7d (see below): ^{1}H NMR (Table I); MS, *m/e* (relative intensity) 478 (M - H_2O, 10), 355 (57), 327 (100), 326 (33), 295 (35), 265 (11), 253 (14), 252 (16), 239 (13), 178 (16), 151 (19).

***threo*-10,11-Dihydro-2,3-dimethoxy-11-[1-(2-methoxyphenoxy)ethyl]-5,10-*o*-benzeno-5*H*-dibenzo[*a*,*d*]cyclohepten-10-ol (7b).**[7] Dehydration of **6b** by general procedure B gave predominantly **2d** (38%) and only a 5% yield of expected product **7b**: ^{1}H NMR (Table I); MS, *m/e* (relative intensity) 494 (M^+, 1), 371 (27), 370 (49), 343 (32), 342 (45), 341 (100), 325 (13), 315 (18), 311 (20), 165 (28), 151 (17).

10,11-Dihydro-2,3-dimethoxy-11-[(2-methoxyphenoxy)methyl]-5,10-*o*-benzeno-5*H*-dibenzo[*a*,*d*]cycloheptene (7c).[7] Dehydration of **6c** by general procedure B gave a crude product (90%) which, upon column chromatography, yielded pure **7c**: 72%; colorless oil; IR (film), no OH or C=O absorbance; ^{1}H NMR (Table I); ^{13}C NMR[7] (acetone-d_6) δ 44.7 (C10), 47.3 (C9), 54.9 (Cα), 56.3 (methoxyls), 72.9 (Cβ), 113.2-117.2 (C2,5, ring A; C3,6, ring B), 121.7, 122.1 (C4,5, ring B), 125.2-149.3 (C1,3,4,6, ring A; C2, ring B; C1-8,4a,8a,9a,10a, anthracenyl), 150.9 (C1, ring B); MS, *m/e* (relative intensity) 464 (M^+, 19), 341 (100), 327 (29), 326 (13), 310 (16), 309 (11), 295 (23), 252 (12), 239 (10), 178 (13), 163 (29).

***threo*-10,11-Dihydro-2,3-dimethoxy-11-[1-(2-methoxyphenoxy)ethyl]-5,10-*o*-benzeno-5*H*-dibenzo[*a*,*d*]cycloheptene (7d).**[7] Reduction of the free phenolic analogue of **2d**, 1-(3-methoxy-4-hydroxyphenyl)-1-(9-oxoanthracen-10-yl)-2-(2-methoxyphenoxy)propane, by general procedure C gave a 91% yield of the corresponding alcohol, 1-(3-methoxy-4-hydroxyphenyl)-1-(9-hydroxyanthracen-10-yl)-2-(2-methoxyphenoxy)propane: MS, *m/e* (relative intensity) 464 (M - H_2O, 2), 341 (23), 313 (34), 312 (12), 287 (51), 194 (41), 193 (68), 178 (21), 165 (40), 164 (63), 163 (100), 151 (31), 124 (19). Dehydration of the alcohol obtained above by general procedure B (6 h) and subsequent methylation with diazomethane gave **6d** (30%) and the expected product **7d**: 31%; IR (film), no OH or C=O absorptions; ^{1}H NMR (Table I); MS, *m/e* (relative intensity) 478 (30, M^+), 355 (95), 327 (100), 295 (28), 151 (12).

Acknowledgment. We are grateful to Lester Zank and Martin Wesolowski for the IR spectra, to Professor Raymond A. Young (Department of Forestry, University of Wisconsin—Madison) for continuing support, to members of the New Zealand Research Advisory Council for partial funding of this project, and to Dr. Kurt L. Loening (Nomenclature Director, Chemical Abstracts Service, Columbus, OH) for help in naming some of the compounds. The use of trade, firm, or corporation names in this publication is for the information and convenience of the reader. Such use does not constitute an official endorsement or approval by the U.S. Department of Agriculture of any product or service to the exclusion of others which may be suitable.

Registry No. **2a**, 74838-65-6; **2b**, 82247-06-1; **3a**, 84064-76-6; **3b**, 84064-68-6; **4a**, 84064-69-7; **5a**, 84064-70-0; **6a**, 84064-71-1; **6b**, 84064-72-2; **6c**, 84107-45-9; **6d**, 84073-42-7; **7b**, 84064-73-3; **7c**, 84064-74-4; **7d**, 84064-75-5; *threo*-1-(3-methoxy-4-hydroxyphenyl)-1-(9-hydroxyanthacen-10-yl)-2-(2-methoxyphenoxy)propane, 84073-43-8.

Stereoselective Addition of Organocopper Reagents to a Novel Carbohydrate-Derived 2,3-Dihydro-4*H*-pyran-4-one[1]

Thomas E. Goodwin,* C. Michael Crowder, R. Bruce White, and John S. Swanson

Department of Chemistry, Hendrix College, Conway, Arkansas 72032

Frederick E. Evans

Division of Chemistry, National Center for Toxicological Research, Jefferson, Arkansas 72079

Walter L. Meyer

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701

Received May 25, 1982

Stereoselective organocopper additions to a novel carbohydrate-derived 2,3-dihydro-4*H*-pyran-4-one are described. Stereochemical orientations are ascertained by scrutiny of high-resolution ^{1}H NMR spectra of these adducts as well as enol acetates derived therefrom.

The development of a convergent synthesis of maytansinoids[2] led to the need for tetrahydro-4*H*-pyran-4-ones of general structure **1** with the indicated absolute configuration. Concordant with this objective, a stereoselective conjugate addition of organocopper reagents to a novel 2,3-dihydro-4*H*-pyran-4-one has been crafted, and the product stereochemistry has been revealed by high-resolution ^{1}H NMR spectroscopy.

2,3-Dihydro-4*H*-pyran-4-one Synthesis

A few 2,3-dihydro-4*H*-pyran-4-ones have been previously prepared from D-glucal (**2**).[3,4] The present synthesis de-

(1) This work was described in part at the 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 1981, Abstract No. ORGN 52.

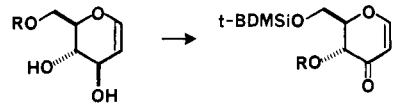
(2) Komoda, Y.; Kishi, T. In "Anticancer Agents Based on Natural Product Models"; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 353.

(3) Inter alia: (a) Fraser-Reid, B.; Walker, D. L.; Tam, S. Y.-K.; Holder, N. L. *Can. J. Chem.* **1973**, *51*, 3950. (b) Collins, P. M. *Carbohydr. Res.* **1969**, *11*, 125 and references contained therein. (c) Sharma, M.; Brown, R. B. *Can. J. Chem.* **1966**, *44*, 2825.

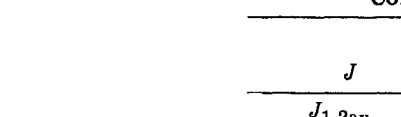
(4) A Diels-Alder route to a racemic analogue of keto alcohol **4** has been reported: (a) Danishefsky, S. "Abstracts of Papers", 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 1981; American Chemical Society: Washington, DC; ORGN 133. (b) Danishefsky, S.; Kerwin, Jr., J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

0022-3263/83/1948-0376$01.50/0

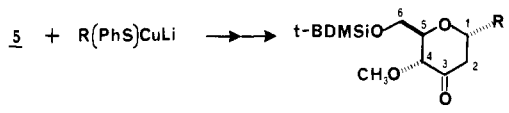
volves from the known[5] *tert*-butyldimethylsilyl ether **3**.



2, R=H
3, R=t-BDMSi



4, R=H
5, R=Me



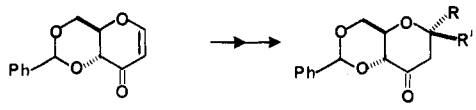
8

1a, R=*n*-Bu; **1b**, R=*t*-Bu;
1c, R=Me; **1d**, R=*s*-Bu.

Oxidation of the allylic hydroxyl group with activated manganese(IV) oxide in dichloromethane provides keto alcohol **4** in good yield. Subsequent methylation with methyl iodide/silver(I) oxide in dichloromethane gives the desired enone **5**. Compounds **4** and **5** are easily prepared and purified, are nicely crystalline, and are conveniently stable at room temperature.[6] They should prove to be useful substrates for a variety of synthesis operations.

Organocopper Conjugate Additions

Fraser-Reid and his co-workers[7] have reported the addition of (dimethylcopper)lithium to enone **6** in ether to provide compounds **7**. The moderate yield and negligible stereoselectivity of this process were not encouraging, therefore alternative reaction conditions were explored.



6

7a, R'=H, R=Me; **20%**
7b, R'=Me, R=H; **18%**

Organo(hetero)cuprate reagents incorporating a variety of adminicular ligands have been successfully employed for many alkyl conjugate addition reactions and often possess distinct advantages over their homocuprate counterparts.[8] Posner et al.[9] have described the use of organo(hetero)cuprates derived from an organolithium reagent and copper thiophenoxide for the conjugate addition of primary, secondary, and tertiary alkyl groups to α,β-unsaturated ketones.

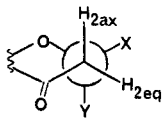
Under carefully controlled conditions the organo(hetero)cuprate reagents **8** conjoin in a 1,4-addition mode with enone **5** in tetrahydrofuran (THF) to provide adducts **1** in preparatively useful yields (~65%).[10] In contrast to the reaction of the simple organocuprate with enone **6**, this addition proves to be highly stereoselective, the product in each case consisting almost exclusively of a single diastereomeric adduct. High-resolution ^{1}H NMR data in support of the stereostructures **1** are detailed below.

Table I. Selected Coupling Constants (hertz) for Adducts 1a-d

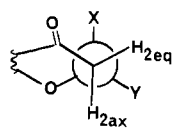
	compd			
J	1a	1b	1c	1d
$J_{1,2ax}$	6.1	11.6	6.3	5.9
$J_{1,2eq}$[14]	3.9	3.2	4.4	5.4
$J_{4,5}$	8.2	4.9	6.8	6.8

Stereochemical Elucidation

If the conformation of adducts **1** is assumed to approximate a chair cyclohexanone,[7,11] the pendant alkyl group at C-1[12] could, a priori, be assumed to reside in an axial or an equatorial position. These possibilities are portrayed in partial structures **9** and **10**, which represent



9a, X=H_1, Y=R
9b, X=R, Y=H_1



10a, X=H_1, Y=R
10b, X=R, Y=H_1

Newman projections down the C-2 to C-1 bond. The Karplus relationship[13] leads to a prediction that $J_{1,2ax}$ and $J_{1,2eq}$ in structures **9a** and **10b** (R axial) should be moderate and similar in magnitude, whereas in structures **9b** and **10a** (R equatorial) $J_{1,2ax}$ should be large, and $J_{1,2eq}$ should be significantly smaller. The data in Table I clearly indicate axial positioning of the alkyl group in adducts **1a,c,d** and an equatorial *tert*-butyl substituent in adduct **1b**.

The simplest explanation for the ^{1}H NMR spectral data in Table I would be that in all four reactions, the incoming alkyl group follows the stereoelectronically preferred "axial" trajectory to give rise to structure **11**. This line of reasoning would require that adducts **1a,c,d** remain in the original chair conformers **11**, while the bulky axial *tert*-butyl group of **1b** causes an interconversion to alternate chair conformer **12**. The diminished magnitude of $J_{4,5}$ for compound **1b** lends some credence to this scenario.[13]

Nonetheless, prudence requires consideration of alternative stereostructures. While the configuration at C-5 is presumed to be immutable in the present circumstance, that at C-4 might have experienced epimerization by way of equilibrating enolates.[15] Although the absence of a

(5) (a) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381. (b) Blackburne, I. D.; Burfitt, A. I. R.; Fredericks, P. R.; Guthrie, R. D. In "Synthetic Methods for Carbohydrates"; El Khadem, H. S., Ed.; American Chemical Society: Washington, 1976; *ACS Symp. Ser. No. 39*, 116.

(6) The triphenylmethyl and *tert*-butyldiphenylsilyl analogues of compound **5** have been prepared and are liquids: Goodwin, T. E.; Loomis, J. F.; Seitzinger, N. K.; White, R. B., unpublished results.

(7) Yunker, M. B.; Plaumann, D. E.; Fraser-Reid, B. *Can. J. Chem.* **1977**, *55*, 4002.

(8) (a) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley-Interscience: New York, 1980. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1.

(9) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

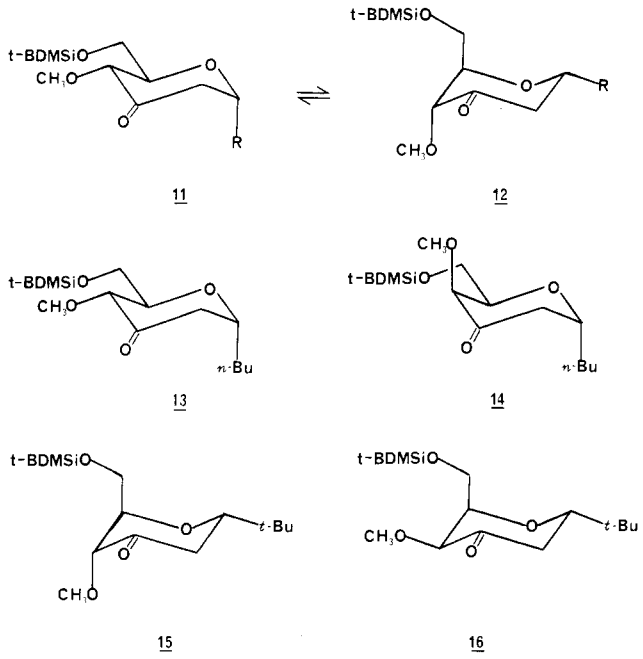
(10) The preparation of adduct **1a** via the conjugate addition of di-*n*-butylcopperlithium to enone **5** in THF has now been optimized to provide a 94% yield of purified product (see Experimental Section).

(11) This conformational approximation has been used successfully for similar compounds: (a) Paulsen, J.; Bünsch, H. *Chem. Ber.* **1978**, 111, 3484. (b) Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3978.

(12) (a) The carbohydrate numbering hierarchy which is depicted on structure **1** is used throughout this manuscript, the sole exception being the current *Chemical Abstracts* nomenclature used as headings in the Experimental Section. (b) In accord with current *Chemical Abstracts* nomenclature, the symbol "α" denotes a substituent orientation which is cis to the $CH_2OSiMe_2(t\text{-Bu})$ group, while "β" refers to a trans relationship.

(13) (a) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870. (b) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969.

(14) The diminished magnitude of $J_{1,2eq}$ can be attributed to the antiperiplanar relationship between H-2_{eq} and the electronegative ring oxygen. See ref 13b and: Booth, H. *Tetrahedron Lett.* **1965**, 411.



11 12 13 14 15 16

facilitating proton source renders such enolate isomerization unlikely,[16] rejection of 4-epi structures without experimental justification seems unwise.

In order to choose among the stereostructures which are diastereomeric at C-1 and/or C-4, additional information was gleaned from 500-MHz ^{1}H NMR spectra of Δ^2 enol acetates which are derived by quenching the appropriate conjugate addition reaction mixtures with acetic anhydride.[17] Spectral assignments (Table II) were deduced from standard chemical shift and coupling constant data[13b,18] and extensive spin-decoupling experiments.[19] A striking feature of these spectra is the remarkable similarity in the chemical shifts and coupling constants between the *n*-butyl and *tert*-butyl compounds. Such agreement would be most unexpected if the two enol acetates differed in configuration at either C-1 or C-4 (or both). The forthcoming conclusion is that both the *n*-butyl group and the *tert*-butyl group added to the same face (α or β) of enone **5** and that either both resulting enolates epimerized at C-4 or neither did.

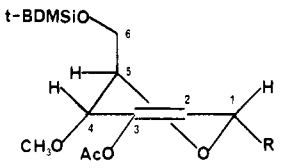
Returning to the proviso that the *n*-butyl group of adduct **1a** must be preferentially axial (vide supra), four chair conformers may be considered which possess the original[12] (α-R) absolute configuration at C-5, and a variety of configurations at C-1 and C-4 (i.e., 1α, 4α; 1α, 4β; 1β, 4α; 1β, 4β). Two of these, viz., those in which the *n*-butyl group was added to the α (top) face of enone **5**, are untenable due to excessive positioning of substituents in the axial orientation; both would contain a 1,3-diaxial interaction between the *n*-butyl group and the 5α-CH_2OSiR_3 substitutent, and in one the 4β-methoxy would be axial as well. These diastereomers would surely exist in the alternate chair conformers with maximal equatorial substituent arrangements and may be excluded from further consideration on that basis. Thus, only structures **13** and **14** should exist with the *n*-butyl group axial, and only these must be considered as possible structures for adduct **1a**.

Table II. Chemical Shifts (ppm from Me_4Si) and ^{1}H Coupling Constants (hertz) for Δ^2 Enol Acetates

	chemical shifts, δ			coupling constants	
proton	*n*-Bu (17a)	*t*-Bu (17b)	*J*	*n*-Bu (17a)	*t*-Bu (17b)
1	4.22	3.84	1,2	2.3	1.9
2	5.63	5.75	1,4	2.1	2.1
4	3.83	3.76	1,5	0	0
5	3.96	4.14	2,4	0.5	0
6a	3.78	3.72	4,5	3.8	1.5
6b	3.77	3.77	5,6a	6.2	7.4
			5,6b	4.8	6.2
			6a,6b	10.4	10.0

Inasmuch as the enol acetate NMR data indicate that congeners **1a** and **1b** have the same relative configurations and the adduct NMR data indicate an equatorial *tert*-butyl group for compound **1b**, the structure of **1b** is logically deduced to be **15** (if **1a** is **13**) or **16** (if **1a** is **14**). Structures **13** and **15** correspond to β addition of the organocuprate with no subsequent C-4 epimerization, while structures **14** and **16** would result from β addition followed by epimerization at C-4.

Finally, dihedral angles were measured from Drieding models of both half-chair conformers of those Δ^2 enol acetates which would correspond in configuration to adduct structures **13** (**15**) and **14** (**16**). The coupling constants predicted for vicinal sp^3–sp^3 and sp^3–sp^2 protons and for allylic sp^3–sp^2 protons[13,18,20] were compared to the observed values. Only half-chair **17** provides reasonable agreement



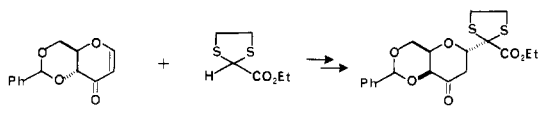
17a, R = *n*-Bu

17b, R = *t*-Bu

(predicted $J_{1,2} \approx 3$ Hz, $J_{2,4} \approx 0$, $J_{4,5} \approx 2$–3 Hz), the other three conformers leading to predicted values for one or more of those couplings which are much larger than those observed (predicted $J_{1,2}$ of ca. 5 Hz and/or $J_{2,4}$ of ca. −2 Hz and/or $J_{4,5}$ of ca. 15 Hz). Structure **17** corresponds in configuration to the putative structures **13** and **15** for the adducts, thus allowing their selection in preference to the **14**/**16** pair.[21]

The adducts discussed herein are therefore assigned the absolute configurations depicted in structures **1a–d**, **11–13**, and **15**. The Δ^2 enol acetates possess structures **17a** and **17b**.

(15) Paulsen and Bünsch[11a] reported epimerization at C-4 through isomerization of the intermediate enolate in the conjugate addition of enone a and ester b to give adduct c as the major product.



a b c

(16) Cf.: House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.

(17) Isolation of a Δ^2 enol acetate rather than the Δ^3 isomer does not, a priori, exclude the possibility of epimerization at C-4.

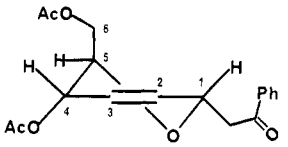
(18) (a) Becker, E. D.; "High Resolution NMR", 2nd ed.; Academic Press: New York, 1980. (b) Williamson, K. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 4623.

(19) Computer-simulated spectra generated from the parameters in Table II were superimposable on the pertinent regions of the experimental spectra.

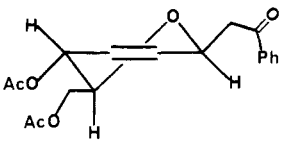
(20) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561.

(21) Half-chair conformers of the enol acetates which would correspond to adducts with a 1α-alkyl group were also subjected to this analysis. With the exception of one half-chair of the 4α-methoxy structure, these also lead to predicted values of one or more coupling constants which are far larger than those observed. The 1α-alkyl-4α-methoxy structure is, of course, excluded by data presented previously.

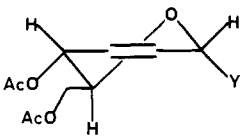
The vicinal C-4/C-5 protons of half-chair conformer 17 have a pseudoequatorial/equatorial relationship as evidenced by coupling constants ($J_{4,5}$) of 3.8 and 1.5 Hz for Δ^2 enol acetates **17a,b**, respectively. This strongly suggests conformational control by the C-1 alkyl substituent, which apparently prefers a pseudoequatorial residence. This phenomenon has also been observed by Dawe and Fraser-Reid[22] for a very close structural and conformational analogue, **18a**, and for its C-1 epimer **18b**. In contrast,



18a



18b



19a, Y = OR

19b, Y = SAc

the presence of an exocyclic heteroatomic C-1 substituent as in carbohydrate derivatives **19a,b**[23] leads to a preponderance of the half-chair conformer in which the C-1 group is pseudoaxial due to an "anomeric effect".[24]

Conclusion

In summary, conjugate organocopper addition to the 2,3-dihydro-4*H*-pyran-4-one **5** is stereoselectively β (bottom face), and C-4 epimerization does not occur.[26] The use of adducts **1a–d** and similar compounds in a maytansinoid synthesis will be described in future publications.

Experimental Section[12]

Boiling points and melting points are uncorrected. For Kugelrohr evaporative bulb-to-bulb distillations, the oven temperature is listed and does not necessarily represent the true boiling point. Infrared spectra were recorded on a Pye-Unicam SP-1000 spectrophotometer. Optical rotations were obtained with a Carl Zeiss polarimeter. ^{1}H NMR spectra were run on $CDCl_3$ solutions with Me_4Si as an internal standard (δ 0) on either a Varian EM-360A (60 MHz), Bruker WH-270 (270 MHz), Bruker WH-400 (400 MHz), or Bruker WM-500 (500 MHz) spectrometer. Column chromatography was carried out by using Merck silica gel 60 (70–230 mesh). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mass spectral data were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln. Solutions of sodium bicarbonate, ammonium chloride, sodium chloride (brine), and cupric sulfate were aqueous and saturated. Tetrahydrofuran was distilled from lithium aluminum hydride immediately before use. Solutions were dried over anhydrous sodium sulfate. The organolithium reagents were purchased from Aldrich Chemical Co.

(A) 2,3-Dihydro-4*H*-pyran-4-one Preparation. (2*R*-*trans*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2,3-dihydro-3-hydroxy-4*H*-pyran-4-one (4). This procedure is similar to one reported by Fraser-Reid et al.[3a] A mixture of 24.30 g of unpurified diol **3**[5a,27,28] and 88.4 g of activated manganese (IV) oxide (Aldrich) in 2.3 L of dichloromethane (chloroform is also a suitable solvent) was stirred in a stoppered flask at ambient temperature for 20 h, filtered over a pad of Celite, and concentrated in vacuo to give a brown crystalline solid. Purification by chromatography over a silica gel column (152 g, 3.5 × 30 cm) with 1:1 ether/petroleum ether as the eluent provided 12.824 g of the desired ketone **4** as a white crystalline solid. The overall yield from tri-*O*-acetyl-D-glucal is 54% (yields ranged from 51% to 72%). One such chromatography provided an analytical sample: mp 114.4–115 °C; IR ($CHCl_3$) 3515 (m), 1678 (s), 1591 (s) cm^{-1}; ^{1}H NMR (60 MHz) δ 0.0 (s, 6 H, $SiMe_2$), 0.78 (s, 9 H, *t*-BuSi), 3.54 (br s, 1 H, OH), 3.73–4.13 (m, 4 H, CH_2 and two methine H), 5.22 (d, 1 H, J = 6.0 Hz, C-1 olefinic H), 7.17 (d, 1 H, J = 6.0 Hz, C-2 olefinic H); $[\alpha]^{20.5}_D$ −275.44° (*c* 0.203, $CHCl_3$). Anal. Calcd for $C_{12}H_{22}O_4Si$: C, 55.78; H, 8.58; Si, 10.87. Found: C, 56.00; H, 8.61; Si, 10.59.

(2*R*-*trans*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2,3-dihydro-3-methoxy-4*H*-pyran-4-one (5). This procedure was suggested by the work of Garden and Thomson.[29] A mixture of 12.824 g (0.0497 mol) of crystalline keto alcohol **4**, 21.325 g (0.150 mol) of methyl iodide, and 23.063 g (0.0995 mol) of freshly prepared[30] and dried (120 °C oven) silver(I) oxide in 188 mL of dichloromethane (chloroform is also a suitable solvent) was stirred at ambient temperature in a stoppered flask for 72 h. Filtration over Celite and concentration in vacuo left a light yellow, crystalline solid. Recrystallization was effected by dissolution in a *minimum* amount of petroleum ether and chilling to provide 9.523 g (70%) of the desired product as colorless needles, mp 53.2–54.5 °C. First crop yields ranged from 68% to 84%. Additional product of lower quality can be obtained from the mother liquor. The first crop served as the analytical sample: IR ($CHCl_3$) 1681 (s), 1602 (s) cm^{-1}; ^{1}H NMR (60 MHz) δ 0.0 (s, 6 H, $SiMe_2$), 0.80 (s, 9 H, *t*-BuSi), 3.49 (s, 3 H, OMe), 3.64–4.31 (m, 4 H, CH_2 and 2 methine H), 5.17 (d, 1 H, J = 6.0 Hz, C-2 olefinic H), 7.12 (d, 1 H, J = 6.0 Hz, C-1 olefinic H); $[\alpha]^{20.5}_D$ −177.05° (*c* 0.200, $CHCl_3$). Anal. Calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.88; Si, 10.31. Found: C, 57.21; H, 8.87; Si, 10.24.

(B) Standardized Conjugate Addition Procedure Using a Mixed Heterocuprate Reagent. [2*R*-(2α,3β,6β)]-6-(1,1-Dimethylethyl)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-4*H*-pyran-4-one (1b). This procedure is patterned after work by Piers and Nagakura[31] and by Posner, Whitten, and Sterling.[9] A 2.0 M solution of *tert*-butyllithium in pentane (1.1 mL; 2.2 mmol of *tert*-butyllithium) was added under nitrogen to a stirred suspension of 373 mg (2.161 mmol) of copper thiophenoxide[32] in 10 mL of dry tetrahydrofuran which was cooled to −20 °C [internal (rather than bath) temperature]. After 5 min the temperature was lowered to −78 °C at which time a solution of 294 mg (1.081 mmol) of crystalline enone **5** in 5 mL of THF was added. After 5 min, the dry ice/acetone bath was replaced by an ice/salt bath (~0° C), and stirring was continued for 2 h. The dark solution was quenched with 1 mL of ammonium chloride solution, diluted with 75 mL of ether, filtered over a pad of Celite, washed twice with brine, and dried. Removal of solvent left 335 mg of pale yellow liquid

(22) (a) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180. (b) The ^{13}C NMR chemical shift values for C-5 of epimers **18a,b** are reversed in the original publication[22a] and should be 68.024 (**18a**) and 73.293 (**18b**) ppm (personal communication from B. Fraser-Reid).

(23) (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570. (b) Holland, C. V.; Horton, D.; Miller, M. J.; Bhacca, N. S. *J. Org. Chem.* **1967**, *32*, 3077.

(24) The de novo stereostructural assignments for Δ^2 enol acetates **17a,b** (and thus for adducts **1a–d**) are further buttressed by the observance of homoallylic couplings of the same magnitude ($J_{1,4} \approx 2$ Hz) for similar 2,3-dideoxy-2-enopyranoside derivatives.[23b,25]

(25) Fraser-Reid, B.; Carthy, B. J.; Holder, N. L.; Yunker, M. *Can. J. Chem.* **1971**, *49*, 3038.

(26) High-resolution ^{1}H NMR spectra of adducts **1a–d** revealed the presence of (isomeric?) impurities. These unidentified impurities generally comprise less than 10% of the mixture, but their presence prevents a claim of complete stereoselectivity for the conjugate additions discussed herein.

(27) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439.

(28) (a) Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405. (b) Tri-*O*-acetyl-D-glucal is commercially available from Pfanstiehl Laboratories, Inc., or the Aldrich Chemical Co.

(29) Garden, J. F.; Thomson, R. H. *J. Chem. Soc.* **1957**, 2483.

(30) Pearl, I. A. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 972.

(31) Piers, E.; Nagakura, I. *J. Org. Chem.* **1975**, *40*, 2694.

(32) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662.

which upon Kugelrohr distillation (72 °C, 0.01 torr) gave the desired adduct **1b**: 228 mg (64%); colorless oil; IR (neat) 1727 (s) cm^{-1}; ^1H NMR (400 MHz) δ 0.05, 0.06 (both s, 3 H each, $SiMe_2$), 0.88, 0.89 (both s, 9 H each, 2 *t*-Bu), 2.32 (dd, 1 H, J_{gem} = 15.7, $J_{1,2\alpha}$ = 3.2 Hz, H-2α), 2.61 (dd, 1 H, $J_{1,2\beta}$ = 11.6 Hz, H-2β), 3.43 (s, 3 H, OMe), 3.83 (m, 2 H, CH_2), 3.91 (d, 1 H, $J_{4,5}$ = 4.9 Hz, H-4), 3.97 (m, 1 H, H-5), 4.02 (dd, 1 H, H-1); mass spectrum, *m/e* (no molecular ion) 273 (M − 57; loss of *t*-C_4H_9), 261, 241, 187, 157, 131, 117 (base), 89; exact mass, *m/e* 273.1509 (calcd for $C_{13}H_{25}O_4Si$, 273.1522).

The methyl, *n*-butyl, and *sec*-butyl analogues were similarly prepared. The Kugelrohr distillation and infrared, ^1H NMR, and mass spectral data follow the names below.

[2*R*-(2α,3β,6β)]-6-Butyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-4*H*-pyran-4-one (1a): 64 °C (0.01 torr); IR (neat) 1735 cm^{-1}; ^1H NMR (400 MHz) δ 0.08, 0.09 (both s, 3 H each, $SiMe_2$), 0.91 (s, 9 H, *t*-Bu), 0.83–0.95 (m, 3 H, Me of *n*-Bu), 1.21–1.41 (m, 6 H, $CH_2CH_2CH_2$ of *n*-Bu), 2.39 (dd, 1 H, J_{gem} = 13.8 Hz, $J_{1,2\beta}$ = 3.9 Hz, H-2β), 2.71 (dd, 1 H, $J_{1,2\alpha}$ = 6.1 Hz, H-2α) [in one 270-MHz spectrum δ 2.66 (ddd, 1 H, J_{gem} = 13.8 Hz, $J_{1,2\alpha}$ = 5.9 Hz, $J_{2\alpha,4}$ = 1.1 Hz, H-2α)], 3.48 (s, 3 H, OMe), 3.72 (dt, 1 H, $J_{4,5}$ = 8.2 Hz, $J_{5,6}$ = 3.1 Hz, H-5), 3.85 (apparent d, 2 H, C-6 CH_2), 3.85 (d, 1 H, H-4) [in one 270-MHz spectrum δ 3.79 (dd, 1 H, $J_{4,5}$ = 8.0 Hz, $J_{2\alpha,4}$ = 1.1 Hz, H-4)], 4.27 (m, 1 H, H-1); mass spectrum, *m/e* (no molecular ion) 273 (M − 57, loss of *t*-C_4H_9), 241, 161, 131 (base), 117, 89; exact mass, *m/e* 273.1521 (calcd for $C_{13}H_{25}O_4Si$, 273.1522).

[2*R*-(2α,3β,6β)]-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-6-methyl-4*H*-pyran-4-one (1c): 69 °C (0.075 torr); IR (neat) 1728 cm^{-1}; ^1H NMR (400 MHz) δ 0.09, 0.10 (both s, 3 H each, $SiMe_2$), 0.92, (s, 9 H, *t*-Bu), 1.23 (d, 3 H, *J* = 8.4 Hz, Me), 2.38 (dd, 1 H, J_{gem} = 13.6 Hz, $J_{1,2\beta}$ = 4.4 Hz, H-2β), 2.71 (dd, 1 H, $J_{1,2\alpha}$ = 6.3 Hz, H-2α), 3.48 (s, 3 H, OMe), 3.80 (m, 1 H, H-5), 3.86 (m, 2 H, CH_2), 3.88 (d, 1 H, $J_{4,5}$ = 6.8 Hz, H-4), 4.54 (m, 1 H, H-1); mass spectrum, *m/e* (no molecular ion) 231 (M − 57; loss of *t*-C_4H_9), 161, 131 (base), 117, 89; exact mass, *m/e* 231.1045 (calcd for $C_{10}H_{19}O_4Si$, 231.1052).

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-6-(1-methylpropyl)-4*H*-pyran-4-one (1d):[33] 71 °C (0.01 torr); IR (neat) 1727 cm^{-1}; ^1H NMR (400 MHz) δ 0.11, 0.12 (both s, 3 H each, $SiMe_2$), 0.92 (s, 9 H, *t*-Bu), 0.82–0.97, 1.41–1.79 (both m, 9 H total, *sec*-Bu), 2.56 (dd, 1 H, J_{gem} = 14.2 Hz, $J_{1,2\beta}$ = 5.4 Hz, H-2β), 2.63 (dd, 1 H, $J_{1,2\alpha}$ = 5.9 Hz, H-2α), 3.47 (s, 3 H, OMe), 3.77 (m, 1 H, H-5), 3.84 (apparent d, 2 H, $J_{5,6}$ = 3.0 Hz, C-6 CH_2), 3.84 (d, 1 H, $J_{4,5}$ = 6.8 Hz, H-4), 4.00 (m, 1 H, H-1), minor diastereomer[34] δ 2.59 (d, 2 H, $J_{1,2}$ = 5.4 Hz, C-2 CH_2); mass spectrum, *m/e* (no molecular ion) 273 (M − 57, loss of *t*-C_4H_9), 241, 161, 156, 131, 117, 89, 87 (base); exact mass, *m/e* 273.1534 (calcd for $C_{13}H_{25}O_4Si$, 273.1522).

(C) Optimized Conjugate Addition Procedure with (Di-*n*-butylcopper)lithium to Prepare Adduct 1a. A 1.6 M solution of *n*-butyllithium in hexane (15.75 mL; 25.20 mmol of *n*-butyllithium) was added under nitrogen to a stirred slurry of copper(I) iodide (Aldrich Gold Label, oven dried at 100 °C; 2.400 g, 12.602 mmol) in 150 mL of dry THF at 0 °C (internally monitored temperature). After 5 min the mixture was cooled to −78 °C, and a solution of 2.2851 g (8.401 mmol) of enone **5** in 5 mL of THF was added at a rate such that the temperature remained at −78 °C. After an additional 1 h and 50 min, the mixture was allowed to warm to −20 °C and maintained at that temperature for 0.5 h. The reaction was quenched with 8 mL of saturated ammonium chloride solution, filtered over Celite, diluted with 500 mL of ether, washed with two 150-mL portions of brine, and dried. Evaporation of the solvent left a cloudy, yellow oil which upon distillation provided 2.599 g (94%) of adduct **1a** as a clear, colorless liquid, bp 104–105 °C (0.005 torr). The spectral data for this compound are recorded above.

(D) Preparation of Enol Acetates. [2*R*-(2α,3β,6β)]-6-Butyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dihydro-3-methoxy-2*H*-pyran-4-ol Acetate (17a). This preparation was carried out as described for **1a** above, except the reaction was quenched with acetic anhydride to provide after Kugelrohr distillation an 87% yield of enol acetate **17a** as a light yellow liquid: 76 °C (0.005 torr); IR ($CHCl_3$) 1757 (s), 1693 (w) cm^{-1}; ^1H NMR (500 MHz) δ 0.06, 0.07 (each s, each 3 H, $SiMe_2$), 0.90 (s, 9 H, *t*-BuSi), 0.85–1.65 (m, 9 H, *n*-Bu), 2.17 (s, 3 H, OAc), 3.41 (s, 3 H, OMe), 3.77, 3.78 (AB of ABX,[18a] 2 H, J_{gem} = 10.4 Hz, C-6 CH_2), 3.83 (ddd, 1 H, $J_{4,5}$ = 3.8 Hz, $J_{1,4}$ = 2.1 Hz, $J_{2,4}$ = 0.5 Hz, C-4 methine), 3.96 (X of ABX,[18a] 1 H, $J_{5,6a}$ = 6.2 Hz, $J_{5,6b}$ = 4.8 Hz, C-5 methine), 4.22 (m, 1 H, C-1 methine), 5.63 (dd, 1 H, $J_{1,2}$ = 2.3 Hz, olefinic H); mass spectrum, *m/e* (no molecular ion) 315 (M − 57, loss of *t*-C_4H_9), 273 (base, *m/e* 315 − 42, loss of CH_2CO), 241, 213, 153, 145, 131, 117, 89; exact mass, *m/e* 315.1547 (calcd for $C_{15}H_{27}O_5Si$, 315.1628), 273.1538 (calcd for $C_{13}H_{25}O_4Si$, 273.1522).

[2*R*-(2α,3β,6β)]-6-(1,1-Dimethylethyl)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dihydro-3-methoxy-2*H*-pyran-4-ol Acetate (17b). This preparation was carried out as described for **1b** above except the reaction was quenched with acetic anhydride to provide after Kugelrohr distillation a 72% yield of enol acetate **17b** as a pale yellow liquid: 71 °C (0.005 torr); IR ($CHCl_3$) 1735 (s), 1695 (m) cm^{-1}; ^1H NMR (500 MHz) δ 0.08 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, *t*-BuSi), 0.95 (s, 9 H, *t*-BuC), 2.18 (s, 3 H, OAc), 3.40 (s, 3 H, OMe), 3.72, 3.77 (AB of ABX,[18a] 2 H, J_{gem} = 10.0 Hz, C-6 CH_2), 3.76 (dd, 1 H, $J_{1,4}$ = 2.1 Hz, $J_{4,5}$ = 1.5 Hz, C-4 methine), 3.84 (dd, 1 H, $J_{1,2}$ = 1.9 Hz, C-1 methine), 4.14 (X of ABX,[18a] 1 H, $J_{5,6a}$ = 7.4 Hz, $J_{5,6b}$ = 6.2 Hz, C-5 methine), 5.75 (d, 1 H, olefinic H); mass spectrum, *m/e* (no molecular ion) 315 (M − 57, loss of *t*-C_4H_9), 273 (base, *m/e* 315 − 42, loss of CH_2CO), 213, 185, 153, 141, 117, 89; exact mass, *m/e* 315.1630 (calcd for $C_{15}H_{27}O_5Si$, 315.1628), 273.1533 (calcd for $C_{13}H_{25}O_4Si$, 273.1522).

Acknowledgment. The financial support of this work by the Research Corp., the donors of the Petroleum Research Fund, administered by the American Chemical Society, and NSF-EPSCOR Grant ISP 8011447 is gratefully acknowledged. The mass spectral data were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln, a National Science Foundation supported Regional Instrumentation Facility. The 60-MHz NMR spectrometer used in this work was purchased with a Research Instrumentation Grant (No. CDP-8006650) from the National Science Foundation. The 400-MHz NMR spectra were graciously provided by Professor S. A. Godleski (University of Rochester). We thank Professor Bert Fraser-Reid for helpful discussions and Dr. K. L. Loening, Nomenclature Director, Chemical Abstracts Service, for nomenclature advice.

Registry No. **1a**, 84010-40-2; **1b**, 84010-41-3; **1c**, 84010-42-4; **1d**, 84010-43-5; **3**, 58871-09-3; **4**, 84010-44-6; **5**, 84010-45-7; **17a**, 84010-46-8; **17b**, 84010-47-9.

(33) No stereodescriptors are given in the name for compound **1d** in the *Chemical Abstracts* system because the configuration about the chiral center in the *sec*-butyl group is unknown.

(34) Apparently a minor isomer is produced which is epimeric about the chiral center in the *sec*-butyl side chain.

(35) **Note Added in Proof**: The stereochemistry portrayed for adduct **1a** has been confirmed by X-ray crystallographic analysis of a derivative (Cordes, A. W.; Noble, M. C.; Goodwin, T. E., unpublished results).

(36) **Note Added in Proof**: The yield of adduct **1b** is routinely >90% with use of a chromatographic (silica gel) rather than a distillative isolation.

(37) **Note Added in Proof**: A pertinent review on the chemistry of hexenuloses (e.g., **4**, **5**) has recently appeared: Holder, N. L. *Chem. Rev.* **1982**, *82*, 287.