Approaches to the Synthesis of the Tetrahydropyran Subunit of the Polyether Nigericin

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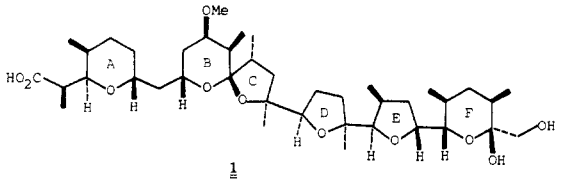
Two approaches were explored for synthesis of a tetrahydropyran with the substitution and stereochemistry of the A ring of the polyether antibiotic nigericin. The lactone **9** was constructed stereoselectively by a sequence of carbamate cyclization and Ireland–Claisen reactions. Conversion to the olefinic derivatives **18** and palladium-induced electrophilic cyclization/carboxylation provide the tetrahydropyran with the correct substitution pattern; selectivity for the desired, axial product is increased by incorporating the nucleophilic oxygen as an acetal derivative; however, the equatorial isomer is still predominant. Lewis acid catalyzed addition of allyl- and enolsilane reagents to a number of acetals derived from **9** was also investigated. Reaction of allyltrimethylsilane under BF_3 catalysis affords products that are consistent with axial attack on a free oxocarbonium ion species (Scheme V); in contrast, addition of the *tert*-butyldimethylsilyl enol ether of *tert*-butyl methyl ketone (**30**) catalyzed by $TiCl_4$ involves S_N2-like displacement of the acetal oxygen which is most readily complexed by the Lewis acid (Scheme VI). This behavior was most dramatically manifested in reaction of the bicyclic acetals **23**, in which the configuration of the methyl group dictates the regiochemistry of ring-opening, oxacane **32** arising from **23**α and tetrahydropyran **31** from **23**β. Conditions were not found that afford control over the propanoic acid side chain stereochemistry in the model compounds.

The stereochemical complexity of the polyether antibiotics and related natural products, coupled with their noncarbacyclic structures,[1] have made their synthesis a proving ground for methods for acyclic stereocontrol as well as cyclic ether formation.[2,3] Our interest in these targets has focussed on the development of strategies for the stereocontrolled construction of α,α'-substituted tetrahydrofurans and -pyrans, utilizing cyclization reactions to introduce successive stereocenters with relative asymmetric induction.[2b,3]

In this regard, the A ring of nigericin (**1**) poses a particular challenge, since the two substituents α to the ether oxygen adopt the thermodynamically less favorable, trans relationship. Utilizing model systems, we have investi-



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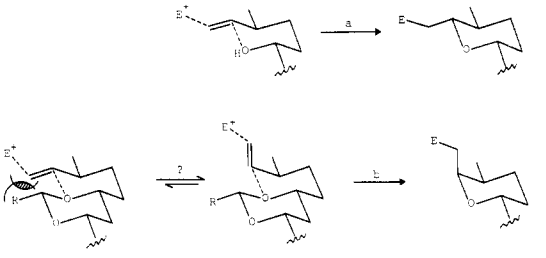
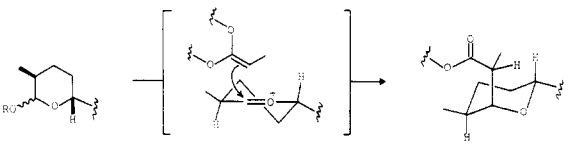
gated two approaches to this problem. In the first, we attempted to perturb the normal course of an alcohol cyclization (path a in Scheme I) by incorporating the nucleophile in an acetal moiety, the added steric constraints of which we hoped would favor axial cyclization (path b).[4]

The second approach embodies a different strategy, namely, the Lewis acid catalyzed condensation of an acetal derivative with an enol ether or equivalent (Scheme II). Strong precedent exists for the generation of related C-glycosides via axial attack,[5] and we were interested in

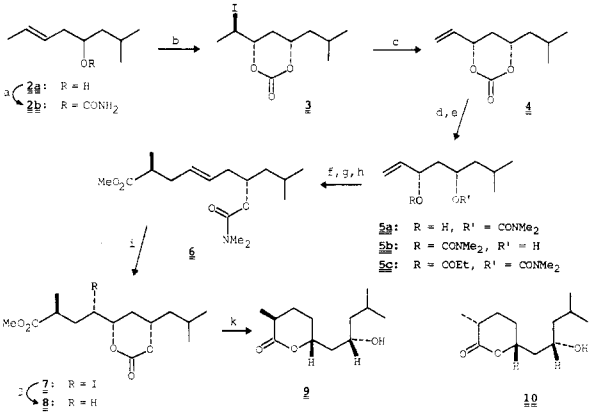
Scheme I



Scheme II



Scheme III[a]



[a] (a) $Cl_3CCONCO$, CH_2Cl_2, then K_2CO_3, aqueous MeOH (quant); (b) I_2, Et_2O, aqueous $NaHCO_3$ (97%, 17:1 ratio); (c) *m*CPBA, CH_2Cl_2, aqueous $NaHCO_3$ (quant); (d) Me_2NH (3.5:1 ratio); (e) $(EtCO)_2O$, DMAP, pyridine, CH_2Cl_2 (76% from **4**); (f) LDA, HMPA/THF, −78 °C, *t*$BuMe_2SiCl$; (g) aqueous H_2SO_4, THF; (h) CH_2N_2, Et_2O (67% from **5c**, 9.7:1 ratio); (i) I_2, Et_2O, aqueous $NaHCO_3$ (quant); (j) *n*Bu_3SnH, THF (87%, >20:1 ratio); (k) K_2CO_3, aqueous MeOH (96%).

(1) (a) Westley, J. W. In *Advances in Applied Microbiology*; Academic Press: New York, 1977; Vol 22, pp 177–223. (b) Dobler, M. In *Ionophores and Their Structures*; J. Wiley and Sons: New York, 1981.

(2) An excellent overview of work in this area is provided in Boivin, T. L. B. *Tetrahedron* **1987**, *43* 3309–3362. Some additional leading references are the following. Brevetoxin: (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1355–1362. (b) Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1986**, *51*, 2230–2240. Lysocellin: (c) Evans, D. A.; Polniasek, R. P. *Tetrahedron Lett.* **1986**, *27*, 5683–5686. Monensin: (d) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105–2106. (e) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106–2108. X-206: (f) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799–802.

(3) (a) Rychnovksy, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964. (b) Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416–2423. (c) Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179–5183. (d) Bartlett, P. A.; Chapuis, C. *J. Org. Chem.* **1986**, *51*, 2799–2806.

(4) Participation of an acetal oxygen in related electrophilic cyclizations is precedented in Still's monensin synthesis (ref 2d) and work of Jalali-Naini, M.; Lallemand, J. J. *Tetrahedron Lett.* **1986**, *27*, 497.

0022-3263/89/1954-0098$01.50/0

exploring the possibility that stereocontrol could be exerted over the side-chain configuration as well.[6]

The common element in these two strategies is use of the stereocenters at C-3 and C-6 of the tetrahydropyran moiety to control the configurations of those at C-2 and of the propanoate side chain, i.e., the assumption that "linear stereocontrol"[3d] would be exerted in a right-to-left direction along the carbon backbone.[7] Lactone **9** was thus a key precursor to model substrates for both approaches.

Synthesis of Lactone 9

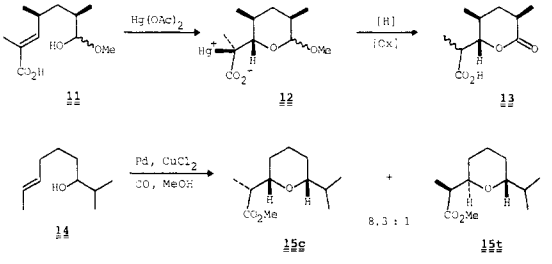
A stereoselective synthesis of intermediate **9** is outlined in Scheme III. The homoallylic alcohol **2a**[8a] was prepared in over 80% yield by addition of diethylpropynylalane to 1,2-epoxy-4-methylpentane[8b] followed by dissolving metal reduction. The double bond of **2** was functionalized stereoselectively by cyclization to the iodo carbonate **3**. We explored several protocols for this transformation, including iodocyclization of the *tert*-butyl carbonate derivative according to our original procedure,[9] of the carbonate monoanion as advocated by Cardillo et al.,[10] and of the carbamate **2b** as first described by Hirama.[11] The latter procedure proved to be the best, affording **3** in 95% yield as a 17:1 ratio of isomers. DBU-induced dehydroiodination occurs predominantly toward the oxygen moiety,[3c,12] so an oxidative elimination procedure was employed instead.[13] Treatment of **3** with 3.5 equiv of *m*-chloroperbenzoic acid in a two-phase system (CH_2Cl_2/aqueous $NaHCO_3$) leads to the allylic carbonate **4** in >90% yield.

The next important element in the synthesis was stereoselective introduction of the methyl substituent via the Ireland–Claisen rearrangement.[14] While we initially investigated this process using the dipropanoate corresponding to **5**, the transformation was complicated by intramolecular Claisen condensation (to give a 2-methyl-3-oxopentanoyl derivative) as well as an unexpected reversal in the stereospecificity of the reaction. Fortunately, the two hydroxyl groups can be distinguished with moderate selectivity by reaction of carbonate **4** with liquid dimethylamine to provide the two dimethylcarbamates **5a** and **5b** in a ratio of 3.5:1. Acylation and chromatographic separation of the mixture affords the desired propanoate **5c** in good overall yield from **4**. Ireland–Claisen rearrangement of ester carbamate **5c**, with enolization of the ester in THF/HMPA, proceeds with good efficiency and high selectivity (69% yield as a ca. 10:1 ratio of isomers, according to capillary GC analysis). Because of the stereochemically "self-immolative"[15] nature of the rearrangement, the hydroxyl group must be reintroduced. In this regard, the earlier introduction of the dimethylcarbamoyl moiety proved to be a key step: in addition to solving a regiochemical problem and serving as an effective protecting group during the Ireland–Claisen rearrangement, it could also be utilized as the precursor for the second iodocyclization reaction. Conversion of **6** to the iodo carbonate, followed by deiodination of the product **7** with tributyltin hydride, affords the carbonate ester **8** in >20:1 selectivity and 85–90% overall yield from olefin **6**. The conversion of carbonate **8** to lactone **9** was accomplished in nearly quantitative yield with K_2CO_3 in methanol.

The primary basis for assigning the indicated stereochemistry to lactone **9** is the known specificity of the iodocyclization and Ireland–Claisen reactions. The reversal in selectivity of the latter transformation when enolization is carried out in pure THF was verified in the rearrangement of **5c** as well; subsequent conversion of *epi*-**6** to the epimeric lactone **10** demonstrated that **10** was indeed the minor isomer present in the preparation of **9**. Epimerization studies, conducted under conditions of thermodynamic as well as kinetic control, demonstrated the interconversion of **9** and **10**, although this process affords at best a 2:1 ratio of **9**:**10** (using KO*t*-Bu/THF).[16]

Electrophilic Cyclization of Olefinic Acetals

A number of cyclization methods have been developed that lead to the 1-carboxyethyl substituent on a pyran ring system. A synthesis of the Prelog–Djerassi lactone, for example, involved mercuricyclization of the α-methyl acrylic acid derivative **11**, followed by reductive demercuration;[17] the latter process was not stereospecific, however. A more general method is the palladium-mediated cyclization/carbonylation process investigated by Semmelhack and his co-workers.[18] The olefinic alcohol **14** affords the tetrahydropyranpropanoate **15** in high yield and stereoselectivity.



(5) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383–2386. Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522–528. Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1983**, *24*, 1563–1566.

(6) Murata, S.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 2601–2602. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383–2386. Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289–4296.

(7) For recent, alternative stereochemical solutions to similarly substituted ethers, see: Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117–8119. Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553–7555. Martin, S. F.; Gwinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588–5593.

(8) (a) Hoffmann, R. W.; Weidmann, U. *J. Organomet. Chem.* **1980**, *195*, 137. (b) Inter alia: Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.*, **1985**, *107*, 5210–5219.

(9) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013–4018.

(10) Bongini, A.; Cardillo, G.; Orena, M.; Prozi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626. See also: Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147.

(11) Hirama, S.; Uei, M. *Tetrahedron Lett.* **1983**, *24*, 5307.

(12) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 701.

(13) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888. Yamamoto, S.; Nagata, W.; Itani, H.; Tsuji, T. *J. Am. Chem. Soc.* **1983**, *105*, 2908. Macdonald, T. L.; Narasimhan, N.; Burka, L. T. *J. Am. Chem. Soc.* **1980**, *102*, 7760 and references cited therein.

(14) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(15) Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Org. Chem.* **1976**, *41*, 303–306, and references therein. Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989–1996.

(16) For related epimerizations, see: Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749. White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Kang, M. C.; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517–6518. In addition to the epimerization studies, the downfield shift of the methyl group in **9** and of the α-hydrogen in **10**, in comparison to their epimeric counterparts, are consistent with the configurational assignment.

(17) Bartlett, P. A.; Adams, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 337–342.

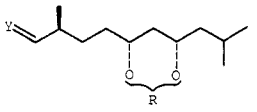
(18) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171. Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.

Table I. Pd(II)-Mediated Acetal Cyclizations

entry	substrate (18, R)	$HC(OMe)_3$[a]	ratio[b] 19c:19t	yield,[c] %
1	**18a**, R = H,H	–	7.9	39
2	**18a**, R = H,H	+[d]	2.2	83
3	**18b**, R = CHPh	–	2.7	93
4	**18b**, R = CHPh	+	2.4	69
5	**18c**, R = CH*p*C_6H_4Br	–	3.7	94[e]
6	**18c**, R = CH*p*C_6H_4Br	+	2.0	90[e]
7	**18d**, R = BHT[f]	–	4.1	90
8	**18e**, R = $CHCH_3$	–	5.7	83[e]
9	**18f**, R = $CHC(CH_3)_3$	–	7.6	39
10	**18f**, R = $CHC(CH_3)_3$	+	2.7	84[e]
11	**18g**, R = $C(CH_3)_2$	–	7.7	66
12	**18h**, R = $CHOCH_3$ (eq)	–	2.1	30[e]
13	**18i**, R = $CHOCH_3$ (ax)	–		*g*

[a] + indicates that reaction was carried out in presence of 5 equiv of $HC(OCH_3)_3$. [b] Ratio determined by capillary GC analysis prior to chromatographic purification. [c] Yields of product after chromatographic purification, unless otherwise indicated. [d] Orthoformates **18h** and **18i** were formed under these conditions. [e] Yield of unpurified product. [f] BHT represents 3,5-di-*tert*-butyl-4-hydroxybenzylidene. [g] No reaction observed.

In addressing the utility of this cyclization procedure for generation of the A ring of nigericin, we first explored the question of axial versus equatorial cyclization with the various acetals **18b–i**. These compounds were prepared



16: Y = H,OH
17: Y = O
18: Y = CH_2

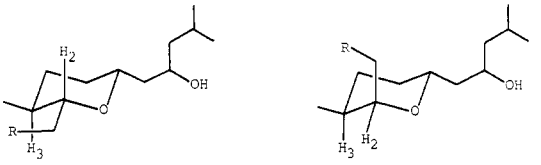
a: R = H,H
b: R = CHPh
c: R = CH–(Br-C$_6$H$_4$)
d: R = CH–(OH-C$_6$H$_3$(t-Bu)$_2$)
e: R = $CHCH_3$
f: R = $CHC(CH_3)_3$
g: R = $C(CH_3)_2$
h: R = CHOMe (*equatorial*)
i: R = CHOMe (*axial*)

straightforwardly from the lactone **9** via the sequence **9** → **16a** → **16b** → **17b** → **18b** → **18a** →→ **18c–i**. Deprotection of the benzylidene derivative **18b** proved to be unexpectedly difficult under acidic conditions; the acetal is recovered unchanged after 12 h in 1 N H_2SO_4. However, the diol **18a** is formed in >95% yield with sodium in ammonia. Acetals **18c–f**, ketal **18g**, and ortho esters **18h,i** were prepared from the diol **18a** by acid-catalyzed condensation with the corresponding aldehyde, 2,2-dimethoxypropane, or trimethyl orthoformate, respectively. Acetals **18b–f** were all formed as a single isomer; the expected all-equatorial stereochemistry was confirmed for the benzylidene derivative by observation of a strong NOE effect between the acetal and carbinol hydrogens in the ^1H NMR spectrum. The isomeric ortho esters **18h** and **18i** were separated chromatographically; the axial methoxy configuration was assigned to the isomer with the downfield ^1H NMR chemical shifts for the acetal and ether hydrogens.[19]

As a control experiment for the palladium-mediated cyclization process, diol **18a** was treated with $PdCl_2$ (0.2–0.5 equiv) and $CuCl_2$ (1.5–2.5 equiv) in methanol under 1 atm of carbon monoxide. As expected, the major isomer formed (7.9:1 ratio) proved to be the diequatorial ester **19c** (Table I, entry 1). The isomers were separated by HPLC and the stereochemical assignment was confirmed by ^1H NMR

(19) Eliel, E. L.; Giza, C. *J. Org. Chem.* **1968**, *33*, 3754–3758. Eliel, E. L.; Nader, F. *J. Am. Chem. Soc.* **1969**, *91*, 536–538.

Table II. ^1H NMR Assignments of Cyclic Ethers[a]



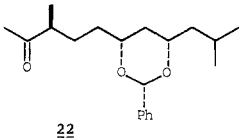
19c R = CO_2Me **19t**
20c R = I **20t**
21c R = H **21t**

compound	R	cis isomer δ_2	cis isomer $J_{2,3}$	trans isomer δ_2	trans isomer $J_{2,3}$
19	CO_2Me	3.47	9.7	4.33	4.7
20	I	2.98	8.7	3.95	4
21	H	3.12	9.0	3.85	3.6

[a] Spectra measured in dilute $CDCl_3$ solution.

(Table II). Cyclization of the benzylidene acetal **18b** shows a marked reduction in the ratio of equatorial:axial product (Table I, entry 3), suggesting that the desired effect (Scheme I) is manifested. Nevertheless, the equatorial product still predominates. Similar results are also obtained when the electronic or steric character of the aryl substituent are varied (substrates **18c** and **18d**, entries 5 and 7). In contrast, the alkylidene acetals (**18e–g**) cyclize more slowly than the aromatic acetals, leading to product ratios similar to those observed on cyclization of the free diol (entries 8, 9, and 11). In these cases, acetal hydrolysis may precede cyclization. In cyclization of the *tert*-butyl-substituted acetal, **18f**, this behavior is suppressed by inclusion of trimethyl orthoformate in the reaction mixture (entry 10), nevertheless the selectivity remains unfavorable. Of the orthoformate isomers themselves, only one could be induced to cyclize in a preliminary experiment, in poor yield and selectivity (entry 12).

While a number of modifications in the standard cyclization procedure were investigated, no improvement in the stereochemical course of the reaction was obtained. Included as acid scavengers, propylene oxide has no effect while excess triethylamine suppresses the reaction entirely. Palladium acetate and $Pd(PhCN)_2Cl_2$ are ineffective at promoting cyclization at all. If carbon monoxide is omitted from the reaction mixture, the benzylidene acetal **18b** is converted to the methyl ketone **22** in 86% yield.[20]



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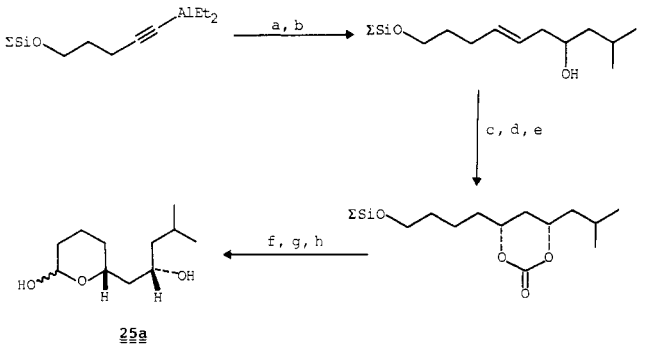
Some alternative electrophilic cyclization reagents were also investigated with the diol **18a** and benzylidene acetal **18b**. With mercuric trifluoroacetate in acetonitrile, followed by methoxycarbonylation ($PdCl_2$, LiCl, $CuCl_2$, and CO in methanol),[21] both the diol and the acetal afford a similar mixture of esters, favoring the equatorial (cis) isomer **19c** over the axial **19t** by ratios of 2.5–3.0:1. This similarity reflects either hydrolysis of the acetal to the diol prior to cyclization or thermodynamic equilibration of the organomercury intermediates. Iodocyclization of acetal **18b** in methylene chloride in the presence of sodium bicarbonate favors the equatorial iodoether **20c** over the axial

(20) Tsuji, J. *Synthesis* **1984**, 369–384. Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 335. Larock, R. C. *Ibid.* **1975**, *40*, 3237.
(21) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 335.

Scheme IV[a]



25a

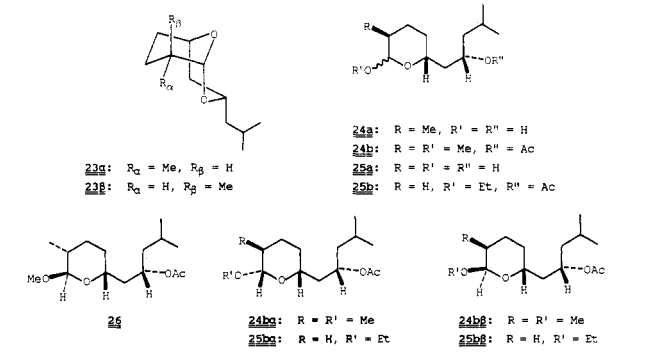
[a] (a) 1,2-epoxy-4-methylhexane, hexane (49%); (b) Na, NH_3, THF; (c) Me_2NCOCl, KH, THF (60% for two steps); (d) I_2, Et_2O, aqueous $NaHCO_3$ (86%); (e) nBu_3SnH, THF (93%, 19:1 ratio); (f) HF, MeCN (86%); (g) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2 (99%); (h) K_2CO_3, aqueous MeOH (92%).

by up to 4:1. In contrast, the axial isomer **20t** is the predominant product (up to 2.9:1 ratio) when cyclization of diol **18a** is carried out under the same conditions. The axial and equatorial isomers were assigned based on the coupling constants $J_{2,3}$ of both the iodides **20** and the corresponding deiodinated materials **21** (Table II). Formation of the less stable isomer has been observed in a number of instances in both iodolactonization and iodoetherification,[22] and it has been attributed to intramolecular delivery of the electrophile via a hypoiodite.[23]

Although a procedure had been found that favors the axial isomer, use of the acetal moiety to control the cyclization as proposed in Scheme I had not been realized. We therefore turned our attention to the alternative mode of synthesis represented by Scheme II.[24]

Nucleophilic Addition to Cyclic Acetals

Two types of acetal substrates were investigated as precursors to the oxonium ion depicted in Scheme II, the bicyclic derivatives **23** and the monocyclic acetals **24b** and **25b**. Reduction of lactone **9** with diisobutylaluminum



hydride followed by azeotropic removal of water from lactol

Table III. Allyltrimethylsilane Additions to Cyclic Acetals

entry	substrate	conditions[a]	product(s)[b]	yield,[c] %
1	**23**[d]	A	**27b, 28b**	62
2	**24bα**	A	**27a**	95
3	**24bβ**	A	**27a**	99
4	**24bβ**	B	**27a**	96
5	**26**	A	**28a**	96
6	**25bα**	A	**28c**	83
7	**25bβ**	A	**28c**	77

[a] A: $BF_3{\cdot}Et_2O$/MeCN, 0 °C; B: $TiCl_4/CH_2Cl_2$, −78 °C. [b] In each case <5% of the α,α'-cis isomer could be identified. [c] Yields of product after chromatographic purification. [d] Mixture of isomers: 78% **23α**, 22% **23β**.

24a under acid catalysis affords the bicyclic acetal **23** as a 3.5:1 mixture of the undesired α-isomer and desired β-isomer, which can be separated by gas chromatography. Acid-catalyzed epimerization via a dihydropyran intermediate is well precedented in related systems.[25] Preference for the α-isomer is understandable in view of the likely chair-boat conformation of the 3-(*endo*)-3-alkyl-2,9-dioxabicyclo[3.3.1]nonane ring system.[26] Although the configuration of these isomers was not readily assigned by NMR (broad singlets are seen for the acetal and adjacent hydrogens in each compound), it was inferred by their conversion without epimerization into the allylated products **27b** and **28b** (see below).

The monocyclic acetal esters **24b** and **25b** were prepared from the corresponding lactols **24a** and **25a** with alcohol/HCl, followed by acetylation; no epimerization was observed in the case of **24b**. The "desmethyl" lactol **25a** was synthesized according to the sequence outlined in Scheme IV.

A sample of the methyl epimer **26**, as a single anomer, was obtained from a stereochemically impure sample of **24a**. For both **24b** and **25b**, the α- and β-anomers were separated chromatographically (ca. 1:1 ratios) and identified by NMR ($J_{1,2}$ = 8.3 and 3.1 Hz for **24bα** and **24bβ**, respectively). Moreover, the anomeric relationship of **24bα** and **24bβ** was demonstrated by their ready interconversion in HCl/methanol; isomer **26** is unaffected under these conditions. The configurations of the desmethyl analogues were deduced from the upfield chemical shift and coupling pattern of the anomeric hydrogens: axial in **25bα** (δ 4.36 ppm, dd, J = 2.3 and 9.3 Hz); equatorial in **25bβ** (δ 4.82 ppm, br s, $w_{1/2}$ = 5.5 Hz).

Our first concern in studying the acetal addition reactions was the stereochemistry at the anomeric (C_2) carbon. Considerable precedent exists for additions of this type, and although axial approach of the nucleophile is the rule, the selectivity is often dependent on the choices of catalyst and solvent as well as nucleophile.[5] As shown by the results presented in Table III, addition of allyltrimethylsilane consistently provides the axial (trans) products **27** or **28**, regardless of the nature or configuration of the acetal precursor. The configurations of **27a** and **28a** were assigned by chemical correlation with the tetrahydropyranacetic acid isomers obtained from the cyclization experiments described above and by ^1H and ^{13}C NMR. For example, in compound **27a**, the axial–equatorial coupling

(22) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 411–454. See also: Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1985**, *86*, 2529. Tamaru, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 2885. Chamberlin, A. R.; Dezube, M.; Dussalt, P.; McMills, M. *J. Am. Chem. Soc.* **1983**, *105*, 5819. Sato, A.; Ogiso, A.; Noguchi, H.; Mitsui, S.; Kaneko, I.; Shimada, Y. *Chem. Pharm. Bull.* **1980**, *28*, 1509.

(23) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950–3952.

(24) While further exploration of the iodocyclization process was considered, the modest selectivity obtained and the potential difficulties with subsequent transformations (e.g., displacement of an α-alkoxy, secondary iodide without elimination) persuaded us that continued pursuit of this approach would not be worthwhile.

(25) For a related epimerization, see: Gore, W. E.; Pearce, G. T.; Silverstein, R. M. *J. Org. Chem.* **1975**, *40*, 1705–1708.

(26) Molecular mechanics calculations (MMPMIX[27] and MacroModel[28]) indicate that the chair-boat conformations depicted for **23α** and **23β** are between 3 and 5 kcal/mol more stable than the alternative double twist-boat forms. A 1.0 kcal/mol difference in energy for the methyl epimers, favoring **23α** as observed, is also predicted by these programs.

(27) Allinger, N. L.; Flanagan, H. L. *J. Comput. Chem.* **1983**, *4*, 399. MMPMIX available from QCPE (J. J. Gajewski, Indiana University).

(28) MacroModel Version 1.5 (W. C. Still, et al., Columbia University).

Scheme V

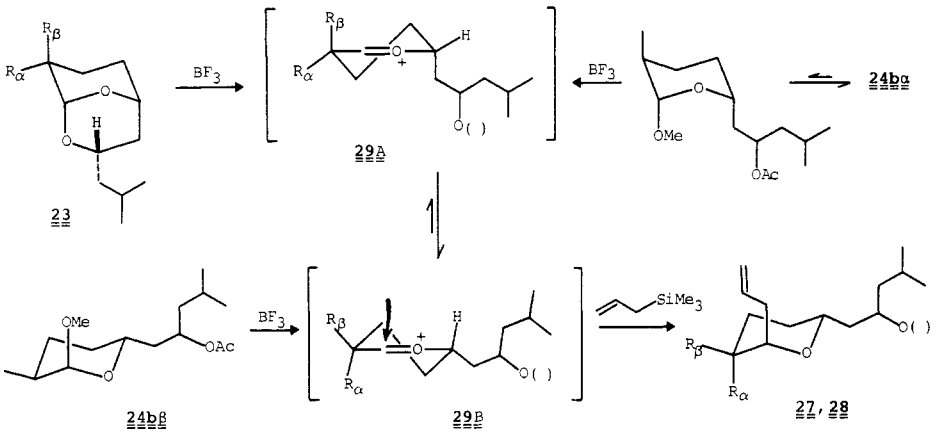
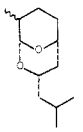
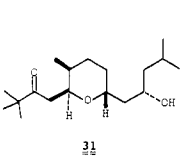
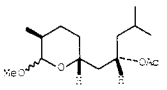
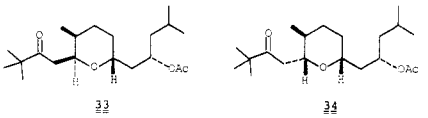
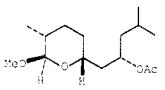
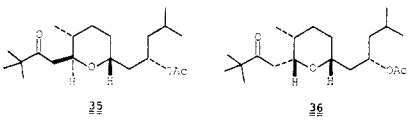


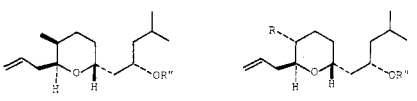
Table IV. Addition of Enolsilane 30 to Cyclic Acetals

30

entry	substrate	catalyst[a]	products[b]	yield,[c] %
			 **31** **32**	
1	78% **23α**, 22% **23β**	$TiCl_4$	23:77	78
2	>95% **23α**	$TiCl_4$	<5:95	86
			 **33** **34**	
3	**24b**	$TiCl_4$	<3:97	57
4	**24b**	$BF_3{\cdot}Et_2O$	92:8	42[d]
5	 **26**		 **35** **36** 33:67	67

[a] Reactions carried out in CH_2Cl_2 solvent at −78 °C. [b] Product ratios determined by capillary gas chromatography. [c] Yields of product after chromatographic purification. [d] Major byproduct is dihydropyran **41** (24% yield).

constant $J_{2,3}$ = 4.4 Hz indicates a cis relationship between the allyl and methyl substituents; the corresponding $J_{2,3}$ = 7.9 Hz in isomer **28a** arises from the allyl–methyl trans-diequatorial conformation. The common stereochemical outcome of all these reactions suggests a common oxonium ion intermediate, **29B**, to which axial addition is strongly preferred (Scheme V).



27a: R" = Ac
27b: R" = H

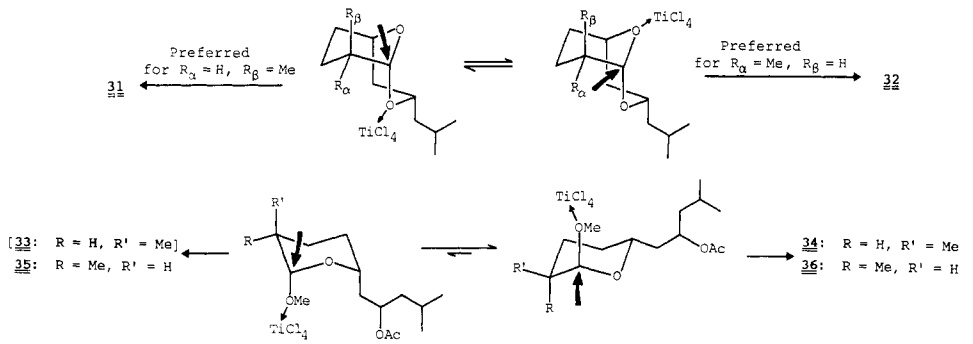
28a: R = Me, R" = Ac
28b: R = Me, R" = H
28c: R = H, R" = Ac

In contrast to the uniform behavior observed with allyltrimethylsilane as the nucleophile, the mode of addition of silyl enol ether **30**[29] is sensitive to the mono- or bicyclic nature of the acetal as well as the Lewis acid catalyst (Table IV). The major products observed on reaction of the mixture of bicyclic acetals **23** (78% α-methyl, 22% β-methyl) with **30** in the presence of $TiCl_4$ are the tetrahydropyran **31** (18% yield) and the eight-membered ring ether **32** (60% yield). That these isomeric products arise separately from the epimeric starting materials was demonstrated by reaction of a purified sample of acetal **23a** under the same conditions: the oxacane **32** was produced in 86% yield as the only significant product (Table IV; entry 2). The oxacane and tetrahydropyran structures were distinguished by ^1H NMR comparison of the corresponding diones obtained on pyridinium chlorochromate oxidation. In the case of the oxacane **32**, oxidation has relatively little effect on the chemical shift or coupling pattern of the resonances of the methylene hydrogens of the isobutyl group. On oxidation of tetrahydropyran **31**, in contrast, a downfield shift of ca. 1 ppm and simplification of the corresponding multiplet pattern to an ABX system demonstrated the presence of an isobutylcarbinol moiety in this isomer.

While addition of enosilane **30** to the monocyclic acetal **24b** (as a mixture of anomers) is also highly stereoselective,

(29) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.

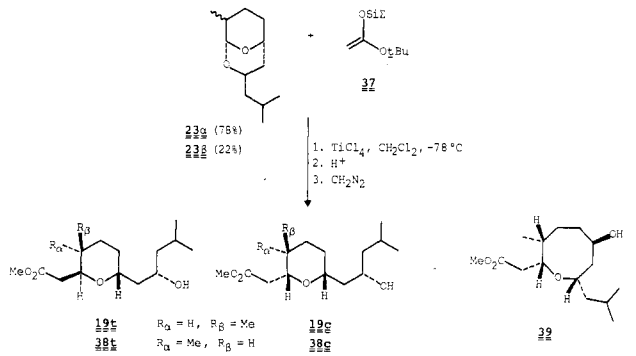
Scheme VI



it is dependent on the Lewis acid (Table IV, entries 3 and 4). Boron trifluoride etherate results in axial attack to give **33**, whereas titanium tetrachloride affords almost exclusively the opposite, cis isomer **34**. The fact that the stereochemical result with BF_3 catalysis (entry 3) is the same as observed for the allyltrimethylsilane additions is consistent with an oxonium ion-type intermediate in this process as well. In contrast, the results with $TiCl_4$ as the Lewis acid are inconsistent with the intermediacy of a free oxonium ion. The dramatically different specificities of the reactions of the bicyclic acetal **23**β (entry 1) and of the monocyclic acetals **24b** with $TiCl_4$ and BF_3 catalysis (entries 3 and 4) indicate that these processes cannot all proceed through the oxonium ion **29b**. The stereo- and regioselectivities observed in the reactions with enolsilane **30** and $TiCl_4$ are consistent with an S_N2-type displacement mechanism. The relative stability of the various isomeric acetal–Lewis acid complexes appears to be the primary factor in determining the course of the reaction. We envisage that the configuration of the coordinated oxygen atom is planar, as observed in a number of titanium–THF complexes;[30] avoidance of $A^{1,3}$ interactions with neighboring equatorial substituents is therefore of major importance. These results thus support the explanation offered previously by Johnson and co-workers for the course of $TiCl_4$-catalyzed additions to 1,3-dioxanes.[31] In bicyclic acetal **23**β, the bridging oxygen atom is hindered sterically by the axial methyl substituent and the flagpole hydrogen across the dioxane ring; coordination with $TiCl_4$ therefore occurs preferentially with the other oxygen and reaction proceeds to give the trans-substituted tetrahydropyran **31** (Scheme VI). The steric congestion in the vicinity of the oxygens is reversed in the epimeric substrate **23a**, hence $TiCl_4$ coordinates to the bridging oxygen and opening to the oxacane is observed. For the monocyclic acetals **24b**, equilibration of the anomers under the reaction conditions and preferential, S_N2-type substitution of the **24b**β isomer would explain formation of the equatorial product **34**. The lower selectivity in the reaction of isomer **26** may also reflect equilibration of the anomers, coupled with a smaller difference in stability between the two reactive conformers (Scheme VI).

Comparable results are obtained on reaction of the bicyclic acetals **23** with ketene acetal **37**,[32] although the selectivities are reduced and the ratio of products is dependent to some extent on the reaction conditions (Scheme VII). $TiCl_4$ was the only effective catalyst that we found for this particular transformation; no reaction was observed with BF_3·OEt_2, $TiCl_4$/$Ti(OiPr)_4$, $SnCl_4$, Et_2AlCl, or *tert*-butyldimethylsilyl triflate, for example. The oxacane **39**

Scheme VII[a]

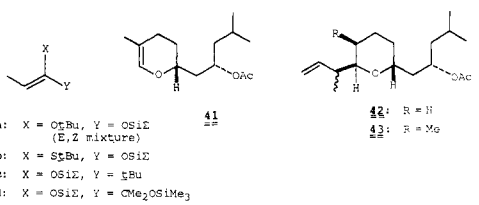


conditions[a]	product composition[b] 19t	19c	38t	38c	39	yield,[c] %
1.4 equiv, 30 + 20 min	44	8	8	2	38	72
5.3 equiv, 25 + 5 min	44	4	7	2	43	56
10 equiv, 5 + 90 min	32	7	4		57	86
5.5 equiv, 25 + 240 min[d]	19	25	21	35		77

[a] Reaction initiated by addition of indicated equivalents of $TiCl_4$ to a solution of equimolar amounts of acetal and enolsilane in CH_2Cl_2 at −78 °C; the times for catalyst addition (via syringe pump) and for continuing reaction prior to workup are given. [b] Product composition determined by capillary GC analysis prior to chromatography. [c] Yield of chromatographed material. [d] Reaction initiated by addition of enolsilane to solution of acetal and $TiCl_4$.

is formed as a single diastereomer, to which we assign the indicated structure based on mass balance and the mechanistic considerations described above.

Our attempts to extend this chemistry to methyl-substituted enolsilanes **40a–d** were less successful.[29,32,33] With the bicyclic acetals **23**, for example, the $TiCl_4$-catalyzed additions proceeded in poor yield and with low selectivity, perhaps reflecting the difficulty of accommodating the bulkier substituted enol derivatives in the S_N2-type transition states. The major byproduct observed in these reactions is the dihydropyran **41**. In contrast, BF_3-catalyzed addition of crotyltributylstannane to the monocyclic acetals **24** and **25** provides the desired trans adduct **42** and **43** in high yield, although they are 1:1 mixtures of epimers at the side-chain position.[34]



(30) Sobota, P.; Utko, J.; Lis, T. *J. Chem. Soc., Dalton Trans.* **1984**, 2077–2079. Folting, K.; Huffman, J. C.; Bansemer, R. L.; Caulton, K. G. *Inorg. Chem.* **1984**, *23*, 3289–3292. Handlovic, M.; Miklos, D.; Zikmund, M. *Acta Crystallogr., Sect. B* **1981**, *B37*, 811–814.

(31) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591–594.

(32) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.

(33) Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth.* **1984**, *63*, 79. Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todesschini, R. *Tetrahedron* **1986**, *42*, 893.

In conclusion, while we did not succeed in our attempt to derive all of the stereocenters in a nigericin A-ring model from that in the progenitor **2a**, the chemistry outlined above provides insight into the nature of acetal cyclization and addition reactions.

Experimental Section[35]

(6*E*)-4-[(Aminocarbonyl)oxy]-2-methyloct-6-ene (2b). To a solution of 1.66 g (11.7 mmol) of (6*E*)-2-methyl-6-octen-4-ol[8a] in 25 mL of CH_2Cl_2 stirred at 0 °C was added a solution of 2.29 g (12.1 mmol) of trichloroacetyl isocyanate in 5 mL of CH_2Cl_2 dropwise over 30 min. After an additional 10 min, a solution of 1.86 g (13.2 mmol) of K_2CO_3 in 15 mL of MeOH and 10 mL of H_2O was added and the mixture was stirred at 0 °C for 4 h and then at 21 °C for 2 h. The mixture was acidified to pH 6 with 0.5 M H_2SO_4 and partitioned between CH_2Cl_2 and H_2O. The organic layer was worked up to give 2.16 g (100%) of carbamate **2b** as a white solid, mp 62–63 °C. An analytical sample was prepared by chromatography (25% EtOAc/hexanes): mp 64–65 °C; IR 3565, 3448, 2970, 1737, 1582, 1327, 1049 cm^{-1}; ^1H NMR δ 0.92 (d, 6, J = 6.6), 1.30 (m, 1), 1.50 (m, 1), 1.64 (m, 1), 1.66 (d, 3, J = 5.5), 2.25 (t, 2, J = 5.5), 4.68 (s, 2), 4.82 (m, 1), 5.45 (m, 1); ^{13}C NMR δ 17.9, 22.1, 23.1, 24.5, 38.1, 42.7, 72.9, 126.0, 128.0, 157.2. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.68; H, 10.47; N, 7.57.

(4*R,6*R**)-4-[(1*S**)-1-Iodoethyl]-6-(2-methylpropyl)-1,3-dioxan-2-one (3).** To a mixture of 112.8 mg (0.609 mmol) of **2b** in 5 mL of Et_2O and 2 mL of saturated $NaHCO_3$ was added 466 mg (1.84 mmol) of I_2. After being stirred for 12 h, the reaction mixture was partitioned between ether and saturated $NaHCO_3/Na_2S_2O_3$. The organic layer was washed with saturated $NaHCO_3$ and $Na_2S_2O_3$ and worked up to give 185 mg (97%) of **3** as a colorless oil, which was used without further purification. An analytical sample was prepared by chromatography (25% EtOAc/hexanes): IR 2975, 1750, 1231, 1119, 1111 cm^{-1}; ^1H NMR δ 0.96 (d, 6, J = 6.6), 1.42 (m, 1), 1.72 (m, 1), 1.92 (m, 1), 1.99 (d, 3, J = 7.0), 2.43 (dt, 1, J = 3.5, 13.8), 4.19 (m, 2), 4.53 (m, 1); ^{13}C NMR δ 21.7, 22.7, 23.2, 23.5, 27.2, 32.7, 43.8, 76.3, 81.3, 148.5. Anal. Calcd for $C_{10}H_{17}IO_3$: C, 38.48; H, 5.49; I, 40.65. Found: C, 38.71; H, 5.59; I, 40.87.

(4*R,6*R**)-4-Ethenyl-6-(2-methylpropyl)-1,3-dioxan-2-one (4).** To a solution of 185 mg (0.609 mmol) of **3** prepared above in 8 mL of CH_2Cl_2 and 4 mL of saturated $NaHCO_3$ was added 469 mg (2.17 mmol based on 80% purity) of *m*-chloroperbenzoic acid (*m*CPBA). After being stirred for 2.5 h, the reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHSO_3/NaHCO_3$. The organic layer was worked up to give 130 mg (>100% crude yield) of allylic carbonate **4** as a colorless oil, which was used without further purification. Capillary GC analysis (column 2) indicated a 17:1 ratio of isomers. An analytical sample was prepared by chromatography (25% EtOAc/hexanes): IR 2980, 1749, 1391, 1234, 1114 cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 6.6), 0.96 (d, 3, J = 6.6), 1.40 (m, 1), 1.55–1.66 (m, 2), 1.88–1.95 (m, 1), 2.13 (dt, 1, J = 4.0, 17.4), 4.44–4.51 (m, 1), 4.90 (m, 1), 5.30 (d, 1, J = 10.5), 5.43 (d, 1, J = 17.2), 5.87 (ddd, 1, J = 6.0, 10.5, 17); ^{13}C NMR δ 21.8, 22.7, 23.6, 33.5, 44.1, 76.9, 78.6, 117.9, 134.2, 148.8. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.98; H, 8.60.

(1*R,3*R**)-3-Hydroxy-1-(2-methylpropyl)-4-pentenyl Dimethylcarbamate (5a).** Into a flask charged with 2.10 g (11.4 mmol) of carbonate **4** cooled to −78 °C was condensed 10 mL of dimethylamine. The cooling bath was removed and the reaction was allowed to warm to reflux temperature (7 °C) for 1 h, and the excess dimethylamine was allowed to evaporate. Further evaporation under 0.1-mm vacuum gave 3.89 g of yellow oil. Chromatography (10–25% EtOAc/hexanes) afforded 1.49 g (57% yield) of **5a** as a colorless oil. An analytical sample was prepared by preparative GC (column 4, 170 °C): IR 3430, 2960, 1685, 1402, 1201 cm^{-1}; ^1H NMR δ 0.90 (d, 6, J = 7), 1.37 (m, 1), 1.65 (m, 2), 1.80 (m, 2), 2.30–2.57 (br s, 1), 2.89 (s, 6), 4.26 (m, 1), 4.96 (m, 1), 5.05 (d, 1, J = 10.2), 5.25 (d, 1, J = 16.3), 5.85 (ddd, 1, J = 5.4, 10.2, 16.4). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.10; N, 6.10. Found: C, 62.59; H, 10.19; N, 5.96.

(1*R,3*R**)-1-(2-Methylpropyl)-3-(propanoyloxy)-4-pentenyl Dimethylcarbamate (5c).** To a solution of 1.47 g (6.39 mmol) of **5a** in 15 mL of CH_2Cl_2 cooled to 0 °C were added 0.90 mL (7.0 mmol) of propanoic anhydride, 20 mg (0.16 mmol) of 4-(dimethylamino)pyridine (DMAP), and 0.80 mL (9.9 mmol) of pyridine. The solution was stirred for 2.5 h and warmed to 21 °C for an additional 4 h, and the reaction mixture was partitioned between CH_2Cl_2 and 1 M H_2SO_4. The organic layer was worked up and the crude product was purified by chromatography (10% EtOAc/hexanes) to give 1.02 g (56% yield) of ester **5c** as a colorless oil. An analytical sample was prepared by preparative GC (column 4, 173 °C): IR 2965, 1741, 1706, 1469, 1398, 1191 cm^{-1}; ^1H NMR δ 0.90 (d, 3, J = 7), 0.91 (d, 3, J = 7), 1.14 (t, 3, J = 7), 1.35 (m, 1), 1.50–1.67 (m, 2), 1.99 (m, 1), 2.36 (q, 2, J = 7), 2.92 (s, 6), 4.89 (m, 1), 5.23 (m, 2), 5.35 (m, 1), 5.83 (ddd, 1, J = 6, 10, 17). Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.53; N, 4.90. Found: C, 63.45; H, 9.69; N, 4.95.

If this procedure is carried out without intermediate purification of carbamate **5a**, a 76% overall yield from carbonate **4** can be realized.

Methyl (2*R,4*E*,7*R**)-2,9-Dimethyl-7-[(dimethylcarbamoyl)oxy]-4-decenoate (6).** A solution of 2.50 mL (17.8 mmol) of diisopropylamine in 40 mL of THF was cooled to 0 °C and was treated with 11.3 mL (16.8 mmol) of 1.49 M *n*-butyllithium in hexanes. After being stirred for 15 min, the solution was cooled to −78 °C and 35 mL of HMPA and 60 mL of THF were added. The resultant yellow slurry was stirred for 15 min and treated with a solution of 961 mg (3.37 mmol) of **5c** in 5 mL of THF. After being stirred for 5 min, a solution of 4.09 g (27.2 mmol) of *tert*-butyldimethylsilyl chloride in 10 mL of THF was added and the mixture was allowed to warm to 21 °C over 1.5 h. After being stirred for 7.5 h, the reaction mixture was partitioned between hexanes and 1 M H_2SO_4, and the organic layer was worked up to give the silyl ester as a slightly yellow oil. This material was dissolved in 75 mL of THF and treated with 3 mL of 6 M H_2SO_4 for 11 h and then made basic with 0.2 M NaOH. The aqueous layer was washed with ether, acidified with 6 M H_2SO_4, and then extracted with ether. The combined organic layer was worked up to give 1.15 g of the acid as a yellow oil. The acid was dissolved in 50 mL of Et_2O at 0 °C and was treated with excess ethereal CH_2N_2 for 10 min. Evaporation of the solvent and chromatographic purification (25% EtOAc/hexanes) of the residue afforded 699 mg (69% yield) of ester **6**. Capillary GC analysis (column 3) showed a 9.7:1 ratio of **6** and its methyl diastereomer: ^1H NMR δ 0.91 (d, 6, J = 7), 1.14 (d, 3, J = 7), 1.27 (m, 2), 1.53 (m, 1), 2.12 (m, 1), 2.24 (m, 2), 2.35 (m, 1), 2.48 (m, 1), 2.88 (br s, 3), 2.90 (br s, 3), 3.66 (s, 3), 4.83 (m, 1), 5.42 (m, 2); ^{13}C NMR δ 16.3, 22.3, 23.1, 24.6, 36.1, 36.2, 36.5, 38.1, 39.4, 42.8, 51.4, 72.8, 127.9, 129.7, 156.4, 176.5; additional ^{13}C resonances for the diastereomer were seen at δ 16.4, 22.3, 23.1, 24.6, 36.1, 36.2, 36.6, 38.2, 39.5, 42.9, 51.5, 72.9, 128.0, 129.9, 156.4, 176.6. Anal.

(34) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239–2246. Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927–3930.

(35) **General**: Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All reactions were performed under a dry nitrogen atmosphere. Tetrahydrofuran, diethyl ether, toluene, and hexanes were distilled from sodium/benzophenone ketal immediately prior to use. Diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), CH_2Cl_2, methanol, and acetonitrile were distilled from calcium hydride. Unless otherwise indicated, reaction workups culminated in washing the organic layer with brine, drying over $MgSO_4$, and removing the solvent on a rotary evaporator under reduced pressure. Chromatography was performed on silica gel 60 (E. Merck, Darmstadt) 100–120 mesh, with the indicated solvents. NMR spectra were acquired in $CDCl_3$ at 250 or 500 MHz (^1H) or at 50.8 or 63.1 MHz (^{13}C). Coupling constants are in hertz. Capillary gas chromatography (GC) was performed with a Hewlett Packard Model 5790A capillary gas chromatograph equipped with a flame ionization detector and helium as carrier gas on one of the following columns: column 1, 5% cross-linked phenylmethyl silicone, 25 m × 0.2 mm; column 2, cross-linked dimethyl silicone, 12.5 m × 0.2 mm; column 3, 5% Carbowax 20M, 25 m × 0.2 mm. Preparative GC was performed on a Shimadzu Model 8A gas chromatograph equipped with a thermal conductivity detector and helium as carrier gas on one of the following columns: column 4, 3% Silicone OV-101 on Chromosorb W-HP, 80/100 mesh, 6 ft × 1/4 in; column 5, 5% Carbowax 20M on Chromosorb W-HP, 80/100 mesh, 6 ft × 1/4 in. Mass spectral data are tabulated as m/z (intensity expressed as percent total ion current).

Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.32; H, 9.72; N, 4.61.

Methyl ($\alpha R^*,\gamma R^*,4R^*,6R^*$)-γ-Iodo-α-methyl-6-(2-methylpropyl)-2-oxo-1,3-dioxane-4-butanoate (7). A mixture of 675 mg (2.25 mmol) of carbamate **6**, 1.89 g (7.46 mmol) of I_2, 40 mL of Et_2O, and 20 mL of saturated $NaHCO_3$ was stirred for 3.5 h and then partitioned between ether and saturated $Na_2S_2O_3/NaHCO_3$. The organic layer was worked up to give 929 mg of the iodo carbonate **7** as slightly yellow oil, which was used immediately without further purification. Material from a separate experiment was purified for analysis by chromatography (25% EtOAc/hexanes): IR 2965, 1742, 1391, 1200, 1125; ^1H NMR δ 0.98 (d, 6, J = 6.6), 1.26 (d, 3, J = 6.6), 1.42 (m, 1), 1.75 (m, 1), 1.93 (m, 1), 2.29 (m, 2), 2.83 (m, 1), 3.71 (s, 3), 4.24 (m, 2), 4.51 (m, 1); ^{13}C NMR δ 18.1, 21.9, 22.8, 23.7, 29.6, 32.8, 34.9, 39.4, 44.0, 51.9, 76.3, 80.6, 148.5, 175.6. Anal. Calcd for $C_{14}H_{23}IO_5$: C, 42.23; H, 5.82; I, 31.87. Found: C, 42.59; H, 6.01; I, 31.50.

Methyl ($\alpha R^*,4S^*,6R^*$)-α-Methyl-6-(2-methylpropyl)-2-oxo-1,3-dioxane-4-butanoate (8). A solution of 929 mg (2.25 mmol) of the crude iodo carbonate **7** described above and 0.74 mL (2.76 mmol) of tributyltin hydride in 50 mL of THF was heated to reflux for 1 h. The solvent was evaporated and the residue taken up in 70 mL of CH_3CN and washed with four 20-mL portions of hexane. The combined hexane phase was extracted with two 10-mL portions of acetonitrile and the combined acetonitrile layer was evaporated to give 724 mg of a colorless oil. Chromatography (25% EtOAc/hexanes) afforded 43.3 mg (6%) of olefin **6** and 500 mg (87% yield from **6**, based on recovered starting material) of carbonate **8** as a colorless oil: IR 2960, 1740, 1466, 1381, 1221, 1122 cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 6.6), 0.96 (d, 3, J = 6.6), 1.19 (d, 3, J = 6.6), 1.31 (m, 1), 1.38 (m, 1), 1.48–1.79 (m, 4), 1.83 (m, 1), 1.90 (m, 1), 2.01 (dt, 1, J = 3.9, 14.5), 2.50 (m, 1), 3.68 (s, 3), 4.45 (m, 2); ^{13}C NMR δ 16.8, 21.8, 22.6, 23.6, 28.0, 32.5, 33.1, 38.6, 44.1, 51.4, 77.0, 78.1, 149.3, 176.3; resonances for the methyl epimer could be discerned at δ 17.0, 28.4, 32.9, 33.3, 38.9, 78.5. Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.50; H, 9.06.

($3R,6S^*$)-6-[($2R^*$)-2-Hydroxy-4-methylpentyl]-3-methyl-2-oxotetrahydropyran (9) and the ($3R^*,6R^*$)-6-[($2S^*$)] Isomer (10). A solution of 3.33 g (12.2 mmol) of **8** and 5.11 g (36.9 mmol) of K_2CO_3 in 120 mL of methanol and 6 mL of H_2O was stirred for 15 h, acidified with 1 M H_2SO_4, and extracted with ether. The organic layer was worked up to give a colorless oil, which was dissolved in 200 mL of benzene with 10 mg of p-toluenesulfonic acid (pTsOH) and heated to reflux for 10 h with azeotropic removal of water. The solvent was evaporated and the residue was chromatographed (25–50% EtOAc/hexanes) to afford 2.52 g (96% yield) of the lactones **9** and **10** as a 5.3:1 mixture: IR 3390, 2965, 1736, 1385, 1100 cm^{-1}; ^1H NMR δ (**9**) 0.93 (d, 6, J = 6.6), 1.31 (d, 3, J = 6.6), 1.47 (m, 2), 1.60 (m, 1), 1.70 (m, 2), 1.84 (m, 2), 2.02 (m, 1), 2.13 (m, 1), 2.45 (m, 1), 3.89 (m, 1), 4.55 (m, 1); (**10**) 0.93 (d, 6, J = 6.6), 1.23 (d, 3, J = 6.6), 1.47 (m, 2), 1.60 (m, 1), 1.70 (m, 2), 1.84 (m, 2), 2.02 (m, 1), 2.13 (m, 1), 2.64 (m, 1), 3.89 (m, 1), 4.55 (m, 1); ^{13}C NMR δ (**9**) 17.2, 22.0, 23.3, 24.5, 25.6, 29.4, 33.2, 36.1, 44.2, 47.0, 67.5, 175.0; (**10**) 16.2, 22.0, 23.3, 24.5, 26.8, 28.5, 33.2, 36.1, 43.2, 47.0, 81.0, 175.0. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.90; H, 10.46.

($2R^*,5S^*,7R^*$)-2,9-Dimethyl-1,5,7-decanetriol (16a). To a solution of 436 mg (1.60 mmol) of carbonate **8** (9:1 mixture of isomers) in 15 mL of Et_2O at 0 °C was added 119 mg (3.14 mmol) of lithium aluminum hydride. After being stirred for 5 min, the reaction mixture was warmed to 21 °C for 1 h before the addition of 6 g (18.6 mmol) of $Na_2SO_4 \cdot 10H_2O$. The suspension was stirred for 12 h, filtered, and evaporated to afford 355 g (100% yield) of triol **16a** as a colorless oil, again as a 9:1 mixture of methyl epimers. This material was carried on to the next step without purification; an analytical sample was prepared separately and purified by preparative GC: IR 3350, 2960, 1470, 1043 cm^{-1}; ^1H NMR ($CDCl_3/D_2O$) δ 0.93 (d, 9, J = 6.6), 1.15–1.29 (m, 2), 1.50 (m, 7), 1.74 (m, 1), 3.45 (m, 2), 3.88 (m, 2); ^{13}C NMR δ (major isomer) 16.6, 22.1, 23.1, 24.1, 28.7, 34.9, 35.5, 43.3, 47.1, 67.1, 70.4, 72.9; (minor isomer) 16.3, 28.2, 34.5, 35.2, 67.3, 72.2. Anal. Calcd for $C_{12}H_{26}O_3$: C, 66.01; H, 12.00. Found: C, 66.35; H, 11.78.

($\beta R^*,2S^*,4S^*,6R^*$)-β-Methyl-6-(2-methylpropyl)-2-phenyl-1,3-dioxane-4-butanol (16b). A solution of 355 mg (≤1.60 mmol) of **16a** (9:1 mixture of isomers), 0.18 mL (1.77 mmol) of benzaldehyde, and 2 mg of pTsOH in 30 mL of benzene was heated to reflux for 6 h with azeotropic removal of H_2O via a Dean–Stark trap. The solution was concentrated and the residue was chromatographed (15% EtOAc/hexanes) to afford 446 mg (91% yield) of **16b** as a colorless oil: IR 3400, 2935, 1345, 1116, 1030 cm^{-1}; ^1H NMR δ 0.94 (d, 9, J = 6.6), 1.15–1.56 (m, 6), 1.57–1.79 (m, 4), 1.90 (m, 1), 3.42–3.51 (m, 2), 3.78–3.89 (m, 2), 5.50 (s, 1), 7.42 (m, 5); ^{13}C NMR δ (major isomer) 16.5, 22.3, 23.0, 23.9, 28.3, 33.2, 35.5, 37.3, 44.9, 67.7, 75.0, 77.2, 100.3, 125.9, 128.0, 128.3, 138.9; (minor isomer) 16.4, 22.3, 23.0, 23.9, 28.2, 33.1, 35.4, 37.3, 44.9, 67.7, 75.0, 77.0, 100.3, 125.9, 128.0, 128.3, 138.9. Anal. Calcd for $C_{18}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.65; H, 10.01.

($\alpha R^*,2S^*,4S^*,6R^*$)-α-Methyl-6-(2-methylpropyl)-2-phenyl-1,3-dioxane-4-butanal (17b). To a solution of 446 mg (1.46 mmol) of alcohol **16b** (9:1 mixture of isomers) and 64 mg (0.78 mmol) of powdered NaOAc in 15 mL of CH_2Cl_2 was added 579 mg (2.69 mmol) of pyridinium chlorochromate. The reaction mixture was stirred for 10 h and then diluted with 50 mL of Et_2O, and the resultant brown slurry was stirred vigorously for 2 h. The solvent was decanted and the residue triturated with ether (3 × 5 mL). The combined ether fractions were concentrated to give 390 mg (88% crude yield) of the aldehyde **17b** as a clear oil, which was used without further purification. An analytical sample was prepared by chromatography (8% EtOAc/hexanes): IR 2965, 1730, 1710, 1460, 1123, 1033 cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 6.6), 0.96 (d, 3, J = 6.6), 1.11 (d, 3, J = 6.6), 1.20–1.45 (m, 2), 1.47–1.84 (m, 5), 1.86–1.95 (m, 2), 2.20 (m, 1), 3.86 (m, 1), 5.50 (s, 1), 7.42 (m, 5), 9.68 (s, 1); ^{13}C NMR δ 13.3, 22.4, 23.1, 24.0, 25.9, 33.3, 37.4, 45.0, 46.1, 75.0, 76.5, 100.4, 126.0, 128.1, 128.4, 138.9, 205.0; resonances for the methyl epimer could be discerned at δ 13.5, 26.0, 33.1, 46.2. Anal. Calcd for $C_{18}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.82; H, 9.49.

($2R^*,4R^*,6S^*$)-4-[($3S^*$)-3-Methyl-4-pentenyl]-6-(2-methylpropyl)-2-phenyl-1,3-dioxane (18b). To a stirring suspension of 802 mg (2.25 mmol) of methyltriphenylphosphonium bromide in 3 mL of THF was added 1.45 mL (2.16 mmol) of 1.49 M n-BuLi in hexane. After 5 min, a solution of 390 mg (1.45 mmol) of aldehyde **17b** in 4 mL of THF was added and the solution was stirred for 5 h. The reaction mixture was partitioned between saturated NH_4Cl and Et_2O, and the organic layer was worked up to give 867 mg of an orange oil. Chromatography (10% EtOAc/hexanes) afforded 357 mg (92% yield) of olefin **18b** as a colorless oil: IR 2960, 1347, 1120, 1030, 700 cm^{-1}; ^1H NMR δ 0.95 (d, 3, J = 6.6), 0.96 (d, 3, J = 6.6), 1.01 (d, 3, J = 6.6), 1.15–1.40 (m, 4), 1.41–1.56 (m, 4), 1.90 (m, 1), 2.14 (m, 1), 3.82 (m, 2), 4.92 (d, 1, J = 10.5), 4.98 (d, 1, J = 17.0), 5.50 (s, 2), 5.70 (ddd, 1, J = 8.0, 10.4, 17.4), 7.42 (m, 5); ^{13}C NMR δ 20.2, 22.4, 23.1, 24.0, 31.8, 33.6, 37.5, 37.7, 45.1, 75.1, 77.1, 100.4, 112.7, 126.0, 128.0, 128.3, 139.2, 144.4. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.59; H, 10.19.

($4R^*,6S^*,9R^*$)-2,9-Dimethyl-10-undecene-4,6-diol (18a). To a solution of 308 mg (1.02 mmol) of **18b** (in this case a 7:1 mixture of isomers) in 7 mL of THF and 40 mL of liquid ammonia at −23 °C was added 40 mg (1.7 mmol) of sodium. The resultant blue solution was stirred for 20 min and then quenched by the addition of MeOH, and the reaction mixture was allowed to warm and evaporate at 21 °C. The residue was partitioned between ether and 1 M H_2SO_4, and the organic layer was worked up to give 252 mg of colorless oil. Chromatography (EtOAc) afforded 14.8 mg (5% yield) of recovered starting material and 199 mg (91% yield) of diol **18a** as a colorless oil. An analytical sample was prepared by preparative GC (column 4, 165 °C): IR 3365, 2970, 1461, 917 cm^{-1}; ^1H NMR δ 0.94 (d, 6, J = 6.7), 1.01 (d, 3, J = 6.7), 1.15–1.33 (m, 2), 1.37–1.68 (m, 6), 1.75 (m, 1), 2.12 (m, 1), 2.85 (br s, 1), 2.99 (br s, 1), 3.70–4.00 (m, 2), 4.96 (m, 2), 5.68 (m, 1). Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.22. Found: C, 72.68; H, 12.40.

Preparation and characterization of the other acetal derivatives of **18** are described in the supplementary material.

General Procedure for Palladium Cyclization of Acetals. A mixture of the acetal (0.100 mmol), $PdCl_2$ (0.030 mmol), and $CuCl_2$ (0.400 mmol) was placed in a flask equipped with a three-way stopcock and was alternately evacuated (0.1 mm) and placed under 1.1 atm of CO three times. Methanol (1–2 mL) and trimethyl orthoformate (50–100 μL) were added and the solution was degassed twice by briefly evacuating and bleeding in CO. The solution was stirred for 1–4 h, during which time the solution changed from bright green to brown/yellow in color; if the solution became colorless with a black precipitate, an additional 1–2 mg

of $PdCl_2$ and 5–10 mg of $CuCl_2$ were added and stirring was continued for 1 h. The reaction mixture was partitioned between 1 M H_2SO_4 and ether, and the combined organic layer was washed (NaCl), dried ($MgSO_4$), and evaporated. The residue was analyzed by capillary GC and purified by chromatography.

Methyl (2*R,3*R**,6*S**)-6-[(2*R**)-2-Hydroxy-4-methylpentyl]-3-methyl-2-tetrahydropyranacetate (19t) and the (2*R**,3*S**,6*R**)-6-[(2*S**)] Isomer (19c) from 18b.** Acetal **18b** (32.1 mg, 0.106 mmol) was cyclized with 9.2 mg (0.052 mmol) of $PdCl_2$ and 69.4 mg (0.52 mmol) of $CuCl_2$ according to the general procedure to furnish the crude product as a colorless oil. Capillary GC analysis (column 1, 125 °C for 1 min, then 5 °C/min to 250 °C) indicated a 1:2.9 ratio of **19t**:**19c**. Chromatography (25% EtOAc/hexanes) of this material gave 22.7 mg (79% yield) of the mixture of isomers as a colorless oil. An analytical sample of the mixture was prepared by preparative GC (column 4, 191 °C): Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.40; H, 10.50. IR 3520, 2965, 1750, 1441, 1200, 1080 cm^{-1}; HPLC separation (7% EtOAc/30% CH_2Cl_2/63% hexanes; 10 × 50 mm Ultrasphere SiO_2) allowed the major isomers to be characterized separately; ^1H NMR δ (**19t**) 0.81 (d, 3, J = 7.0), 1.10 (ddd, 1, J = 4.8, 8.3, 13.4), 1.25–1.42 (m, 4), 1.45–1.52 (m, 3), 1.60 (m, 1), 1.62–1.83 (m, 1), 1.95 (br s, 1), 2.35 (dd, 1, J = 4.2, 14.1), 2.83 (dd, 1, J = 11.5, 14.1), 3.74 (s, 3), 3.74–3.91 (m, 2), 4.33 (ddd, 1, J = 4.7, 4.7, 11.2); (**19c**) δ 0.84 (d, 3, J = 7.0), 0.88 (d, 3, J = 6.8), 0.90 (d, 3, J = 6.8), 1.14 (ddd, 1, J = 5.1, 8.6, 13.3), 1.18–1.35 (m, 1), 1.35–1.47 (m, 3), 1.48–1.64 (m, 3), 1.70–1.85 (m, 2), 2.37 (dd, 1, J = 9.8, 14.9), 2.65 (dd, 1, J = 2.8, 14.9), 2.85–3.10 (br s, 1), 3.47 (ddd, 1, J = 2.8, 9.7, 9.7), 3.58 (m, 1), 3.71 (s, 3), 3.80–3.93 (m, 1); ^{13}C NMR (**19t**) δ 17.2, 22.2, 23.3, 24.3, 26.4, 31.9, 32.2, 32.7, 43.1, 47.6, 51.9, 69.8, 71.0, 74.4, 172.3; (**19c**) δ 17.5, 22.3, 23.2, 24.3, 32.3, 34.9, 38.7, 43.2, 46.7, 51.8, 70.0, 79.4, 80.3, 172.3.

Preparation and characterization of the (iodomethyl)- and methyl-substituted tetrahydropyrans **20** and **21**, respectively, are described in the supplementary material.

(3-*endo*,8-*exo*)-8-Methyl-3-(2-methylpropyl)-2,9-dioxabicyclo[3.3.1]nonane (23β) and the (3-*endo*,8-*endo*) Isomer (23α). A solution of 65 mg (0.148 mmol) of lactol **24a** and 3 mg of *p*-toluenesulfonic acid in 40 mL of benzene was heated to reflux for 2.5 h with azeotropic removal of water. The solution was diluted with ether, washed with saturated $NaHCO_3$, and worked up, and the residue was chromatographed (10% EtOAc/hexanes) to afford 13.1 mg (45% yield from lactone **9**) of the bicyclic acetals **23α** and **23β** as a 3:1 mixture of isomers. An analytical sample was prepared by preparative GC (column 4, 136 °C): IR 2960, 2892, 1421, 1123 cm^{-1}; ^1H NMR δ (**23α**) 0.87 (d, 3, J = 6.7), 0.93 (d, 3, J = 6.7), 0.94 (d, 3, J = 6.7), 1.17–1.31 (m, 1), 1.31–1.51 (m, 4), 1.57–1.69 (m, 3), 2.06–2.18 (m, 1), 3.96 (m, 1), 4.17 (m, 1), 5.01 (br s, 1); (**23β**) 0.93 (d, 6, J = 6.7), 1.05 (d, 3, J = 6.7), 1.17–1.30 (m, 2), 1.35–1.55 (m, 2), 1.70–1.85 (m, 3), 2.00–2.20 (m, 2), 2.26–2.42 (m, 1), 3.97–4.09 (m, 1), 4.13–4.23 (m, 1), 4.95 (br s, 1). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.87; H, 11.15.

A pure sample of **23α** (>20:1 ratio of isomers) was isolated by preparative GC (column 4, 136 °C).

(2*RS*,3*R,6*S**)-2-Hydroxy-6-[(2*R**)-2-hydroxy-4-methylpentyl]-3-methyltetrahydropyran (24a).** To a solution of 140 mg (0.653 mmol) of lactone **9** (as a 7:1 mixture of isomers) in 5 mL of THF cooled to −78 °C was added 1.60 mL (1.60 mmol) of 1.0 M diisobutylaluminum hydride (DIBAL) in hexanes. The reaction mixture was stirred for 30 min and then quenched by the addition of 0.5 mL of methanol followed by acidification with 1 M H_2SO_4. The mixture was extracted with ether and the organic layer was washed with saturated $NaHCO_3$ and worked up, and the residue was chromatographed (50% EtOAc/hexanes) to afford 142 mg (100% yield) of the lactol **24a** as a colorless oil: IR 3400, 2965, 1466, 1078 cm^{-1}; ^1H NMR δ 0.89 (d, 3, J = 6.6), 0.90 (d, 3, J = 6.6), 0.91 (d, 3, J = 6.6), 1.20 (m, 2), 1.55 (m, 3), 1.75 (m, 2), 3.52 (m, 1), 3.70 (m, 1), 4.35 (m, 1), 5.00 (m, 1). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.24; H, 10.98.

(2*R,3*S**,6*R**)-6-[(2*S**)-2-Acetoxy-4-methylpentyl]-2-methoxy-3-methyltetrahydropyran (24bβ), the (2*R**,3*R**,6*S**)-6-[(2*R**)] Isomer (24bα), and the (2*R**,3*R**,6*R**)-6-[(2*S**)] Isomer (26).** To a solution of 1.90 g (8.88 mmol) of lactone **9** (5:1 mixture of isomers) in 150 mL of Et_2O at −78 °C was added 25.0 mL (20.0 mmol) of a 0.80 M solution of DIBAL in hexane. An additional 8.0 mL (6.4 mmol) of the DIBAL solution was added in two 4-mL portions after 30 min and 1 h. After being stirred for an additional 1.5 h, the reaction mixture was quenched by the addition of 3 mL of methanol and 3 mL of 1 M H_2SO_4. The mixture was warmed to room temperature, acidified to pH 2 with 6 M H_2SO_4, and extracted with ether, and the organic layer was worked up to afford 2.86 g of a colorless oil. The residue was dissolved in 20 mL of anhydrous methanol and treated with 30 mg of acetyl chloride and 1 mL of trimethyl orthoformate for 30 min. The solution was partitioned between saturated $NaHCO_3$ and ether, and the organic layer was worked up to afford 2.54 g of the crude mixture of methyl acetals. This material was chromatographed (5% EtOAc/5% CH_2Cl_2/hexanes) to give 615 mg (30%) of desacetyl-**24bβ** and desacetyl-**24bα** (first and third diastereomers to elute), 201 mg (10%) of desacetyl-**26** (second diastereomer to elute), and 731 mg (36%) of mixed fractions containing all three diastereomers: MS, m/z 229 (M − 1, 0.2), 226 (1), 212 (3), 141 (24), 87 (73); HRMS, calcd for $C_{13}H_{25}O_3$ (M − 1) m/z 229.1803, found m/z 229.1792. Careful chromatography under the same conditions afforded pure samples of each diastereomer for analysis.

Desacetyl-24bβ: IR 3525, 2940, 1468, 1109, 1055 cm^{-1}; ^1H NMR δ 0.92 (m, 9), 1.11–1.23 (m, 1), 1.25–1.37 (m, 1), 1.39–1.64 (m, 6), 1.67–1.91 (m, 3), 3.39 (s, 3), 3.85–3.97 (m, 2), 4.49 (d, 1, J = 3.1).

Desacetyl-24bα: IR 3510, 2960, 1467, 1170, 1066, 1008 cm^{-1}; ^1H NMR δ 0.92 (d, 3, J = 6.4), 0.93 (d, 3, J = 6.4), 1.12–1.36 (m, 3), 1.37–1.58 (m, 4), 1.60–1.72 (m, 2), 1.74–1.85 (m, 2), 3.47 (s, 3), 3.61–3.73 (m, 1), 3.87–3.96 (m, 1), 3.97 (d, 1, J = 8.4).

Desacetyl-26: IR 3500, 2940, 1471, 1286, 1144, 1104, 1047 cm^{-1}; ^1H NMR δ 0.84 (d, 3, J = 6.7), 0.85 (d, 3, J = 6.7), 0.97 (d, 3, J = 7.2), 1.10 (ddd, 1, J = 4.3, 8.2, 12.6), 1.17–1.56 (m, 7), 1.64–1.80 (m, 2), 1.85–2.02 (m, 1), 3.34 (s, 3), 3.77–3.95 (m, 2), 4.32 (br s, 1).

A solution of 608 mg (2.64 mmol) of desacetyl-**24bα** and desacetyl-**24bβ**, 1.00 mL (12.4 mmol) of pyridine, 0.75 mL (7.95 mmol) of acetic anhydride, and 64 mg (0.52 mmol) of 4-(dimethylamino)pyridine (DMAP) in 10 mL of CH_2Cl_2 was stirred at 21 °C for 5 h and then partitioned between CH_2Cl_2 and water. The organic layer was washed with 1 M H_2SO_4 and worked up, and the residue was chromatographed (10% EtOAc/5% CH_2Cl_2/hexanes) to give 662 mg (92% yield) of **24bα** and **24bβ** as a colorless oil. Further chromatographic purification (5% EtOAc/5% CH_2Cl_2/hexanes) afforded analytical samples of each diastereomer.

24bβ: IR 2965, 2940, 1727, 1374, 1253, 1051 cm^{-1}; ^1H NMR δ 0.86 (d, 3, J = 6.8), 0.92 (d, 3, J = 6.5), 0.93 (d, 3, J = 6.5), 1.18–1.38 (m, 2), 1.41–1.72 (m, 6), 1.74–1.92 (m, 2), 2.04 (s, 3), 3.36 (s, 3), 3.63–3.76 (m, 1), 4.45 (d, 1, J = 3.1), 5.08–5.20 (m, 1); MS, m/z 271 (M − 1, 0.2), 241 (36), 212 (43), 170 (90), 129 (79); HRMS, calcd for $C_{15}H_{27}O_4$ (M − 1) m/z 271.1909, found m/z 271.1898.

24bα: IR 2965, 1727, 1375, 1249, 1059, 1020 cm^{-1}; ^1H NMR δ 0.90 (d, 6, J = 6.7), 0.92 (d, 3, J = 6.6), 1.13–1.49 (m, 4), 1.50–1.72 (m, 4), 1.74–1.83 (m, 1), 1.85–2.01 (m, 1), 2.04 (s, 3), 3.37–3.48 (m, 1), 3.47 (s, 3), 3.86 (d, 1, J = 8.3), 5.09–5.20 (m, 1); MS, m/z 271 (M − 1, 0.9), 212 (37), 170 (84), 129 (89); HRMS, calcd for $C_{15}H_{27}O_4$ (M − 1) m/z 271.1909, found m/z 271.1897.

In a similar manner desacetyl-**26** was converted to **26** (79% yield): IR 2960, 1726, 1371, 1250, 1043, 944 cm^{-1}; ^1H NMR δ 0.90 (d, 3, J = 6.5), 0.91 (d, 3, J = 6.5), 1.03 (d, 3, J = 7.2), 1.32–1.66 (m, 7), 1.70–2.02 (m, 3), 2.04 (s, 3), 3.37 (s, 3), 3.75 (m, 1), 4.36 (br s, 1), 5.08–5.20 (m, 1); MS, m/z 257 (M − 15, 1.2), 240 (100), 212 (42), 180 (35), 170 (93), 129 (73), 110 (54); HRMS, calcd for $C_{14}H_{25}O_4$ (M − 15) m/z 257.1752, found m/z 257.1754.

General Method for the Reaction of Alkyl Acetals with Boron Trifluoride Etherate and Allyltrimethylsilane. A solution of the methyl acetal (0.05 mmol) in 1–2 mL of CH_3CN is cooled to 0 °C and treated sequentially with allyltrimethylsilane (0.2–0.3 mmol) and $BF_3{\cdot}OEt_2$ (0.1–0.2 mmol). After being stirred for 30 min, the reaction is quenched with saturated $NaHCO_3$ (2 mL) and the mixture is extracted with ether. The organic layer is worked up to afford the crude allyltetrahydropyran. The crude product mixture is analyzed by capillary GC and then purified by chromatography.

(2*R,5*S**,6*S**)-2-[(2*S**)-2-Acetoxy-4-methylpentyl]-5-methyl-6-(2-propenyl)tetrahydropyran (27a) from 24bα.** Following the general procedure above, 15.0 mg (0.055 mmol) of **24bα** was treated with 30 mg (0.28 mmol) of trimethylallylsilane and 16 μL (0.13 mmol) of $BF_3{\cdot}OEt_2$ to afford after workup 17 mg of a colorless oil. Capillary GC analysis (column 1) indicated that

a single diastereomer had been formed. Chromatography (10% EtOAc/hexanes) afforded 14.7 mg (95% yield) of adduct **27a** as a colorless oil: IR 2960, 1727, 1373, 1253, 1029 cm^{-1}; ^1H NMR δ 0.86 (d, 3, J = 7.4), 0.90 (d, 3, J = 7.0), 0.91 (d, 3, J = 7.0), 1.15–1.30 (m, 1), 1.32–1.71 (m, 6), 1.73–1.95 (m, 3), 1.95–2.13 (m, 1), 2.03 (s, 3), 2.37–2.52 (m, 1), 3.56–3.68 (m, 1), 3.83 (ddd, 1, 4.8, 4.8, 10.4), 5.01–5.13 (m, 3), 5.79–5.96 (m, 1); ^{13}C NMR δ 16.1, 21.3, 22.0, 23.2, 24.6, 26.5, 29.6, 31.5, 32.6, 39.9, 43.0, 66.1, 70.1, 75.5, 116.1, 136.0, 170.6. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.08; H, 10.79.

(2*R,5*R**,6*S**)-2-[(2*S**)-2-Acetoxy-4-methylpentyl]-5-methyl-6-(2-propenyl)tetrahydropyran (28a) from 26.** Following the general procedure above, 13.4 mg (0.049 mmol) of **26** was treated with 35 μL (0.22 mmol) of trimethylallylsilane and 20 μL (0.163 mmol) of BF_3·OEt_2 to afford after workup 15 mg of a colorless oil. Capillary GC analysis (column 1) indicated that a single diastereomer had been formed. Chromatography (5% EtOAc/5% CH_2Cl_2/hexanes) produced 13.9 mg (100% yield) of **28a** as a colorless oil: IR 2965, 2940, 1740, 1373, 1249, 1030 cm^{-1}; ^1H NMR δ 0.87–0.93 (m, 9), 1.25–1.54 (m, 7), 1.57–1.68 (m, 1), 1.70–1.84 (m, 1), 2.04 (s, 3), 2.07–2.26 (m, 2), 2.35–2.46 (m, 1), 3.40 (ddd, 1, J = 3.8, 7.9, 7.9), 3.90 (m, 1), 5.00–5.13 (m, 3), 5.83–5.99 (m, 1); ^{13}C NMR δ 18.1, 21.3, 21.8, 23.4, 24.6, 26.9, 28.1, 33.9, 36.3, 37.6, 42.6, 68.5, 70.4, 75.4, 116.1, 135.8, 170.6. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.35; H, 10.83.

(2*R,5*S**,6*S**)-2-[(2*S**)-2-Hydroxy-4-methylpentyl]-5-methyl-6-(2-propenyl)tetrahydropyran (27b) and the (2*R**,5*R**,6*R**)-2-[(2*R**)] Isomer (28b).** To a solution of 24.8 mg (0.125 mmol) of the mixture of bicyclic acetals **23α** and **23β** (78:22 ratio) and 43 mg (0.38 mmol) of allyltrimethylsilane in 2 mL of CH_3CN cooled to 0 °C was added 30 μL (0.24 mmol) of BF_3·OEt_2 over 2 min. The mixture was stirred for 1.25 h and partitioned between ether and saturated $NaHCO_3$, the organic layer was worked up, and the residue was chromatographed (10–25% EtOAc/hexanes) to afford 14.2 mg (47% yield) of a mixture of **27b** and **28b** in the ratio of 25:75 according to capillary GC analysis (column 1). An analytical sample was prepared by preparative GC (column 4, 172 °C): IR 3495, 2950, 1485, 1099 cm^{-1}; ^1H NMR δ (**27b**) 0.84 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 1.15 (ddd, 1, J = 4.7, 8.5, 16.9), 1.26–1.56 (m, 6), 1.60–1.82 (m, 3), 1.89 (m, 1), 2.35 (m, 2), 3.52 (dt, 2, J = 7.0, 7.0), 3.64 (br s, 1), 3.87 (m, 1), 4.03 (m, 1), 5.11 (m, 2), 5.75–5.93 (m, 1); (**28b**) 0.90 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 1.15 (ddd, 1, J = 4.7, 8.5, 16.9), 1.26–1.56 (m, 6), 1.60–1.82 (m, 3), 1.89 (m, 1), 2.35 (m, 2), 3.52 (dt, 2, J = 7.0, 7.0), 3.64 (br s, 1), 3.87 (m, 1), 4.03 (m, 1), 5.11 (m, 2), 5.75–5.93 (m, 1). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 74.75; H, 11.77.

General Method for the Reaction of Acetals with Titanium Tetrachloride and Enolsilanes. A solution of acetal (0.050 mmol) and the enolsilane (0.20–0.30 mmol) in CH_2Cl_2 (2–3 mL) was cooled to −78 °C and a solution of 0.80 M $TiCl_4$ (0.15–0.20 mmol) was added via syringe pump over 20–30 min. After being stirred for 10–60 min, the reaction was quenched by the addition of methanol (0.5 mL), acidified with 1 M H_2SO_4, warmed to 21 °C, and extracted with ether. The organic layer was worked up and the crude product mixture was analyzed by capillary GC and purified by chromatography.

(2*R,3*R**,6*S**)-2-(3,3-Dimethyl-2-oxobutyl)-6-[(2*R**)-2-hydroxy-4-methylpentyl]-3-methyltetrahydropyran (31) and (2*R**,3*R**,6*R**,8*S**)-2-(3,3-Dimethyl-2-oxobutyl)-3-methyl-8-(2-methylpropyl)-4-oxacyclooctan-6-ol (32).** Following the general procedure above, a solution of 21.1 mg (0.106 mmol) of the mixture of bicyclic acetals **23α** and **23β** (78:22 ratio) and 73 mg (0.42 mmol) of enolsilane **30**[27] in 4 mL of CH_2Cl_2 was treated with 0.39 mL (0.32 mmol) of 0.81 M $TiCl_4$ in CH_2Cl_2 to afford, after workup and chromatographic purification (10–25% EtOAc/hexanes), 5.7 mg (18% yield) of **31** and 18.9 mg (60% yield) of **32** as colorless oils.

31: IR 3500, 2960, 1709, 1474, 1371, 1080 cm^{-1}; ^1H NMR δ 0.80 (d, 3, J = 7.2), 0.88 (d, 6, J = 7.2), 1.05–1.17 (m, 1), 1.17 (s, 9), 1.24–1.37 (m, 2), 1.39–1.51 (m, 3), 1.53–1.84 (m, 3), 1.90–2.05 (m, 1), 2.46 (dd, 1, J = 4.2, 17.0), 2.95 (dd, 1, J = 8.9, 17.0), 3.49 (br s, 1), 3.70–3.82 (m, 2), 4.48 (ddd, 1, J = 4.5, 4.5, 9.0); ^1H NMR (C_6D_6) δ 0.57 (d, 3, J = 7.1), 0.80–1.10 (m, 17), 1.17–1.37 (m, 3), 1.48–1.76 (m, 4), 1.94–2.06 (m, 1), 2.09 (dd, 1, J = 4.0, 16.7), 2.85 (dd, 1, J = 9.3, 16.7), 3.48–3.58 (m, 1), 3.60 (br s, 1), 3.75–3.87 (m, 1), 4.50 (ddd, 1, J = 4.6, 4.6, 9.2); ^{13}C NMR δ 16.9, 22.2, 23.4, 24.3, 26.5, 26.7, 31.3, 32.6, 33.5, 42.6, 44.0, 46.8, 69.7, 71.3, 72.1 (no C=O carbon observed); MS, m/z 298 (M^+, 0.6), 280 (7), 241 (51), 181 (46), 155 (44), 109 (54), 57 (100); HRMS, calcd for $C_{18}H_{34}O_3$ m/z 298.2507, found m/z 298.2512.

32: IR 3610, 2960, 2935, 1705, 1470, 1371, 1082 cm^{-1}; ^1H NMR δ 0.82 (d, 3, J = 6.5), 0.84 (d, 3, J = 6.5), 0.90 (d, 3, J = 7.0), 1.05–1.15 (m, 1), 1.13 (s, 9), 1.33–1.47 (m, 2), 1.48–1.66 (m, 4), 1.82–1.86 (m, 2), 2.08–2.21 (m, 2), 2.25 (dd, 2, J = 3.4, 17.0), 2.87 (dd, 1, J = 8.7, 17.0), 3.73 (m, 1), 4.04 (m, 1), 4.23 (ddd, 1, J = 3.1, 3.1, 8.6); ^{13}C NMR δ 13.9, 22.3, 23.2, 24.6, 26.2, 27.2, 30.7, 34.6, 38.1, 40.8, 44.3, 44.5, 67.8, 72.5, 74.1 (no C=O carbon observed). Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.19; H, 11.56.

(2*R,3*R**,6*R**,8*S**)-2-(3,3-Dimethyl-2-oxobutyl)-3-methyl-8-(2-methylpropyl)-1-oxacyclooctan-6-ol (32) from 23α.** Following the general procedure above, 4.8 mg (0.0242 mmol) of **23α** and 19 mg (0.011 mmol) of enolsilane **30** were treated with 100 μL (0.0810 mmol) of 0.80 M $TiCl_4$ at −78 °C for 45 min to afford after workup and chromatography (10% EtOAc/5% CH_2Cl_2/hexanes) 6.2 mg (86% yield) of **32** as a colorless oil. GC analysis indicated that a single isomeric product had been formed.

(2*R,3*R**,6*S**)-6-[(2*R**)-2-Acetoxy-4-methylpentyl]-2-(3,3-dimethyl-2-oxobutyl)-3-methyltetrahydropyran (33) from BF_3-Catalyzed Addition to 24b.** A solution of 40.8 mg (0.150 mmol) of **24b** (1:1 mixture of anomers) and 200 mg (1.16 mmol) of enolsilane **30** in 50 μL of CH_2Cl_2 was cooled to 0 °C and treated with 50 μL (0.41 mmol) of BF_3·OEt_2. After being stirred for 15 min, the reaction mixture was quenched by the addition of $NaHCO_3$ and extracted with ether. The organic layer was worked up to afford 49 mg of a colorless oil. Capillary GC analysis (column 1) indicated a ratio of **33:34** of 10.6:1. Chromatography (5% EtOAc/5% CH_2Cl_2/hexanes) of this material afforded 8.6 mg (24% yield) of the dihydropyran **41** and 21.2 mg (42% yield) of adduct **33** as a colorless oil. An analytical sample of **33** was prepared by preparative GC (column 4, 232 °C): IR 2965, 1728, 1377, 1256, 1025 cm^{-1}; ^1H NMR δ 0.78 (d, 3, J = 7.0), 0.88 (d, 3, J = 6.4), 0.89 (d, 3, J = 6.4), 1.16 (s, 9), 1.19–1.35 (m, 3), 1.46–1.97 (m, 7), 2.01 (s, 3), 2.41 (dd, 1, J = 5.1, 17.1), 2.84 (dd, 1, J = 7.4, 17.1), 3.53–3.65 (m, 1), 4.44 (ddd, 1, J = 4.9, 4.9, 7.3), 4.99–5.10 (m, 1); ^{13}C NMR δ 16.0, 21.3, 22.1, 23.1, 24.6, 26.4, 26.7, 29.3, 32.4, 34.8, 40.0, 43.7, 44.4, 67.6, 70.2, 71.6, 170.8. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.25; H, 10.79.

(2*R,3*S**,6*R**)-6-[(2*S**)-2-Acetoxy-4-methylpentyl]-2-(3,3-dimethyl-2-oxobutyl)-3-methyltetrahydropyran (34) from $TiCl_4$-Catalyzed Addition to 24b.** Following the general procedure above for $TiCl_4$-catalyzed addition, 10.8 mg (0.0396 mmol) of a mixture of **24b** (1:1 mixture of anomers) was treated with 27 mg (0.16 mmol) of enolsilane **30** and 0.145 mL (0.118 mmol) of 0.80 M $TiCl_4$ to afford after workup 17 mg of a colorless oil. Capillary GC analysis (column 1, 125 °C for 1 min, then 5 °C/min to 250 °C) indicated a ratio of **33:34** of 1:36. Chromatography (5% EtOAc/hexanes) afforded 7.7 mg (57% yield) of **34** as a colorless oil: IR 2965, 1726, 1374, 1256, 1091, 1026 cm^{-1}; ^1H NMR δ 0.79 (d, 3, J = 6.3), 0.87 (d, 3, J = 6.7), 0.89 (d, 3, J = 6.7), 1.14 (s, 9), 1.19–1.38 (m, 4), 1.41–1.67 (m, 4), 1.69–1.83 (m, 2), 2.02 (s, 3), 2.39 (dd, 1, J = 2.8, 16.1), 2.79 (dd, 1, J = 9.0, 16.1), 3.24–3.36 (m, 1), 3.53 (ddd, 1, J = 2.8, 9.2, 9.2), 4.98–5.10 (m, 1); ^{13}C NMR δ 17.8, 21.3, 21.9, 23.3, 24.5, 26.0, 32.1, 32.7, 35.1, 40.6, 41.2, 42.9, 44.3, 69.9, 74.1, 79.8, 170.6, 200.0; MS, m/z 340 (M^+, 2.4), 283 (59), 241 (77), 223 (100), 181 (83); HRMS, calcd for $C_{20}H_{36}O_4$ 340.2613, found 340.2621.

(2*R,3*S**,6*S**)-6-[(2*R**)-2-Acetoxy-4-methylpentyl]-2-(3,3-dimethyl-2-oxobutyl)-3-methyltetrahydropyran (35) and the (2*R**,3*R**,6*R**)-6-[(2*S**)] Isomer (36).** Following the general procedure above, 19.7 mg (0.0723 mmol) of acetal **26** was treated with 53 mg (0.31 mmol) of enosilane **30** and 0.270 mL (0.219 mmol) of 0.80 M $TiCl_4$ to afford, after workup, 25 mg of a colorless oil. Capillary GC analysis (column 1) showed a ratio of **35:36** of 1:2. Chromatography (5% EtOAc/hexanes) afforded 11.5 mg (47% yield) of **36** and 4.9 mg (20% yield) of **35** as colorless oils.

35: IR 2965, 1729, 1470, 1374, 1256, 1029 cm^{-1}; ^1H NMR δ 0.90 (d, 3, J = 7.0), 0.91 (d, 6, J = 6.5), 1.04 (s, 9), 1.25–1.74 (m, 9), 1.93–2.07 (m, 1), 2.03 (s, 9), 2.56 (dd, 1, J = 4.4, 16.6), 2.73 (dd, 1, J = 7.3, 16.6), 3.75–3.84 (m, 1), 3.88 (ddd, 1, J = 4.5, 7.5, 7.5), 4.98–5.09 (m, 1); ^{13}C NMR δ 18.2, 21.3, 22.2, 23.2, 24.6, 26.2, 26.7, 27.7, 34.0, 36.6, 40.2, 43.3, 44.3, 68.9, 70.5, 72.4, 170.8; MS, m/z 340 (M^+, 4.2), 283 (66), 241 (100), 197 (27), 163 (42); HRMS, calcd

for $C_{20}H_{36}O_4$ m/z 340.2613, found m/z 340.2605.

36: IR 2965, 1726, 1473, 1374, 1253, 1056 cm^{-1}; ^1H NMR δ 0.87 (d, 3, J = 6.4), 0.90 (d, 3, J = 6.4), 0.92 (d, 3, J = 6.8), 1.13 (s, 9), 1.25–1.45 (m, 3), 1.46–1.85 (m, 7), 2.03 (s, 3), 2.25 (dd, 1, J = 5.0, 16.8), 2.80 (dd, 1, J = 7.8, 16.8), 3.31–3.43 (m, 1), 3.97 (ddd, 1, J = 2.1, 5.0, 7.4), 5.03–5.15 (m, 1); ^{13}C NMR δ 12.0, 21.3, 22.0, 23.3, 24.5, 26.0, 26.1, 30.0, 30.9, 40.2, 41.4, 43.2, 44.3, 69.9, 75.2, 76.0, 170.6; MS, m/z 340 (M^+, 4.6), 283 (86), 280 (81), 223 (100), 181 (39); HRMS, calcd for $C_{20}H_{36}O_4$ m/z 340.2613, found m/z 340.2608.

Methyl (2*R,3*R**,6*S**)-3-Methyl-6-[(2*R**)-2-methyl-4-hydroxypentyl]-2-tetrahydropyranacetate (19t) and the (2*R**,3*S**,6*S**)-6-[(2*R**)] (38t), (2*R**,3*S**,6*R**)-6-[(2*S**)] (19c), and (2*R**,3*R*,6*R**)-6-[(6*S**)] (38c) Isomers from Addition to 23aβ.** To a solution of 5.8 mg (0.029 mmol) of the mixture of bicyclic acetals **23**α and **23**β (78:22 ratio) in 1 mL of CH_2Cl_2 at −78 °C was added 0.20 mL (0.16 mmol) of 0.81 M $TiCl_4$ in CH_2Cl_2 to give a yellow-brown solution. After 15 min, a solution of 40 mg (0.17 mmol) of ketene acetal **37**[30] in 0.30 mL of CH_2Cl_2 was added over 25 min. The solution became deep red in color as the silyl ketene acetal was added. The reaction was quenched after 4 h by the addition of 0.5 mL of MeOH, the mixture was warmed to 21 °C and partitioned between ether and 1 M H_2SO_4, and the organic layer was worked up. The residue was dissolved in 2 mL of THF and hydrolyzed with 0.5 mL of 6 M H_2SO_4 for 9.5 h. The solution was made basic with 1 M NaOH, washed with Et_2O, acidified with 1 M H_2SO_4, saturated with NaCl, and extracted with ether, and the organic layer was worked up to give a colorless oil. This material was dissolved in 5 mL of ether and treated at 0 °C with excess diazomethane. After concentration, capillary GC analysis (column 1) indicated, in the order of elution, a 25:21:35:19 mixture of **19c**:**38t**:**38c**:**19t** (retention times 19.23, 19.79, 20.14, and 20.57 min, respectively). Chromatography (25% EtOAc/hexanes) afforded 6.1 mg (77% yield) of the pyran mixture. Isomer **38t** had been isolated and purified from a previous reaction: ^1H NMR δ 0.87 (d, 3, J = 6.6), 0.88 (d, 3, J = 6.6), 0.96 (d, 3, J = 7.0), 1.13 (ddd, 1, J = 4.9, 8.1, 13.2), 1.25–1.55 (m, 6), 1.60–1.85 (m, 4), 2.28 (dd, 1, J = 3.8, 15.2), 2.52 (dd, 1, J = 9.6, 15.2), 3.57–3.68 (m, 1), 3.69 (s, 3), 3.87 (m, 1), 3.96 (ddd, 1, J = 2.1, 3.8, 9.6).

Methyl (2*R,3*R**,6*R**,8*S*)-6-Hydroxy-3-methyl-8-(2-methylpropyl)-1-oxacyclooctane-2-acetate (39).** To a solution of 12.4 mg (0.0625 mmol) of the mixture of bicyclic acetals **23**α and **23**β and 59 mg (0.26 mmol) of ketene acetal **37** in 3 mL of CH_2Cl_2 at −78 °C was added over 30 min via syringe pump a solution of 10 μL (0.091 mmol) of $TiCl_4$ in 2 mL of CH_2Cl_2. The reaction was quenched after 20 min by the addition of 0.5 mL of MeOH and was allowed to warm to 21 °C before being partitioned between CH_2Cl_2 and 1 M H_2SO_4. The organic layer was worked up and the residue was esterified with excess etheral diazomethane in ether at 0 °C. Subsequent evaporation of the solvent and chromatographic purification of the product (25% EtOAc/hexanes) afforded 9.0 mg (53% yield) of the pyrans **19t** and **19c** and 3.2 mg (19% yield) of **39** as colorless oils. An analytical sample of **39** was prepared by preparative GC (column 4, 199 °C): IR, 3480, 2960, 2930, 1731, 1462, 1371, 1240, 1176 cm^{-1}; ^1H NMR δ 0.86 (d, 3, J = 6.7), 0.89 (d, 3, J = 6.7), 0.92 (d, 3, J = 6.7), 1.12 (ddd, 1, J = 4.3, 8.2, 13.4), 1.40–1.67 (m, 5), 1.67–1.90 (m, 3), 2.03–2.18 (m, 2), 2.42 (dd, 1, J = 4.3, 15.14), 2.52 (dd, 1, J = 9.0, 15.1), 3.68 (s, 3), 3.73 (m, 1), 4.07 (m, 2). Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 65.84; H, 10.43.

The crotylstannane additions to provide adducts **42** and **43** are described in the supplementary material.

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Registry No. 1, 28380-24-7; (±)-**2a**, 117270-10-7; (±)-**2b**, 117270-11-8; (±)-**3**, 117270-12-9; (±)-**4**, 117270-13-0; (±)-**5a**, 117270-14-1; (±)-**5c**, 117270-15-2; (±)-**6**, 117270-18-5; (±)-**6** (methyl epimer), 117270-19-6; (±)-**6** (SiΣ ester), 117270-16-3; (±)-**6** (acid), 117270-17-4; (±)-**7**, 117270-20-9; (±)-**8**, 117270-21-0; (±)-**9**, 117308-00-6; (±)-**10**, 117270-22-1; (±)-**16a**, 117270-23-2; (±)-**16a** (methyl epimer), 117404-79-2; (±)-**16b**, 117404-85-0; (±)-**16b** (methyl epimer), 117270-24-3; (±)-**17b**, 117404-86-1; (±)-**17b** (methyl epimer), 117270-25-4; (±)-**18a**, 117270-27-6; (±)-**18a** (methyl epimer), 117404-87-2; (±)-**18b**, 117404-88-3; (±)-**18b** (methyl epimer), 117270-26-5; (±)-**18c**, 117270-28-7; (±)-**18d**, 117270-29-8; (±)-**18e**, 117270-30-1; (±)-**18f**, 117270-31-2; (±)-**18g**, 117270-32-3; (±)-**18h**, 117270-33-4; (±)-**18i**, 117404-80-5; (±)-**19c**, 117270-35-6; (±)-**19t**, 117270-34-5; (±)-**20c**, 117270-61-8; (±)-**20t**, 117270-62-9; (±)-**21c**, 117270-63-0; (±)-**21t**, 117270-64-1; (±)-**23**α, 117270-38-9; (±)-**23**β, 117404-81-6; (±)-**24a**α, 117270-36-7; (±)-**24a**β, 117270-37-8; (±)-**24b**α, 117270-42-5; (±)-**24b**β, 117270-43-6; (±)-**24b**α (R″ = H), 117270-40-3; (±)-**24b**β (R″ = H), 117270-39-0; (±)-**25a**α, 117270-73-2; (±)-**25a**β, 117404-89-4; (±)-**25b**α, 117270-45-8; (±)-**25b**β, 117404-82-7; (±)-**25b** (2,3-anhydro deriv.), 117270-74-3; (±)-**26**, 117270-44-7; (±)-**26** (desacetyl deriv.), 117270-41-4; (±)-**27a**, 117270-48-1; (±)-**27b**, 117270-46-9; (±)-**28a**, 117270-49-2; (±)-**28b**, 117270-47-0; (±)-**28c**, 117270-50-5; **30**, 17510-46-2; (±)-**31**, 117270-51-6; (±)-**32**, 117270-52-7; (±)-**33**, 117270-54-9; (±)-**34**, 117270-55-0; (±)-**35**, 117270-56-1; (±)-**36**, 117270-57-2; **37**, 74786-02-0; (±)-**38c**, 117270-59-4; (±)-**38t**, 117270-58-3; (±)-**39**, 117270-60-7; (±)-**41**, 117270-53-8; (±)-**42** (isomer 1), 117270-75-4; (±)-**42** (isomer 2), 117404-84-9; (±)-**43** (isomer 1), 117270-76-5; (±)-**43** (isomer 2), 117270-77-6; $Cl_3CCONCO$, 3019-71-4; $Ph_3PMe^+Br^-$, 1779-49-3; (±)-$\Sigma SiO(CH_2)_3C{\equiv}CCH_2CH(OH)Bu$-*i*, 117270-65-2; $\Sigma SiO(CH_2)_3C{\equiv}CH$, 61362-77-4; (±)-(*E*)-$\Sigma SiO(CH_2)_3CH{=}CHCH_2CH(OH)Bu$-*i*, 117270-66-3; (±)-(*E*)-$HO(CH_2)_3CH{=}CHCH_2CH(OH)Bu$-*i*, 117270-67-4; $ClCONMe_2$, 79-44-7; (±)-(*E*)-$\Sigma SiO(CH_2)_3CH{=}CHCH_2CH(OCONMe_2)Bu$-*i*, 117270-68-5; (*E*)-$Bu_3SnCH_2CH{=}CHCH_3$, 35998-93-7; (*Z*)-$Bu_3SnCH_2CH{=}CHCH_3$, 35998-94-8; (±)-isobutyloxirane, 96553-67-2; (±)-(4*R**,6*R**)-4-[(1S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-iodobutyl]-6-(2-methylpropyl-1,3-dioxan-2-one, 117270-69-6; (±)-(4*S**,6*R**)-4-[(1*R**)-4-[(*tert*-butyldimethylsilyl)oxy]-1-iodobutyl]-6-(2-methylpropyl)-1,3-dioxan-2-one, 117404-83-8; (±)-*cis*-4-[[(*tert*-butyldimethylsilyl)oxy]butyl]-6-(2-methylpropyl)-1,3-dioxan-2-one, 117270-70-9; (±)-*cis*-6-(2-methylpropyl)-2-oxo-1,3-dioxane-4-butanol, 117270-71-0; (±)-*cis*-6-(2-methylpropyl)-2-oxo-1,3-dioxane-4-butanal, 117270-72-1.

Supplementary Material Available: Experimental procedures and characterization for compounds not described above (10 pages). Ordering information is given on any current masthead page.