63** is that derived from apparent Cram–Felkin[2,5] facial control.

The finding, with respect to the cyclocondensation reaction, is in keeping with the results of experiments described above. It was also discovered that the same pyrone, **68**, is the only one obtained upon reaction of aldehyde **66** with diene mixture **67b** with magnesium bromide in benzene. This is a much more rapid reaction and leads to the formation of an intermediate β-aldol. Heterocyclization was achieved in the usual way with trifluoroacetic acid. Under these conditions, **68** was the only pyrone obtained (79% yield). The high selectivity toward eventual formation of *trans*-dihydropyrone via high threo selectivity in the β-aldol forming reaction by magnesium bromide could not have been predicted in advance. It stands in contrast to the absence of selectivity in the formation of **42** and **43** from **34** and **16** under catalysis by magnesium bromide in benzene.

While the precise factors leading to this result are not completely understood, an interesting stereoselective route to carbon-linked disaccharides has been developed. This, and the synthesis of the mouse androgen **32** are but two examples of the kinds of applications that can be realized if facial selectivity and topological selectivity in the cyclocondensation reaction can be coordinated. Further possibilities in this regard are receiving close attention in our laboratory.

Many of these advances involve the highly functionalized diene system **67**. The preparation of such dienes and their application to problems in carbohydrate chemistry are described in the next paper of this series.[38]

Experimental Section

2-(Benzyloxy)butyraldehyde (2a). A solution of the ether **1a** (5.00 g, 26.3 mmol) in dichloromethane (250 mL) containing methanol (60 mL) and sodium bicarbonate (1.3 g) was cooled to −78 °C and ozone[18b] was passed through until the blue color persisted. Nitrogen was bubbled through to remove the excess ozone, and dimethyl sulfide (8 mL) was added. After warming to room temperature and stirring overnight, a small aliquot was removed and concentrated. Analysis by ^{1}H NMR showed a mixture of the desired product (minor) and another compound (major), which was assigned as the ozonide. The entire reaction mixture was filtered and concentrated. Water (17 mL) and acetic acid (6 mL) were added followed by zinc dust (4.0 g). After stirring vigorously for 1 h, the mixture was filtered and the residue was washed with ether. The filtrate was extracted with ether and the organic layer was washed with brine and saturated aqueous sodium bicarbonate, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on 100 g of silica gel (15% ether/pentane) to give 3.60 g (77%) of the title compound as a clear, colorless oil (R_f 0.4): IR ($CHCl_3$) 1725, 1482, 1445, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.68 (d, J = 2 Hz, 1 H), 7.38 (m, 5 H), 4.67, 4.55 (AB, J = 11 Hz, 2 H), 3.70 (dt, J = 2, 6 Hz, 1 H), 1.75 (quintet, J = 7 Hz, 2 H), 1.00 (t, J = 7 Hz, 3 H); MS, m/e (%) 178 (M^+, 0.4), 177 (2), 149 (6), 148 (2), 108 (3), 107 (21), 106 (2), 105 (7), 92 (15), 91 (100).

(2S*,1'S*)-2-[(1'-Benzyloxy)propyl]-6-methyl-2,3-dihydro-4H-pyran-4-one (5). Magnesium Bromide Catalysis. A solution of the aldehyde **2a** (3.00 g, 16.9 mmol) in THF (80 mL) was cooled to 0 °C and magnesium bromide[43] (5.7 mL of a 2.95 M solution in 10% benzene/ether, 16.9 mmol) was added over 2 min. After 10 min, the diene **4**[12] (9.10 g, 42.1 mmol) was added, and the solution was allowed to warm slowly to room temperature. After stirring 14 h, the solution was poured into saturated aqueous sodium bicarbonate and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resultant oil[44] was dissolved in 100 mL of dichloromethane and trifluoroacetic acid (4 mL) was added. After 3 h, the solution was washed with water, saturated aqueous sodium bicarbonate, and brine, then dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (40% ethyl acetate/hexane) gave 3.41 g (78%) of the title compound as a clear, colorless oil (R_f 0.40): IR ($CHCl_3$) 1655, 1605, 1442, 1397, 1335, 1235, 1100, 1027, 901 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.28 (m, 5 H), 5.33 (s, 1 H), 4.68, 4.63 (AB, J = 11.7 Hz, 2 H), 4.45 (ddd, J = 14.5, 4.8, 3.5 Hz, 1 H), 3.48 (td, J = 7.2, 4.8 Hz, 1 H), 2.67 (dd, J = 16.6, 14.5 Hz, 1 H), 2.27 (ddd, J = 16.6, 3.5, 1.0 Hz, 1 H), 2.02 (s, 3 H), 1.80–1.65 (m, 2 H), 1.01 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 192.30, 173.72, 137.64, 127.99 (2x), 127.56 (2x), 127.45, 104.53, 79.99, 79.45, 72.62, 36.70, 22.39, 20.55, 9.45; MS, m/e (%) 261 (M + 1, 3), 203 (0.6), 202 (3), 169 (3), 159 (1), 154 (6), 144 (7), 118 (6), 112 (9), 111 (93), 96 (7), 92 (15), 91 (100), 85 (11), 72 (12). Anal. ($C_{16}H_{20}O_3$) C, H. Examination of the crude and purified products by GLC[45] (retention time 10.1 min) and 500-MHz ^{1}H NMR showed no detectable amount of the alternative diastereomer **6**. In separate experiments, purified yields ranged from 76% to 80% using 4.22 and 4.38 mmol of the aldehyde **2a**, respectively.

(36) (a) Horton, D.; Nakadate, M.; Tronchet, J. M. J. *Carbohydr. Res.* **1968**, *7*, 56. (b) Howarth, G. B.; Lance, D. G.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1969**, *47*, 75. (c) Arrick, R. E.; Baker, D.; Horton, D. *Carbohydr. Res.* **1973**, *26*, 441.

(37) (a) Hems, R.; Horton, D.; Nakadate, M. *Carbohydr. Res.* **1972**, *25*, 205. (b) Hoppe, I.; Schöllkopf, U. *Ann. Chem.* **1983**, 372.

(38) For the preparation of diene **67**, see: Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.*, following paper in this issue.

(39) The following library of crystallographic programs was used: MULTAN 80, University of York, York, England, 1980. Structure Determination Package V18.0, Enraf-Nonius Corporation, Delift, Holland, 1981. ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN 1970.

(40) See supplementary material for the fractional coordinates, temperature parameters, bond distances, bond angles and an ORTEP drawing for **68**.

(41) Feldmann, L.; Fischer, H. O. L. *Arch. Biochem.* **1947**, *14*, 17.

(42) Kinoshita, M.; Aburaki, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279.

(43) Prepared from 1,2-dibromoethane and magnesium turnings in ether. Benzene (ca. 10%) was added to homogenize the two-phase mixture. The molarity was calculated by weighing the residual magnesium. The resultant solution could be stored for several months at room temperature.

(44) Crude ^{1}H NMR analysis indicated that aldol products were present.

(45) Column: 4 ft, 3% OV-17. Temperature program: 180 °C for 2 min, heat at 16 °C min to 210 °C. Flow rate: 30 mL/min.

(2*S*,1′*S)- and (2*R**,1′*S**)-2-[(1′-Benzyloxy)propyl]-6-methyl-2,3-dihydro-4*H*-pyran-4-one (5 and 6). Boron Trifluoride Catalysis.** Boron trifluoride etherate (80 mg, 0.56 mmol) was added to a solution of the aldehyde **2a** (0.100 g, 0.56 mmol) and diene **4** (0.24 g, 1.1 mmol) in 2.2 mL of dichloromethane at −78 °C. After 1 h, the solution was added to saturated aqueous sodium bicarbonate and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resultant oil[44] was dissolved in 3 mL of dichloromethane and trifluoroacetic acid (6 drops) was added. After 4 h, the solution was washed with water, saturated aqueous sodium bicarbonate, and brine, then dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography as above afforded 112 mg (77%) of the title compound as a clear, colorless oil. Examination of the crude and purified materials by 500-MHz ^1H NMR showed a 1:1.4 ratio of **5**/**6**. GLC analysis[45] showed similar ratios (retention times: **6**,(9.6 min); **5**,(10.1 min). ^1H NMR ($CDCl_3$, 500 MHz) (in addition to the signals reported above for **5**, the following signals were assigned to **6**) δ 7.38–7.28 (m, 5 H), 5.33 (s, 1 H), 4.70, 4.66 (AB, *J* = 11.3 Hz, 2 H), 4.41 (dt, *J* = 14.5, 3.8 Hz, 1 H), 3.68 (td, *J* = 7.5, 3.8 Hz, 1 H), 2.69 (dd, *J* = 17.0, 14.5 Hz, 1 H), 2.44 (ddd, *J* = 17.0, 3.8, 1.0 Hz, 1 H), 2.02 (s, 3 H), 1.70–1.58 (m, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H).

Zinc Chloride/THF Catalysis. The aldehyde **2a** (0.100 g, 0.562 mmol) in 0.5 mL of THF was added to a solution of freshly fused zinc chloride (76 mg, 0.56 mmol) in THF (3 mL). After 10 min the diene **4** (0.36 g, 1.7 mmol) was added. After 18 h at room temperature, the solution was added to water and extracted with ether (2x). The organic layers were washed with saturated aqueous sodium bicarbonate and brine, then dried ($MgSO_4$), and concentrated in vacuo. The resultant oil[44] was dissolved in 2 mL of CH_2Cl_2 and treated with 6 drops of trifluoroacetic acid for 2 h. Workup and flash chromatography as above gave 115 mg (79%) of the title compound as a clear, colorless oil. GLC[45] and 90-MHz ^1H NMR analysis as described above showed a 1:1.4 ratio of **5**/**6**.

Zinc Chloride/Benzene Catalysis. The aldehyde **2a** (50.0 mg, 0.28 mmol) was added to a mixture of freshly fused zinc chloride (38 mg, 28 mmol) in benzene (1.5 mL). After 5 min, the diene **4** (0.18 g, 0.84 mmol) was added. After 24 h at room temperature, the dark solution was worked up as above to give an oil[44] which was treated with 3 drops of trifluoroacetic acid in 2 mL of CH_2Cl_2 for 2 h. Workup and chromatography as above gave 38 mg (52%) of the title compound as a pale yellow oil. GLC[45] and 90-MHz ^1H NMR analysis as described above showed a 1.2:1 ratio of **5**/**6**.

Yb(fod)$_3$ Catalysis. A solution of the aldehyde **2a** (50 mg, 0.28 mmol), the diene **4** (120 mg, 0.56 mmol), and Yb(fod)$_3$ (15 mg, 0.014 mmol) in 0.5 mL of deuteriochloroform was allowed to stand at room temperature. After 3 h, no **2a** was observed by ^1H NMR. The solution was diluted with ether and stirred with 3 drops of trifluoroacetic acid for 5 min. Workup and chromatography as above gave 54 mg (74%) of the title compound as a clear, colorless oil. GLC[45] and 500-MHz ^1H NMR analysis as described above showed a 1.1:1 ratio of **5**/**6**.

(2*S,1′*S**)-2-[(1′-Benzyloxy)propyl]-2,3-dihydro-4*H*-pyran-4-one (8a).** A solution of the aldehyde **2a** (0.227 g, 1.27 mmol) in 5 mL of THF was cooled to 0 °C and magnesium bromide[43] (0.47 mL of a 2.7 M solution in 10% benzene/ether, 1.3 mmol) was added dropwise. The mixture was warmed to room temperature and the diene **7** (0.44 g, 2.6 mmol) was added. After 2.5 h, 50% aqueous acetic acid (2 mL) was added and the mixture was stirred 10 min and then extracted with ether (2x). The organic layer was washed with brine and saturated aqueous sodium bicarbonate, then dried, and concentrated in vacuo. Flash chromatography (40% ethyl acetate/hexane) afforded 0.272 g (87%) of the title compound as a clear, colorless oil (R_f 0.37). Analysis by 500-MHz ^1H NMR and 22.5-MHz ^{13}C NMR showed the presence of a single diastereomer, which was assigned the 2*S**,1′*S** configuration based on analogy with **5**. IR ($CDCl_3$) 1672, 1600, 1443, 1400, 1342, 1279, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.28 (m, 6 H), 5.40 (dd, *J* = 5.9, 1.2 Hz, 1 H), 4.66, 4.60 (AB, *J* = 11.5 Hz, 2 H), 4.48 (dt, *J* = 14.7, 3.5 Hz, 1 H), 3.48–3.45 (m, 1 H), 2.80 (dd, *J* = 16.7, 14.7 Hz, 1 H), 2.33 (ddd, *J* = 16.7, 3.5, 1.2 Hz, 1 H), 1.77–1.62 (m, 2 H), 0.99 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 192.12, 162.65, 137.56, 128.08 (3x), 127.54 (2x), 106.74, 79.91, 79.48, 72.55, 37.82, 22.27, 9.48; MS, *m*/*e* (%) 247 (18, M + 1), 246 (8, M$^+$), 225 (2), 223 (2), 217 (2), 211 (2), 207 (2), 205 (2), 203 (4), 201 (2), 200 (2), 199 (2), 190 (2), 189 (15), 188 (100), 155 (5), 149 (19), 144 (5), 97 (7), 91 (16).

(2*S,1′*S**)-2-[((1′-Methoxyethoxy)methoxy)propyl]-2,3-dihydro-4*H*-pyran-4-one (8b).** A solution of the aldehyde **2b** (80.9 mg, 0.460 mmol) in 2 mL of THF was cooled to 0 °C and magnesium bromide[43] (0.17 mL of a 2.7 M solution in 10% benzene/ether, 0.46 mmol) was added followed after 5 min with the diene **7** (0.16 g, 0.92 mmol). The ice bath was removed and the solution was stirred 2 h at room temperature, poured into water, and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant oil[46] was stirred with THF (2 mL), H_2O (1 mL), and acetic acid (0.5 mL) for 1 h. Water was added, and the mixture was extracted with ether (2x). The organic layers were washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (60% ethyl acetate/hexane) gave 67 mg (60%) of the title compound as a clear, colorless oil (R_f 0.32). Examination of the crude and purified products by GLC[45] (retention time 5.6 min) and ^1H NMR analysis showed a single diastereomer, which was assigned the 2*S**,1′*S** configuration on the basis of analogy with **5**. IR ($CHCl_3$) 1672, 1600, 1452, 1401, 1350, 1279, 1210, 1103, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.37 (d, *J* = 5.8 Hz, 1 H), 5.41 (d, *J* = 5.8 Hz, 1 H), 4.83, 4.79 (AB, *J* = 6.9 Hz, 2 H), 5.53 (dt, *J* = 14.7, 3.5 Hz, 1 H), 3.77–3.49 (m, 5 H), 3.38 (s, 3 H), 2.75 (dd, *J* = 16.5, 14.7 Hz, 1 H), 2.38 (dd, *J* = 16.5, 3.5 Hz, 1 H), 1.79–1.61 (m, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H); MS, *m*/*e* (%) 245 (0.2, M + 1), 244 (0.1, M$^+$), 186 (6), 167 (1), 113 (11), 110 (7), 97 (37), 89 (100), 71 (9), 59 (43).

(2*S,1′*S**)- and (2*R**,1′*S**)-2-[(1′-Benzyloxy)ethyl]-2,3-dihydro-4*H*-pyran-4-one (9 and 11).** A solution of the aldehyde **3** (0.180 g, 1.10 mmol), the diene **7** (0.283 g, 1.65 mmol), and Yb(fod)$_3$ (35 mg, 0.033 mmol) in 1 mL of deuteriochloroform was allowed to stand at room temperature for 12 h. The solution was then stirred 1 h with 50% aqueous acetic acid (1 mL) and ether (1 mL), poured into water, and extracted with ether. The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (43% ethyl acetate/hexane) gave 185.3 mg (73%) of the title compounds as a clear, colorless oil (R_f 0.40). Integration of several regions of the 500-MHz ^1H NMR spectrum showed a 1.56:1 ratio of **9**/**11**. Assignment of the stereochemistry was based on analogy with **5** and **6**. Spectral data assigned to the minor diastereomer **11**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.27 (m, 6 H), 5.40 (dd, *J* = 6, 1.0 Hz, 1 H), 4.66, 4.58 (AB, *J* = 11.8 Hz, 2 H), 4.35 (ddd, *J* = 14.3, 4.4, 3.4 Hz, 1 H), 3.82 (dq, *J* = 6.4, 4.4 Hz, 1 H), 2.71 (dd, *J* = 16.9, 14.3 Hz, 1 H), 2.53 (ddd, *J* = 16.9, 3.4, 1.0 Hz, 1 H), 1.26 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 191.91, 162.33, 137.56, 127.87 (2x), 127.27 (2x), 127.16, 106.57, 81.54, 74.44, 70.87, 36.63, 15.12.

Spectral data for the major diastereomer **9** are reported below.

(2*S,1′*S**)-2-[(1′-Benzyloxy)ethyl]-2,3-dihydro-4*H*-pyran-4-one (9).** A solution of the aldehyde **3** (0.210 g, 1.28 mmol) in THF (5 mL) was cooled to 0 °C and magnesium bromide[43] (0.47 mL of a 2.7 M solution in 10% benzene/ether, 1.28 mmol) was added dropwise. After 10 min, the diene **7** (0.44 g, 2.6 mmol) was added, and the mixture was stirred 1 h at 0 °C and 2 h at room temperature. Water (1 mL) and acetic acid (0.5 mL) were added, and the mixture was stirred 15 min then extracted with ether (2x). The organic layer was washed with saturated aqueous sodium bicarbonate and brine, then dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (35% ethyl acetate/hexane) gave 255 mg (86%) of the title compound as a clear, colorless oil (R_f 0.35). Integration of several areas of the 500-MHz ^1H NMR spectrum showed a >40:1 ratio of **9**/**11**. Assignment of the stereochemistry was based on analogy with **5** and **6**. Spectral data for **9**: IR ($CHCl_3$) 1668, 1599, 1400, 1278, 1210, 1085, 1035, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.27 (m, 6 H), 5.40 (dd, *J* = 5.9, 1.2 Hz, 1 H), 4.69, 4.54 (AB, *J* = 11.8 Hz, 2 H), 4.38 (ddd, *J* = 14.6, 4.4, 3.4 Hz, 1 H), 3.71 (dq, *J* = 6.4, 4.4 Hz, 1 H), 2.77 (dd, *J* = 16.8, 14.6 Hz, 1 H), 2.40 (ddd, *J* = 16.8, 3.4, 1.2 Hz, 1 H), 1.30 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 191.85, 162.43, 137.46, 127.92, 127.27 (4x), 106.46, 80.84, 73.79, 70.87, 37.38, 14.57; MS, *m*/*e* (%) 232 (0.2, M$^+$), 189 (2), 188 (17), 144 (10), 141 (6), 135 (12), 126 (7), 118 (7), 97 (63), 92 (23), 91 (100), 71 (7). Anal. ($C_{14}H_{16}O_3$) C, H. See above for spectral data of the minor diastereomer **11**.

(2*S,1′*S**,6*R**)-2-[(1′-Benzyloxy)propyl]-4-[(triethylsilyl)oxy]-6-[4′-((*tert*-butyldimethylsilyl)oxy)butyl]-2,3-dihydro-6*H*-pyran (13).** Magnesium bromide[43] (0.12 mL of a 2.7 M solution in 10% ether/benzene, 0.321 mmol) was added to a solution of the aldehyde **2a** (57.1 mg, 0.321 mmol) in 1.5 mL of THF. After 5 min, the diene **12**[16] (0.119 g, 0.321 mmol) was added. After 36 h, triethylamine (0.05 mL) was added dropwise, and the mixture was passed through a short column of silica gel (deactivated with 1% triethylamine/ether) using ether as the eluant. Concentration of the filtrate in vacuo gave an oil, which was purified by flash chromatography (5% ethyl acetate/hexane) to give 92 mg (52%) of the title compound as a clear, colorless oil as a single isomer by 90-MHz ^1H NMR (R_f 0.28): IR ($CDCl_3$) 1660, 1447, 1400, 1372, 1348, 1245, 1193, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.37–7.22 (m, 5 H), 4.86–4.76 (m, 1 H), 4.63 (s, 2 H), 4.34–4.08 (m, 1 H), 3.92–3.64 (m, 1 H), 3.49 (t, *J* = 6 Hz, 2 H), 3.39–3.14 (m, 1 H), 2.34–0.49 (m, 28 H), 0.88 (s, 9 H), 0.05 (s, 6 H); MS, *m*/*e* (%) no M$^+$, 491 (1, M−*t*-Bu), 459 (5), 458 (13), 457 (36), 400 (9), 399 (25), 362

(46) Crude ^1H NMR was consistent with a cyclic enolsilane.

(27), 361 (100), 313 (15), 267 (37), 253 (23), 215 (19).

(2S*,1'S*)-2-[(1'-Benzyloxy)propyl]-6-[4'-((*tert*-butyldimethylsilyl)oxy)butyl]-2,3-dihydro-4*H*-pyran-4-one (14). Palladium acetate (20.9 mg, 0.093 mmol) was added to a solution of **13** (51.0 mg, 0.093 mmol) in 0.7 mL of acetonitrile. After 24 h, the mixture was filtered through Florisil, washing with ether. Evaporation and flash chromatography (23% ethyl acetate/hexane, R_f 0.30) gave 28.0 mg (70%) of the title compound as a clear, colorless oil as a single diastereomer by 500-MHz ^{1}H NMR. Assignment of stereochemistry was based on analogy with **5**. IR ($CDCl_3$) 1650, 1595, 1444, 1386, 1332, 1237, 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.28 (m, 5 H), 5.33 (s, 1 H), 4.66, 4.62 (AB, J = 11.5 Hz, 2 H), 4.42 (ddd, J = 14.7, 4.4, 3.5 Hz, 1 H), 3.61 (t, J = 6.2 Hz, 2 H), 3.47 (m, 1 H), 2.66 (dd, J = 16.6, 14.7 Hz, 1 H), 2.35–2.23 (m, 3 H), 1.75–1.52 (m, 6 H), 0.99 (t, J = 7.5 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 193.04, 177.44, 138.00, 128.41 (2x), 127.92 (2x), 127.81, 104.24, 80.46, 79.86, 72.98, 62.53, 37.33, 34.46, 32.08, 26.69, 25.90, 22.76, 18.31, 9.91 (3x), −5.31 (2x); MS, m/e (%) no M$^+$, 417 (1, M − CH_3), 376 (13), 375 (37), 317 (1), 283 (12), 197 (14), 157 (10), 91 (100).

(2S*,3S*)- and (2S*,3R*)-2-Phenyl-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one (17c and 17t). Magnesium bromide[43] (0.56 mL of a 2.7 M solution in benzene/ether, 1.52 mmol) was added to a solution of benzaldehyde (0.161 g, 1.52 mmol) in 2 mL of THF. After 5 min, the diene **16** (0.152 g, 0.76 mmol) was added and the solution was stirred overnight then stirred 1 h with 50% aqeuous acetic acid (1 mL). The mixture was poured into water and extracted with ether (2x). The organic phase was washed with saturated aqueous sodium bicarbonate, then dried ($MgSO_4$), and concentrated in vacuo. The resultant oil was purified by flash chromatography (10% ethyl acetate/hexane) to give 2.0 mg (1.3%) of **17t** (R_f 0.30) and 75.0 mg (49%) of **17c** (R_f 0.25). These materials were identical with authentic samples previously prepared in these laboratories[11] by ^{1}H NMR, IR, and MS.

(2S*,1'S*,3R*)-2-[(1'-Benzyloxy)propyl]-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one (18t). Magnesium bromide[43] (0.26 mL of a 2.95 M solution in 10% benzene/ether, 0.76 mmol) was added to a solution of the aldehyde **2a** (135.2 mg, 0.760 mmol) in 2 mL of THF. After 5 min, the diene **16** (0.15 g, 0.76 mmol) was added, and the mixture was stirred 19 h at room temperature. Ether (1 mL) and 50% aqeuous acetic acid (1 mL) were added, and the mixture was stirred 0.5 h, then added to water, and extracted with ether (2x). The organic phase was washed with saturated aqueous sodium bicarbonate and brine, then dried ($MgSO_4$), and concentrated in vacuo. No **18c** could be detected by ^{1}H NMR or TLC. Flash chromatography (15% ethyl acetate/hexane, R_f 0.35) gave 0.141 g (68%) of the title compound as a clear, pale yellow oil: IR ($CDCl_3$) 1661, 1636, 1455, 1380, 1348, 1309, 1270, 1180, 1158, 1103, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.26 (m, 6 H), 4.71, 4.48 (AB, J = 11.5 Hz, 2 H), 4.02 (dd, J = 12.7, 2.2 Hz, 1 H), 3.47 (ddd, J = 8.3, 5.8, 2.2 Hz, 1 H), 2.83 (dq, J = 12.7, 6.8 Hz, 1 H), 1.98–1.75 (m, 2 H), 1.65 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 195.54, 158.21, 137.73, 128.19 (2x), 127.81 (2x), 127.65, 112.32, 83.01, 78.29, 71.63, 39.88, 21.73, 10.46, 9.81 (2x); MS, m/e (%) 274 (M+, 0.1), 201 (10), 149 (13), 132 (5), 131 (3), 128 (8), 125 (100), 97 (6), 92 (12), 91 (85), 85 (5). Anal. ($C_{17}H_{22}O_3$) C, H.

(2S*,6R*)- and (2S*,6S*)-2-Phenyl-6-methoxy-2,3,5,6-tetrahydro-4*H*-pyran-4-one (20c and 20t). Magnesium bromide[43] (0.39 mL of a 2.7 M solution in 10% benzene/ether, 1.04 mmol) was added to a solution of benzaldehyde (0.110 g, 1.04 mmol) in THF (6 mL). After 10 min, the diene **7** (0.36 g, 2.1 mmol) was added and the mixture was stirred overnight at room temperature, then poured into water, and extracted with ether (2x). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant oil was dissolved in 0.5 mL of triethylamine and treated with 0.5 mL of methanol for 1 h. The solution was added to water and extracted with ether (2x). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (20% ethyl acetate/hexane, R_f 0.30) gave 140 mg (65%) of a 3.6:1 mixture of **20c**/**20t** as judged by crude and purified 90-MHz ^{1}H NMR spectra. These materials were identical with authentic samples previously prepared in these laboratories[17] by ^{1}H NMR, IR, and MS.

(2S*,1'S*,6R*)- and (2S*,1'S*,6S*)-2-[(1'-Benzyloxy)propyl]-6-methoxy-2,3,5,6-tetrahydro-4*H*-pyran-4-one (21c and 21t). Magnesium bromide[43] (0.45 mL of a 2.7 M solution in 10% benzene/ether, 1.2 mmol) was added to a solution of the aldehyde **2a** (0.216 g, 1.21 mmol) in 5 mL of THF. After 5 min, the diene **7** (0.42 g, 2.4 mmol) was added, and the mixture was stirred 5 h. Triethylamine (0.5 mL) and methanol (1 mL) were added, and the solution was stirred 3 h, added to water, and extracted with ether (2x). The organic phase was washed with saturated aqueous ammonium chloride and brine, then dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (23% ethyl acetate/hexane, R_f 0.30) gave 0.270 g (80%) of the title compounds as a clear, colorless oil. Examination of the 500-MHz ^{1}H NMR spectrum showed a 1:18 ratio of **21c**/**21t**: IR ($CHCl_3$) 1716, 1441, 1395, 1339, 1280, 1210, 1108, 1060, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.28 (m, 5 H), 5.16 (d, J = 4.4 Hz, 1 H), 4.67, 4.60 (AB, J = 11.6 Hz, 2 H), 4.15 (dt, J = 11.6, 3.2 Hz, 1 H), 3.74* (ddd, J = 11.9, 4.6, 2.5 Hz, 1 H), 3.54* (s, 3 H), 3.36 (s, 3 H), 3.30 (td, J = 6.5, 3.8 Hz, 1 H), 2.64 (dd, J = 14.9, 4.4 Hz, 1 H), 2.61 (dd, J = 14.5, 11.6 Hz, 1 H), 2.46 (dt, J = 14.9, 2.0 Hz, 1 H), 2.24 (dt, J = 14.5, 2.0 Hz, 1 H), 1.77–1.66 (m, 2 H), 0.99 (t, J = 7.5 Hz, 3 H); MS, m/e (%) no M$^+$, 260 (5), 248 (2), 247 (9), 246 (20), 172 (25), 149 (30), 141 (13), 129 (55), 92 (12), 91 (100), 85 (68), 71 (12). (*Indicates signals assigned to the minor diastereomer **21c**.) Assignment of stereochemistry rests on analogy with compounds **5**, **20c**, and **20t**.

(2S,4'R)- and (2R,4'R)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-4*H*-pyran-4-one (23 and 24). Magnesium bromide[43] (1.31 mL of a 2.7 M solution in 10% benzene/ether, 3.54 mmol) was added dropwise to a 0 °C solution of the aldehyde **22** (0.460 g, 3.54 mmol) in THF (7 mL). After 10 min, the diene **7** (0.91 g, 5.3 mmol) was added and the mixture was warmed to room temperature over 2 h then stirred 2 h more. After stirring with 50% aqueous acetic acid (2 mL) for 0.5 h, the mixture was diluted with ether and washed with water, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (45% ethyl acetate/hexane) gave 0.256 g (36.6%) of the known[15] **23** (R_f 0.28) and 21.6 mg (3.08%) of **24** (R_f 0.16). Compound **23** was identical with an authentic sample previously prepared in these laboratories[15] (^{1}H NMR, IR, TLC). Spectral data for the minor diastereomer **24**: IR ($CHCl_3$) 1668, 1599, 1397, 1375, 1362, 1274, 1210, 1165, 1065, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, J = 6.0 Hz, 1 H), 5.43 (dd, J = 6.0, 1.1 Hz, 1 H), 4.42 (ddd, J = 14.4, 5.4, 3.4 Hz, 1 H), 4.30 (td, J = 6.5, 5.4 Hz, 1 H), 4.10 (dd, J = 8.5, 6.8 Hz, 1 H), 3.89 (dd, J = 8.5, 6.4 Hz, 1 H), 2.69 (dd, J = 16.7, 14.4 Hz, 1 H), 2.37 (ddd, J = 16.7, 3.4, 1.1 Hz, 1 H), 1.46 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 191.17, 162.58, 110.37, 107.34, 79.07, 76.02, 64.97, 37.89, 26.24, 25.21; MS, m/e (%) 199 (0.4, M + 1), 198 (2, M$^+$), 184 (3), 183 (29), 141 (9), 123 (13), 102 (5), 101 (100), 99 (5), 97 (9), 95 (8), 83 (12), 81 (35), 73 (19), 72 (19), 71 (30).

(2S*,1'S*)-2-[(1'-Hydroxy)propyl]-6-methyl-2,3-dihydro-4*H*-pyran-4-one (25). Boron trifluoride etherate (1.1 mL, 1.3 g, 8.9 mmol) was added dropwise to a solution of the dihydropyrone **5** (0.463 g, 1.78 mmol) in dichloromethane (3.5 mL) and dimethyl sulfide (3.5 mL) at room temperature. After heating at reflux for 24 h, the solution was added to water and extracted with dichloromethane (3x). The organic phase was washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (60% ethyl acetate/hexane, R_f 0.3) gave 0.26 g (86%) of the title compound as a clear, colorless oil: IR ($CHCl_3$) 1658, 1609, 1398, 1329, 1220, 901 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.32 (s, 1 H), 4.26 (dt, J = 14, 4 Hz, 1 H), 3.60 (m, 1 H), 2.65 (dd, J = 16.5, 14 Hz, 1 H), 2.5 (br s, 1 H, exchange), 2.25 (dd, J = 16.5, 4 Hz, 1 H), 2.03 (s, 3 H), 1.8–1.5 (m, 2 H), 1.03 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 192.68, 173.83, 104.64, 81.02, 73.27, 37.08, 25.32, 20.72, 9.61; MS, m/e (%) 171 (2, M + 1), 170 (11, M$^+$), 154 (1), 153 (2), 152 (16), 113 (12), 112 (60), 111 (66), 97 (18), 86 (7), 85 (100), 57 (17). Anal. ($C_9H_{14}O_3$) C, H.

***exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-3-one (26).** A solution of the alcohol **25** (0.100 g, 0.589 mmol) in dichloromethane (5 mL) was stirred with 1.0 g of Woelm neutral alumina (activity grade 1) for 24 h, then filtered, and concentrated (80 mmHg, 0 °C). Flash chromatography (30% ether/pentane, R_f 0.4) and careful concentration gave 56.0 mg (56%) of the title compound as volatile colorless needles, mp 24.5–25.0 °C. GLC[47] (retention time 6.5 min) and 270-MHz ^{1}H NMR showed the presence of only one isomer: IR ($CDCl_3$) 1704, 1371, 1318, 1230, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.48 (d, J = 5.2 Hz, 1 H), 3.82 (t, J = 6.5 Hz, 1 H), 2.72 (dd, J = 16.5, 5.2 Hz, 1 H), 2.62, 2.53 (AB, J = 16.4 Hz, 2 H), 2.44 (dt, J = 16.5, 1.3 Hz, 1 H), 1.61–1.48 (m, 2 H), 1.57 (s, 3 H), 0.92 (t, J = 7.4 Hz, 3 H); MS, m/e (%) no M$^+$, 149 (1), 144 (1), 143 (2), 142 (1), 141 (2), 110 (49), 95 (14), 81 (100), 74 (33), 71 (13), 68 (26), 67 (11), 59 (65), 57 (11), 45 (25), 43 (53), 41 (11).

***exo*-7-Ethyl-3-hydroxy-5-methyl-6,8-dioxabicyclo[3.2.1]octane (28).** Mercuric acetate (61.2 mg, 0.192 mmol) was added to a solution of the alcohol **25** (27.2 mg, 0.160 mmol) in THF (2 mL). After 1 h, the mixture was cooled to 0 °C and sodium borohydride (0.6 mL of a 1 M solution in ethanol) was added dropwise. After 10 min at room temperature, the mixture was added to saturated aqueous ammonium chloride and extracted with ether (2x). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give 28.0 mg (100%) of the title compound as a clear, colorless oil, which was used in the preparation of

(47) Column: 4 ft, 3% OV-17, 100 °C, 30 mL/min flow rate.

29 without further purification. In a separate experiment, the alcohol **25** (57.2 mg, 0.336 mmol) was treated with mercuric acetate (129 mg, 0.404 mmol) in THF (3 mL) followed by sodium borohydride (1.7 mL of a 1 M solution in ethanol) to give a crude oil which was purified by flash chromatography (50% ethyl acetate/hexane). The two epimeric alcohols **28** were cleanly separated to give 19.1 mg (33%) of the *endo*-alcohol (R_f 0.40) and 28.9 mg (50.0%) of the *exo*-alcohol (R_f 0.30). Spectral data for the minor (endo) alcohol: IR ($CDCl_3$) 3525, 1440, 1378, 1208, 1186, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.28 (t, J = 6.8 Hz, 1 H), 4.20 (d, J = 4 Hz, 1 H), 4.05 (t, J = 4.4 Hz, 1 H), 3.05 (br s, 1 H, exchange), 2.07 (dt, J = 14.6, 4.4 Hz, 1 H), 1.99 (dd, J = 14.6, 4.8 Hz, 1 H), 1.90 (d, J = 14.6 Hz, 1 H), 1.87 (d, J = 14.6 Hz, 1 H), 1.6–1.45 (m, 2 H), 1.47 (s, 3 H), 0.92 (t, J = 7.5 Hz, 1 H); MS, *m/e* (%) no M^+, 145 (7), 125 (27), 111 (15), 105 (13), 98 (10), 97 (59), 92 (16), 91 (100), 85 (19), 83 (15), 69 (14). Spectral data for the major (exo) alcohol: IR ($CDCl_3$) 3580, 1438, 1378, 1211, 1188, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.23 (t, J = 2.5 Hz, 1 H), 4.22–4.16 (m, 1 H), 3.79 (t, J = 6.5 Hz, 1 H), 3.20 (br s, 1 H, exchange 2.21 (dd, J = 12.6, 6.2 Hz, 1 H), 2.03 (ddt, J = 12.9, 6.2, 1.4 Hz, 1 H), 1.93–2.40 (m, 4 H), 1.47 (s, 3 H), 0.90 (t, J = 7.5 Hz, 3 H); MS, *m/e* (%) no M^+, 155 (5), 149 (2), 128 (35), 114 (13), 112 (38), 95 (12), 86 (100), 85 (34), 83 (22), 71 (17), 69 (22), 68 (36), 58 (12), 57 (23), 43 (58).

***exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (Brevicomin) (29).** A solution of the crude alcohol **28** (see above, 28.0 mg, 0.160 mmol) in THF (0.7 mL) and TMEDA (0.18 mL) was cooled to 0 °C and treated with *n*-butyllithium (0.077 mL of a 2.3 M solution in hexane, 0.18 mmol). After 10 min, bis(dimethylamino) phosphorochloridate (0.14 g, 0.80 mmol) was added and the solution was stirred overnight at room temperature. Ether and saturated aqueous sodium carbonate were added. After 0.5 h, the mixture was extracted with ethyl acetate. The organic phase was dried (K_2CO_3), concentrated, and subjected to vacuum (0.2 mmHg) for 0.5 h to provide a clear, pale yellow oil. The crude product was mixed with THF (0.8 mL) and *tert*-butyl alcohol (0.047 g, 0.64 mmol), and the resultant solution was added over 40 min to ethylamine (2.5 mL) containing lithium wire (11 mg, 1.6 mmol) at 0 °C. After an additional 10 min, saturated aqueous ammonium chloride was added until the blue color had dissipated. Water was added, and the mixture was extracted with pentane (3x). The organic phase was washed with saturated aqueous cupric sulfate and dried. The solvent was distilled off through a 6-cm Vigreux column, and the residue was purified by flash chromatography (15% ether/pentane, R_f 0.35). The eluant was concentrated carefully on a rotary evaporator at 0 °C and 130 mmHg to give 12.5 mg (50% overall from **25**) of the title compound as a clear, colorless oil whose spectral data were consistent with those reported in the literature:[48] IR (CCl_4) 2943, 1462, 1385, 1345, 1339, 1247, 1239, 1196, 1183, 1175, 1137, 1107, 1085, 1033, 1016, 1005, 986, 967, 877, 856 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 3.95 (s, 1 H), 3.75 (t, J = 6.5 Hz, 1 H), 1.9–1.1 (m, 8 H), 1.30 (s, 3 H), 0.87 (t, J = 7 Hz, 3 H); MS, *m/e* (%) 156 (M^+, 3), 127 (2), 115 (2), 114 (22), 99 (5), 98 (11), 86 (15), 85 (33), 83 (14), 81 (20), 68 (13), 67 (12), 57 (14), 43 (100).

***exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (32).** Diisobutylaluminum hydride (2.7 mL of a 1.0 M solution in toluene, 2.7 mmol) was added dropwise to a solution of the dihydropyrone **25** (0.182 g, 1.07 mmol) in benzene (9 mL) at ca. 5 °C. After warming to room temperature over 1 h, the solution was stirred 2 h then recooled to ca. 5 °C. Ammonium chloride (150 mg), water (0.1 mL), and methanol (0.1 mL) were added, and the mixture was stirred vigorously for 30 min. Dichloromethane, magnesium sulfate, and Celite were added, and the mixture was filtered while washing with dichloromethane. The filtrate was concentrated in vacuo to give 180 mg (98%) of the crude diol **30** as a clear, colorless oil. In previous runs, it was found that this material was chromatographically unstable, hence the crude product was used immediately in the next step. Mercuric acetate (0.40 g, 1.26 mmol) was added to a solution of **30** (180 mg, 1.05 mmol) in 4 mL of THF. After 12 h, the solution was concentrated in vacuo to give a colorless solid, which was suspended in 5 mL of dichloromethane and cooled to 0 °C. Triethylamine (1.1 g, 11 mmol) was added, followed by the dropwise addition of methanesulfonyl chloride (0.60 g, 5.3 mmol). After stirring overnight at room temperature, water was added, and the mixture was filtered through Celite while washing with dichloromethane. The organic phase was washed with 5% aqueous hydrochloric acid, water, and saturated aqueous sodium bicarbonate then dried ($MgSO_4$). The solvent was removed by distillation through a 6-cm Vigreux column, and the residue was flash chromatographed (10% ether/pentane, R_f 0.25) to give 83 mg (51%) of the title compound **32** after concentration on a rotary evaporator at 0 °C and 130 mmHg. In a separate experiment 88 mg of the diol **30** (0.51 mmol) gave 56.6 mg (72%) of the title compound after a similar sequence. Spectral data were in excellent agreement with those previously reported[23-25] (IR, 90-MHz ^1H NMR, MS): IR (CCl_4) 2940 (s), 1637 (w), 1456 (m), 1450 (m), 1424 (m), 1393 (s), 1376 (s), 1253 (s), 1250 (s), 1195 (s), 1180 (m), 1144 (m), 1109 (m), 1085 (m), 1021 (s), 1014 (s), 963 (s), 900 (m), 861 (s) cm^{-1}, ^1H NMR ($CDCl_3$, 270 MHz) δ 5.83 (ddd, J = 9.3, 2.1, 1.5 Hz, 1 H), 5.71 (dddd, J = 9.3, 4.3, 2.1, 2.1* Hz, 1 H), 4.24 (m, $w_{1/2}$ = 8 Hz, 1 H), 3.79 (td, J = 6.3, 1.8* Hz, 1 H), 2.65 (dddd, J = 17.6, 4.3*, 2.1, 2.1 Hz, 1 H), 1.86 (dddd, J = 17.6, 4.3, 1.5, 1.0* Hz, 1 H), 1.65–1.55 (m, 2 H), 1.53 (s, 3 H), 0.95 (t, J = 7.4 Hz, 3 H); MS (70 ev), *m/e* (%) 155 (2, M + + 1), 154 (15 M^+), 136 (7), 125 (51), 121 (9), 119 (13), 117 (16), 121 (22), 111 (100), 97 (33), 96 (50), 95 (87), 94 (16), 93 (12), 83 (44), 81 (48), 57 (26), 43 (80), 41 (23), 39 (22). *Indicates couplings that were removed upon irradiation of the multiplet at 4.24 ppm.

(2*S,1′*R**,3*R**)-2-(1′-Hydroxypropyl)-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one.** Boron trifluoride etherate (0.36 g, 2.5 mmol) was added dropwise to a solution of the dihydropyrone **18t** (69.1 mg, 0.252 mmol) in dichloromethane (1.0 mL) and dimethyl sulfide (0.5 mL) at room temperature. After it was refluxed 18 h, the solution was added to water and extracted twice with ether. The organic phase was washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (37% ethyl acetate/hexane, R_f 0.32) gave 30.2 mg (65%) of the title compound as a clear, colorless oil: IR ($CDCl_3$) 3550, 3430, 1670, 1622, 1449, 1380, 1305, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.22 (br s, 1 H), 3.90 (dd, J = 12, 2 Hz, 1 H), 3.63 (td, J = 6, 2 Hz, 1 H), 2.83 (dq, J = 12, 7 Hz, 1 H), 2.1 (br s, 1 H, exchange), 1.80–1.55 (m, 2 H), 1.68 (s, 3 H), 1.16 (d, J = 7 Hz, 3 H), 1.02 (t, J = 7.5 Hz, 3 H); MS, *m/e* (%) 185 (3, M + 1), 184 (20, M^+), 166 (1), 156 (2), 155 (2), 126 (8), 125 (7), 112 (9), 111 (100), 99 (17), 85 (72), 71 (20).

(1*S,2*S**,5*R**,7*S**)-2,4-Dimethyl-7-ethyl-6,8-dioxabicyclo[3.2.1]-oct-3-ene (33t).** Diisobutylaluminum hydride (0.13 mL of a 1.0 M solution in toluene, 0.13 mmol) was added to a solution of the above dihydropyrone (11.0 mg, 0.060 mmol) in 0.5 mL of benzene at ca. 5 °C. After 24 h at room temperature, ammonium chloride (20 mg) and water (5 mL) were added. After 1 h, magnesium sulfate and Celite were added and the mixture was filtered while washing with dichloromethane. The filtrate was concentrated in vacuo to give the diol as a clear, colorless oil. A solution of this crude material in THF (0.20 mL) was treated with mercuric trifluoroacetate (31 mg, 0.072 mmol) at room temperature for 15 min. Dichloromethane (0.20 mL) was added followed by triethylamine (36 mg, 0.36 mmol). The mixture was cooled to ca. 0 °C and methanesulfonyl chloride (44 mg, 0.30 mmol) was added slowly. After 15 min, the mixture was filtered through Celite while washing with ether. Pentane was added to the filtrate, which was then washed with saturated aqueous ammonium chloride, dried ($MgSO_4$), and concentrated on a rotary evaporator (0 °C at ca. 120 mmHg) to give a crude oil. Flash chromatography (10% ether/pentane, R_f 0.5) gave the title compound as a clear, colorless volatile oil: IR ($CHCl_3$) 1690, 1450, 1360, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.24 (m, $w_{1/2}$ = 8 Hz, 1 H), 5.23 (s, 1 H), 3.91 (m, $w_{1/2}$ = 4 Hz, 1 H), 3.71 (td, J = 6.4, 1.7 Hz, 1 H), 1.94 (m, $w_{1/2}$ = 15 Hz, 1 H), 1.71 (s, 3 H), 1.64–1.55 (m, 2 H), 1.14 (d, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.4 Hz, 3 H); MS, *m/e* (%) 168 (2, M^+), 140 (2), 139 (11), 125 (34), 111 (17), 108 (25), 107 (23), 97 (12), 95 (74), 93 (13), 85 (29), 83 (49), 82 (29), 71 (28), 69 (15), 67 (39), 57 (27), 55 (44), 43 (100), 41 (21).

(1*S,2*R**,5*R**,7*S**)-2,4-Dimethyl-7-ethyl-6,8-dioxabicyclo[3.2.1]-oct-3-ene (33c).** By the procedure given for the synthesis of **33t** from **18t**, **18c** (30.8 mg, 0.11 mmol) was debenzylated and cyclized to give bicyclic compound **33c** (10.0 mg, 65%): IR ($CHCl_3$) 2950, 2850, 1440, 1370, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.26 (s, 1 H), 5.16 (br s, 1 H), 3.95 (m, $w_{1/2}$ = 7.5 Hz, 1 H), 3.90 (td, J = 6.5, 1.7 Hz, 1 H), 2.86–2.83 (m, 1 H), 1.70–1.69 (m, 3 H), 1.66–1.59 (m, 1 H), 1.55–1.49 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.93 (d, J = 7.4 Hz, 3 H); MS, *m/e* (%) 168 (M^+, 5.0), 167 (47.5), 150 (10.5), 149 (100), 113 (14.8), 112 (10.18), 84 (6.2), 83 (9.5), 71 (20.3), 70 (18.6), 57.2 (15.9).

(2*R,1′*S**)- and (2*S**,1*S**)-2-[2′-(Benzyloxy)-1′-methylethyl]-6-methyl-2,3-dihydro-4*H*-pyran-4-one (36 and 37).** A solution of 3-(benzyloxy)-2-methylpropanal (**34**)[29] (101.8 mg, 0.57 mmol) and 2,4-bis-[(trimethylsilyl)oxy]-1,3-pentadiene (**4**) (190 mg, approximately 95% pure, 0.74 mmol) in benzene (4.0 mL) and Et_2O (1.0 mL) was cooled to −15 °C and treated with $MgBr_2$[43] (193 μL of a 2.96 M solution in 10% benzene/ether). After 1 h at −10 °C, this mixture was cooled to −78 °C and 5 mL of saturated $NaHCO_3$ solution was added. After warming to room temperature, the aqueous phase was extracted with ether and the combined organics were dried over K_2CO_3. After removal of solvents in vacuo the crude material was dissolved in CH_2Cl_2 (2.0 mL) and treated with trifluoroacetic acid (0.4 mL) for 1 h. Removal of solvents in vacuo followed by silica gel chromatography gave 135.2 mg (91%) of a 9:1

(48) (a) Silverstein, R. M. *J. Chem. Educ.* **1968**, *45*, 794. (b) Mori, K. *Tetrahedron Lett.* **1974**, 4223.

mixture of dihydropyrones **36** and **37**. Analytical samples were prepared by HPLC (12% ethyl acetate/hexane).

36: IR ($CDCl_3$) 1650, 1605, 1395, 1330, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39–7.29 (m, 5 H), 5.32 (s, 1 H), 4.51 (br s, 2 H), 4.48 (ddd, J = 14.0, 6.1, 3.8 Hz, 1 H), 3.49 (m, 2 H), 2.47 (dd, J = 16.7, 14.0 Hz, 1 H), 2.33 (ddd, J = 16.7, 3.9, 0.9 Hz, 1 H), 2.28–2.21 (m, 1 H), 1.98 (s, 3 H), 1.03 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 192.73, 174.09, 138.01, 128.15, 127.39, 127.28, 104.58, 80.04, 72.94, 70.82, 37.23, 37.07, 20.71, 12.42; MS, m/e (%) 261 (0.1), 260 (0.1), 169 (2.2), 161 (3.4), 160 (25.5), 152 (1.5), 151 (1.5), 146 (1.4), 145 (12.3), 139 (2.1), 131 (1.9), 127 (1.6), 118 (2.1), 112 (6.3), 111 (57.2), 109 (2.3), 107 (2.4), 105 (2.1), 97 (2.7), 96 (7.9), 92 (11.8), 91 (100.0), 85 (19.9).

37: IR ($CDCl_3$) 1645, 160, 1395, 1335, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.36–7.29 (m, 5 H), 5.32 (s, 1 H), 4.51 (multiplet containing an apparent d, J = 3.7 Hz, 3 H), 3.53 (dd, J = 9.3, 7.2 Hz, 1 H), 3.44 (dd, J = 9.3, 5.4 Hz, 1 H), 2.55 (dd, J = 16.6, 14.7 Hz, 1 H), 2.29 (dd, J = 16.6, 3.2 Hz, 1 H), 2.12–2.05 (m, 1 H), 1.97 (s, 3 H), 1.05 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 193.16, 174.36, 138.12, 128.31, 127.50, 104.74, 79.55, 73.10, 71.20, 38.48, 37.29, 20.87, 11.82; MS, m/e (%) 260 (M^+, 0.2), 202 (0.2), 169 (2.9), 161 (2.7), 160 (18.1), 152 (2.9), 151 (1.8), 146 (1.1), 145 (10.0), 144 (1.5), 139 (2.6), 131 (2.3), 127 (1.7), 123 (1.2), 118 (2.6), 112 (8.7), 111 (84.1), 109 (21), 107 (2.0), 105 (1.9), 100 (2.5), 97 (3.2), 96 (5.5), 92 (12.4), 91 (100.0), 8.5 (17.9).

(2*R,1′*S**)- and (2*S**,1′*S**)-2-[2′-(Benzyloxy)-1′-methylethyl]-2,3-dihydro-4*H*-pyran-4-one (38 and 39).** A solution of 3-(benzyloxy)-2-methylpropanal (**34**)[29] (464 mg, 0.26 mmol) and 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (**8**) in benzene (4.0 mL) and ether (1.0 mL) was cooled to −10 °C and treated with $MgBr_2$ (96 μL of a 2.7 M solution in 10% benzene/ether, 0.26 mmol). After warming to 0 °C for 0.5 h, Et_3N (3.0 mL) was added and the crude reaction mixture was poured into 10 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether, and the organics were combined and dried over K_2CO_3. After removal of solvents in vacuo the crude material was dissolved in CH_2Cl_2 (2.0 mL) and treated with trifluoroacetic acid (0.2 mL) for 1 h. Removal of solvents in vacuo followed by silica gel chromatography gave 45.4 mg (71%) of an 85:15 mixture of 2,3-dihydropyrones **38** and **39**. Analytical samples were prepared by HPLC (15% ethyl acetate/hexane).

38: IR ($CDCl_3$) 3050–2800, 1670, 1600, 1405, 1275, 1225; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39–7.29 (m, 6 H), 5.41 (dd, J = 6.0, 1.3 Hz, 1 H), 4.51 (s, 2 H), 4.49 (ddd, J = 14.2, 6.0, 3.5 Hz, 1 H), 3.49 (apparent dd, J = 5.8, 0.7 Hz, 2 H), 2.59 (dd, J = 16.7, 14.5 Hz, 1 H), 2.42 (ddd, J = 16.7, 3.5, 1.2 Hz, 1 H), 2.31–2.21 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 192.83, 163.37, 128.36, 127.66, 127.54, 107.02, 80.63, 73.21, 70.93, 38.59, 37.29, 12.63; MS, m/e (%) 247 (M + 1, 0.3), 246 (M, 0.2), 204 (0.1), 203 (0.5), 160 (5.4), 155 (3.8), 145 (6.3), 107 (3.0), 97 (100.0), 91 (77). Anal. ($C_{15}H_{18}O_3$) C, H.

39: IR ($CDCl_3$) 1670, 1595, 1400, 1275, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39–7.29 (m, 6 H), 5.40 (dd, J = 5.9, 1.3 Hz, 1 H), 4.57 (apparent dt, J = 15.0, 3.6 Hz, 1 H), 4.51 (s, 2 H), 3.52 (dd, J = 9.3, 7.3 Hz, 1 H), 3.47 (dd, J = 9.3, 5.4 Hz, 1 H), 2.66 (dd, J = 16.7, 14.9 Hz, 1 H), 2.35 (ddd, J = 16.7, 3.3, 1.3 Hz, 1 H), 2.13–2.02 (m, 1 H), 1.05 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 192.94, 163.32, 138.18, 128.43, 127.70, 127.60, 107.02, 79.96, 73.27, 71.28, 39.70, 37.42, 11.74; MS, m/e (%) 247 (M + 1, 0.1), 246 (0.1), 245 (0.1), 204 (0.1), 203 (0.7), 160 (3.6), 155 (3.7), 145 (5.5), 107 (3.0), 98 (7.1), 97 (100.0), 92 (6.9), 91 (56.8).

(2*R,1′*S**)- and (2*S**,1′*S**)-2-[1′-((Benzyloxy)methyl)propyl]-2,3-dihydro-4*H*-pyran-4-one (40 and 41).** A solution of 2-[(benzyloxy)-methyl]butyraldehyde (**35**) (99.3 mg, 0.517 mmol) and 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (**8**) (110 mg, 0.64 mmol) in benzene (4.0 mL) and ether (1.0 mL) was cooled to −15 °C and treated with $MgBr_2$[43] (175 μL of a 2.95 M solution in 10% benzene/ether, 0.516 mmol). After it was warmed to −10 °C for 1 h the mixture was cooled to −78 °C and quenched with Et_3N (2.0 mL) and $NaHCO_3$ (5.0 mL). After it was warmed to room temperature, the aqueous phase was extracted with ether. The organics were dried over K_2CO_3 and concentrated in vacuo. This crude material was dissolved in CH_2Cl_2 (2.0 mL) and treated with trifluoroacetic acid (200 mL). Concentration in vacuo and silica gel chromatography gave 90.3 mg (67%) of a 9:1 mixture of dihydropyrones **40** and **41**, which were separable by HPLC (10% ethyl acetate/hexane).

40: IR ($CDCl_3$) 1665, 1595, 1400, 1275, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39–7.28 (m, 6 H), 5.41 (dd, J = 5.9, 1.2 Hz, 1 H), 4.58 (ddd, J = 14.8, 4.8, 3.4 Hz, 1 H), 4.50 (s, 2 H), 3.59–3.48 (m, 2 H), 2.66 (dd, J = 16.7, 14.8 Hz, 1 H), 2.41 (ddd, J = 16.7, 3.3, 1.2 Hz, 1 H), 1.99–1.90 (m, 1 H), 1.63–1.35 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 193.00, 163.41, 138.13, 128.36, 127.66, 127.55, 107.01, 80.09, 73.26, 68.33, 43.90, 39.13, 19.89, 11.71; MS, m/e (%) 260 (M^+, 0.2), 203 (1.0), 174 (1.8), 169 (4.2), 152 (1.2), 146 (1.2), 145 (11.1), 125 (3.8), 123 (1.3), 110 (2.7), 109 (4.1), 107 (4.0), 99 (2.1), 98 (7.3), 97 (100.0), 96 (3.9), 92 (8.4), 91 (68.6).

41: IR ($CDCl_3$) 1660, 1595, 1400, 1275, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.38–7.29 (m, 6 H), 5.41 (dd, J = 5.9, 0.7 Hz, 1 H), 4.58 (apparent dt, J = 14.8, 4.2 Hz, 1 H), 4.50 (apparent d, J = 3.3 Hz, 2 H), 3.54 (apparent d, J = 5.3 Hz, 2 H), 2.67 (dd, J = 16.7, 14.9 Hz, 1 H), 2.41 (ddd, J = 16.7, 3.3, 1.1 Hz, 1 H), 1.89–1.80 (m, 1 H), 1.65–1.40 (m, 2 H), 0.96 (t, J = 7.5 Hz, 3 H); MS, m/e (%) 260 (M^+, 0.1), 203 (0.8), 174 (1.1), 169 (4.2), 152 (1.0), 146 (0.8), 145 (7.7), 139 (1.2), 125 (2.3), 123 (1.4), 111 (1.1), 110 (1.6), 109 (1.7), 107 (2.8), 98 (6.2), 97 (100.0), 92 (6.7), 91 (61.4).

(2*S,3*R**,1′*S**)-, (2*S**,3*S**,1′*S**)-, (2*R**,3*R**,1′*S**)-, and (2*R**,3*S**,1′*S**)-2-[2′-(Benzyloxy)-1′-methylethyl]-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one (42, 43, 44, and 45). $MgBr_2$ catalysis.** A solution of diene **16** (320 mg, 1.6 mmol) and aldehyde **34**[29] (141.0 mg, 0.79 mmol) in benzene (4.0 mL) and ether (1.0 mL) was cooled to −10 °C and treated with $MgBr_2$[43] (0.43 mL of a 2.95 M solution of MgBr in 10% benzene/ether, 1.27 mmol). After it was stirred for 2 h at 0 °C, the solution was cooled to −78 °C, quenched with 5.0 mL of saturated $NaHCO_3$ solution, warmed to room temperature, and extracted with ether. The organic layer was dried (K_2CO_3) and concentrated in vacuo. The resultant oil was dissolved in CH_2Cl_2 (4 mL) and treated with trifluoroacetic acid (0.5 mL) for 0.5 h. Concentration in vacuo followed by column chromatography gave 95.5 mg of **43** (44%) and 76.6 mg of **42** (36%).

BF_3·Et_2O Catalysis. A solution of diene **16** (130 mg, 0.65 mmol) and aldehyde **34** (91.0 mg, 0.51 mmol) in CH_2Cl_2 (5.1 mL) was cooled to −78 °C and treated with BF_3·Et_2O (72.7 mg, 0.51 mmol). After 1 h at −78 °C, saturated $NaHCO_3$ solution (5.0 mL) was added. The solution was warmed to room temperature and extracted with ether. After drying (K_2CO_3) and concentration in vacuo the resultant oil was dissolved in CH_2Cl_2 (4.0 mL) and treated with TFA (0.5 mL). Concentration in vacuo and column chromatography gave 131.8 mg (94%) of a mixture of four 2,3-dihydropyrones. HPLC (7% ethyl acetate/hexane) and NMR analysis showed this to be a 22:4:4:1 mixture of **44**, **45**, **43**, and **42**, respectively.

$TiCl_4$ catalysis. A solution of aldehyde **34**[29] (38.4 mg, 0.21 mmol) in CH_2Cl_2 (2.1 mL) was cooled to −78 °C and treated with $TiCl_4$ (44.8 mg, 0.24 mmol). After 5 min, diene **16** (63 mg, 0.31 mmol) was added. After an additional 10 min, MeOH (1.0 mL) and saturated $NaHCO_3$ solution (3.0 mL) were added and warmed to room temperature. Extraction with ether, drying ($MgSO_4$), and concentration in vacuo gave an oil, which was dissolved in CH_2Cl_2 (5.0 mL) and treated with TFA (0.5 mL) for 1 h. Concentraton in vacuo and silica gel chromatography gave 32.4 mg (55%) of 2,3-dihydropyrone **42**.

42: IR ($CDCl_3$) 1660, 1615, 1455, 1390, 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.38–7.28 (m, 5 H), 7.18 (br s, 1 H), 4.53 (m, 2 H), 4.17 (dd, J = 10.4, 2.7 Hz, 1 H), 3.62 (dd, J = 9.0, 3.2 Hz, 1 H), 3.57 (dd, J = 9.0, 5.5 Hz, 1 H), 2.43 (dq, J = 7.3, 2.8 Hz, 1 H), 2.19–2.12 (m, 1 H), 1.67 (d, J = 1.1 Hz, 3 H), 1.06 (d, J = 7.4 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 197.55, 158.81, 138.33, 128.04, 127.23, 111.78, 81.88, 72.94, 70.82, 40.97, 34.20, 12.69, 10.30, 9.11; MS, m/e (%) 274 (M^+, 2.2), 259 (10.5), 168 (5.0), 153 (2.7), 150 (3.2), 147 (2.2), 142 (2.1), 139 (3.8), 126 (3.6), 125 (26.7), 109 (6.0), 107 (4.3), 91 (100.0), 85 (16.7), 69 (26.1).

43: IR ($CDCl_3$) 1660, 1625, 1450, 1380, 1310 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.38–7.29 (m, 5 H), 7.19 (br s, 1 H), 4.51 (s, 2 H), 4.00 (dd, J = 11.3, 3.7 Hz, 1 H), 3.66 (dd, J = 9.4, 6.1 Hz, 1 H), 3.41 (dd, J = 9.4, 6.3 Hz, 1 H), 2.68 (dq, J = 11.3, 6.9 Hz, 1 H), 2.32–2.23 (m, 1 H), 1.66 (d, J = 1.1 Hz, 3 H), 1.18 (d, J = 7.0 Hz, 3 H), 1.10 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 195.55, 158.20, 138.17, 128.15, 127.33, 127.23, 112.22, 86.16, 72.99, 70.66, 41.68, 34.14, 14.91, 11.12, 10.52; MS, m/e (%) 274 (M^+, 0.5), 259 (1.4), 183 (0.5), 165 (0.6), 160 (0.8), 153 (1.0), 147 (0.9), 145 (1.8), 139 (2.0), 137 (1.1), 125 (100.0), 109 (2.4), 107 (2.3), 91 (69.6), 85 (8.6), 69 (17.8).

44: IR ($CDCl_3$) 1655, 1620, 1445, 1370, 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39–7.28 (m, 5 H), 7.19 (br s, 1 H), 4.53 (s, 2 H), 4.25 (dd, J = 13.5, 2.3 Hz, 1 H), 3.57 (apparent t, J = 8.8 Hz, 1 H), 3.43 (dd, J = 9.2, 6.0 Hz, 1 H), 2.54 (apparent sextet, J = 6.8 Hz, 1 H), 2.19–2.13 (m, 1 H), 1.67 (br s, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 195.65, 158.81, 138.33, 128.36, 127.55, 112.54, 82.85, 73.10, 71.74, 40.81, 34.52, 10.68, 9.71, 9.55; MS, m/e (%) 274 (0.2), 259 (2.3), 153 (1.7), 147 (1.0), 145 (1.5), 139 (3.2), 125 (100.0), 91 (63.6), 85 (19.1), 69 (17.1). Anal. ($C_{17}H_{22}O_3$) C, H.

45: IR ($CDCl_3$) 1660, 1620, 1450, 1380, 1290, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.38–7.29 (m, 5 H), 7.18 (br s, 1 H), 4.47 (s, 2 H),

4.15, (dd, J = 9.7, 2.8 Hz, 1 H), 3.37 (apparent d, J = 4.7 Hz, 2 H), 2.50 (qd, J = 7.3, 2.8 Hz, 1 H), 2.23–2.14 (m, 1 H), 1.67 (br s, 3 H), 1.16 (d, J = 6.7 Hz, 3 H), 1.07 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 198.11, 159.31, 138.05, 128.40, 127.66, 127.50, 112.07, 84.08, 73.37, 71.60, 42.16, 34.43, 14.35, 10.52, 10.11; MS, *m/e* (%) 274 (M^+, 2.6), 260 (15.1), 259 (7.7), 189 (3.1), 183 (4.7), 168 (4.2), 165 (6.6), 160 (7.5), 153 (8.4), 151 (5.0), 147 (5.7), 145 (5.0), 139 (13.8), 125 (81.4), 91 (100.0), 69 (15.0).

(2*R,3*S**)- and (2*R**,3*R**)-6-Phenyl-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one (17t and 17c).** A solution of benzaldehyde (41.76 mg, 0.39 mmol) in CH_2Cl_2 (3.9 mL) was cooled to −78 °C and treated with $TiCl_4$ (74.5 mg, 0.39 mmol) for 3 min. Diene **16** was then added, and after 10 min MeOH (1.0 mL) and saturated $NaHCO_3$ solution (1.0mL) were added sequentially. After the solution warmed to room temperature and was extracted with ether, the organics were dried (K_2CO_3) and concentrated in vacuo. The resultant oil was dissolved in CH_2Cl_2 (4.0 mL) and treated with TFA (1.0 mL) for 1 h. Concentration in vacuo followed by silica gel chromatography gave 70.5 mg (89%) of an 8:1 mixture of dihydropyrones **49** and **50**. Spectroscopic and analytical data for these compounds have been previously reported.[11]

(2*R,3*R**,1′*R**)-2-[(1′-benzyloxy)propyl]-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one (18c).** A solution of aldehyde **35** (31.9 mg, 0.18 mmol) in CH_2Cl_2 (1.8 mL) was cooled to −78 °C and treated with $TiCl_4$ (34.5 mg, 0.18 mmol) for 3 min. Diene **16** (52.3 mg, 0.26 mmol) was added, and after 15 min MeOH (1.0 mL) was added followed by saturated $NaHCO_3$ solution (1.0 mL). After the solution warmed to room temperature, H_2O (2.0 mL) was added and the aqueous layer was extracted with ether. Drying (K_2CO_3) and concentration in vacuo gave an oil, which was diluted with CH_2Cl_2 (4.0 mL) and treated with TFA (1.0 mL). Concentration in vacuo followed by silica gel chromatography gave 45.8 mg (93%) of dihydropyrone **18c**: IR ($CHCl_3$) 1660, 1620, 1455, 1385, 1300, 1175, 1115, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.41–7.29 (m, 6 H), 4.70 (AB, J = 11.3 Hz, 2 H), 4.32 (dd, J = 8.4, 3.0 Hz, 1 H), 3.68 (ddd, J = 8.4, 7.3, 3.8 Hz, 1 H), 2.42 (qd, J = 7.3, 3.0 Hz, 1 H), 1.68 (d, J = 1.1 Hz, 3 H), 1.70–1.40 (m, 2 H), 1.09 (d, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.4 Hz, 3 H); MS, *m/e* (%) 274 (M^+, 1.5), 201 (4.6), 168 (5.1), 149 (9.5), 132 (3.6), 131 (2.1), 125 (31.7), 97 (31.7), 97 (3.1), 92 (11.6), 91 (100.0), 85 (6.9). Anal. ($C_{17}H_{22}O_3$) C, H.

(1*R,4*R**,5*S**)-4-Methyl-2,9-dioxabicyclo[3.3.1]nonan-7-one (50).** Dihydropyrone **38** (45.2 mg, 0.18 mmol) was debenzylated and cyclized by following the procedure given for **25** and **26** to give 12.2 mg (43%) of bicyclic acetal **50**: IR ($CDCl_3$) 1720, 1225, 1120, 1135; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.51 (br d, J = 4.5 Hz, 1 H), 4.25 (br d, J = 6.9 Hz, 1 H), 4.01 (dd, J = 13.0, 3.0 Hz, 1 H), 3.55 (apparent dt, J = 13.0, 1.5 Hz, 1 H), 2.95 (dd, J = 16.8 7.5 Hz, 1 H), 2.78–2.70 (m, 2 H), 2.55 (br d, J = 16.0 Hz, 1 H), 1.63–1.55 (m, 1 H), 1.38 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 205.35, 94.07, 73.21, 62.16, 46.33, 46.12, 33.60, 17.78; MS, *m/e* (%) 156 (M^+, 11.4), 110 (6.5), 97 (9.6), 91 (8.7), 86 (27.9), 84 (45.3), 82 (22.1), 71 (79.5), 69 (25.4), 68 (100.0), 67 (33.9), 58 (22.3), 57 (20.5), 56 (28.4), 55 (60.1).

(1*R,4*S**,5*S**)-4-Methyl-2,9-dioxabicyclo[3.31]nonan-7-one (52).** A solution of aldehyde **34**[29] (211.5 mg, 1.19 mmol) and diene **8** (255 mg, 1.48 mmol) in ether (10 mL) was cooled to −78 °C and treated with $BF_3{\cdot}Et_2O$ (168 mg, 1.19 mmol). After 0.5 h at −78 °C, Et_3N (1.0 mL) and saturated $NaHCO_3$ solution (1.0 mL) were added. After warming to room temperature the organics were separated and the water layer was extracted with ether. Drying (K_2CO_3) and concentration in vacuo gave a brown oil, which was dissolved in CH_2Cl_2 (4 mL) and treated with TFA (0.5 mL). After 1 h, saturated $NaHCO_3$ solution (50 mL) was added. Extraction with ether, drying (K_2CO_3), concentration in vacuo, and silica gel chromatography gave 86.7 mg (30%) of an approximately 1.5:1 mixture of dihydro pyrones **39** and **38**, respectively. This mixture was deprotected and cyclized to give 22.3 mg of a mixture of bicyclic compounds **52** and **50**. HPLC (10%, ethyl acetate/hexane) was used to obtain a highly enriched sample (~15:1) of **52**: IR ($CDCl_3$) 1720, 1225, 1130, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.53 (br d, J = 4.7 Hz, 1 H), 4.38 (br dd, J = 6.1, 5.4 Hz, 1 H), 3.44 (apparent t, J = 12.4 Hz, 1 H), 2.80–2.50 (m, 5 H), 0.77 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 205.35, 93.74, 72.61, 63.40, 46.28, 40.75, 32.90, 13.07; MS, *m/e* (%) 156 (M^+, 21.3), 105 (26.5), 97 (100.0) 95 (21.3), 91 (84.5), 86 (42.6), 85 (43.9), 84 (67.1), 83 (54.2), 82 (31.0), 71 (94.8), 69 (43.2), 68 (91.0), 67 (32.9), 57 (43.2), 55 (38.1).

(1*R,4*R**,5*S**)-4-Ethyl-2,9-dioxabicyclo[3.3.1]nonan-7-one (54).** Dihydropyrone **40** (70.0 mg, 0.27 mmol) was debenzylated and cyclized following the procecdure given for compounds **25** and **26** to give 28.4 mg (62%) of bicyclic compound **54**: IR ($CHCl_3$) 2935, 1710, 1220, 1115, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.49 (br d, J = 4.1 Hz, 1 H), 4.36 (br d, J = 7.0 Hz, 1 H), 3.95 (dd, J = 13.1, 3.4 Hz, 1 H), 3.65 (apparent dt, J = 13.1, 1.6 Hz, 1 H), 2.95 (dd, J = 16.4, 7.3 Hz, 1 H), 2.79–2.64 (m, 2 H), 2.52 (br d, J = 16.4 Hz, 1 H), 1.92–1.76 (m, 2 H), 1.30–1.24 (m, 1 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 205.24, 94.12, 71.53, 59.99, 46.28, 46.17, 40.75, 24.07, 11.77; MS, *m/e* (%) 170 (M^+, 31.5), 124 (20.1), 111 (22.8), 109 (25.5), 97 (25.5), 96 (51.0), 95 (33.6), 86 (53.7), 85 (33.6), 84 (87.9), 83 (35.6), 82 (91.9), 81 (36.9), 71 (93.3), 69 (57.7), 68 (22.8), 67 (100.0), 57 (35.6), 56 (78.5), 55 (45.0).

(1*R,4*S**,5*S**)-4-Ethyl-2,9-dioxabicyclo[3.3.1]nonan-7-one (56).** Using the procedure given for the synthesis of **52**, aldehyde **35** (90.9 mg, 0.47 mmol) under $BF_3{\cdot}Et_2O$ catalysis gave 64.0 mg (52%) of a 1:1 mixture of dihydropyrones **40** and **41**. 55.0 mg of this mixture was deprotected and cyclized (see above) to give 20.8 mg (58%) of a mixture of bicyclic compounds **54** and **56**. HPLC (10%, ethyl acetate/hexane) gave a sample enriched (7.5:1) in compound **56**: IR ($CHCl_3$) 2940, 1715, 1220, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.54 (br d, J = 4.5 Hz, 1 H), 4.46 (br t, J = 5.9 Hz, 1 H), 3.81 (ddd, J = 12.9, 5.4, 1.1 Hz, 1 H), 3.45 (apparent t, J = 12.4 Hz, 1 H), 2.81–2.57 (m, 4 H), 2.40–2.28 (m, 1 H), 1.20–1.08 (m, 2 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 205.41, 94.10, 71.48, 62.34, 46.43, 41.04, 39.54, 21.48, 10.14; MS, *m/e* (M^+, %) 170 (M^+, 28.3), 111 (29.0), 109 (21.8), 96 (31.6), 95 (25.8), 85 (22.4), 83 (24.8), 82 (88.5), 81 (26.9), 71 (100.0), 69 (47.0), 67 (93.4), 57 (26.3), 55 (39.1).

(3*R,4*S**)-Methyl-3-acetoxy-5-(benzyloxy)-4-methylpentanoate (57).** Ozone was bubbled through a cold (−78 °C) solution of **38** (25.0 mg, 0.10 mmol) in CH_2Cl_2 (4.0 mL) and methanol (4.0 mL) until blue. After the mixture was flushed with nitrogen 30%, H_2O_2 solution (2.0 mL) and NaOH (150 mg) were added. After the solution was warmed to room temperature and stirred for 1 h, the organic layer was separated. After acidification with 10% HCl the aqueous phase was extracted with Et_2O, and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The crude hydroxy acid was dissolved in ether (2.0 mL) and treated with CH_2N_2 (in ether). After concentration in vacuo the crude hydroxy ester was treated with acetic anhydride (0.6 mL) and pyridine (0.4 mL) in CH_2Cl_2 (1.0 mL) and stirred overnight. After the reaction was quenched with saturated $NaHCO_3$ solution and extracted with ether, the organics were dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel to give 18.3 mg (61%) of **57**. Application of the same procedure to dihydropyrone **36** (104.0 mg) gave 60.2 mg (51%) of **57**: IR ($CDCl_3$) 2935, 2840, 1730, 1430, 1365, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.38–7.28 (m, 5 H), 5.36–5.29 (m, 1 H), 4.48 (br s, 2 H), 3.67 (s, 3 H), 3.48–3.32 (ABX, 2 H), 2.71–2.53 (ABX, 2 H), 2.71–2.14 (m, 1 H), 2.01 (s, 3 H), 0.98 (d, 3 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 171.13, 170.14, 138.27, 128.28, 127.52, 127.49, 73.04, 72.03, 71.65, 51.64, 36.71, 36.39, 20.88, 13.09; MS, *m/e* (%) (no M^+) 251 ($M^+ - C_2H_3O$, 1.2), 235 ($M^+ - C_2H_3O_2$, 1.3), 234 (9.0), 161 (14.0), 160 (100.0), 145 (43.6), 128 (20.5), 113 (12.8), 111 (13.1), 96 (10.1), 92 (12.2), 91 (78.2), 68 (11.1).

(1*R,4*R**,5*R**,6*S**,8*S**)-4,6,8-Trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-one (58).** Dihydropyrone **42** (65.0 mg, 0.23 mmol) was debenzylated and cyclized following the procedure given for compounds **25** and **26** to give 12.0 mg (28%) of bicyclic compound **58**: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.30 (d, J = 4.7 Hz, 1 H), 4.06 (br d, J = 6.4 Hz, 1 H), 3.60 (dd, J = 12.8, 3.5 Hz, 1 H), 3.38 (apparent dt, J = 12.8, 1.6 Hz, 1 H), 3.05–2.99 (m, 1 H), 2.74–2.68 (m, 1 H), 1.70–1.62 (m, 1 H), 1.35 (d, J = 7.0 Hz, 3 H), 1.12 (d, J = 6.9 Hz, 3 H), 1.08 (d, J = 7.0 Hz, 3 H); MS, *m/e* (%) 184 (M^+, 6.5), 128 (7.4), 123 (6.5), 118 (27.4), 107 (10.1), 86 (14.1), 85 (28.8), 84 (22.2), 83 (40.4), 82 (84.8), 72 (57.7), 71 (8.7), 69 (36.9), 67 (22.1), 59 (6.7), 58 (13.7), 57 (34.9), 56 (100), 55 (13.7), 51 (8.0).

(1*R,4*R**,5*R**,6*R**,8*S**)-4,6,8-Trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-one (59).** Dihydropyrone **43** (85.0 mg, 0.31 mmol) was debenzylated and cyclized following the procedure given for compounds **25** and **26** to give 20.3 mg (35%) of bicyclic compound **29**: IR ($CDCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.24 (d, J = 4.9 Hz, 1 H), 3.84 (s, 1 H), 3.76 (dd, J = 13.0, 3.3 Hz, 1 H), 3.45 (apparent dt, J = 12.9, 1.4 Hz, 1 H), 2.81 (qd, J = 7.0, 4.9 Hz, 1 H), 2.53 (br q, J = 7.4 Hz, 1 H), 1.60–1.50 (m, 1 H), 1.40 (d, J = 7.3 Hz, 3 H), 1.38 (d, J = 6.5 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 22.50 MHz) δ 211.86, 97.97, 79.93, 61.99, 49.91, 44.98, 33.39, 18.48, 17.78, 9.06; MS, *m/e* (%) 184 (M^+, 11.5), 128 (6.3), 125 (6.5), 123 (7.3), 87 (8.9), 85 (73.6), 84 (10.0), 83 (99.7), 82 (100.0), 71 (6.1), 69 (34.5), 67 (17.1), 58 (7.9), 57 (19.8), 56 (69.1), 55 (8.8).

6-*O*-Benzyl-7,8-dideoxy-1,2,3,4-di-*O*-isopropylidene-D-glycero(and L-glycero)-α-D-galactooct-7-enopyranose (64 and 65). To a solution of 1,2,3,4-di-*O*-isopropylidene-α-D-galactohexodialdo-1,5-pyranose (**63**) (0.99 g, 3.84 mmol) in THF (20 mL) at 0 °C was added vinyl magnesium bromide (4.22 mL, 1 M in THF) slowly over 5 min. The reaction was stirred at 0 °C for 0.5 h then an additional 6.5 h at room temperature. The reaction was quenched with 10% aqueous ammonium chloride (5 mL) and diluted with ether (60 mL). The ether layer was washed with

water, dried ($MgSO_4$), and concentrated in vacuo. A solution of the above crude product in THF (20 mL) was treated with sodium hydride (0.7 g of a 60% dispersion in mineral oil, 10.0 mmol) and then benzyl bromide (0.97 g, 5.6 mmol). After 16 h the reaction was quenched with water (5 mL) and diluted with ether (75 mL). The ether layer was washed with water and brine and dried ($MgSO_4$). Flash chromatography of the crude product (10% ethyl acetate/hexane) gave **64** and **65** (0.759 g, 52%) in a 2:1 ratio.

64: IR ($CHCl_3$) 1449, 1379, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.37–7.30 (m, 5 H), 5.97–5.83 (m, 1 H), 5.51 (d, J = 5 Hz, 1 H), 5.43–5.35 (m, 2 H), 4.65–4.44 (m, 4 H), 4.28 (dd, J = 5.0, 2.2 Hz, 1 H), 4.05 (dd, J = 6.7, 7.9 Hz, 1 H), 3.73 (dd, J = 9.2, 1.4 Hz, 1 H), 1.50 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H),1.31 (s, 3 H); MS, m/e (%) 361 (5.8 M^+ – 15), 171 (86.9), 91 (93.5), 71.1 (100).

65: IR ($CHCl_3$) 1445, 1381, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.42–7.30 (m, 5 H), 5.99–5.85 (m, 1 H), 5.62 (d, J = 5.0 Hz, 1 H), 5.47–5.29 (m, 2 H), 4.70–4.54 (m, 3 H), 4.29 (dd, 5.1, 2.3 Hz, 1 H), 4.24 (dd, J = 7.9, 1.7 Hz, 1 H), 4.11 (dd, J = 7.9, 6.7 Hz, 1 H), 3.81 (dd, J = 7.9, 1.7 Hz, 1 H), 1.55 (s, 3 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H); MS, m/e (%) 361 (M^+ – 15, 1.6), 171 (31.6), 91 (57.4), 71 (100).

6-*O*-Benzyl-1,2,3,4-di-*O*-isopropylidene-D-glycero-α-D-galactohepto-dialdo-1,5-pyranose (66). A solution of the alkene **64** (100 mg, 0.266 mmol) in dichloromethane (5 mL) and methanol (2 mL) was cooled to −78 °C and ozone was bubbled through the solution until the blue color persisted. The reaction was purged with nitrogen to remove the excess ozone, and dimethyl sulfide (2 mL) was added at −78 °C. The reaction was warmed to room temperature and stirred for 15 h. Concentration of the reaction followed by flash chromatography (20% ethyl acetate/hexane) gave **66** (90 mg, 89%): IR ($CHCl_3$) 1730, 1445, 1376 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.76 (d, J = 1.8 Hz, 1 H), 7.40–7.28 (m, 5 H), 5.51 (d, J = 4.9 Hz, 1 H), 4.72 (d, J = 11.2 Hz, 1 H), 4.64 (dd, J = 8.0, 2.4 Hz, 1 H), 4.56 (d, J = 11.2 Hz, 1 H), 4.40 (dd, J = 8.0, 2.4 Hz, 1 H), 4.32 (dd, J = 4.9, 2.4 Hz, 1 H), 4.12–4.03 (m, 2 H), 1.50 (s, 3 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.32 (s, 3 H); MS, m/e (%) 379 (M + 1, 0.1), 363 (M^+ – 15, 1.9), 349 (0.9), 305 (1.3), 91 (100).

(2*R*,3*R*)-2-(6-*O*-Benzyl-1,2,3,4-*O*-isopropylidene-D-glycero-α-D-galacto-1,5-pyranosyl)-3-(benzoyloxy)-2,3-dihydro-4*H*-pyran-4-one (68). To a solution of the aldehyde **66** (35 mg, 0.092 mmol) and the diene mixture **67a** (61 mg, 0.184 mmol) in THF (1.1 mL) was added magnesium bromide[43] (0.031 mL of a 2.95 M solution in 10% benzene/ether). The reaction was stirred at room temperature. After 2 days an additional equivalent of diene was added (30 mg, 0.09 mmol in THF, 0.15 mL). The reaction was quenched after 5 days with aqueous saturated sodium bicarbonate (1 mL) and diluted with ether (20 mL). The ether layer was washed with aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and then concentrated in vacuo. Flash chromatography (20% ethyl acetate/hexane) afforded **68** (24.6 mg, 47%): mp 184–185 °C (MeOH); IR ($CHCl_3$) 1747, 1690, 1598, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.16–8.13 (m, 2 H), 7.63–7.30 (m, 9 H), 6.05 (d, J = 13.3 Hz, 1 H), 5.53 (d, J = 4.8 Hz, 1 H), 5.49 (d, J = 5.8 Hz, 1 H), 5.02 (dd, J = 13.3, 0.5 Hz, 1 H), 4.72–4.45 (m, 4 H), 4.33 (dd, J = 4.8, 2.3 Hz, 1 H), 4.24 (dd, J = 9.8, 1.3 Hz, 1 H), 3.96 (dd, J = 9.8, 0.7 Hz, 1 H), 1.54 (s, 3 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H).

68–Magnesium Bromide in Benzene. To a solution of the aldehyde **66** (90 mg, 0.238 mmol) and the diene mixture **67** (172 mg, 0.59 mmol) in benzene (5 mL) at room temperature was added magnesium bromide[43] (0.1 mL of a 2.95 M solution in 10% benzene/ether, 0.295 mmol). The reaction was stirred for 6 h at room temperature and then quenched with saturated aqueous sodium bicarbonate (2 mL) and diluted with ether (70 mL). The ether layer was washed with aqueous saturated sodium bicarbonate and brine, then dried ($MgSO_4$), and concentrated in vacuo. The crude product mixture was redissolved in carbon tetrachloride (6 mL) and treated with trifluoroacetic acid (0.66 mL) for approximately 2 h. Concentration of the reaction in vacuo and chromatography (20% ethyl acetate/hexane) gave **68** (107 mg, 79%).

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Registry No. 1a, 91860-77-4; **2a**, 89279-49-2; **2b**, 91860-80-9; **3**, 53346-05-7; (*E*)-**4**, 63446-76-4; (*Z*)-**4**, 63446-77-5; **5**, 89279-50-5; **6**, 91860-78-5; **7**, 54125-02-9; **8a**, 89279-53-8; **8b**, 91860-79-6; **9**, 89279-54-9; **11**, 91860-81-0; **12**, 91860-83-2; **13**, 91860-82-1; **14**, 89279-55-0; **16**, 72486-93-2; **17c**, 83378-98-7; **17t**, 83379-03-7; **18c**, 89363-68-8; **18t**, 89378-00-7; **20c**, 85613-00-9; **20t**, 89363-65-5; **21c**, 91926-25-9; **21t**, 89363-67-7; **22**, 15186-48-8; **23**, 81277-28-3; **24**, 91860-84-3; **25**, 89279-51-6; **26**, 91860-85-4; **28** (isomer 1), 91860-86-5; **28** (isomer 2), 91926-26-0; **29**, 20290-99-7; **30** (isomer 1), 91860-87-6; **30** (isomer 2), 91926-27-1; **31**, 91861-03-9; **32**, 62255-25-8; **33c**, 91926-28-2; **33t**, 91860-89-8; **34**, 73814-73-0; **35**, 89279-56-1; **36**, 89279-61-8; **37**, 89279-62-9; **38**, 89279-59-4; **39**, 89279-60-7; **40**, 89279-57-2; **41**, 89279-58-3; **42**, 89363-64-4; **43**, 89363-66-6; **44**, 91860-90-1; **45**, 91860-91-2; **50**, 91860-92-3; **52**, 91860-93-4; **54**, 91860-94-5; **56**, 91860-95-6; **57**, 91860-96-7; **58**, 91860-97-8; **59**, 91926-29-3; **63**, 4933-77-1; **64**, 91860-98-9; **65**, 91860-99-0; **66**, 91861-00-6; **67a**, 91861-02-8; **67b**, 91861-04-0; **68**, 91861-01-7; magnesium bromide, 7789-48-2; boron trifluoride etherate, 109-63-7; zinc chloride, 7646-85-7; benzaldehyde, 100-52-7; (2*S**,1′*R**, 3*R**)-2-(1′-hydroxypropyl)-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one, 91860-88-7; vinyl bromide, 593-60-2; $Yb(fod)_3$, 18323-96-1; $TiCl_4$, 7550-45-0.

Supplementary Material Available: ORTEP drawing as well as tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for **68** and general experimental, experimental details, and spectral data for compounds **1a**, **1b**, **2b**, **3**, and **35** (9 pages). Ordering information is given on any current masthead page.

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