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ACYCLIC STEREOCONTROL BY HETEROCONJUGATE ADDITION—4

ANTI-DIASTEREOSELECTION BY A β-CHELATION EFFECT[1]

MINORU ISOBE,* YOSHIYASU ICHIKAWA, YASUNORI FUNABASHI, SHIGERU MIO and TOSHIO GOTO
Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University, Chikusa, Nagoya 464, Japan

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Abstract—High selectivity in heteroconjugate addition for C—C bond formation with complete *syn*-diastereoselection has been attributed to the chelation effect between the α-oxygen atom of the substrate and the nucleophile anions through metal cations. Herein is described a new method exhibiting *anti*-diastereoselection based on a different chelation effect caused by the ligands on the β-carbon atom to the heteroolefin. Most of the examples are taken as the heteroolefin connected at the C-5 position to D-hexopyranosides with a C-4 hydroxyl group. Thus, the methodology was expanded to an optically active system starting from glucose as a chiral source for asymmetric synthesis. The results are very clear in the case of a Grignard reagent as the nucleophile instead of methyllithium, and so one of the compounds was used for the synthesis of the A-segment of okadaic acid.

INTRODUCTION

Acyclic stereocontrol has become an extremely important field in the synthesis of stereocomplex natural products. We have developed new synthetic methodology which we have named "heteroconjugate addition"[2] during the course of the synthesis of an ansamacrocyclic lactam, maytansine,[3] with introduction of its methyl side chain in the *syn*-orientation. The methodology is remarkable for 100% complete *syn*-diastereoselectivity in the addition. It should also be noted for its feasibility in carbon skeleton elongation by utilizing the sulfonyl carbanion in the adduct; thus, the heteroatoms played additional roles for further functionalization, such as carboxylic acid formation as shown in Scheme 1. *Syn*-carboxylic acid (**3**) was prepared by *syn*-addition of methyl to **1** in the synthesis of the Prelog–Djerassi lactonic acid.[4] On the other hand, *anti*-carboxylic acid (**5**) was synthesized by *syn*-addition of ethoxy-vinyllithium to **1** followed by reduction of the sulfonyl and by ozonolysis.

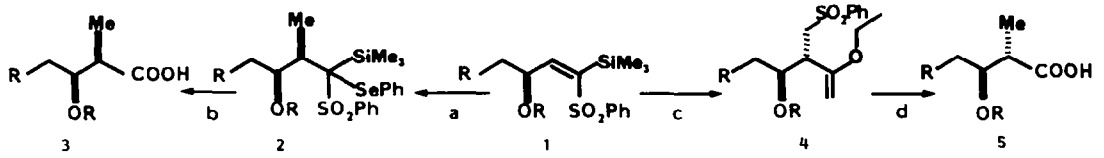
The utility of heteroconjugate addition methodology would be expanded if the diastereoselectivity could be switched to select either the *syn*- or *anti*-orientation as required by the synthetic target. In fact, this is the situation in the case of our current target natural product, okadaic acid, a toxic marine polyether with a molecular weight of 804, having 17 asymmetric centers.[5] *Syn*-selective heteroconjugate addition was used for the C-segment synthesis of okadaic acid. It also contains the *anti*-orientation in the A-segment, for which reverse selectivity is necessary. One of the solutions is described in this paper. We would like to contribute this paper as a useful general method for the synthesis of optically active compounds.

RESULTS AND DISCUSSION

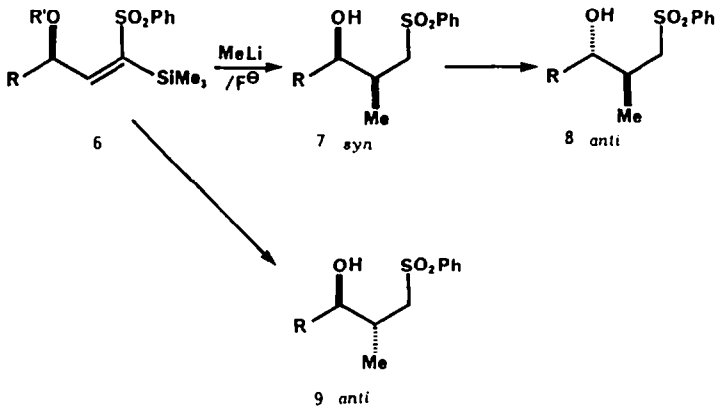
Chelational and conformational effects determining the diastereoselectivity

A simple method to obtain *anti* by means of heteroconjugate addition (**6** to **8**) was facilitated by inverting the secondary hydroxyl group of the 100%-*syn*-adducts **7** under Mitsunobu[6] conditions to yield **8**, which is a 100%-*anti*-diastereoisomer,[7] as shown in Scheme 2. The principal selectivity (**6** to **7**) is due to the chelational effect caused by the α-hydroxyl group, which renders a faster attack of the nucleophile from the chelation face as shown in Fig. 1. On the other hand, the opposite (non-chelation) face may not have such a highly accelerating effect; thus, a slow reaction gave little adduct from this face. The product via the attack from the oxygen face in Fig. 1 should produce the *syn*-diastereoisomer (**7**); on the other hand, the product from the carbon face should give the *anti*-diastereoisomer (**9**), the enantiomer of **8**. The following consideration should lead us to survey the direction searching for the *anti*-selectivity.

The *syn*-selectivity in the heteroconjugate addition was originally designed as shown in Fig. 1 so that the nucleophile (MeLi) can attack the heteroolefin exclusively from its top (oxygen) face due to the following two regulating factors. First, the nucleophile carbanion should coordinate with the oxygen atom by a chelation effect through the lithium cations so that the nucleophile will have a higher opportunity for attacking the olefin from the oxygen face than from the non-chelating carbon face. Second, the electrophile should exist in one of the conformers shown in Fig. 2. This argument is based on a restricted orientation of the olefin relative to the asymmetric carbon such that the



Scheme 1. (a) MeLi/PhSeCl; (b) H_2O_2; (c) CH_2=C(OEt)Li; (d) Na/Hg then O_3.



Scheme 2.

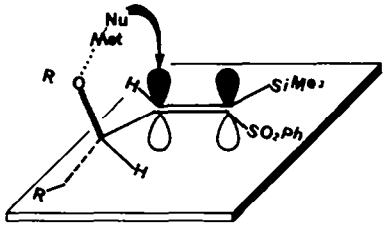


Fig. 1.

bulky substituents R and OR should be away from overlapping with X. As a result, the least bulky substituent (H) should be located around the eclipsing olefin, as in conformations **B**, **C** and **D** in Fig. 2. When the asymmetric carbon is twisted clockwise (to **A**), the potential energy of **A** will be extremely enhanced because of the steric hindrance between the olefinic substituent X and R. Therefore, the oxygen atom should be restricted only to the left side of the olefin in conformations **B**, **C** and **D**. Both conformers **B** and **D** are expected to be significant for chelationally accelerated introduction of the nucleophile to the olefin. Since in conformer **D** the nucleophile should attack through the high steric bulk between R and OR, the attack should take place via conformation **B** from the left side to exhibit *syn*-diastereoselectivity. Conformer **C** is of importance as a transition state for electronic control,[8] which is not significant under the conditions employed in this work.[9] Incidentally, the potential energy of the conformer having X eclipsed with OR or R is extremely high; e.g. even in the case of small substituents such as OH, X = R = Me, the values are nearly 8 and 58 kcal mol^{-1} higher than the value in **B**, respectively.[9] The bulkier substituents in the heteroolefin should retain a higher potential energy difference, so that no conformer having the α-oxygen atom on the right side of the olefin should exist either in the ground state or in the transition state at all.

The above argument for *syn*-diastereoselection suggests that the *anti*-addition could be achieved by coordination of the nucleophile to the opposite face of the α-oxygen atom. We became interested in heteroolefins that have a hydroxyl functionality on the β-carbon atom in order to examine the new chelation effect occurring on the other face as shown in Fig. 3, or conformation **E** in Fig. 2. In this case, the new coordination with the β-oxygen atom should favor β-face addition to give the *anti*-product. To make the discussion convenient, the coordination concerning the α-oxygen or β-oxygen atom is called "α-chelation" or "β-chelation", respectively. In the following sections, we will discuss the preparation of the heteroolefins carrying a β-oxygen atom and the reaction conditions to produce an *anti*-adduct.

Preparation of heteroolefins **12**, **16** *and* **18** *from* D-*glyceraldehyde*

D-Glyceraldehyde acetonide **10** was the chiral precursor of these heteroolefins, which were prepared

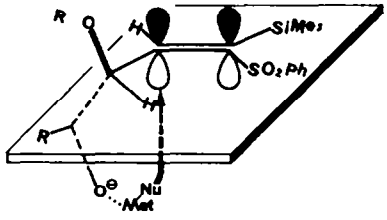


Fig. 3.

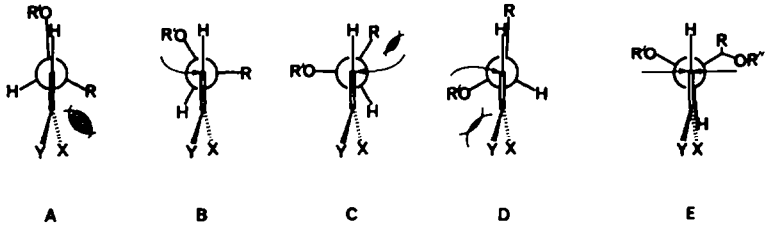
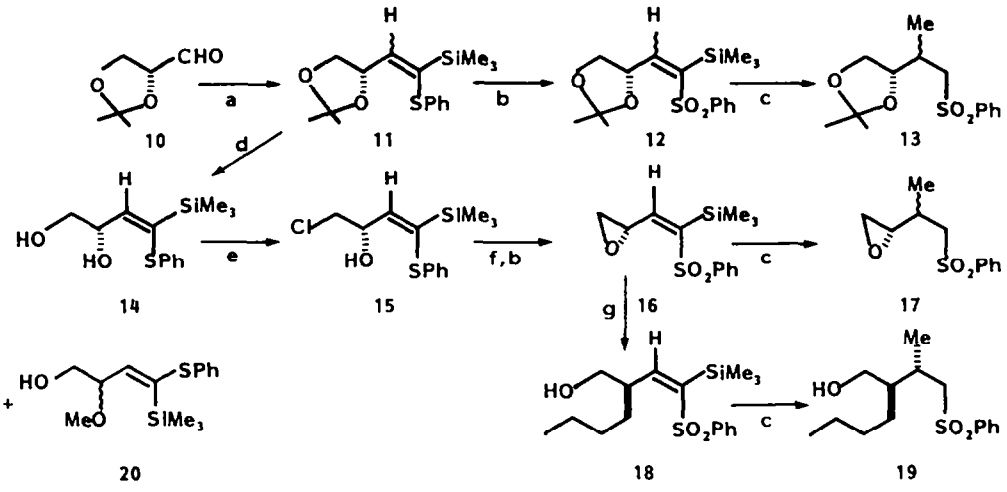


Fig. 2.



Scheme 3. (a) $PhS(Me_3Si)_2CLi$; (b) MCPBA; (c) MeLi; (d) H_3O^+; (e) *p*-TsCl/DMAP; (f) t-BuOK; (g) n-BuCuCN.

according to Scheme 3. Peterson-type olefination of aldehyde **10** with bis(trimethylsilyl)phenylthiomethyllithium $[PhS(Me_3Si)_2CLi]$[2,10] afforded a mixture of *E*- and *Z*-vinylsilylsulfides **11**, which was utilized for the preparation of three types of the title heteroolefins, **12**, **16** and **18**. Oxidation of the vinylsulfides **11** produced the corresponding sulfones as a mixture of *E*- and *Z*-**12**. When the acetonide of the sulfide **11** was hydrolyzed under acidic conditions, one of the regioisomers of the olefins survived to produce the corresponding chiral diol *Z*-**14**, but the other isomer *E*-**11** decomposed to give the racemic methoxy derivative **20**. The primary hydroxyl group of **14** was selectively chlorinated to **15**, which was converted into the epoxide **16** in two steps with potassium t-butoxide and MCPBA. Since the heteroolefin was known to have very little electrophilicity toward dialkyl cuprates, the epoxide was treated with di-n-butylcuprate, which added to the oxiran ring selectively at its allylic position to give the adduct **18**. The following section examines the roles of the oxygen atoms in these three heteroolefins.

Addition of methyllithium to the heteroolefins **12**, **16** *and* **18**

The simple heteroolefin **18** carrying a free hydroxyl group on the β-carbon was treated with 2 equiv of methyllithium to examine whether or not the current β-chelation would lead to an enhanced reaction velocity to give exclusive *anti*-adduct. The reaction course was designed so that the transition state would be the one shown in Fig. 4; thus, methyllithium should coordinate with the alkoxide to attack from the back face. The adduct **19**, in fact produced quantitatively, was then analyzed to be 100% of a single isomer (Me δ 1.03 ppm, d, J = 8); the purity was further confirmed by comparison with authentic samples which were prepared as a mixture of *syn*-isomer (δ 1.05 ppm, d) and *anti*-isomer (δ 1.03 ppm, d) by converting **19** in two steps involving dehydration and hydration with diborane.

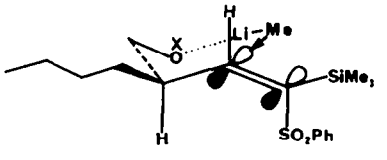
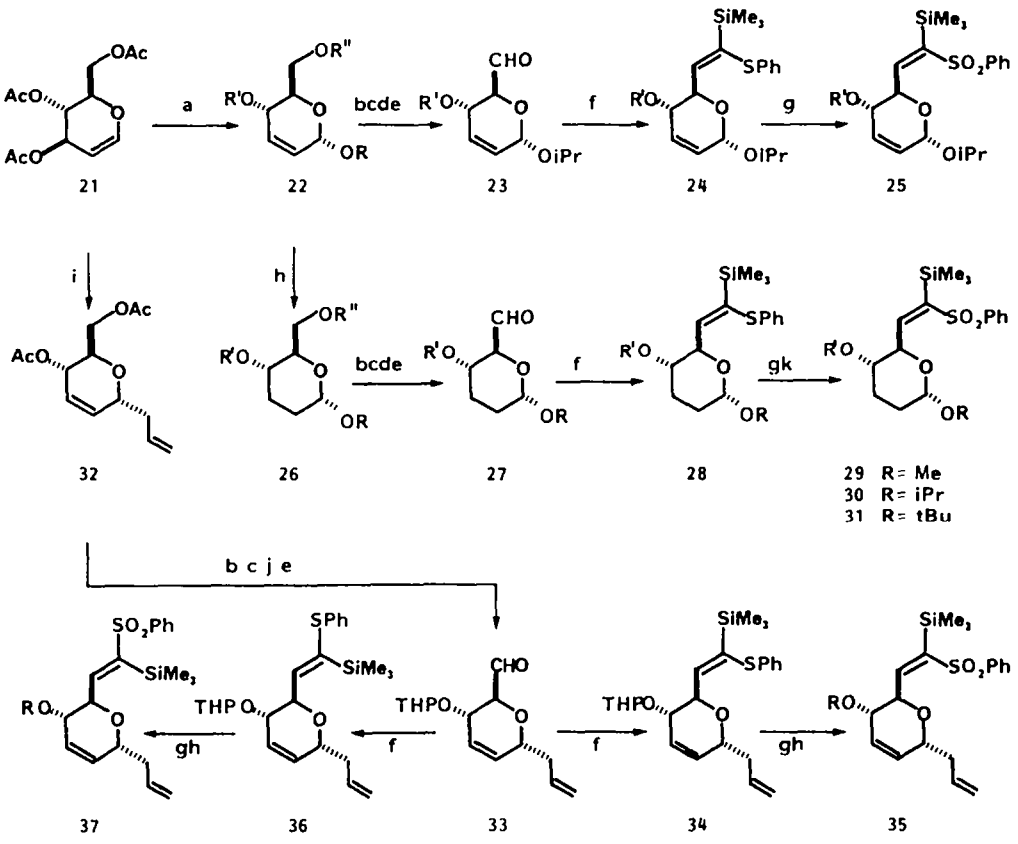


Fig. 4.

Methyllithium addition to heteroolefins such as **12** and **16** afforded an essentially 50:50 mixture of *syn*- and *anti*-adducts **13** and **12**, respectively. In these two cases, the nucleophile methyllithium can coordinate on both faces of the olefin, which suggests the significance of β-chelation effects. Since the diastereoselectivity was not clearly predictable in these systems, we utilized the following cyclic ethers to make the analysis of the reaction course easier.

Preparation of 4*-hydroxypyranosylheteroolefins* **25**, **29**, **30**, **31**, **35** *and* **37**

The chelation effect with the hydroxyl group on the β-carbon is best examined in pyranosides, which are readily available from hexoses. Many of the 4-deoxypyranosides established in our previous work demonstrate exclusive *syn*-diastereoselection.[3,4,11] For the preparation of the 4-hydroxy derivatives from a sugar, we chose a commercially available glucose derivative, tri-O-acetyl D-glucal (**21**)[12] as the starting material for the current purpose. The syntheses of the six heteroolefins are summarized in Scheme 4. The first step is glycosidation, for which we employed O—Me, O—2-Pr,[5b] O—t-Bu,[13] C-propenyl,[14] by treatment with methanol, 2-propanol, t-butanol or trimethyl-2-propenylsilane, respectively, in the presence of BF_3–Et_2O in dichloromethane solvent to afford **22** or **32**. (Heteroolefins **29**, **30** and **31** were prepared to examine the effect of the α-glycoside moieties in addition to the 4-hydroxyl group.) After manipulation of the protective groups on the hydroxyl groups at the 4- and 6-positions, the latter was oxidized into aldehyde, **23**, **27** or **33**. Peterson olefination was employed to couple the corresponding aldehyde with $[PhS(Me_3Si)_2CLi]$ at the 6-position of the sugar to afford the vinylsulfide **24**, **28**, **34** or **36**. Since the sulfides were unstable to acid, they



Scheme 4. (a) BF_3–Et_2O/ROH [R = Me, i-Pr, t-Bu] [R' = Ac, H, EOE or MOP] [R'' = Ac, H, Bz, H]; (b) Et_3N/MeOH; (c) BzCl/Py; (d) CH_2=CHOEt or CH_2=CMeOEt/H^+, KOH/MeOH; (e) $(COCl)_2$/DMSO/Et_3N; (f) $PhS(Me_3Si)_2CLi$; (g) MCPBA; (h) Pd–C/H_2; (i) CH_2=$CHCH_2SiMe_3$/BF_3–Et_2O; (j) dihydropyran/H^+; KOH/MeOH; (k) H_3O^+.

were first oxidized to sulfones, in principle, and then the protective group on each 4-position was removed to give the heteroolefins **25**, **29**, **30**, **31**, **35** and **37**. When we prepared the 4-hydroxypyranosylheteroolefins by Peterson-type olefination, all the major products were *Z*-isomers, which were readily separated by crystallization and/or by chromatography. But the 1-(C-2-propenyl)-4-hydroxypyranosylheteroolefin was produced as an essentially 75:25 mixture of *Z*- and *E*-isomers. So **37** was only the *E*-heteroolefin separated in an amount useful for the following studies.

Stereochemistry of the pyranosylheteroolefins

The simple Me-O-pyranosylheteroolefin **29** has the conformation shown in Fig. 5, in which the OMe group is located in an axial orientation due to the anomeric effect[15] and the bulky heteroolefin is located in an equatorial orientation. This fact was indicated by the coupling constant $J_{4,5}$ = 9.0 Hz in **25**, **29**, **30** and **31** as shown in Table 1. The conformation that the heteroolefin is eclipsed with H-5 is supported by the fact that all the C-6 olefinic protons couple with the C-5 H's in *ca* 9 Hz (Table 1). All the other 1-alkoxy-4-hydroxypyranosylheteroolefins showed the same tendency. Conformation **E** in Fig. 2 was confirmed to be the case in the ground state of these heteroolefins. But 1-C-(2-propenyl)heteroolefins **35** and **37** exhibited different reactivity under the addition conditions (*vide infra*). Although the *Z*-heteroolefin **35** exists in the normal conformation shown in Fig. 6, the conformation of this special *E*-heteroolefin (**37**) is different from those of the other heteroolefins. Thus, the *E*-heteroolefin assumes an axial orientation because of $J_{4,5}$ = 3.5 Hz; on the other hand, the 1-C-(2-propenyl) group assumes an equatorial orientation as illustrated in Fig. 7. This phenomenon is due to the strong electronegativity of an *E*-sulfonyl group in an axial orientation, that is to say, "extended anomeric effect". The current conformational difference led the two regio-isomers to show different selectivity in the addition (Table 1).

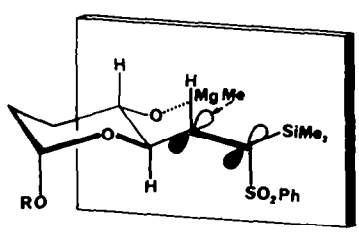
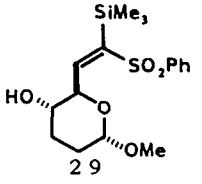
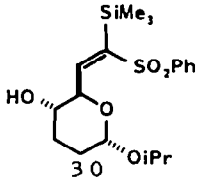
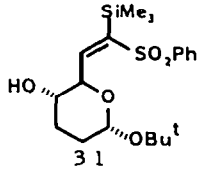
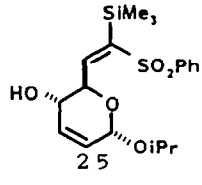
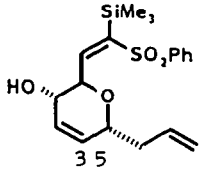
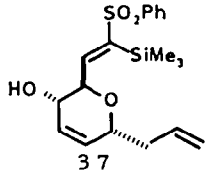


Fig. 5.

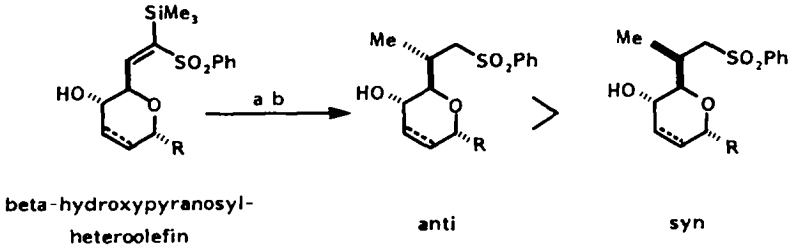
Table 1. Effects of β-chelation in β-oxyheteroolefins

Heteroolefin	H-6, ppm H-5, ppm (J in Hz)	Nucleophile	Reaction condition Solvent–co-solvent	Reaction temp (°)	Product ratio *anti*:*syn*	Yield (%)
 29	6.52 4.90 (9, 9)	MeLi	THF	−78	50:50	76
 30	6.50 5.28 (9, 9)	MeMgBr	THF–hexane (1:9)	−20	95:5	98
		MeLi	THF	−78	48:52	90
		MeLi	THF–HMPA	−78	40:60	99
		MeLi	THF–hexane (1:9)	−78	25:75	91
		t-BuLi	THF	−78	99:1	95
 31	6.38 5.26 (9, 9)	MeLi	THF	−78	85:15	88
 25	6.51 5.31 (9, 9)	MeMgBr	THF	−20	91:9	80
 35	6.60 5.20 (9, 7.5)	MeMgBr	THF	−40	90:10	98
		MeLi	THF	−78	40:60	95
 37	7.34 4.60 (9, 3.5)	MeMgBr	THF	−20	—:—	<25
		MeLi	THF	−78	91:9	99

Addition of methyllithium to pyranosylheteroolefins and proof of stereochemistry

β-Oxyheteroolefins **25**, **29**, **30**, **31**, **35** and **37** were treated with 2.5 equiv of methyllithium (LiBr complex in Et_2O) in THF at −78° and then with KF in MeOH to give the adduct shown in Scheme 5; the results are summarized in Table 1.

The stereochemistry of the product was proven by comparison with the authentic *syn*-adduct in the heteroconjugate addition of a pyranosylheteroolefin which had been confirmed by leading to further authentic compounds, such as Prelog–Djerassi lactonic acid,[4] maytansinoids[3] or acyclic derivatives.[11] In the course of those studies, an experimental rule was established to assign the *syn*- and *anti*-diastereoisomers according to their ^{13}C-NMR signals of the methyl



Scheme 5. (a) MeLi, MeMgBr or t-BuLi; (b) KF/MeOH.

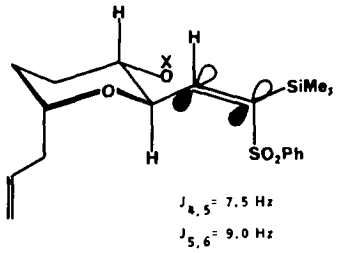


Fig. 6.

group: that *syn*-isomers appear at δ 14.0 $\pm$ 0.4 ppm and *anti*-isomers at δ 17.20 $\pm$ 0.4 ppm.[16] The empirical rule was not directly applicable for the assignment of adducts having a β-hydroxyl group as in the above cases. Determination of such adducts was achieved by reducing the hydroxyl group of **38** in order to convert **38** into an assignable system by the ^{13}C-NMR chemical shifts of the methyl groups. For this purpose, we employed Barton's radical reduction via the xanthate[17] of the alcohol shown in Scheme 6; thus, the hydroxyl group in **38** was first converted into the methyl xanthate **39**, which was further heated with tri-n-butyltin hydride in the presence of AIBN as a radical initiator. The products **40** exhibited a ^{13}C-NMR Me signal at δ 17.0 ppm. When treated with 1,3-propanedithiol in the presence of HCl–$ZnCl_2$, **40** (R = t-Bu) was converted into an acyclic derivative **41**, which showed its Me signal at δ 17.4 ppm. The ratio of *anti*: *syn* was finally analyzed on **41** by NMR and HPLC to be 85: 15. The 2-propyl-glycoside **30** also gave a similar result. For comparison, an authentic *syn*-isomer **44** (showing the Me signal at δ 13.8 ppm) was prepared from **42** by simple addition of MeLi (to **43**[16]) followed by acidic treatment with the dithiol.

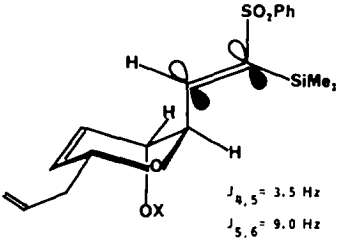
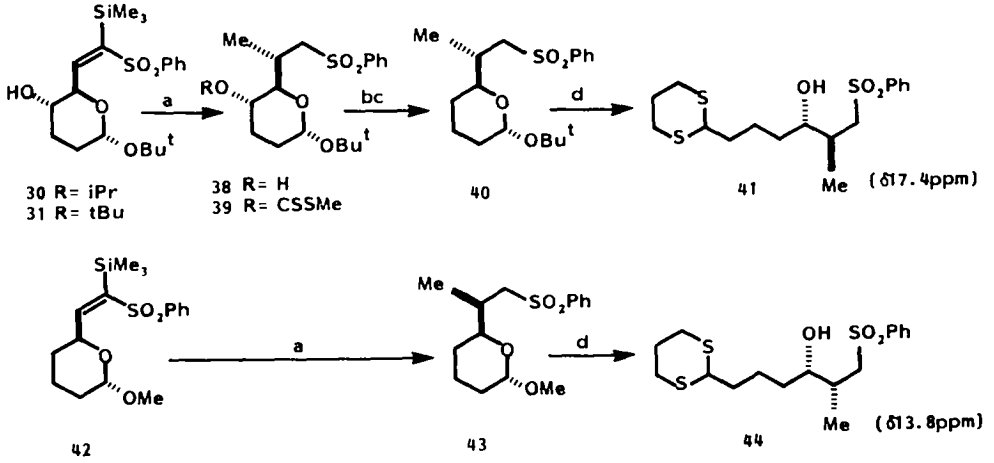


Fig. 7.

Highly selective addition of a Grignard reagent to a β-oxyheteroolefin

The β-chelation effects in the 4-hydroxypyranosyl-heteroolefin are basically in competition with α-chelation effects for assembling the nucleophile MeLi. And on both of the faces can be constructed effective aggregates with the nucleophiles for the addition to result in a mixture of two diastereoisomers. The structure may not be such a simple feature that involves one methyl anion and one oxygen atom sharing a lithium cation, since the simple model cannot inter-



Scheme 6. (a) MeLi/KF; (b) CS_2/NaH, MeI; (c) n-Bu_3SnH; (d) $HS(CH_2)_3SH/BF_3$.

pret the significant difference in the diastereoselectivity (50, 52 and 85% *anti*) among the same "methyllithium" addition to the same heteroolefins **29**, **30** and **31**, different in 1-OR, namely O—Me, O—2-Pr, O—t-Bu, respectively. Only the most bulky t-butyl glycoside (**31**) showed a high selectivity. On the other hand, addition of a bulky t-BuLi instead of MeLi to **30** afforded a single product. It can be rationalized in only the above two cases that the formation of the aggregates should be spatially prohibited on the α-face due to steric congestion between the (glycosidic) isopropyl and (nucleophilic) t-butyl groups, or the t-butyl and methyl groups, respectively, to yield the *anti*-adduct. Selective addition with MeLi from the β-face, in general, was unsuccessful except in the case of a C-glycoside heteroolefin, **37**.

The solvent effect in the diastereoselection was studied on **30**; in either THF, THF–HMPA or THF–hexane the addition was *syn*-dominant. The results may suggest an electrostatic repulsion between the 4-oxide and methylanion due to the ionic character of Li. The Grignard reagent should show an important interaction owing to the more covalent character of Mg^{2+}. In our previous work, however, the heteroconjugate addition of methylhalogenomagnesium to α-alkoxy-β-methylenheteroolefins was found to be extremely slow (by more than the order of 10^{-3}) relative to the addition of methyllithium.[16] This implies that the enhancement of the reaction velocity from the α-face is not the case for the Grignard reagent, which may interact strongly with the free alkoxy group on the β-face to produce an *anti*-adduct as shown in Fig. 5. Seebach claims a beautiful solution suggesting the structure of aggregates which are significant in the transition state model involving the chelation effect.[18] The Grignard reagent indeed added to the heteroolefin at an accelerated velocity when it could interact with a free β-hydroxyl group. The reactions of heteroolefins **25**, **30** and **35** with MeMgBr gave largely the corresponding *anti*-adducts (91, 95 and 90%, respectively) due to the β-chelation effect. *E*-Heteroolefin **37** gave a low yield of the adduct with MeMgBr at −20° due to the intramolecular attack of the β-alkoxide on the silicon atom. But a rapid addition with MeLi took place to give the 91%-*anti*-product at −78° without silicon migration to oxygen, so that the reaction took place not in the axial conformation (as in Fig. 7) but in the equatorial one (Fig. 6).

The *anti*-product of **25** was indeed used for the synthesis of the okadaic acid A-segment; the *anti*-stereochemistry was proven using a different method in this case.[7] The above methodology is being expanded for introduction of functionalized nucleophiles other than a methyl group, and is expected to solve further stereochemical problems in organic syntheses of stereocomplex molecules.

EXPERIMENTAL

Preparation of the heteroolefins **12**, **16** *and* **18** *from* D-*glyceraldehyde.* To a soln of bis(trimethylsilyl)phenylthiomethane[10] in THF (2.0 l) was added n-BuLi (1.7 M, 288.4 ml) at −78° in *ca* 2 h, and the mixture was kept at −40° for 1 h and then at room temp for 2 h, while the mixture became deep yellow in colour. The mixture was again cooled to −78° and mixed with D-glyceraldehyde acetonide (**16**, 59.9 g in 35 ml of THF), and the temp was allowed to rise gradually to −10° in 3 h. To this mixture was added NH_4Cl soln and the mixture was extracted with Et_2O. The extracts were combined, washed with H_2O and NaCl soln, dried (Na_2SO_4) and evaporated to give crude products (147 g). Purification by silica gel column chromatography afforded the adduct **11** (114.9 g, 80% yield), which was dissolved in MeOH (1.5 l) and stirred with *p*-toluenesulfonic acid (7.0 g) at 0° for 10 min and then at room temp for 4 h. The mixture was poured into $NaHCO_3$ and extracted with CH_2Cl_2. The crude products were crystallized from a mixture of n-hexane and Et_2O to give 14.7 g of *Z*-sulfide (**14**) and the residual mother liquor was separated by preparative HPLC to give *Z*-sulfide (8.27 g) in 46% (60% in a small scale) yield. **14**: m.p. 92.0–93.0°; $[\alpha]_D$ +193.2° (*c* 0.327, $CHCl_3$) (analyzed to be a single enantiomer as MTPA-ester); ^{1}H-NMR δ 6.42 (1H, d, J = 8.1 Hz), 7.22 (5H, br s). (Found: C, 58.22; H, 7.47. Calc for $C_{13}H_{20}O_2SiS$: C, 58.16; H, 7.51%.)

The sulfide acetonide **14** (4.92 g, 16.9 mmol) was oxidized with MCPBA (80%, 9 g, 41.7 mmol) in CH_2Cl_2 (100 ml) at 0° for 40 min. The excess reagent was decomposed by Na_2SO_3 until KI–starch paper became negative and the reaction mixture was worked up to give a mixture of heteroolefins (*E*/*Z* = 1 : 1) which was separated by silica gel prep-HPLC (EtOAc–hexane, 1 : 10) to give *E*-**12** (2.2 g): ^{1}H-NMR δ 0.22 (9H, s), 1.44 (6H, s), 3.70 (1H, dd, J = 8.5, 7), 4.14 (1H, dd, J = 8.5, 6), 4.86 (1H, ddd, J = 9, 7, 6), 7.20 (1H, d, J = 9) and *Z*-**12** (2.2 g) δ 0.22 (9H, s), 1.36 (3H, s), 1.48 (3H, s), 3.68 (1H, dd, J = 8.5, 6.5), 4.22 (1H, dd, J = 8.5, 7), 5.42 (1H, ddd, J = 7.5, 7, 6.5), 6.56 (1H, d, J = 7.5); 82% yield.

The *Z*-diolsulfide **14** (3.00 g) was dissolved in CH_2Cl_2 (60 ml) and stirred with pyridine (9.0 ml), dimethylaminopyridine (689 mg) and *p*-toluenesulfonyl chloride (4.69 g) at room temp for 12 h, when the mixture was diluted with Et_2O (60 ml) and filtered through an Na_2SO_4 column. The filtrate was concentrated to *ca* 60 ml and stirred with a mixture of Me_2CO–H_2O (4 : 1) for 30 min. The chlorohydrin (**15**) was taken up with Et_2O and purified on a silica gel column to give 1.6 g (50% yield), which was treated with t-BuOK (1.2 M, 5.2 ml) in THF at −20°. After 10 min, the mixture was diluted with Et_2O (400 ml) and passed through a silica gel column. The eluate was cooled to 0° and stirred with MCPBA (2.7 g) for 0.5 h and then at room temp for 4 h. The work-up afforded the epoxyheteroolefin **16** (0.74 g, 50% yield) as crystals, m.p. 58.6–59.0°; $[\alpha]_D$ +63.0° (*c* 1.45, $CHCl_3$); ^{1}H-NMR δ 0.24 (9H, s), 2.65 (1H, dd, J = 5.2, 2.5), 3.02 (1H, dd, J = 5.2, 4.6), 4.43 (1H, ddd, J = 8.0, 4.6, 2.5), 5.96 (1H, d, J = 8). (Found: C, 55.28; H, 6.42. Calc for $C_{13}H_{18}O_3SiS$: C, 55.29; H, 6.40%.)

To a suspension of copper(I) cyanide (72.1 mg) in anhyd Et_2O (2.4 ml) was added dropwise a soln of n-BuLi (1.7 M, 0.47 ml) at −78° and then the temp was raised to −30°. This soln was added to a soln of epoxyheteroolefin **16** (52.4 mg in 1.7 ml Et_2O) at −30° and stirred for 20 min at this temp. Ethereal work-up afforded the butyl adduct (44.2 mg, 70% yield; analyzed to be a single enantiomer as MTPA-ester) **18**, m.p. 89–90°; $[\alpha]_D$ −55.9° (*c* 1.13, $CHCl_3$); ^{1}H-NMR δ 0.34 (9H, s), 0.72 (3H, br t), 6.32 (1H, d, J = 10.9). (Found: C, 60.13; H, 8.31. Calc for $C_{17}H_{28}O_3SiS$: C, 59.96; H, 8.28%.)

Addition of methyllithium to **12**, **16**, **18**. The acetonid-heteroolefin **12** (120 mg) was dissolved in 2.5 ml of THF and then stirred with MeLi (1.5 M LiBr complex) at −78° for 10 min. The adduct obtained by ethereal work-up was treated further with KF (80 mg) in hot MeOH (3 ml) for 20 min. The final product (58 mg, 56% yield) was analyzed by ^{1}H-NMR to be a mixture of two diastereoisomers of **13**, the ratio being 60 : 40; ^{1}H-NMR δ 1.08 (1.8H, d, J = 8), 1.10 (1.2H, d, J = 8), 1.26 (3H, s), 1.36 (3H, s).

The epoxyheteroolefin **16** (40 mg) was similarly treated with MeLi to give a mixture of two diastereoisomers (**17**) showing δ 1.16 (d, J = 6.8) and 1.22 (d, J = 6.8) in a ratio of 55 : 45.

The β-hydroxyheteroolefin **18** (56.4 mg) was dissolved in THF (1.9 ml) and mixed with MeLi (1.55 M, 0.24 ml) at −78° and then stirred at −40° for 3 h. The product was extracted with Et_2O and treated further with KF (30 mg) in a mixture of MeOH–CH_2Cl_2 (1 ml : 0.5 ml) for 2 h at room temp to give the adduct, 48.5 mg (100%), **19**, oil, $[\alpha]_D$ +7.4° (*c* 0.97, $CHCl_3$); IR

ν 3620 (sh), 3530 cm^{-1}; ^{1}H-NMR δ 0.88 (3H, m), 1.04 (3H, d, J = 7), 1.22 (6H, m), 1.66 (1H, m), 2.11 (1H, br s), 2.30 (1H, m), 2.99 (1H, dd, J = 14.2, 7.5), 3.40 (1H, dd, J = 14.2, 4.4), 3.55 (2H, m), 7.6 (3H, m), 7.9 (2H, m); ^{13}C-NMR δ 14.0, 16.5, 22.9, 27.6, 29.2, 30.0, 44.6, 60.5, 63.3, 127.7, 129.0, 133.3 ppm.

Preparation of the 1 - (2' - *propyl*)4 - *hydroxy* - 2,3 - *dehydropyranosylheteroolefins* **25**. Tri-O-acetyl D-glucal (100 g) was dissolved in CH_2Cl_2 (450 ml dried over Al_2O_3) and stirred with 2-propanol (115 ml) and to this soln was added dropwise BF_3–Et_2O (70 ml) at room temp under N_2 over a period of 15 min. After stirring a further 15 min at room temp, the mixture was poured into ice-cold $NaHCO_3$ aq (500 g in 3 l) with vigorous stirring and the stirring was continued for 45 min. The organic layer was separated, washed with H_2O, passed through a column containing Na_2SO_4 and silica gel, and then evaporated to give oily residue (*ca* 100 g). It was dissolved in MeOH (2 l) and stirred with H_2O (250 ml) and Et_3N (250 ml) at 50° for 14 h. The mixture was evaporated to dryness *in vacuo* to afford a solid which was crystallized by washing with a mixture of Et_2O and hexane to give crude crystals (65–94% yield), which was recrystallized to give 56 g (81%) pure diol **22** (R' = R'' = H); m.p. 95.5–97.5°; $[\alpha]_D$ +75.3° (*c* 1.10, $CHCl_3$); ^{1}H-NMR δ 1.18 (3H, d, J = 6), 1.24 (3H, d, J = 6), 1.50 (1H), 1.82 (1H, br d, J = 5), 3.6–4.1 (4H), 4.20 (1H, br t, J = 6), 5.08 (1H, t, J = 1), 5.71 (1H, ddd, J = 10, 3, 2), 5.95 (1H, d, J = 10). (Found: C, 57.44; H, 8.54. Calc for $C_9H_{16}O_4$: C, 57.43; H, 8.57%.)

The diol **22** (R' = R'' = H; 6.9 g) was monobenzoylated by mixing with benzoyl chloride (4.3 ml) and pyridine (60 ml) in CH_2Cl_2 (150 ml) at 0° overnight. The product was taken up by extracting with Et_2O to give crude benzoate (10.5 g). Part of it was purified to give an oil **22** (R' = H, R'' = Bz); $[\alpha]_D$ +9.8° (*c* 1.18, $CHCl_3$); ^{1}H-NMR δ 1.15 (3H, d, J = 6), 1.21 (3H, d, J = 6), 3.07 (1H, br s), 3.9–4.2 (2H), 4.5–4.7 (2H, AB), 5.10 (1H, br s), 5.72 (1H, dt, J = 10, 3), 5.98 (1H, d, J = 10), 7.4–7.6 (3H), 8.0–8.2 (2H). (Found: C, 65.74; H, 6.98. Calc for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90%.)

The benzoate **22** was stirred with ethylvinylether (5 ml) and PPTS (0.5 g) in CH_2Cl_2 (200 ml) at room temp for 1.8 h affording the ethoxyethylether (crude 12 g), which was treated further with KOH (8.7 g) in MeOH (300 ml) at room temp overnight to be worked up with Et_2O. The product primary alcohol (crude 9.6 g) was purified by silica gel (100 g eluant ether–hexane, 1 : 3 then 2 : 1) to give pure alcohol **22** (R' = *EE*; R'' = H) (6.0 g in 63% overall yield in 3 steps). A large scale from 61.5 g of the diol afforded 44.4 g. The alcohol (12.2 g) was oxidized by introducing it into a mixture of oxalyl chloride (5.3 ml), DMSO (11.5 ml) and Et_3N (31 ml) in CH_2Cl_2 (350 ml) at −78° and the mixture was stirred at −30° for 1 h.[19] The mixture was diluted with hexane and then extracted with a mixture of Et_2O–hexane (1 : 1) to give 13.9 g of **23**, which was mixed with bis(trimethylsilyl)phenylthiomethyllithium [prepared from 15 ml of the methane and n-BuLi (1.55 M, 36 ml) in THF (320 ml) at −78°]. The product was purified by silica gel column chromatography (gel 270 g, eluant ether–hexane, 5 : 1) to produce 12.4 g (61% overall yield) of **24**. It was oxidized with MCPBA (12.3 g) in a mixture of CH_2Cl_2 (350 ml) and sat $NaHCO_3$ aq (300 ml) to give the product (13.9 g); its geometry being *Z* : *E* = 27 : 1. Its ethoxyethyl group was hydrolyzed by stirring it in a mixture of PPTS (1.4 g), 2-propanol (50 ml) and CH_2Cl_2 (300 ml) at 40° for 55 min and the mixture was poured into $NaHCO_3$. Extraction with CH_2Cl_2 afforded 14.1 g of **25** (R' = H); oil, $[\alpha]_D$ −82.5° (*c* 0.81, $CHCl_3$); ^{1}H-NMR δ 0.23 (9H, s), 1.06 (3H, d, J = 6), 1.13 (3H, d, J = 6), 1.47 (1H, d, J = 8), 1.8–2.1 (2H), 5.04 (1H, br s), 5.31 (1H, t, J = 9), 5.64 (1H, dt, J = 10, 1), 6.06 (1H, d, J = 10), 6.51 (1H, d, J = 9), 7.4–8.0 (5H). (Found: C, 57.55; H, 7.06. Calc for $C_{19}H_{28}O_5SiS$: C, 57.55; H, 7.12%.)

Preparation of the 1 - (2' - *propyl*)4 - *hydroxypyranosylheteroolefins* **30**. The olefin **26** (R' = R'' = Ac) (8.5 g) was dissolved in EtOAc (250 ml) and stirred with Pd–C (5%, 0.05 g) under H_2 at room temp for 10 h. The mixture was filtered through Celite and the filtrate was evaporated to dryness to give an oil (8.8 g), which (8 g) was hydrolyzed by stirring in MeOH (200 ml) containing Et_3N (40 ml) and H_2O (40 ml) at room temp for 6 h. The mixture was concentrated to dryness to give an oil (5.4 g, 97% yield). To a soln of **26** (R' = R'' = H; 5.4 g) in CH_2Cl_2 (300 ml) was added pyridine (45 ml) and benzoyl chloride (3.41 ml) soln in CH_2Cl_2 (10 ml) at −20° and the mixture was stirred at room temp for 8 h. The mixture was poured into cold H_2O and extracted with Et_2O to afford **26** (R' = H, R'' = Bz) [^{1}H-NMR δ 1.15 and 1.22 (3H × 2, d, J = 6.2), 1.9 (4H), 2.80 (1H), 3.52 (1H, m), 3.84 (1H, m), 3.94 (1H, q × 2, J = 6.2), 4.42 (1H, dd, J = 12, 2), 4.82 (1H, dd, J = 12, 4.2), 4.93 (1H), 7.5 (3H), 8.05 (2H). The alcohol (7.3 g) was treated with vinylethylether (5.2 ml) in CH_2Cl_2 (120 ml) in the presence of pyridinium-*p*-toluenesulfonate (PPTS) (0.57 g) at room temp for 13 h. The mixture was poured into $NaHCO_3$ and then extracted with a mixture of Et_2O and hexane to give **26** (R' = *EE*, R'' = Bz) (8.5 g, 94% yield). It was stirred in MeOH (170 ml) containing KOH (85%, 10.7 g) at room temp, and after 15 min the mixture was poured into cold 1 N HCl (160 ml). The mixture (pH 7) was extracted with EtOAc 5 times and the combined extracts were washed with NaCl soln and evaporated to dryness to give an oil, which was purified by silica gel chromatography to give **26** (R' = *EE*, R'' = H) (3.9 g, 69% yield). It was dissolved in CH_2Cl_2 (30 ml) and then added to a cold (−78°) mixture of oxalylchloride (1.96 ml) and DMSO (3.2 ml) in CH_2Cl_2 (100 ml) and to this mixture was added Et_3N (13.5 ml) at −78°.[19] After stirring the mixture at 0° for an additional 1 h, it was poured into a buffered soln of NH_4Cl–HCl and extracted at pH 6 with a mixture of Et_2O and hexane (2 : 1) to give **27** (R' = *EE*) [3.6 g in 93% yield, δ 9.75 (1H, d, J = 9)]. The aldehyde was dissolved in THF (40 ml) and introduced into a soln of bis(trimethylsilyl)phenylthio-methyllithium [prepared from the methane (4.2 ml) and n-BuLi (9.55 ml) in THF (140 ml)] at −78° over a period of 10 min and the mixture was stirred without the cooling bath for 1 h. The mixture was poured into NH_4Cl and then extracted with hexane 3 times to give **28** (R' = *EE*) (5.1 g, 78% yield). It was treated further in CH_2Cl_2 with a mixture of MCPBA (80%, 5.5 g), $NaHCO_3$ (2.2 g) and H_2O (30 ml) for 1 h at room temp, and the mixture was stirred with Na_2SO_3, concentrated to *ca* 70 ml *in vacuo* and then extracted with Et_2O. The residue (5.6 g) was successively treated with D,L-10-camphorsulfonic acid (0.54 g) in 2-propanol (180 ml) at 0° for 10 min and at room temp for 10 min. The mixture was poured into cold $NaHCO_3$ and extracted with Et_2O to give crude oil (4.8 g), which was crystallized from a mixture of hexane and Et_2O to give **30** (R' = H) (3.46 g, 75% yield); m.p. 87.5–89.5°; $[\alpha]_D$ −82.1° (*c* 0.98, $CHCl_3$); ^{1}H-NMR δ 0.20 (9H, s), 1.08 and 1.14 (3H × 2, d, J = 6), 1.8–1.9 (4H, br), 2.94 (1H, m), 3.32 (1H, br), 3.80 (1H, m), 4.88 (1H, br), 5.28 (1H, t, J = 9), 6.50 (1H, d, J = 9), 7.5 (3H, m), 7.9 (2H, m). (Found: C, 59.14; H, 7.60. Calc for $C_{19}H_{30}O_5SiS$: C, 59.25; H, 7.59%.)

Preparation of the 1-(t-*butyl*)4-*hydroxypyranosylheteroolefin* **31**. A soln of **21** (30.0 g) in C_6H_6 (900 ml) was stirred with t-BuOH (27 ml) and BF_3–Et_2O (7.2 ml) under argon at room temp for 100 min and the mixture was poured into cold $NaHCO_3$, extracted with Et_2O, washed with H_2O and NaCl, dried (Na_2SO_4) and evaporated to give 32.3 g (97% yield) of t-butylglycoside. It was dissolved in EtOAc (900 ml) and stirred with Pd–C (5%, 4.5 g) and $NaHCO_3$ (1.2 g) under H_2 for 12 h. The mixture was filtered through Celite, and the filtrate was concentrated to give the dihydrodiacetate (30.2 g). It was hydrolyzed by stirring with Et_3N (150 ml) and H_2O (100 ml) in MeOH (800 ml) at room temp affording the diol **26** (R' = R'' = H, R = t-Bu) (22.5 g quantitative yield).

To a soln of the diol (7.0 g) in CH_2Cl_2 (300 ml) was added pyridine (150 ml) in one portion and then benzoyl chloride (4.4 ml in 20 ml CH_2Cl_2) dropwise at 0°. After stirring the mixture at room temp overnight, it was diluted with Et_2O (500 ml) and washed with H_2O, dilute HCl, $NaHCO_3$ and NaCl, dried (Na_2SO_4) and evaporated to give crude monobenzoate (*ca* 11.6 g). It was treated with 2-methoxypropene (9 ml) and CSA (0.5 g) in CH_2Cl_2 (250 ml) at room temp for 1.5 h and the mixture was poured into $NaHCO_3$ soln. The organic layer was separated, washed with H_2O and half-sat NaCl, dried and evaporated to give the 2-methoxy-2-propylether (10.6 g in 86%

yield). The benzoate **26** (R′ = CMe_2OMe, R″ = Bz) was dissolved in MeOH (200 ml) and stirred with KOH (6.8 g) and H_2O at room temp for 1.75 h. To the mixture was added solid CO_2 and the solvent was removed by evaporation to give an oily residue, which was extracted with Et_2O to give **26** (R′ = CMe_2OMe, R″ = H) (7.0 g in 93% yield). Oxidation of its hydroxymethyl (5.8 g) was better achieved (than by Swern oxidation) by dipyridinium chromate (40.0 g) in CH_2Cl_2 (220 ml) at room temp for 10 min. The product was diluted with Et_2O and filtered through Celite and the filtrate was passed through a silica gel column to give 4.5 g (78% yield) of **27** (R′ = CMe_2OMe). Peterson olefination of this aldehyde (2.5 g) with bis(trimethylsilyl)phenylthiomethyllithium [generated from the corresponding methane (3.4 ml) and n-BuLi (1.6 M, 8.0 ml) in THF (70 ml)] at −45° as followed by purification with silica gel (55 g, hexane–Et_2O, 1:3 as eluant) to yield 1 g (30% yield) of **28** (R′ = CMe_2OMe, R = t-Bu). The sulfide (145 mg) was stirred with MCPBA (0.26 g) and sat $NaHCO_3$ (3 ml) in CH_2Cl_2 at 0° for 1.5 h and at room temp for 20 min to give the heteroolefin (152 mg in 95% yield) **31** (R′ = H): oil; ^{1}H-NMR δ 0.20 (9H, s), 1.10 (9H, s), 1.6–1.9 (4H), 3.3 (2H), 4.95 (1H, br s), 5.26 (1H, t, J = 9), 6.38 (1H, d, J = 9), 7.5 (3H), 7.8 (2H).

Preparation of 1 - *C* - (2 - *propenyl*) - 4 - *hydroxypyranosylheteroolefin* **35** *and* **37**. Tri-O-acetyl-D-glucal **21** (100 g) was dissolved in CH_2Cl_2 (1.1 l) and stirred with trimethyl-2-propenylsilane (89 ml) and BF_3–Et_2O (48 ml) at −40° for 1.5 h and then at 0° for 1 h. The mixture was poured into $NaHCO_3$ and the organic layer was washed, dried and evaporated to give 108 g of a crude oil (analyzed to be a mixture of α/β-C-glycoside in a ratio of 16:1 by HPLC). The oil (**32**, 11.4 g) was first hydrolyzed in a mixture of Et_3N (40 ml), H_2O (20 ml) and MeOH (240 ml) at room temp for 2 days and then evaporated to dryness; second, the residue was acetylated by stirring with acetyl chloride (3.2 ml), pyridine (20 ml) and CH_2Cl_2 (300 ml) at 0° for 2 h to give crude monoacetate (11.8 g). It was treated further with dihydropyran (7.1 ml) and CSA (2.0 g) in CH_2Cl_2 at room temp for 2 h and the product was successively treated with Et_3N (40 ml) and H_2O (20 ml) in refluxing MeOH (200 ml) for 2 days. After evaporation, the mixture was purified by silica gel (170 g, eluant Et_2O–hexane, 1:1) to afford THP-monool (7.18 g in 63% overall yield in 4 steps). The alcohol (6.40 mg) was subjected to Swern oxidation[19] [oxalyl chloride (7.5 ml), DMSO (14 ml), Et_3N (56 ml) in CH_2Cl_2 (320 ml)] to give the aldehyde which was mixed with bis(trimethylsilyl)phenylthiomethyllithium [generated from 10 ml of the methane, n-BuLi (1.65 M, 23.5 ml) in THF (300 ml) at −78° for 0.5 h and at −50° for 4 h] at −45°. The crude product was purified on a silica gel column (150 g eluant Et_2O–hexane, 1:50) to give **34** and **36** (4.87 g in 40% yield). The sulfide (3.40 g) was oxidized with MCPBA (6.8 g) in CH_2Cl_2 (120 ml) at 0° for 2.4 h and the product sulfone was hydrolyzed with PPTS (pyridinium *p*-toluenesulfonate 0.40 g) in EtOH (100 ml) at 60° for 2 h and the hydrolysate was purified by silica gel (100 g eluant Et_2O–hexane, 1:3 then 1:1) to afford the heteroolefins in 74% yield *E*-**37** (0.6 g); oil; $[\alpha]_D$ +20.8° (*c* 1.18, $CHCl_3$); ^{1}H-NMR δ 0.24 (9H, s), 1.10 (1H, OH), 1.3–1.5 (2H), 3.84 (1H, br s), 4.24 (1H, ddd, J = 8, 5, 2), 4.60 (1H, dd, J = 9, 3.5), 5.08–5.20 (2H), 5.7–6.10 (3H), 7.34 (1H, d, J = 9), 7.5–7.6 (3H), 7.7–8.0 (3H); and *Z*-**35** (1.6 g); m.p. 68.5°; $[\alpha]_D$ −105° (*c* 1.05, $CHCl_3$); ^{1}H-NMR δ 0.14 (9H, s), 1.8–2.1 (2H), 3.5 (1H, OH), 4.0–4.2 (2H), 4.8–5.0 (2H), 5.20 (1H, dd, J = 9, 7.5), 5.38 (1H, ddd, J = 10, 3, 2), 5.4–5.7 (1H), 5.96 (1H, dt, J = 10, 2), 6.60 (1H, d, J = 9), 6.9–7.0 (3H), 7.8–8.0 (2H). (Found: C, 60.20; H, 6.92. Calc for $C_{19}H_{28}O_4SiS$: C, 60.28; H, 6.92%.)

Preparation of 1 - (2′ - *propyl*) - 4 - *dimethyl* - t - *butylsilyl*)*oxyheteroolefin* **30** (R′ = $SiMe_2Bu^t$). A soln of **30** (0.19 g) was stirred with t-butyldimethylsilyl-O-triflate (0.12 ml) and pyridine (0.078 ml) in THF (6 ml) at 0° for 40 min to give **30**; oil; $[\alpha]_D$ +72.5° (*c* 0.97, $CHCl_3$). (Found: C, 58.79; H, 8.69. Calc for $C_{25}H_{44}O_5Si_2S_1$: C, 58.55; H, 8.60%.)

Methyllithium addition to t-*butylheteroolefin* **31**. The heteroolefin **31** (152 mg) was dissolved in THF (5 ml) and cooled in a dry-ice bath to −78° and then stirred with MeLi (LiBr complex, 2.05 M, 0.7 ml) for 15 min at this temp. The mixture was then mixed with NH_4Cl, extracted with Et_2O and the extracts were combined, washed with H_2O and NaCl soln, dried and evaporated to give 127 mg of oil. It was treated further with KF (20 mg) in MeOH (2.5 ml) at room temp for 1.5 h and then worked up to afford the adduct **38** (62 mg in 88% yield).

The alcohol **38** (62 mg) was dissolved in THF (2 ml) and mixed with NaH (18 mg, 60%, preliminarily washed with hexane) and CS_2 at −20° for 30 min and then at 0° for 15 min with stirring. To this mixture was added MeI (0.1 ml) and imidazole (*ca* 1 mg) and stirring was continued for 40 min to give the xanthate (77 mg, 99% yield). It was heated with a mixture of n-Bu_3SnH [0.25 ml of the soln which was preliminarily prepared from n-Bu_3SnCl (2.5 ml) and $LiAlH_4$ (0.2 g) in Et_2O (13 ml)] and AIBN (*ca* 2 mg of 2,2′-azobisisobutylonitrile) in toluene (2.5 ml) at 90° for 20 min. The product was separated by TLC to afford an oil (22 mg in 38% yield) **40**; ^{13}C-NMR of Me δ 17.0 ppm.

Hydrolysis of the t-butylglycoside (**40**, 22 mg) was carried out with 1,3-propanedithiol (0.01 ml), $ZnCl_2$ (10 mg) and conc HCl (0.1 ml) to afford a crude product (30 mg), which was purified by silica gel TLC to yield in 70% the acyclic molecule **41**; ^{13}C-NMR of Me δ 17.4 ppm. The corresponding *syn*-isomer showed the signal at δ 13.8 ppm. The ratio of *anti*:*syn* product was 85:15.

Reduction of the hydroxyl group of **38a**. To a suspension of NaH (14 mg 60% in oil/0.27 mmol), imidazole (0.2 mg) and THF (0.2 ml) was added with stirring a soln of **38a** (46 mg, 0.134 mmol) in THF (0.8 ml) at room temp under N_2. The mixture was stirred for 30 min and then mixed with CS_2 (0.05 ml, 0.8 mmol). After stirring for an additional 1 h, the mixture was stirred further with MeI (0.03 ml, 0.5 mmol) for 30 min and then worked up with NH_4Cl soln and Et_2O to give crude xanthate (64 mg); δ 2.51 (3H, s, SMe), 4.84 (1H, br s), 5.32 (1H, m); ν 2920, 1380, 1370 cm^{-1}. It was heated with n-Bu_3SnH (0.07 ml, 0.26 mmol) and AIBN (*ca* 2 mg) in toluene (2.1 ml) at 90° under argon for 7 h. The mixture was evaporated to dryness and the residue was purified by silica gel TLC to give **40a**; ^{1}H-NMR δ 1.08 and 1.14 (3H × 2, d, J = 6), 1.09 (3H, d, J = 6.5), 1.5 (6H), 2.0 (1H), 2.83 (1H, dd, J = 14, 9.5), 3.46 (1H, dd, J = 14.5, 2.5), 3.5 (1H), 3.78 (1H, q × 2, J = 6), 4.80 (1H, br s), 7.6 (3H), 7.9 (2H); ^{13}C-NMR δ 16.9, 17.7, 21.1, 23.3, 28.2, 30.0, 33.8, 58.4, 67.1, 71.4, 94.3, 127.8, 129.1, 133.4, 140.1.

Typical addition of methyllithium to pyranosyl heteroolefins **30**. An ethereal soln of MeLi (0.2 ml, 1.29 M LiBr complex) was added dropwise to a soln of the heteroolefins (such as **30**) (90 mg, 0.175 mmol) dissolved in THF (3.0 ml) at −78° under argon with stirring. The stirring was continued for 50 min at this temp and the mixture was quenched with NH_4Cl soln and extracted with Et_2O. The extracts were combined, washed with NH_4Cl soln, water and NaCl soln, dried (Na_2SO_4) and evaporated under reduced pressure to afford the adduct. It was successively stirred with KF (40 mg) in MeOH (2.0 ml) at room temp for 1 h. The solvent was removed by evaporation *in vacuo* and the residue was extracted with Et_2O to give the product, which was purified by silica gel TLC with a mixture of Et_2O and hexane as developing agent. The yields were 50–95%.

Typical addition of methylbromomagnesium to **30**. To a cold soln of **30** (0.82 g, 2.06 mmol) in a mixture of THF (13 ml) and n-hexane (13 ml) was added dropwise an ethereal soln of MeMgBr (2 M, 5.1 ml, 5.15 mmol) at −78° under argon and the mixture was stirred for 2.4 h at −20°. After mixing with NH_4Cl soln, the mixture was extracted with Et_2O to give the crude adduct (0.94 g), which was successively stirred with KF (0.6 g) in MeOH (24 ml) at room temp for 65 min. Evaporation of the mixture, ethereal work-up and purification by silica gel TLC afforded pure **38a** (0.69 g in 98% overall yield); ^{1}H-NMR δ 1.06 (3H, d, J = 7), 1.11 (3H × 2, d, J = 6), 1.70 (4H), 1.81 (1H, m), 2.67 (1H), 2.82 (1H, dd, J = 15, 6), 3.45 (1H, dd, J = 15, 3.5), 3.47 (1H), 3.51 (1H, td, J = 10, 2), 3.82 (1H, q × 2, J = 6), 4.80 (1H, br s), 7.6 (3H), 7.9 (2H); ^{13}C-NMR δ 18.9, 21.0, 23.3, 26.9, 27.8, 29.9, 57.4, 66.8, 67.1, 76.2, 93.2, 127.8, 129.3, 133.8, 139.4; IR ν 3520, 2940, 1380, 1370 cm^{-1}. (Found: C, 59.73; H, 7.67. Calc for $C_{17}H_{26}O_5S_1$: C, 59.63; H, 7.65%.)

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