should be no more stable than **2**, suggesting that the conformational stability of **2** in solution has been overestimated.[2,10]

Finally, the experimental (or calculated) differences in ground-state strain energies of 2.6 kcal/mol (2.2 kcal/mol) and in activation energies of 7.0 kcal/mol (5.7 kcal/mol) for **2** and **3** provide estimates for the difference in the strain energies for the transition states of **2** and **3** of 9.6 kcal/mol (7.9 kcal/mol). Not surprisingly, the buttressing effect of the 3,6-methyl groups is considerably greater in the transition state than in the ground state.

Acknowledgment. This work was supported by NSF Grant DMB 84 13502 to R.N.A. R.N.A. is the recipient of a NIH Research Career Development Award (ES 00133). The authors are particularly grateful to Prof. M. S. Newman for his generous gift of the title compounds and Prof. N. L. Allinger for a copy of ref 23 prior to publication. Support by the National Science Foundation (CHE-84-02155) for purchase of the X-ray diffractometer is gratefully acknowledged. We thank Dr. D. M. Barnhart for assistance with the preliminary X-ray work on **3**.

Supplementary Material Available: Tables of U values, intramolecular distances and angles, atomic positional parameters, and atomic coordinates for **2** and **3** (17 pages); listing of structure factors (25 pages). Ordering information is given on any current masthead page.

A Concise and Stereoselective Route to the Predominant Stereochemical Pattern of the Tetrahydropyranoid Antibiotics: An Application to Indanomycin

Samuel J. Danishefsky,* Shari DeNinno, and Paul Lartey

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received September 2, 1986*

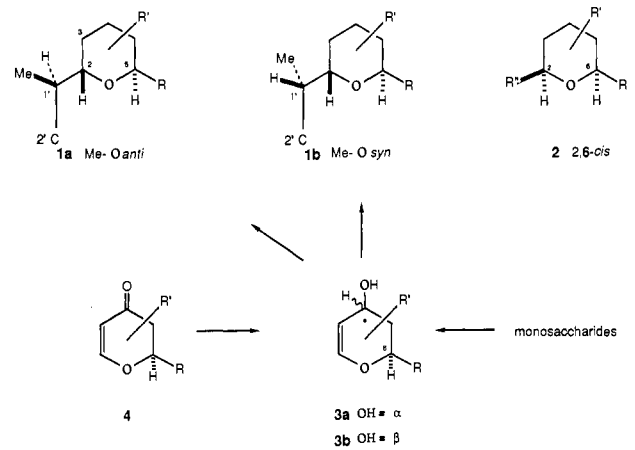
Abstract: The reactions of (*E*)- and (*Z*)-crotylsilanes of the type $R_3Si—CH_2—CH=CH—CH_3$ with activated glycal derivatives in the presence of BF_3 etherate have been examined. In all cases, the reactions were regiospecific, resulting in incorporation of a 3-methylprop-1-ene-3-yl function at the 2-position of the pyran with formation of a 3,4 double bond. The reactions also demonstrate virtual facial specificity. The carbon nucleophile enters trans to the substituent at the 6-position, leading to a 2,6-anti relationship. The topographic selectivity which defines the relationship of the configuration of the *sec*-butenyl group relative to C_2 of the pyran is a function of several variables. The most significant of these is the stereochemistry (*E* or *Z*) of the crotyl group and the presence or absence of substitution at the 3-position of the pyran. Some sensitivity to the electronegativity of the activating group is also manifested. By combining the most favorable features for topographic selectivity, a highly concise and highly stereoselective (Zimmerman definition) construction of the primary pattern (1′-anti 2,6-trans) of the title compounds is achieved. A synthesis of the pyranoid segment of indanomycin in optically active form based on this chemistry is described.

I. Background

When the repertoire of extensively oxygenated natural products is examined, the widespread occurrence of the trialkylated tetrahydropyrans becomes apparent.[1] Compounds housing such substructures commonly exhibit significant ionophoric, antibacterial, or antifungal activity. The 2-position of the ring is often substituted with an isopropyl or a sec-butyl group, usually in oxidized form. The 6-position is generally connected to a longer chain which contains extensive oxygenation. There is usually a trans relationship between the substituents at positions 2 and 6 (see structures **1a** and **1b**).[2,3]

Another little noted connectivity involves the stereogenic centers at $C_{1'}$ of the side chain and at the 2-position of the pyran.[4] If the side chain $C_{1'}$–$C_{2'}$ bond is drawn antiperiplanar to the 2–3 bond of the ring, the branching substituent (usually methyl, occasionally ethyl) at $C_{1'}$ and the ring oxygen are anti (see structure **1a**).[2] Only rarely is the syn pattern (see structure **1b**) encountered.[3]

Scheme I



As part of a broader program directed toward the synthesis of highly oxygenated natural products, we focused on these substructural features. A particularly attractive solution would be one which exploited intermediates of the type **3**. Depending on the nature of R and R′, such intermediates might well be readily available via transformation of monosaccharides.[5a] An alternative

(1) For an extensive compilation of such compounds see: (a) Westley, J. W., Ed. *Polyether Antibiotics*; Marcel Dekker: New York, 1083; Vol. I and II. (b) For the structure of zincophorin see: Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501.

(2) For instance, several compounds with the common 2,6-*trans*-1′-*anti* relationship, cf. inter alia, nigericin, salinomycin, narasin, lasalocid A, indanomycin (X-14547A), grisorixin,[1a] and zincophorin.[1b]

(3) Alborixin and X-206[1a] are examples of 2,6-cis ionophores. It is interesting to note that they also possess the 1′-syn relationship. A 1′-syn relationship in a more oxidized spiro ketal substrate is encountered in the avermectins.

(4) For consistency, the numbering system used throughout this paper is that of a pyran nucleus (oxygen is position 1). This system is maintained even for sugar derivatives.

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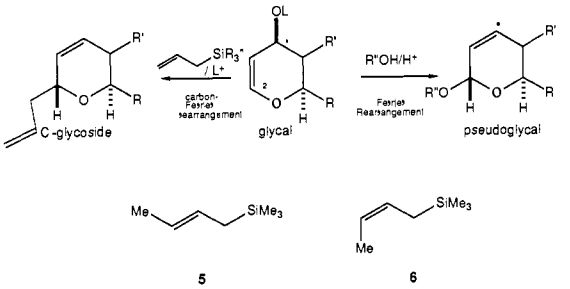
Scheme II



route to type **3** systems, which was developed in these laboratories, involves the formation of dihydropyrones **4** via the Lewis acid catalyzed cyclocondensation of dienes with aldehydes, RCHO.[5b] By this method, essentially any R function can be accommodated in the cyclocondensation reaction. The R′ function can emerge at either the 3- or 5-position depending on its placement in the diene. By careful selection of the Lewis acid catalyst, an R′ function at the 5-position may be generated cis or trans to the R function at the 6-position.[6a,b]

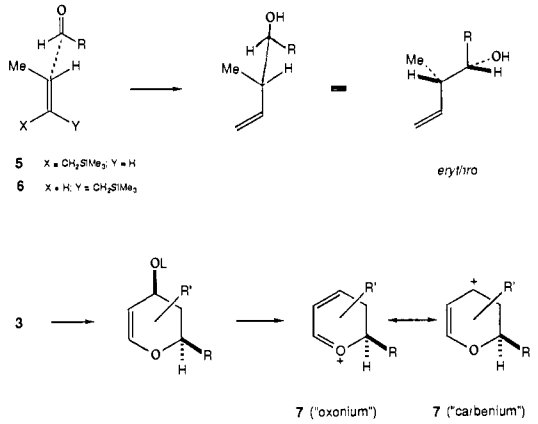
We note, however, that regardless of whether the allylic alcohol precursor is derived from carbohydrate sources or from de novo synthesis, these substrates are only readily available as the equatorial alcohols, wherein the hydroxyl group at position 4 is cis to the alkyl group at position 6[4] (cf. **3b**). The two primary monosaccharide sources, glucal and galactal, contain this relationship. Also, 1,2-reduction of fully synthetic systems of the type **4** feeds into the same stereochemical series.[7]

This situation poses a major limitation upon the applicability of suprafacial bond reorganization reactions of the Claisen variety. To reach the naturally prevalent 2,6-trans systems of the type **1**, such routes require access to the 4,6-trans alcohols (see **3a**).[8a,b] By suprafacial reactions, the more available 4,6-cis systems (cf. **3b**) can only be used to reach the less prevalent C_2–C_6 cis series of products (see structure **2**).[3]

In formulating our plan we were mindful of the tendency of glycals or activated glycals to undergo solvolytic displacement via nucleophilic attack in an S_N2' sense. Ordinarily the incoming heterofunction in such Ferrier displacements[9a] emerges axial in the "pseudoglycal". We wondered whether the Y function could also be a suitable carbon nucleophile which might undergo a "carbon–Ferrier" displacement. In addition to the feasibility of the reaction, the stereochemistry of the resultant *C*-glycoside would be of considerable interest.

Our first investigations into the possibility of the "carbon–Ferrier" displacement involved the use of trimethylallylsilane as the nucleophile in the presence of $TiCl_4$ as a Lewis acid catalyst.[9b] These experiments revealed very high positional specificity favoring S_N2' attack, i.e., the allyl group indeed entered at C_2. Moreover, high stereoselectivity was observed. Almost independently of the stereochemistry at position 4, the allyl group emerged at position 2 trans to the R group at position 6. It seemed likely that this result reflected a kinetic preference for quasiaxial attack by the allylic nucleophile while C_2 underwent rehybridization.

Scheme III



While this easily executed reaction on readily available substrates did indeed solve the problem of trans 2,6-stereochemistry found in most of the targets,[2] it did not address the question of stereochemistry at $C_{1'}$. Toward that end we investigated the use of (*E*)- and (*Z*)-crotylsilanes **5** and **6**.[10]

Kumada and co-workers had studied the reactions of crotylsilanes with aldehydes under catalysis by titanium tetrachloride.[11] A high erythro selectivity was noted with the *E* isomer **5**. With the *Z* isomer **6**, a more modest erythro selectivity resulted. It should be noted that erythro selectivity in the aldehyde series would correspond to a syn preference in the case of the carbon-Ferrier displacement. In a subsequent investigation Sakurai[12] reported that the reaction of *either* geometric crotylsilane isomer with aliphatic acetals was highly syn selective.

Both Kumada and Sakurai interpreted their findings in terms of acyclic transition states. This type of antiperiplanar arrangement had been invoked by Yamamoto[13] to explain the high erythro selectivity manifested by both (*E*)- and (*Z*)-crotylstannanes in their reactions with aldehydes under the influence of titanium tetrachloride.

On the basis of a simple reading of these precedents, the carbon–Ferrier-like reaction of crotylsilanes with a derivative of **3** might have been expected to afford syn product **1b**. However, system **3** represents a structural type which had not yet been investigated. Thus, the electrophile derived from **3** is at once an incipient oxonium species and an incipient allylic carbenium ion (see resonance forms **7**). Given this unique situation, and the generally "after the fact" nature of theoretical analysis in the whole field of acyclic stereoselection, a broadly based experimental program seemed to be in order.

II. Reaction of Crotylsilanes, 5 and 6, with Various Glycal Derivatives

Initial experiments were carried out with silanes **5** and **6** with D-glucal triacetate **8**. Catalysis with titanium tetrachloride in methylene chloride gave rather complex mixtures. However, the use of BF_3OEt_2 gave an interesting and potentially useful result. With the (*E*)-silane **5**, a 3:1 ratio of "carbon-Ferrier" products was obtained in a combined yield of 58%. Only traces of compounds belonging to the 2,6-cis series (compounds **46** and **47**, vide infra) could be detected. Subsequent correlations (vide infra) showed the major compound to be the anti system **10**, while the minor product is the $C_{1'}$ epimer **11**. Surprisingly, the same reaction

(5) (a) See: Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: New York, 1983; Vol. 3. (b) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

(6) (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(7) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.

(8) For examples where silylketeneacetal bond reorganization reactions have been used, cf., inter alia: Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *Ibid.* **1985**, *107*, 3285. See also: (b) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002. For an alternate solution to control of the configuration at $C_{1'}$ see ref 25a.

(9) (a) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. Ferrier, R. J.; Prasad, N. J. *Chem. Soc. C* **1969**, 570. (b) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803.

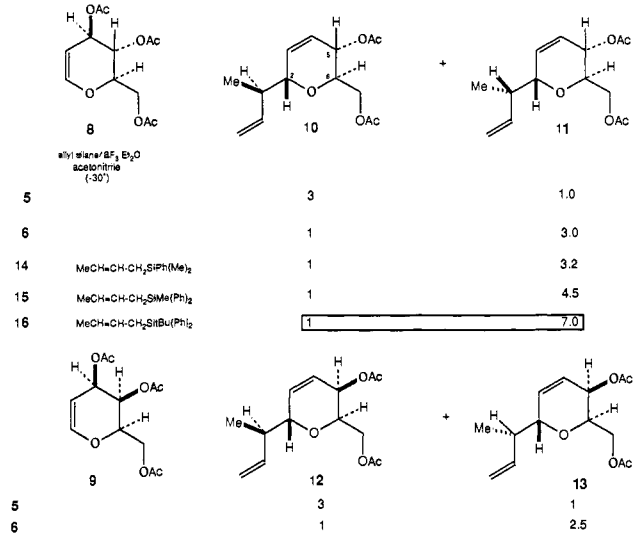
(10) For the preparation of these compounds from the corresponding chlorides, see: Cadiot, P.; Matarasso-Tchiroukhine, E. *J. Organomet. Chem.* **1976**, *121*, 155.

(11) Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865.

(12) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *29*, 2589. For a paper which contains a single example of a reaction of a crotyl silane with a sugar glycoside see: Hosomi, A.; Sakata, Y.; Sakurai, H. *Ibid.* **1984**, *25*, 2383. The stereochemical situation both in terms of starting silane and product *C*-glycoside is left vague.

(13) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7109.

Scheme IV



carried out with the (*Z*)-silane **6** afforded the same products, but now in a 1:3 ratio. *Thus, unlike the cases cited above, the carbon-Ferrier reaction with crotylsilanes exhibited modest stereoselectivity which is responsive to olefin geometry.*

A similar situation pertained with galactal triacetate **9**. With (*E*)-crotylsilane **5**, a 3.2:1 ratio of $C_{1'}$ anti:$C_{1'}$ syn epimers **12** and **13** was obtained. Conversely, with (*Z*)-crotylsilane **6**, a 1:2.5 ratio of **12**:**13** was produced.

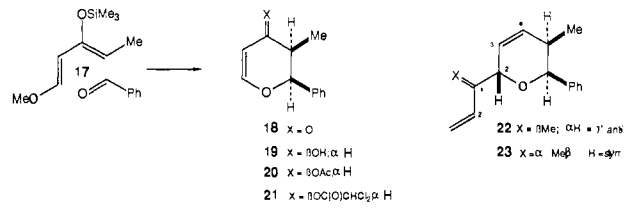
The presence of the two additional acetoxy functions in the glucal and galactal substrates was seen to be a complicating factor in realizing high yields in this carbon-Ferrier reaction. Moreover, the actual target systems which we had in mind in the natural products domain were not envisioned to be derivable from these substrates. Therefore, extensive optimization experiments on yields and ratios were not conducted in these series. However, one experiment did suggest some opportunities for manipulating the epimer ratio at $C_{1'}$. When the more encumbered (*Z*)-silane **14** was employed, the syn:anti ratio was improved slightly to 3.2:1. The use of (*Z*)-silane **15** afforded a 4.5:1 ratio of **11**:**10**. Finally, with (*Z*)-silane **16**, this ratio improved to 7:1. The use of the *E* version of **14**, **15**, and **16** led, in each case, to worse anti:syn product mixtures than were obtained with the parent trimethylsilyl system.

We next addressed the reactions of the synthetic glycal-like system **19**. This compound was obtained by Luche[14] reduction of dihydropyrone **18**. The latter was in turn available in 90% yield from the cyclocondensation of diene **17** with benzaldehyde under the influence of $ZnCl_2$.[6a] Acetylation of **19** under standard conditions (Ac_2O, pyridine, DMAP) afforded **20**. Reaction of **20** with (*E*)-crotylsilane gave a 5:1 ratio of anti:syn products **22**:**23** in combined yield of 67%. Conversely, (*Z*)-crotylsilane afforded a 4:1 ratio of **23**:**22**. As in the cases of glucose and galactose derivatives, the carbon–Ferrier processes are quite responsive to the olefin geometry of the crotylsilanes.

The effect of varying the electronegativity of the leaving group was examined. With (*E*)-silane **5**, the dichloroacetate **21** gave rise to a 7:1 ratio of anti:syn products **22**:**23**. With (*Z*)-silane **6**, this modification tended to erode the ratio of syn:anti product. A 2.5:1 ratio of **23**:**22** was obtained.

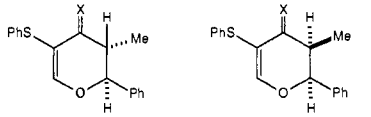
A sharp increase in the anti:syn ratio was realized by incorporating a substituent at position 3 of the pyran. The use of a potentially disposable thiophenyl function at the 3-position was probed first. The requisite glycal-like structures **26** and **27** were obtained from the corresponding dihydropyrones **24** and **25**.[15]

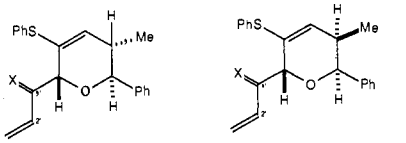
Scheme V



Substrate	Silane	22 *anti*	23 *syn*
20	5 *E*	5	1
21	5 *E*	7	1
20	6 *Z*	1	4
21	6 *Z*	1	2.5

These compounds were in turn converted to the corresponding acetates **28** and **29**. Reaction of the 5,6-trans compound **28** with (*E*)-silane **5** afforded a 10:1 anti(**30**):syn(**31**) ratio. Similarly, reaction of **5** with the 5,6-cis acetate **29** afforded a 7:1 ratio of anti(**32**):syn(**33**) products. With each of these substrates, the syn:anti ratio with the (*Z*)-silane **6** was eroded relative to that obtained with the corresponding des-thiophenyl compound **20**. Thus, the overall effect of incorporation of a 3-thiophenyl substituent is that of favoring formation of the anti isomer for both silanes. In the case of (*E*)-silane **5**, the anti selectivity seen with the 3 H compounds is improved in going from **20** to **28**. In the case of (*Z*)-silane **6**, the same substrate structure change results in a weakened syn selectivity.





Substrate	Silane	30 *anti*	31 *syn*
28	5 (E)	7	1
28	6(Z)	1	1.5

Substrate	Silane	32 *anti*	33 *syn*
29	5 (E)	10	1
29	6(Z)	1	1

An analogous effect is manifested with a 3-methyl substituent. Here we combined the salutory effects of increasing the electron-withdrawing capacity of the leaving group with incorporation of the additional methyl substituent. Thus, glycal-like structure **35**, prepared from the previously reported dihydropyrone **34**,[6a,16] was converted to the acyloxy derivatives, **36** and **37**. Carbon–Ferrier reaction with (*E*)-silane **5** with acetate **36** under catalysis by BF_3 etherate afforded a 30:1 ratio of anti(38):syn(39) products. With dichloroacetate **37** the ratio of **38**:**39** was 28:1. The anti directing effect of the methyl group leads to a 2:1 anti(**38**):syn(**39**) ratio with **36** even via the usually cis selective crotylsilane, **6**.

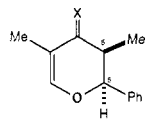
We sought to investigate the effect of a 3-methyl group in the 5,6-trans series. Accordingly, the glycal-type system **40a** was

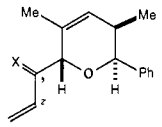
(14) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 5848.

(15) These compounds were prepared through the use of 1-methoxy-2-(phenylthio)-3-(trimethylsiloxy)-1,3-pentadiene with benzaldehyde under BF_3 etherate catalysis. If the reaction is run in methylene chloride, the trans compound, **24**, is the predominant product. If the reaction is run in toluene, cis compound, **25**, becomes the major product. D. Myles, Yale University, unpublished results.

(16) These compounds were prepared by reduction[14] followed by acetylation with acetic anhydride or dichloroacetyl chloride, respectively.

(17) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *25*, 3927. The crotyl stannanes were used as a mixture of geometric isomers.





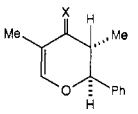
34 X = O
35 X = β OH; α H
36 X = β OAc; α H
37 X = βOCOCHCl$_2$

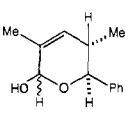
38 X = β Me; α H (1′*anti*)
39 X = α Me; β H (1′*syn*)

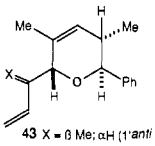
36	+ 5	⟶	38 (1′*anti*) 3039 (1′*syn*) 1
36	+ 6	⟶	38 2.5 : 39 1
37	+ 5	⟶	38 26 : 39 1
37	+ 6	⟶	38 2 : 39 1

prepared from the corresponding dihydropyrone **40**. Initially, attempted acylation of **40a** under standard conditions (Ac_2O, DMAP, pyridine) did not provide the expected acetate **41**. Instead, there was obtained the pseudo-glycal **42** as the major product after aqueous workup. It was of interest to determine whether such a pseudoglycal would serve as a substrate for the carbon–Ferrier displacement. Indeed, the reactions proceeded quite smoothly in good overall yield. The data are given below.

Subsequently the unstable glycal acetate **41** was obtained by acetylation of **40b** under different conditions (AcCl, Et_3N, DMAP, CH_2Cl_2). It was of interest to compare the glycal and pseudoglycal cases. In fact, reaction of **41** with silane **5** afforded a 12:1 ratio of **43**:**44**. Thus, the $C_{1'}$ anti selectivity improves in going from the pseudoglycal **42** to the glycal acetate **41**. This difference may reflect the fact that the allylically related substrates **42** and **41** are not converging upon the same type **7** cation. More likely, it reflects subtle differences in the "leaving" group arrangement or solvation arrangement of the "same" species.







40 X = O
40a X = βOH; α H
41 X = β OAc; α H

42

43 X = β Me; αH (1′*anti*)
44 X = αMe; β H (1′*syn*)

42	+ 5	⟶	43 (1′*anti*) 7 : 44 (1′*syn*)
42	+ 6	⟶	43 1.3 : 44 1
41	+ 5	⟶	43 12 : 44 1
41	+ 6	⟶	43 1.7 : 44 1

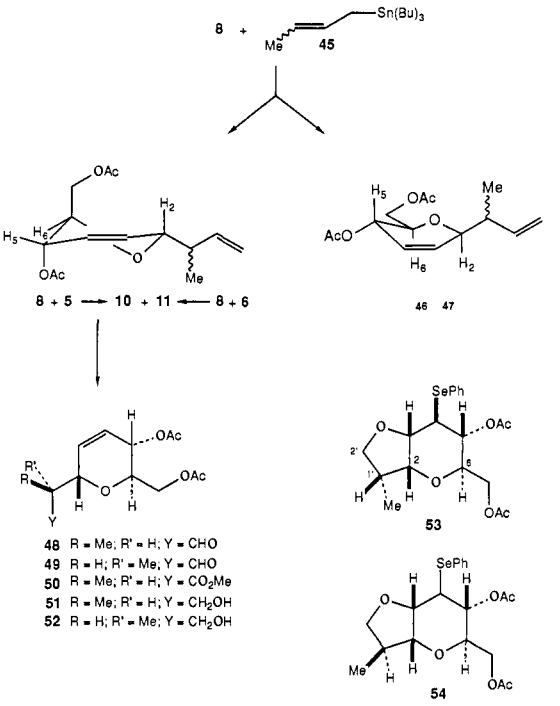
We conclude this survey section by noting that a stereospecific entry to the 2,6-trans series has been achieved in each case via the use of crotylsilanes under catalysis by BF_3 etherate in acetonitrile. Moreover, strongly stereoselective routes to the prevalent $C_{1'}$ anti series have been achieved via the reactions of the (*E*)-silane **5** with suitably activated glycals bearing substitution at position 3. With the technology currently in hand the route to $C_{1'}$ syn compounds, using (*Z*)-crotylsilane **6**, is less selective.

III. Transformations and Structural Correlations of Carbon–Ferrier Products

NOE experiments on compound set **10** and **11** revealed that in each instance the isomers differed in configuration at $C_{1'}$ rather than at position 2 of the pyran. In each instance, no enhancement of H_2 was observed upon irradiation of H_6. This is in contrast to the 5.8% enhancement observed for H_5 via irradiation of H_6.

While the reaction of **8** with **5** and **6** under BF_3 etherate catalysis produced bearly detectable traces of the C_2–C_6 cis products **46** and **47**, the corresponding reactions with the crotylstannane isomers **45**[17] produced a four-component mixture of **10**, **11**, and cis compounds **46** and **47**. The ratio of 1′-2 anti:syn isomers was essentially the same as was obtained from the silanes (**10**:**11** ~ 3:1; **46**:**47** ~ 4:1). However, there resulted a virtually complete loss of C_2–C_6 trans selectivity. While of no synthetic utility, the stannane process provided access to these cis isomers as reference materials.

Scheme VI



48 R = Me; R′ = H; Y = CHO
49 R = H; R′ = Me; Y = CHO
50 R = Me; R′ = H; Y = CO_2Me
51 R = Me; R′ = H; Y = CH_2OH
52 R = H; R′ = Me; Y = CH_2OH

^{1}H NMR spectroscopy reveals that in cis compounds **46** and **47**, both the butenyl side chain at position 2 and the acetoxymethyl group at position 6 are equatorial, as is the acetoxyl function at position 5. In compounds **46** and **47**, in contrast to **10** and **11**, a strong NOE enhancement is observed at H_2 upon irradiation of H_6. Also, comparison of $J(H_{5,6})$ in both sets of compounds is revealing. In the **10**–**11** set, $J_{5,6}$ = 3–4 Hz, whereas in the **46**–**47** set the corresponding $J_{5,6}$ is 9–10 Hz. Thus, in the 2,6-trans series (**10**–**11**) the 5,6-substituents are shown to be substantially axial with the branched 2-substituent equatorial.

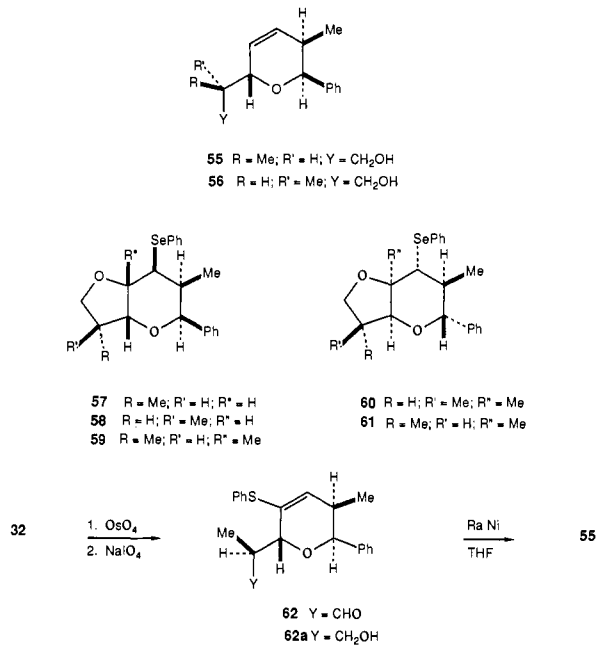
In the C_2–C_6 cis series (**46**–**47**) all substituents are equatorial. The assignment of configuration to the $C_{1'}$ stereogenic center in compounds **10** and **11** followed from oxidative transformations of these products. Such conversions are not without their own element of interest in suggesting applications of such *C*-glycosides to other synthetic problems.

Hydroxylation of the $C_{1'}$–$C_{2'}$ double bond of both **10** and **11** under Van Rheenan conditions[18] was possible. The crude diols were cleaved with sodium periodate in aqueous ethanol to afford aldehydes **48** and **49**. The former was converted by oxidation and esterification to methyl ester **50**. Reduction of aldehydes **48** and **49** with sodium borohydride afforded carbinols **51** and **52**, respectively. These carbinols underwent selenoetherification[19] to provide compounds **53** and **54**. ^{1}H NMR analysis with particularly revealing NOE measurements identified these compounds to be those shown and established the series to be as indicated.[20] The galactose derived compounds **12** and **13** were assigned to be in the C_2–C_6 trans series on the basis of the similarity of their ^{1}H NMR spectra to those of **10** and **11**. The assignment for $C_{1'}$ epimers **12** and **13** arose from analogy to compounds **10** and **11**, respectively.[20]

The fully synthetic compounds **22** and **23** were transformed as above to selenoethers **57** and **58** via alcohols **55** and **56**, re-

(18) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(19) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
(20) The NOE data for compounds **53**, **54**, **55**, and **56** are provided as supplementary material for the microfilm edition.

Scheme VII



spectively. ^{1}H NMR NOE measurements revealed these compounds to be as indicated. A similar sequence starting with the $C_{1'}$ anti isomers **38** and **43** gave rise to selenoethers **59**, **60**, and **61**.[20]

The thiophenyl compound **32** was correlated chemically with the des-thiophenyl series. Thus the double bond of the side chain was oxidized [(i) OsO_4; (ii) $NaIO_4$]. The derived aldehyde **62** was reduced with sodium borohydride to afford alcohol **62a**. Desulfurization with Raney Nickel (W-4) served to convert compound **62a** to previously encountered **55**. This transformation correlates the $C_{1'}$ anti thiophenyl compound **32** with the des-thiophenyl anti compound **22**.

IV. Stereochemical Rationalizations

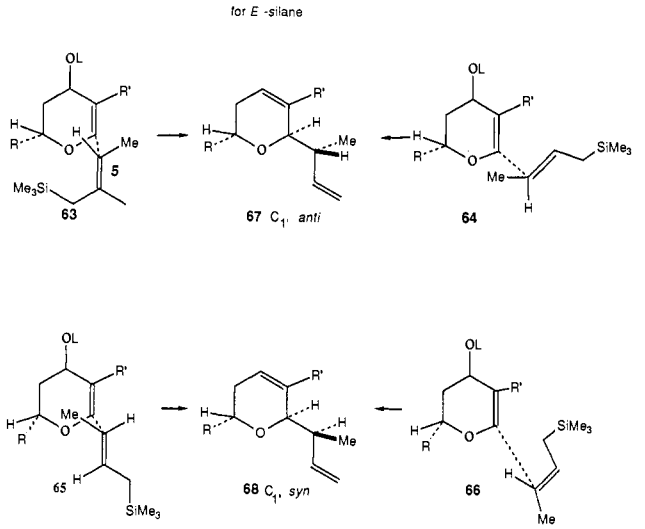
The proclivities of the (*E*)-silane **5** to give $C_{1'}$ anti products (cf. **67**) by this chemistry can be rationalized in terms of ensemble **63**. It is seen that this arrangement corresponds to one of the synclinal forms[21,22] where the allylsilane is gauche to the oxonium segment of the O→C_4 unsaturated network (see resonance forms **7**). Of course while synclinal with respect to the oxonium segment, the relationship of the crotylsilane to the carbenium segment is antiperiplanar. This duality is a unique feature of the substrates for the carbon–Ferrier displacement.

Leakage to $C_{1'}$ syn product **68** with the (*E*)-silane might occur from two ensembles, i.e., the alternate oxonium synclinal arrangement **65** or the carbenium synclinal lineup shown as **66**. It is readily seen that the presence of a substituent (R′ = SPh or Me) might raise the energy of the **66** ensemble and thus would promote selectivity in favor of $C_{1'}$ anti product. A large R′ function would be likely to raise the energy of oxonium antiperiplanar form **64** which also leads to **67**, but this arrangement is probably not operative in any case since it places the methyl group of the silane in a hindered environment.

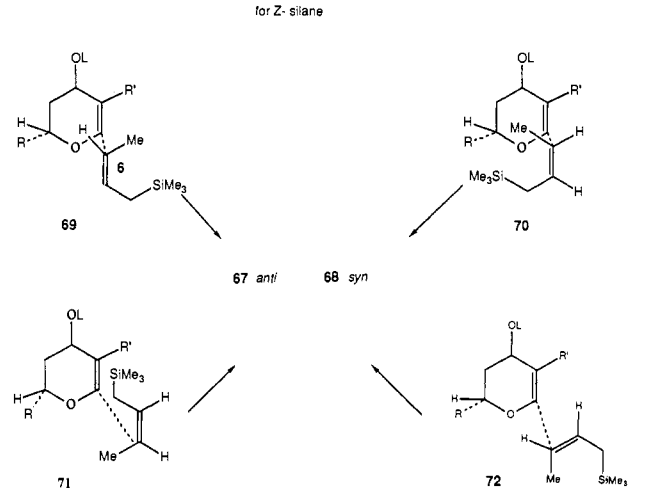
The syn selectivity of the (*Z*)-silane **6** reactions is less readily explained. In the absence of specific attractions between the trialkylsilyl region and the ring oxygen, it might have been expected that reaction would occur through oxonium synclinal form **69**. However, this would have led to anti product **67**. Since the process is in fact syn selective, alignments **70** or **72** would seem to be preferred. The effect of substitution (see R′) at position 3 in eroding the syn selectivity (vide supra) can possibly be explained by its disfavorment of ensemble **72**, presumably rendering oxonium synclinal form **69** more competitive.

(21) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.
(22) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

Scheme VIII



Scheme IX



Thus the preference for oxonium synclinal form **63** in the *E*-series is not manifested for the corresponding form **69** in the *Z*-series. It would appear to be necessary to invoke a favorable interactivity between the silyl sector and the ring oxygen (present in **63** but absent in **69**) to explain this difference. The nature of this apparently favorable interactivity is not known.

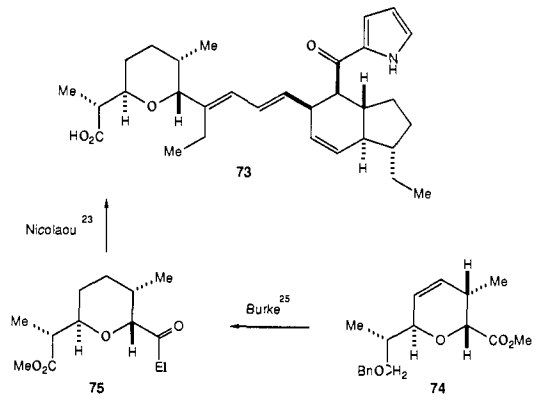
V. An Application to the Indanomycin Problem

As mentioned above, in earlier research we developed the capacity through cycloaddition reactions to synthesize pyranoid systems. Through the chemistry described herein we developed the crotylsilane carbon–Ferrier displacement to the point where it provides a stereoselective route to the C_2–C_6 trans $C_{1'}$ anti family of tetrahydropyranoid natural products. There are in principle many targets[1a] which fall within range of the combination of these methods.

The first target system to which we attempted to apply this capability was the dihydropyranoid substructure of indanomycin[1a] **73**. Of course, the total synthesis of indanomycin had been achieved in a landmark effort by Nicolaou and co-workers.[23,24]

(23) For a full account of this work see: Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.
(24) For some subsequent synthetic routes to indanomycin see: (a) Edward, M. P.; Ley, S. V.; Lister, S. G. *Tetrahedron Lett.* **1981**, *22*, 361. (b) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630. (c) Roush, W. F.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (d) Roush, W. F.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3432. (e) Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90. (f) Boeckman, R. K.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3423. (g) Whitney, R. A. *Chem. J. Chem.* **1986**, *64*, 803.

Scheme X



A synthesis of both the dihydropyranoid[25] and hydrindanoid[26] components was achieved by Burke and Armistead. These workers passed through intermediate **74** en route to the synthesis of **75**. Compound **75** had been an intermediate in the Nicolaou total synthesis.[23] For our purposes, intermediate **74** would serve as a suitable target.

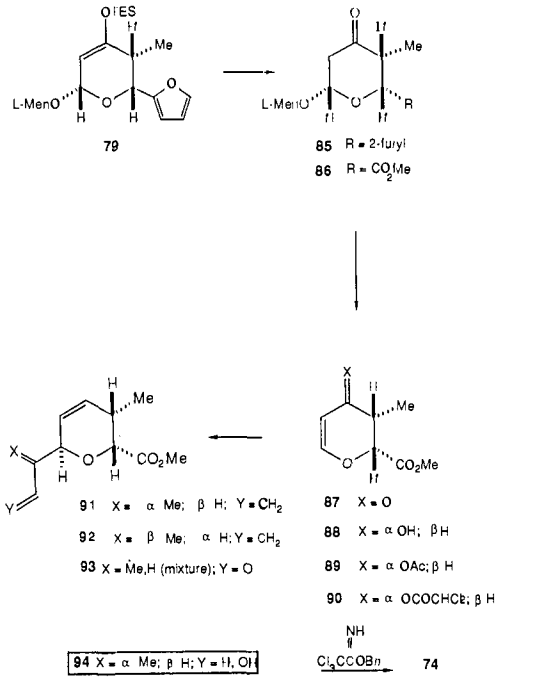
Indanomycin has two individual chiral sectors. The separation of these regions is such that in a synthetic sense it would be difficult to imagine how the stereochemical information built up in one sector could be effectively communicated to control the emergence of the other. Accordingly, all workers in this field have recognized the need to couple subunits of properly correlated absolute configuration. This goal would be furthered by a synthesis of the subunits wherein the desired enantiomer was produced from the outset. We took account of this standard in our synthesis of **74**.

For this purpose we synthesized the triethylsilyl L-menthyloxy diene **78**. This compound was prepared from enone **77** which in turn arose by an exchange reaction of L-menthol[27] with the known enone **76**.[28] At this juncture, we could take advantage of the previously demonstrated use of chiral shift reagents ($Eu(hfc)_3$ or $Yb(hfc)_3$)[29] in conjunction with the use of chiral auxilliary menthyloxydienes. Previous work from our laboratory had shown that the combination of these chiral elements can provide diastereomeric excesses far beyond those which would be expected by strictly arithmetic factoring of the selectivities of the individual components.

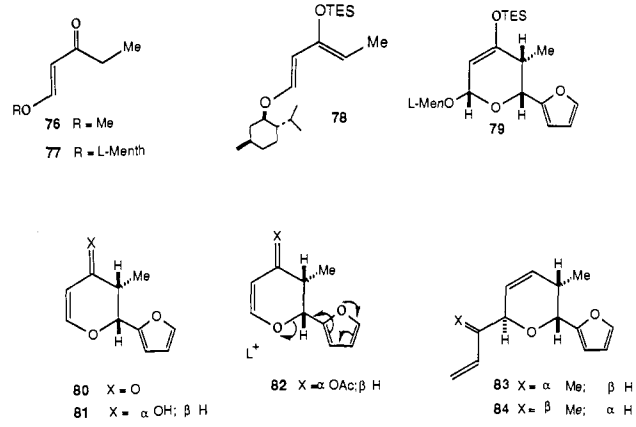
In the event, cycloaddition was carried out between **78** and furfural in the presence of $Eu(hfc)_3$ as a catalyst in hexanes at −30 °C. ^1H NMR analysis of the crude reaction mixture indicated the formation of two products in a 5:1 ratio. Chromatography on silica gel allowed for isolation of the major product in 66% yield. ^1H NMR spectroscopic analysis of this structure and those of its transformation products reveal it to have the C_2–C_5–C_6 cis–cis arrangement. In the light of subsequent conversion to the target system of the correct absolute configuration, this product can be assigned structure **79**.

The initial approach involved attempted carbon–Ferrier displacement on compound **82** obtained from **79** via compounds **80** and **81**. Reaction of **82** with **5** did indeed occur with apparently good stereoselectivity (ca. 5:1 $C_{1'}$ anti **83**:$C_{1'}$ syn **84** products). However, the yield of this transformation under catalysis by BF_3 etherate under a variety of conditions was very low. A variety

Scheme XI



of difficulty characterized byproducts were produced. We reasoned that this difficulty might reflect the instability of the furyl ether linkage of **82** in the presence of Lewis acids (see arrows).



Our response to this problem called for degrading the furan to a suitable carbonyl derivative, prior to the stage of the carbon–Ferrier displacement. It was therefore necessary to find a point in the synthesis where the total functionality was consistent with such a degradation. It seemed unlikely that we could achieve this oxidative transformation with either compound **79**, **80**, or **81**. Fortunately, it was possible to cleave the silyl enol ether of **79** without elimination of the menthyloxy group through the action of HF–pyridine in methanol at −30 °C. In this fashion, compound **85** was obtained in 80% yield.

Ozonolytic degradation of the furan ring was achieved, leading after esterification with diazomethane to ester **86** in 77% yield. Treatment of **86** with trifluoroacetic acid afforded **87** (72%). Luche reduction of **87**[14] followed by acylation with either acetic anhydride or dichloroacetyl chloride afforded **89** and **90**, respectively.

The stage was now set for the all crucial carbon–Ferrier displacement. It will be recognized that substrate **89** is less than ideally suited to favor high anti selectivity in the displacement since it is unsubstituted at C_3. Furthermore, the presence of the electron-withdrawing carbomethoxyl group would serve to discourage full carbonium ion character in the transition state for the reaction. Previous studies (vide supra) involving variation of leaving groups suggested that fuller carbonium ion character is favorable for anti selectivity. In the event, reaction of **89** with

(25) (a) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163. (b) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron.* **1986**, *42*, 2787.

(26) (a) Armistead, D. M. Ph.D. Thesis, University of South Carolina, 1986. (b) Burke, S. D.; Armistead, D. M.; Shankaran, K. *Tetrahedron Lett.* **1986**, *27*, 6295.

(27) Danishefsky, S.; Bednarski, M.; Izawa, T.; Maring, C. *J. Org. Chem.* **1984**, *49*, 2290.

(28) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(29) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968.

(30) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

Table I. Combined Yields of Carbon–Ferrier Products Derived from Reactions of **5** and **6** with Activated Glycals

glycal	silane	product (yield, %)
8	5	10,11 (58)
8	6	10,11 (59)
9	5	12,13 (76)
9	6	12,13 (44)
20	5	22,23 (67)
20	6	22,23 (42)
21	5	22,23 (75)
21	6	22,23 (56)
28	5	30,31 (62)
28	6	30,31 (73)
29	5	32,33 (67)
29	6	32,33 (53)
36	5	38,39 (67)
36	6	38,39 (51)
37	5	38,39 (82)
37	6	38,39 (50)

(*E*)-silane **5** afforded a 3.5:1 mixture of $C_{1'}$ anti (**91**):$C_{1'}$ syn (**92**) products. The ratio was upgraded to 4.5:1 by the use of dichloroacetate substrate **90**.

The mixture was converted to **93** (39%) by treatment with osmium tetraoxide followed by sodium periodate. Reduction of **93** with sodium borohydride and separation of the $C_{1'}$ epimers afforded homogeneous **94** in 68% yield. Benzylation of this base sensitive substance was achieved by the method of Bundle[30] with benzyltrichloroacetimidate. There was thus obtained the target system **74** whose infrared and ^{1}H NMR (490 MHz) spectra were identical with those provided by Professor Steven Burke. In addition, the optical rotation $[\alpha]_D$ +150.8° (*c* 2.02, $CHCl_3$) corresponded closely with that previously reported.[25]

The applicability of this methodology to other targets is an ongoing project in our laboratory.

VI. Experimental Section

All commercial chemicals were used as obtained without further purification, except for solvents which were purified and dried, where appropriate, before use by standard methods. Preparative column chromatography was carried out on silica gel 60 (E. Merck, 9285, 230–400 mesh) with the flash technique. Thin-layer chromatography was carried out on silica gel 60 GF 254 (E. Merck). Melting points were determined by using a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were determined on a Bruker WH 250 250-MHz instrument, and all chemical shifts are reported relative to internal $(CH_3)_4Si$. IR spectra were measured in solution ($CHCl_3$) on a Perkin-Elmer 1420 spectrophotometer with NaCl cells. Mass spectra were determined on an Hewlett-Packard 5985 GC/MS system. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

A. A Typical Procedure for the BF_3 Etherate Catalyzed Addition of Crotyltrimethylsilane to Acylated Glycals: Preparation of Compounds 12 and 13. (*E*)-Crotylsilane **5** (126 mg, 0.984 mmol) was added to 134 mg (0.492 mmol) of tri-*O*-acetyl-D-galactal in 5 mL of dry CH_3CN. The solution was cooled to −30 °C and 0.121 mL (0.984 mmol) of BF_3 etherate was added. The cooling bath was removed and the mixture stirred until the reaction was complete (monitored by TLC, 10 min). The mixture was poured into 5 mL of saturated aqueous $NaHCO_3$ solution and partitioned twice with 10 mL of CH_2Cl_2. The combined organic layers were washed once with brine, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The oily residue was chromatographed (5:1 hexanes:ethyl acetate) over silica gel to afford a mixture of diastereomers (107 mg, 76% combined yield). HPLC separation (11% ethyl acetate in hexanes) afforded the pure compounds **12** and **13**.

α-*anti*-D-Galactal adduct **12**: ^{1}H NMR (250 MHz) δ 6.15 (dd, *J* = 9.8, 2.3 Hz, 1 H), 6.0 (dd, *J* = 9.8, <1 Hz, 1 H), 5.89 (m, 1 H), 5.04 (dd, *J* < 1, 3.13 Hz, 2 H), 4.20 (m, 3 H), 4.09 (m, 1 H), 2.52 (m, 1 H), 2.11 (s, 3 H), 2.09 (s, 3 H), 1.09 (d, *J* = 6.7 Hz, 3 H); IR ($CHCl_3$) 1740, 1370, 1230, 1050 cm^{-1}; $[\alpha]_D$ −200.7° (*c* 1.5, $CHCl_3$).

α-*syn*-D-Galactal adduct **13**: ^{1}H NMR (250 MHz) δ 6.18 (dd, *J* = 10.4, 2.5 Hz, 1 H), 6.0 (dd, *J* = 10.4, 2.8 Hz, 1 H), 5.75 (m, 1 H), 5.1 (m, 3 H), 4.1–4.3 (m, 3 H), 4.0 (m, 1 H), 2.54 (m, 1 H), 2.10 (s, 6 H), 1.14 (d, *J* = 6.7 Hz, 3 H); IR ($CHCl_3$) 1740, 1370, 1230, 1050 cm^{-1}; $[\alpha]_D$ −233.7° (*c* 0.51, $CHCl_3$).

B. A Typical Procedure for Degradation of the Side Chain of the Carbon–Ferrier Adduct Mixture and for Separation of the Epimeric Alcohols: Conversion of a Mixture of 22 and 23 to 55 and 56. The mixture of **22** and **23** (40 mg, 0.175 mmol) was dissolved in 10 mL of THF. *N*-Methylmorpholine *N*-oxide (20 mg, 0.175 mmol) was dissolved in 1 mL of H_2O. To the combined solutions was then added 0.56 mL of a 25-mg/mL solution of OsO_4 in THF (14 mg, 0.055 mmol). The reaction was monitored by TLC and was complete after 3 **h**. A saturated aqueous solution of sodium dithionite (1 mL) was added and the solution was allowed to stir for 2 h. The solution was then poured into 20 mL of ethyl acetate and washed with H_2O (1×, 15 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated in vacuo to afford 30 mg (65%) of a mixture of diols. The mixture (0.114 mmol) was redissolved in EtOH (6 mL) and 30 mg (0.140 mmol) of $NaIO_4$ was added in 500 μL of H_2O. The solution was stirred for 30 min and was poured into 20 mL of $CHCl_3$ and washed with H_2O (3×, 15 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The mixture was purified by chromatography (3:2 hexanes:ethyl acetate) to afford 17 mg (40% overall) of a mixture of aldehydes. The aldehyde mixture (10 mg, 0.043 mmol) was dissolved in 5 mL of absolute EtOH at 0 °C. $NaBH_4$ (1.6 mg, 0.043 mmol) was added in 2 mL of EtOH and the mixture stirred until the reaction was complete by TLC (30 min). Five drops of glacial acetic acid were added until H_2 evolution ceased. The solution was diluted with MeOH and then concentrated under reduced pressure. Silica gel chromatography (3:2 hexanes/ethyl acetate) yielded 10 mg (100%) of the mixture of **55** and **56**. HPLC separation of the two compounds (2:1 hexanes/ethyl acetate) afforded the pure alcohols.

Alcohol **55**: ^{1}H NMR (250 MHz) δ 7.3 (m, 5 H), 6.05 (dd, *J* = 12.5, 2.5 Hz, 1 H), 5.88 (dd, *J* = 12.5, 4.17 Hz, 1 H), 4.98 (d, *J* = 3.34 Hz, 1 H), 4.22 (dd, *J* = 4.22, <1 Hz, 1 H), 3.64 (m, 2 H), 2.35 (m, 1 H), 2.16 (m, 1 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.70 (d, *J* = 8.33 Hz, 3 H); IR ($CHCl_3$) 3560, 3019, 2973, 2932, 2890, 2876, 1520, 1420, 1210, 1085, 1031, 928 cm^{-1}.

Alcohol **56**: ^{1}H NMR (250 MHz) δ 7.3 (m, 5 H), 6.12 (m, 1 H), 5.79 (dd, *J* = 10, 4.2 Hz, 1 H), 4.93 (d, *J* = 3.75 Hz, 1 H), 4.42 (dd, *J* = 6.25, <1 Hz, 1 H), 3.74 (m, 2 H), 2.46 (m, 1 H), 1.96 (m, 1 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); IR ($CHCl_3$) 3553, 2910, 2897, 2885, 2871, 1520, 1450, 1220 cm^{-1}.

C. Typical Procedure for Selenoetherification of the Purified Alcohols. Conversion of Alcohol 51 to Selenoether 53. The alcohol **51** (10.3 mg, 0.036 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C. Phenyl selenenyl chloride (16 mg, 0.08 mmol) was added. The cooling bath was removed and the mixture allowed to stir at room temperature for 22 h. The mixture was poured into 15 mL of saturated $NaHCO_3$ solution, diluted with 20 mL of CH_2Cl_2, and partitioned. The CH_2Cl_2 phase was washed with brine (1×, 15 mL), dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. Chromatography over silica gel (5:1 hexanes:ethyl acetate) afforded 8 mg (52%) of selenoether **53**.

Selenoether **53**: ^{1}H NMR (500 MHz) δ 7.63 (m, 2 H), 7.30 (m, 3 H), 4.95 (dd, *J* = 8.3, 8.3 Hz, 1 H), 3.95–4.05 (m, 3 H), 3.60 (dd, *J* = 7.9, 8.3 Hz, 1 H), 3.45 (dd, *J* = 8.7, 6.4 Hz, 1 H), 2.35 (m, 1 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H); IR ($CHCl_3$) 1750, 1525, 1425, 1220, 1100, 930, 800 cm^{-1}; MS, *M*/*e* 427 (M^+), 428 (M^+ + 1), 429 (M^+ + 2), 430 (M^+ + 3).

D. The Synthesis of Compound 74. Synthesis of Menthyloxydiene 78. Enone **77**[29] (12 g, 0.051 mol) was dissolved in 115 mL of ether at −78 °C. To the solution was added 14.2 mL (0.102 mol) of triethylamine and 16 g (0.061 mol) of triethylsilyl trifluoromethanesulfonate. The solution was warmed to −30 °C and allowed to stir for 2 h. The solution was poured onto 100 mL of saturated aqueous $NaHCO_3$ and extracted with ether (2×, 100 mL). The combined ether extracts were washed with H_2O and brine (1×, 50 mL, respectively). The solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 17.7 g (98%) of **78**.

Synthesis of Cycloadduct 79. Furfural (2.1 mL, 0.025 mol) was added to L-menthyloxydiene **78** (8.9 g, 0.025 mol) in 450 mL of dry hexanes at room temperature. $Eu(hfc)_3$ (4.5 g, 0.0038 mol) was added with stirring. The solution was cooled to −30 °C and allowed to stir for 48 h. After the solution was warmed to room temperature, Et_3N (10 mL) and MeOH (20 mL) were added and the solution was stirred for 15 min. The solvent was removed in vacuo and the resulting brown oil was chromatographed (2% ether/hexanes) over silica gel to afford a 5:1 mixture of presumed diastereomers. Separation of the major product was accomplished through use of preparative HPLC (eluant: 0.64% ether/hexanes) to afford 5.5 g (61% overall) of pure **79**: ^{1}H NMR (250 MHz) δ 7.39 (br s, 1 H), 6.35 (m, 2 H), 5.39 (br s, 1 H), 4.85 (d, *J* = 3.18 Hz, 1 H), 4.78 (d, *J* = 1.09 Hz, 1 H), 3.45 (dt, *J* = 10.6, 4.29 Hz, 1 H), 2.42–2.19 (m, 3 H), 1.72–1.58 (m, 2 H), 1.48–1.23 (m, 2 H), 1.06–0.85 (m, 13 H), 0.83–0.65 (m, 12 H); IR ($CHCl_3$) 3000, 2960, 2880, 1660, 1458, 1350, 1150, 1130, 1089, 1000, 865 cm^{-1}; $[\alpha]_D$ +38.8 (*c* 3.61, CH_2Cl_2); anal. C, H, N; MS, *m*/*e* 448 (3.7, M^+), 447 (3.5, M^+ − 1), 449 (1.2, M^+ + 1), 293 (100, M^+ − 155.3, menthol).

Synthesis of Menthyloxy Ketone 85. To a cold (−30 °C) solution of pyridine (13 mL), MeOH (13 mL), and concentrated HF (0.865 mL) was added silyl enol ether **79** in MeOH (10 mL). After 2 h at −30 °C, the solution was warmed to room temperature and quenched by addition of Et_3N (5 mL) and saturated $NaHCO_3$ solution (25 mL). After dilution with H_2O (50 mL), the aqueous phase was extracted with ether (4×, 50 mL) and the combined organics were dried (K_2CO_3). Concentration in vacuo and silica gel chromatography (9:1 hexanes/ethyl acetate) gave ketone **85** (0.594 g, 80%): mp 56.1 °C; ^1H NMR (250 MHz) δ 7.37 (br s, 1 H), 6.40–6.32 (m, 2 H), 4.82 (m, 2 H), 3.40 (dt, J = 10.6, 4.59 Hz, 1 H), 2.82–2.55 (m, 3 H), 2.29 (d, J = 12.9 Hz, 1 H), 2.24–1.98 (m, 1 H), 1.41–1.05 (m, 4 H), 1.00 (d, J = 10.4 Hz, 3 H), 0.95–0.80 (m, 7 H), 0.72 (d, J = 8.34 Hz, 3 H); IR ($CHCl_3$) 2960, 2920, 2862, 1730, 1450, 1280, 1250, 1140, 1035, 990 cm^{-1}; $[\alpha]_D$ −8.68° (c 3.4, CH_2Cl_2); anal. C, H, N.

Synthesis of Menthyloxy Keto Ester 86. Compound **85** (250 mg, 0.747 mmol) in 10 mL of a CH_2Cl_2 and MeOH solution (1:1) was treated with ozone at −78 °C until the solution remained blue. The flask was purged with N_2 and after warming to room temperature was concentrated in vacuo. The colorless oil was redissolved in ether and treated with CH_2N_2 until the yellow color persisted. Concentration of the solution in vacuo and subsequent silica gel chromatography (5:1 hexanes/ethyl acetate) afforded **86** (187 mg, 77%): mp 75–76 °C; ^1H NMR (250 MHz) δ 4.75 (dd, J = 3.24, 8.67 Hz, 1 H), 4.30 (d, J = 3.25 Hz, 1 H), 3.81 (s, 3 H), 3.47–3.32 (dt, J = 10.6, 4.55 Hz, 1 H), 2.85–2.53 (m, 3 H), 2.43–2.28 (m, 1 H), 2.13–1.95 (m, 1 H), 1.65 (m, 3 H), 1.48–1.19 (m, 3 H), 1.18 (d, J = 8.26 Hz, 3 H), 0.98–0.85 (m, 7 H), 0.68 (d, 8.26 Hz, 3 H); IR ($CHCl_3$) 3010, 2960, 2922, 2880, 1760, 1720, 1455, 1250, 1120, 1020 cm^{-1}; $[\alpha]_D$ −35.73° (c 1.85, $CHCl_3$); anal. C, H, N; MS, m/e 326 (M^+), 171 (M^+ − 155.3, menthol).

Synthesis of Dihydropyrone 87. Trifluoroacetic acid (4 mL, 52 mmol) was added to a stirring solution of **86** (324 mg, 1.61 mmol) in 25 mL of CH_2Cl_2 at room temperature. After 2 h, the solution was concentrated in vacuo. The reddish oil was immediately chromatographed (3:2 hexanes/ethyl acetate) over silica gel to yield 111 mg (65%) of **87**. The unreacted starting material was resubmitted to the same conditions (10 mL of CH_2Cl_2, 2 mL of TFA) and allowed to stir an additional 2 h. Concentration in vacuo yielded 7.0 mg of **87**: total yield, 118 mg (70%) of pure **87**; ^1H NMR (250 MHz) δ 7.37 (d, J = 5.98 Hz, 1 H), 5.24 (d, J = 5.95 Hz, 1 H), 4.98 (d, J = 3.69 Hz, 1 H), 3.86 (s, 3 H), 2.88–2.75 (m, 1 H), 1.12 (d, J = 7.36 Hz, 3 H); IR ($CHCl_3$) 3020, 2960, 1760, 1680, 1600, 1451, 1440, 1300, 1270, 1252, 1118, 1090, 1022, 910, 820 cm^{-1}; $[\alpha]_D$ −113.3° (c 2.0, CH_2Cl_2); MS, m/e 170 (M^+), 171 (M^+ + 1), 111 (M^+ − 59, methyl ester).

Reduction of 87. Formation of Alcohol 88. To a cooled (−78 °C) solution of dihydropyrone **87** (145 mg, 0.82 mmol) in 20 mL of MeOH was added cerium chloride heptahydrate (335 mg, 0.90 mmol) with stirring. $NaBH_4$ (38 mg, 0.90 mmol) in 10 mL of EtOH was added over a 1-h period via syringe pump. The solution was stirred at −78 °C for an hour after addition was complete and was then warmed to room temperature and quenched with pH 7 phosphate buffer. Extraction of the aqueous phase was accomplished with ethyl acetate (1×, 50 mL), ether (2×, 50 mL), and methylene chloride (1×, 50 mL). After the mixture was dried with $MgSO_4$, the filtrate was concentrated in vacuo. The yellow oil was chromatographed over silica gel (3:2 hexanes/ethyl acetate) to give **88** (114 mg, 81%): ^1H NMR (250 MHz) δ 6.41 (dd, J = 6.18, 1.24 Hz, 1 H), 4.84 (dd, J = 5.60, 3.86 Hz, 1 H), 4.55 (d, J = 3.82 Hz, 1 H), 4.35–4.27 (br m, 1 H), 3.78 (s, 3 H), 2.49–2.36 (m, 1 H), 3.00–2.03 (br s, 1 H), 1.05 (d, J = 8.30 Hz, 3 H); IR ($CHCl_3$) 3605, 3500, 3080, 3008, 2960, 2905, 1745, 1650, 1440, 1265, 1158, 1085, 1010, 910, 870, 840 cm^{-1}; $[\alpha]_D$ −35.4° (c 1.86, CH_2Cl_2); anal. C, H, N; MS, m/e 172 (M^+), 173 (M^+ + 1), 113 (M^+ − 59, methyl ester).

Acetylation of 88. Formation of 89. To a solution of alcohol **88** (80 mg, 0.465 mmol) in 1 mL of pyridine was added acetic anhydride (176 μL, 1.86 mmol) and catalytic DMAP with stirring. The solution stirred for 1 h and was concentrated in vacuo. The resulting yellow oil was redissolved in $CHCl_3$ and washed with H_2O (1×, 15 mL) and brine (1×, 15 mL). The filtrate was dried over $MgSO_4$, and the solvent was removed in vacuo. Silica gel chromatography (3:2 hexanes/ethyl acetate) yielded 87 mg (95%) of **89**: ^1H NMR δ 6.45 (dd, J = 5.00, 1.58 Hz, 1 H), 5.39–5.33 (m, 1 H), 4.75 (dd, J = 6.25, 4.04 Hz, 1 H), 4.58 (d, J = 3.96 Hz, 1 H), 3.75 (s, 3 H), 2.64 (m, 1 H), 2.00 (s, 3 H), 1.00 (d, J = 8.30 Hz, 3 H); IR ($CHCl_3$) 3010, 2980, 2960, 2885, 1755, 1740, 1730, 1650, 1440, 1371, 1160, 1110, 1090, 1065, 1040, 1020, 990, 915, 850 cm^{-1}; $[\alpha]_D$ +30.38 (c 1.06, CH_2Cl_2); MS, m/e 171 (M^+ − 43, acetate), 155 (M^+ − 59, methyl ester), 112 (M^+ − 102, acetate and methyl ester).

Reaction of 89 with (*E*)-Silane 5. Formation of 91 and 92. (*E*)-Crotylsilane **5**[10] (214 mg, 1.67 mmol) was added to **89** (179 mg, 0.836 mmol) in 5 mL of propionitrile. The solution was cooled to −78 °C and BF_3 etherate was added. The cooling bath was removed and the mixture stirred until the reaction was complete (monitored by TLC, 5 min). The solution was quenched with 1 mL of saturated $NaHCO_3$ solution and was extracted (3×, 10 mL of CH_2Cl_2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was chromatographed (5:1 hexanes:ethyl acetate) over silica gel to afford 60 mg (90%) of a 3.5:1 mixture of compounds (**91**,**92**). The mixture was carried on and used in the next reaction.

Preparation of Alcohol 94. A solution of OsO_4 in THF (5.3 mL, 0.837 mmol of 40-mg/mL solution in THF) was added to the mixture of **91** and **92** (160 mg, 0.761 mmol) in 10 mL of THF at room temperature. The solution immediately turned black. After the solution was stirred at room temperature overnight, 240 mg (3.04 mmol) of solid $NaHSO_3$, 100 mg of florisil, and 1 mL H_2O were added with stirring. The solution was stirred until the organic layer was very light (~1 h). The solution was diluted with ether, dried with $MgSO_4$, filtered through a plug of Celite, and concentrated in vacuo. The crude diol (147 mg, 0.645 mmol) was redissolved in 20 mL of EtOH and $NaIO_4$ (207 mg, 0.968 mmol) in 500 μL of H_2O was added. The solution became thick with a white precipitate and after 2 h the reaction was complete. The mixture was poured onto $CHCl_3$ and extracted with H_2O (1×, 20 mL) and brine (1×, 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 63 mg (39% overall) of aldehyde mixture **93**. To a solution of this material in 1 mL of ethanol at 0 °C was added $NaBH_4$ (11 mg, 0.295 mmol). The reaction was monitored by TLC and was complete after warming to room temperature and stirring for 35 min. The reaction was quenched with 5 drops of glacial acetic acid, diluted with MeOH, and concentrated in vacuo. Silica gel chromatography (3:2 hexanes/ethyl acetate) afforded 41 mg (87%) of a mixture of alcohols. HPLC separation (2:1 hexanes/ethyl acetate) afforded 32 mg of optically active alcohol **94**. ^1H NMR (250 MHz) δ 5.97–5.77 (m, 2 H), 4.45 (d, J = 3.41 Hz, 1 H), 4.19 (d, J = 9.94 Hz, 1 H), 3.78 (s, 3 H), 3.75–3.55 (m, 2 H), 2.91–2.65 (br s, 1 H), 2.61–2.49 (m, 1 H), 2.12–1.98 (m, 1 H), 0.98 (d, J = 6.93 Hz, 3 H), 0.85 (d, J = 6.89 Hz, 3 H); IR ($CHCl_3$) 3510, 3000, 2960, 2930, 2880, 2860, 1750, 1460, 1440, 1265, 1190, 1090, 1030 cm^{-1}; $[\alpha]_D$ +221.8° (c 1.63, $CHCl_3$).

Reaction of Alcohol 94 with Benzyltrichloroacetimidate. Formation of Benzyl Ether 74. Cyclohexane (36 μL, 0.332 mmol) and benzyltrichloroacetimidate (62 μL, 0.332 mmol) were added to a solution of **94** (35.5 mg, 0.166 mmol) in 1 mL of CCl_4 at room temperature. Trifluoromethanesulfonic acid (2 μL) was added with stirring. The reaction was quenched with 1 mL of saturated $NaHCO_3$ solution after 45 min and extracted with H_2O (1×, 15 mL) and brine (1×, 15 mL). The organic phase was dried over $MgSO_4$. The filtrate was concentrated to yield **74**. Silica gel chromatography (10:1 hexanes/ether) yielded 32 mg (64%) of desired 74. The spectra for compound 74 was identical with spectra of authentic material provided by Professor Steven Burke.

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Supplementary Material Available: Spectral data for compounds **10**, **11**, **48**, **49**, **50**, **51**, **52**, **54**, **57**, **58**, **59**, **60**, **61**, and alcohols derived from a mixture of **32**, **33** and **43**, **44**; also, NOE data on compounds **53**, **54**, **57**, and **58** are available (8 pages). Ordering information is given on any current masthead page.