Carbohydrate Research, 129 (1984) 73–86
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CHIRAL SYNTHONS FROM LEVOGLUCOSENONE: SHORT ROUTES FOR (−)-δ-MULTISTRIATIN AND (+)-PRELOG–DJERASSI LACTONIC ACID

MASATAKA MORI, TATSUJI CHUMAN, AND KUNIO KATO

Central Research Insitute, The Japan Tobacco Public Corporation, Umegaoka 6-2, Midori-ku, Yokohama 227 (Japan)

(Received July 28th, 1983; accepted for publication in revised form, November 9th, 1983)

ABSTRACT

Levoglucosenone (**1**) was used as the starting material for short and stereoselective routes to chiral synthons for (−)-δ-multistriatin (**2**) and (+)-Prelog–Djerassi lactonic acid (**3**). The stereochemistry of these synthons is discussed on the basis of high-resolution ^{1}H-n.m.r. data.

INTRODUCTION

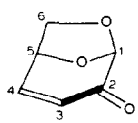
Levoglucosenone (**1**) is a carbohydrate-derived enone obtainable by acid-catalyzed pyrolysis of cellulosic materials under controlled conditions[1]. To examine the utility of **1** from so-called "biomass", its behavior in several reactions has been investigated[2]. The rigid 1,6-anhydro-D-sugar ring-system provides high stereoselectivity for introducing additional chirality in the ring, and we expected **1** to be a versatile precursor for the synthesis of natural products having chiral carbon atoms. This work outlines stereoselective syntheses of chiral synthons for two natural compounds, (−)-δ-multistriatin (**2**), a portion of which work has been reported in preliminary form[3], and (+)-Prelog–Djerassi lactonic acid (**3**) from **1**, to establish short and stereoselective routes for them.

Multistriatin is a component of the aggregation pheromones of the elm-bark beetle *Scolytus multistriatis*[4]. It has recently been reported[5] that the (−)-δ-isomer (**2**) is biologically active toward the European population of the beetle, and the (−)-α-isomer (**4**) is active for the American population. (+)-Prelog–Djerassi lactonic acid[6] (**3**), a degradation product of methymycin, pikromycin, and narbomycin, has been of value in the chemistry of macrolide antibiotics. Synthetic chemists have focused much attention on stereocontrolled syntheses of **3**, including several studies employing carbohydrates[7].

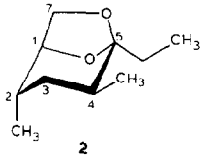
The structural relationship of these compounds may be observed in the formulas of **2** and **3**, drawn in the $^1C_4$(D) conformation. The D-*arabino* and D-*ribo* configurations of the 2,3,4-trideoxy-2,4-di-*C*-methyl sugar ring-systems in compounds **2** and **3** are formally derived from a common precursor having the D-*erythro* con-

0008-6215/84/$ 03.00

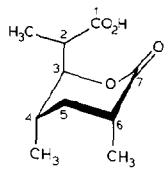
figuration at C-4 and -5. Thus, the main aspects of these syntheses were (*1*) *exo*-selective methylation at C-4 of **1**; (*2*) stereocontrol in introducing the additional C-2 methyl group in the precursor molecule; and (*3*) transformations of the 2,4-dimethyl derivatives of **1** into compounds relevant for the further conversions into **2** and **3**.



1



2



3

4

RESULTS AND DISCUSSION

Preparation of the C-4 *exo*-methyl adduct of **1** was our first objective. It was expected that steric factors in the conjugate-addition to **1** caused by the bulky 1,6-anhydro bridge upon the upper side of the pyranoid ring of **1** would favor the *exo*-adduct.

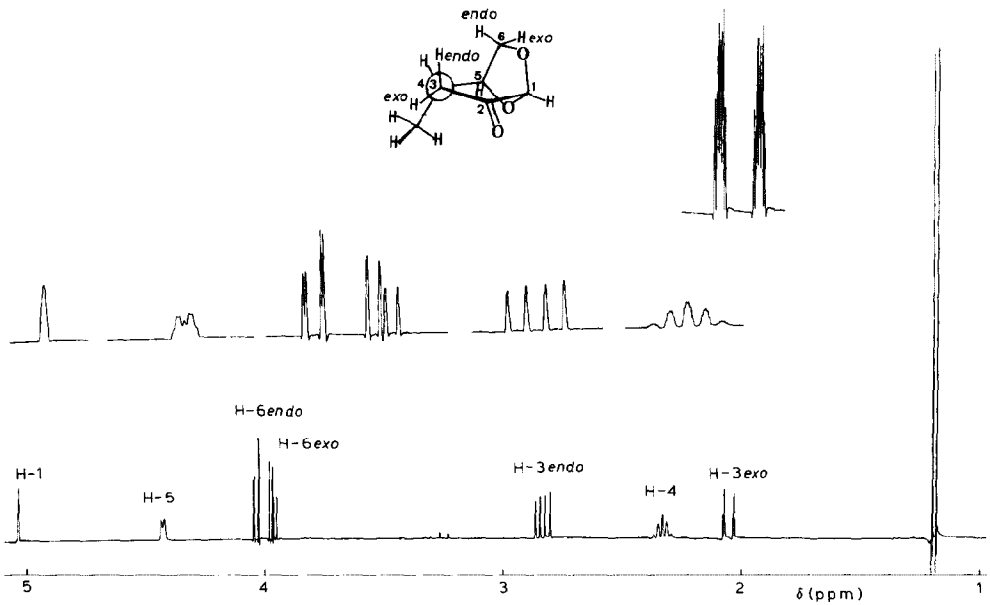


Fig. 1. Resolution-enhanced ^{1}H-n.m.r. (400 MHz) spectrum of **5** (1,6-anhydro-3,4-dideoxy-4-*C*-methyl-β-D-*erythro*-hexopyranos-2-ulose). The spectrum was recorded in chloroform-*d* with tetramethylsilane as the internal standard. For resolution enhancement, the free-induction decay was multiplied by the Gaussian transformation function.

TABLE I

PROTON-N M R (400 MHz) DATA FOR COMPOUND **5**

Protons	*H-1*	*H-3*endo	*H-3*exo	*H-4*	*H-5*	*H-6*exo	*H-6*endo	*Me-4*
	br s	*dd*	*ddt*	*m*	*m*	*dd*	*dd*	*d*
δ (p.p.m.)	5.03	2.83	2 05	2.33	4.43	3.60	4.03	1.19
J (Hz)	$J_{3endo,3exo}$ 16.25	$J_{4,3exo}$ 1.06	$J_{1,3exo}$ 1.06	$J_{5,3exo}$ 2.01	$J_{4,3endo}$ 7.83	$J_{4,5}$ <1		
	$J_{4,Me-4}$ 7.05	$J_{5,6exo}$ 5.15	$J_{5,6endo}$ 1.15	$J_{6exo,6endo}$ 7.50				

The crude levoglucosenone (**1**) used contained some impurities, mostly furan derivatives, and a facile purification-procedure was established (see Experimental section).

The purified sample (>98%) of **1** was treated with lithium dimethyl cuprate to give the C-4 methyl adduct **5** as a single product in 86% yield. Shafizadeh *et al.*[2a] had prepared compound **5**, accompanied by the C-2 adducts, in lower yield by another method, and the orientation of the methyl group was tentatively assigned as *exo* from the lack of coupling between H-4 and H-5 in the ^{1}H-n.m.r. spectrum.

The precise stereochemistry of **5** was established from its high-resolution (400 MHz) ^{1}H-n.m.r. spectrum (Fig. 1, Table I). Characteristic features include well-separated signals for the geminal H-3 protons (at δ 2.05 and 2.83); the one at higher field showed complex multiplicity because of long-range couplings. The resolution-enhanced spectrum showed the signal at δ 2.05 to be a doublet of doublets of triplets. The largest coupling (16.25 Hz) was clearly the geminal splitting. Decoupling experiments showed that H-3 (δ 2.05) exhibited long-range couplings with H-1 (*J* 1.06 Hz) and H-5 (*J* 2.01 Hz), plus a small vicinal coupling with H-4 (*J* 1.06 Hz). Therefore, H-3 (δ 2.05) must be coplanar (W-shaped geometry) with both H-1 and H-5, and, therefore, the pyranoid ring of **5** may adopt a chair-like conformation, and the signal at δ 2.05 becames assignable to H-3*endo*. The upfield shift of H-3*exo*

TABLE II

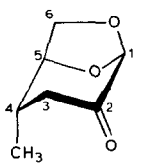
COMPARISONS OF PROTON-N M R DATA FOR COMPOUNDS **7a** AND **7b**, AND β- AND δ-MULTISTRIATIN

Compound	*Me-2*	*Me-4*	*H-5*	*H-6*
7a	1.12	1.26	4.25	3.86
7b	0.81	1.17	4.22	3.80
	Me-4	*Me-2*	*H-1*	*H-7*
β-Multistriatin[a]	1.10	1.24	4.26	3.85
δ-Multistriatin[a]	0.81	1.15	4.22	3.85

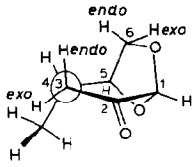
[a]Data from ref. 4b.

relative to H-3*endo* probably arises from anisotropic deshielding[8] by the C-2 carbonyl group of **5**. All the coupling constants are listed in Table I. Based on the foregoing, the most plausible conformation of **5** is proposed as **5'**, and the stereochemistry is thus 1*R*,4*S*,5*S*.

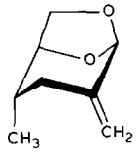
Subsequent Wittig reaction at C-2 of **5** gave the *exo*-methylene derivative **6** in 75% yield, and this was employed as the common precursor for synthesis of **2** and **3**.



5



5'

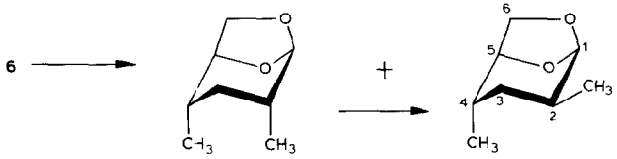


6

Synthesis of (−)-δ-multistriatin (**2**). — If compound **6** adopts a conformation similar to that of **5'**, the stereoselectivity on the hydrogenation of the *exo*-alkene at C-2 may be influenced by both the 1,6-anhydro bridge and the C-4 methyl group.

In practice, hydrogenation of the *exo*-alkene **6** with palladium-on-charcoal catalyst in ether afforded the two 2-epimers, **7a** (T_R 23.5 min) and **7b** (T_R 22.2 min), in the ratio of 4:1, and these were separated by preparative g.l.c.

As shown in Table II, because of the structural analogy[4b], the good agreement of the ^{1}H-n.m.r. data for **7a** and **7b** with those for β- and δ-multistriatin allowed assignment of the orientations of the 2- and 4-methyl groups of **7a** and **7b** as *exo–exo* and *endo–exo*, respectively.



7a **7b**

These assignments are supported by the following evidence. During the ^{1}H-n.m.r. measurements for **7a** in chloroform-*d* solution, epimerization occurred; after 18 h, only the spectrum of **7b** was observed. This finding may be explained in terms of the instability of **7a** (having 1,3-diaxial methyl groups), which causes epimerization of the C-2*exo*-methyl group of **7a** adjacent to the enolizable acetal group, to give at equilibrium[4b] the stable C-2*endo*-methyl isomer **7b**.

The absolute stereochemistries of **7a** and **7b** were, therefore, assigned as D-*ribo* (1*R*,2*R*,4*S*,5*S*) and D-*arabino* (1*R*,2*S*,4*S*,5*S*), respectively.

Thus, in the hydrogenation of **6**, steric hindrance by the C-4 methyl group was the most influential factor.

As compound **7b** possesses the correct absolute stereochemistry (D-*arabino*) of **2**, the isomerization of the epimers of **7** into **7b** was investigated by g.l.c. When the epimers of **7** (50 mg) in chloroform with a catalytic amount of *p*-toluenesulfonic acid were boiled for 4 h under reflux and then refrigerated overnight, the ratio **7a**:**7b** changed to 1.8:98.2. With a larger sample (1 g), the isomerization was relatively slow, but after boiling for 5 h under reflux with *p*-toluenesulfonic acid in dichloromethane and keeping for one week, **7b** was obtained in 95.2% diastereomeric purity and was used for further conversions.

Following Weiler's procedures[9], compound **7b** was alkylated at C-1. A solution of **7b** in dichloromethane was treated with propanedithiol and boron trifluoride etherate to give the dithiane **8a**, and the free glycol group was isopropylidenated to afford **8b**. Lithiation of the dithiane **8b** proceeded incompletely under standard conditions. In the synthesis of α-multistriatin, Weiler *et al.*[9] succeeded by using *tert*-butyllithium in hexane and then alkylated with ethyl iodide in hexamethylphosphoric triamide. Our alternatively method[10] using butyllithium–tetramethylethylenediamine complex in THF was facile, and subsequent addition of ethyl iodide readily gave **9**. Treatment of **9** with mercuric chloride in the presence of calcium carbonate regenerated the carbonyl group and caused transacetalation to afford **2**, as almost the sole product. Alternatively, degradation of the C-2′ epimeric mixture of **9** derived from **7a** and **7b** with mercuric chloride led to the same result.

The spectroscopic data for g.l.c.-purified **2**, $[\alpha]_D^{23}$ −84.7° (*c* 0.155, pentane), were completely identical with those reported for (−)-δ-multistriatin[5b].

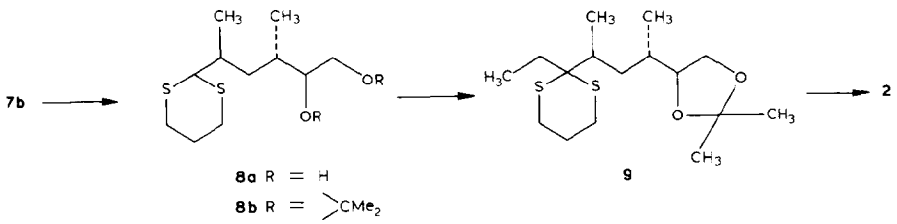


TABLE III

HYDROGENATION OF **6** AND **12a**

Substrate	*Catalyst*	*Solvent*	*Products*	*(Rel. ratio)*[a]
6	Raney-Ni(W8)	MeOH	**7a** + **7b**	2.6:1
6	Pd–C[b]	EtOAc		3.6:1
6	Pd–C	Et_2O		4.0:1
6	PtO_2	Et_2O		12.5:1
12a[c]	Pd–C	EtOAc	**10a** + **10a**′[d]	4:1
12a	PtO_2	Et_2O		6.0:1

[a]Determined by g.l.c. [b]Palladium on charcoal. [c]From ref. 7c. [d]C-2 epimer of **10a**.

TABLE IV

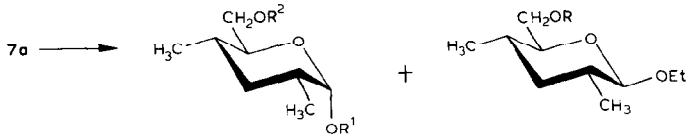
PROTON-N M R (400 MHz) DATA FOR COMPOUNDS **10b** AND **11b**

Compound		*H-1*	*H-2,H-4*	*H-3*ax	*H-3*eq	*H-5*	*H-6*	*H-6'*	*Me-2,Me-4*
		d	*m*	*q*	*dt*	*m*	*m*		*d*
10b	δ (p.p.m.)	4.65	1.73 1.83	1.27	1.44	3.45	3.55		0.78 0.88
	J (Hz)	$J_{1,2}$ 3.42, $J_{2,3ax} = J_{4,3ax} = J_{3ax,3eq}$ = 13.25, $J_{2,3eq} = J_{4,3eq}$ = 3.9							
11b	δ (p.p.m.)	3.99	1.6 (2H)	0.94	1.75	3.22	3.68[a]	3.57[a]	0.81 0.90
	J (Hz)	$J_{1,2}$ 8.55, $J_{2,3ax} = J_{4,3ax} = J_{3ax,3eq}$ = 13.2, $J_{2,3eq} = J_{4,3eq}$ = 4.3							

[a]Doublet of doublets.

Synthesis of (+)-Prelog–Djerassi lactonic acid (**3**). — Compound **7a** includes the three chiral carbon atoms having the correct absolute configurations (D-*ribo*) corresponding to those at C-3,-4, and -6 (but not at C-2) of **3**. Employing **10c** as the key intermediate, Jarosz and Fraser-Reid[7b] have described a route to **3** from methyl α-D-glucoside. Isobe *et al.*[7c] also used **10a** for their synthesis of **3**. Compounds **10c** and **10a** may be obtained by transglycosylation of **7a**. In this work, we selected **10a** as the precursor for **3**, and, thus, high diastereomeric purity of **7a** and its transformation into **10a** were required. In order to increase the diastereomeric purity of **7a**, we further examined the hydrogenation conditions for **6**. As shown in Table III, excellent stereoselectivity was obtained by the use of platinum dioxide catalyst and diethyl ether as solvent (**7a**:**7b** = 25:2).

Unfortunately, ethanolysis of **7a** with use of various acid catalysts always gave the α and β anomers (**10a** and **11a**) in almost equal amounts, accompanying the C-2 epimers. The benzylated derivatives of the ethanolyzates could be resolved by column chromatography. The stereochemistry of the major products **10b** (R_F 0.37) and **11b** (R_F 0.15) was elucidated by high-resolution (400 MHz) ^{1}H-n.m.r. spectroscopy (Table IV).



10a R^1 = Et, R^2 = H
10b R^1 = Et, R^2 = Bn
10c R^1 = Me, R^2 = H

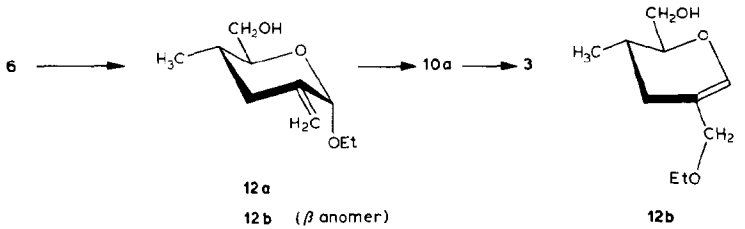
11a R = H
11b R = Bn

In each spectrum, the H-3 signals were well separated, and that appearing at higher field was assigned to be the axial one; it gave a quartet displaying large cou-

pling-constants. The large and equal couplings $J_{3ax,3eq} \simeq J_{3ax,2} \simeq J_{3ax,4} \simeq 13$ Hz indicated the chair conformation of the pyranoid ring and the diequatorial orientations of the C-2 and C-4 methyl groups on the rings of **10b** and **11b**. The magnitudes of $J_{1,2}$ for the anomers **10b** (3.4 Hz) and **11b** (8.6 Hz) indicated the anomeric configurations to be α and β, respectively.

As the transglycosylation of **7a** produced a mixture of anomers and often caused partial epimerization at C-2, another route to afford better selectivity was investigated.

The allylic glycoside **6** was quite sensitive toward acidic ethanol, and, under mild conditions (1% trifluoroacetic acid in ethanol for 1 h at 50°), it was converted into an equilibrated mixture of **6** and the transglycosylation products (**12**), which were separable by chromatography. The major product (**12a**), obtained in 52% yield, was identical by ^{1}H-n.m.r. spectroscopy to the precursor[7c] of Isobe's intermediate **10a**, indicating the α-anomeric configuration. From the chromatography, ~30% of the starting compound (**6**) was recovered, and a small amount (4%) of the unusual ethanol adduct (**12c**) was also obtained. Capillary g.l.c.–m.s. analysis of **12a** revealed the presence of the β anomer (**12b**), which showed essentially the same fragmentation pattern as **12a**; the ratio **12a**:**12b** was 47:3. The favoring of α anomers upon preparation or equilibration has been observed for some allylic glycosides[11].



12a

12b (β anomer)

12b

As established in the conversion of **5** into **6**, the stereoselectivity of hydrogenation of **12a** was improved by the use of platinum dioxide in ether to give **10a** and its C-2 epimer in the ratio of 6:1. Spectroscopic data for the hydrogenation products were essentially identical with those of Isobe's key intermediate for the synthesis[7c] of **3**. Moreover, the nature of **10a** on g.l.c. under various conditions were in complete agreement with those of debenzylated **10b**, whose stereochemistry was earlier determined. Our four-step route for **10a** is advantageous in its facility; Isobe *et al.* required ten steps from D-glucal.

By the method of Isobe[7c], compound **10a** was converted into **3**. The minor diastereomeric impurities could be removed during the transformations. As, in their[7c] stereocontrolled heteroconjugate addition-reaction, at C-2 to produce **3**, the corresponding β anomer showed incomplete stereoselectivity, the foregoing α-selective transglycosylation of **6** was of great value. The spectral data for **3** [m.p. 124°, $[\alpha]_D^{23}$ +40.3° (*c* 0.24, chloroform)] are in good agreement with those reported in the literature[12].

In conclusion, this work provides stereoselective routes for precursors of (−)-δ-multistriatin (**2**) and (+)-Prelog–Djerassi lactonic acid (**3**) from levoglucosenone (**1**). The rigid framework of **1** affords high stereoselectivity in introducing the C-2 and C-4 methyl groups. Employing **1** as the starting material eliminates the tedious blocking–deblocking and dehydrating processes in conventional transformations of carbohydrates into non-carbohydrate products.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were determined with a Jasco DIP-181 digital polarimeter. Elemental analyses were performed by Mrs. Y. Naito, Department of Agricultural Chemistry, the University of Tokyo. I.r. spectra were recorded with a Jasco A-3 spectrophotometer. G.l.c. was performed in a Shimadzu GC-7A gas chromatograph having a flame-ionization detector, employing nitrogen as the carrier gas. Two capillary columns (50 m × 0.3 mm o.d.) coated with (*A*) OV-101, (*B*) PEG-20M, and (*C*) a glass column (1 m × 3 mm) packed with Chromosorb W coated with 5% OV-101 were used for separations. The chromatographic peaks were quantified with a Hewlett–Packard 3380A digital integrator. Preparative g.l.c. was conducted with a Hitachi 063 gas chromatography fitted with a thermal-conductance detector and column packing *C*. Low- and high-resolution g.l.c.–m.s., and f.d.–m.s. measurements were obtained with a Hitachi M-80 instrument and column packings *B* and *C*. T.l.c. was conducted on silica gel sheets (Eastman) and spots were detected with vanillin–sulfuric acid.

N.m.r. spectrometry. — All n.m.r. spectra were recorded for chloroform-*d* solutions with tetramethylsilane as the internal standard. ^{1}H-N.m.r. (100 MHz) spectra were recorded with a Jeol PS-100 instrument, and ^{1}H-n.m.r. (99.6 MHz) for the small-scale sample and ^{13}C-n.m.r. (25.1 Hz) spectra were recorded with a Jeol FX-100 instrument. High-resolution 400-MHz ^{1}H-n.m.r. spectra were recorded with a Bruker WM-400 spectrometer. For resolution enhancement, the free-induction decay were multiplied by the Gaussian transformation function as included in the Bruker software package.

*Facile purification procedure for crude levoglucosenone (1,6-anhydro-3,4-dideoxy-β-*D*-glycero-hex-3-enopyranos-2-ulose,* **1**). — Crude **1** was obtained from Shiono Koryo Kaisha Ltd., where **1** had been prepared from cellulose by the method of Shafizadeh[2a]. Crude **1** (60 g) was passed through a 100-mL charcoal column with methanol–water (1:1) as eluant, to remove most of the furfural and its derivatives. The eluate was evaporated to remove methanol, and the resulting suspension was extracted with 3 100-mL portions of dichloromethane. The extract was washed with aq. sodium hydrogencarbonate, dried over anhydrous magnesium sulfate, and concentrated to low volume (100 mL). The sample contained 2-(hydroxyacetyl)furan (**13**) as the major impurity. T.l.c. showed that the best separation

between **1** (R_F top) and **13** (R_F 0.3) was achieved with dichloromethane as the developing solvent. The sample was therefore applied to a column of silica gel (Merck 60, 100 g), which was eluted with dichloromethane to give almost pure **1** (t.l.c.). Solvents were removed by evaporation and the product was distilled *in vacuo* to afford ~40 g of pure **1** (98% pure as judged by g.l.c.); b.p. 65°/0.7 torr, $[\alpha]_D^{23}$ +538° (*c* 1.1, chloroform) (lit.[2a] $[\alpha]_D$ +530°). All spectroscopic data for this sample were identical with those reported in the literature[1].

1,6-Anhydro-3,4-dideoxy-4-C-methyl-β-D-erythro-hexopyranos-2-ulose (**5**). — A solution of lithium dimethyl cuprate[13] was prepared by dropwise addition of methyllithium in ether (1.5M, 107 mL) to a stirred suspension of copper(I) bromide–dimethyl sulfide complex (16.4 g) in dry diethyl ether at −78° under argon. The mixture was warmed until clear (~1 h, −40°) and then cooled to −60°. To this was added dropwise a solution of **1** (5 g, 40 mmol) in dry diethyl ether (10 mL). The mixture was maintained for an additional 0.5 h at −60° and allowed to warm during 1 h to 20°. It was then poured into ice-cooled, saturated ammonium chloride solution (200 mL) and the mixture was stirred for 1 h. The ether layer was separated and the blue aqueous layer extracted twice with dichloromethane (100 mL). The combined organic layer was washed with brine, dried (magnesium sulfate), and passed through a short column of silica gel. The solution was evaporated to remove solvents and the residue distilled to give 4.85 g (86%) of **5**. Capillary g.l.c. analysis of **5** showed >99% diastereomeric purity; b.p. 63°/5 torr, $[\alpha]_D^{23}$ −299.4° (*c* 0.35, diethyl ether); ν_{max}^{film} 2960, 2900, 1750, 1730, 1480, 1455, 1420, 1380, 1320, 1295, 1240, 1130, 1110, 985, 950, 910, 850, and 740 cm^{-1}; n.m.r. see Table I; *m/z* 67 (90%), 68 (100), 85 (10), 96 (35), and 114 (7%, $M^+ - CO$); 2,4-dinitrophenylhydrazone: m.p. 217–219°, $[\alpha]_D^{23}$ −179.3° (*c* 0.56, chloroform) (lit.[2a] m.p. 215–216°, $[\alpha]_D$ −150°).

1,6-Anhydro-2,3,4-trideoxy-4-C-methyl-2-C-methylene-β-D-erythro-hexopyranoside (**6**). — Butyllithium (1.3M, 38 mL) in hexane was added dropwise to a stirred suspension of triphenylmethylphosphonium bromide (16.3 g, 47 mmol) in dry diethyl ether (150 mL) at room temperature under argon. After 1 h, the ketone **5** (5 g, 35 mmol) in diethyl ether (10 mL) was added dropwise to the mixture, which was then stirred for 2 days. Next it was poured into saturated sodium hydrogencarbonate solution, and the mixture was stirred for 0.5 h. The ether layer was separated, washed with brine, and dried (magnesium sulfate). The solution was decolorized by passage through a short column of aluminum oxide, and concentrated at atmospheric pressure to low volume. During evaporation, crystals of triphenylphosphine oxide precipitated and were removed by filtration. The crystals were washed with a little pentane, and the combined filtrate and washings were applied to a column of aluminum oxide. Washing of this with two column-volumes of pentane gave phosphine oxide and the degraded products, and the succeeding 1:1 pentane–diethyl ether eluate was evaporated at atmospheric pressure to afford pure **6** (3.85 g, 78%). The distilled sample crystallized spontaneously as waxy needles; m.p. 32.5°, b.p. 55°/4 torr, $[\alpha]_D^{23}$ −227.7° (*c* 0.4, diethyl ether); ν_{max}^{film} 2970, 2900,

1455, 1440, 1380, 1335, 1310, 1130, 1100, 1085, 1045, 980, 960, and 900 cm^{-1}; δ_H 1.1 (d, 3 H, *J* 7 Hz, Me-4), 1.9 (m, 2 H, H-3), 2.7 (m, 1 H, H-4), 3.9 (m, 2 H, H-6), 4.3 (m, 1 H, H-5), 4.76 and 4.83 (2 d, 2 H, *J*2 Hz, *exo*-alkene), and 5.5 (br.s., 1 H, H-1); δ_C 17.43, 31.12, 33.93, 68.10, 77.81, 104.19, 109.75, and 142.86; *m/z* 41 (80%), 55 (90), 79 (100), 95 (70), 97 (60), 110 (50), and 140 (90, M^+); high-resolution m.s.: calc. for $C_8H_{14}O_2$: 140.0837 a.m.u.; found: 140.0821.

Anal. Calc. for $C_8H_{14}O_2$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.60.

*1,6-Anhydro-2,3,4-trideoxy-2,4-di-*C*-methyl-β-*D*-ribo- and arabino-hexopyranoside* (**7a** and **7b**). — Alkene **6** (1 g) was dissolved in diethyl ether (100 mL) and hydrogenated with 5% palladium-on-charcoal (100 mg) at atmospheric pressure and room temperature until g.l.c. indicated complete reaction. G.l.c. (column *A*, 60 + 3°/min) indicated two products having T_R 23.5 min (**7a**) and T_R 22.2 min (**7b**) in 4:1 ratio. Analytical samples of **7a** and **7b** were obtained by preparative g.l.c. Compound **7a** had $[\alpha]_D^{23}$ −91.4° (*c* 0.4, pentane); ν_{max}^{film} 2950, 2900, 1470, 1380, 1320, 1160, 1110, 1055, 1035, 960, and 895 cm^{-1}; δ_H 1.13 (d, 3 H, *J* 8 Hz, Me-2), 1.28 (d, 3 H, *J* 7 Hz, Me-4), 1.7–2.1 (m, 4 H, H-2,3,4), 3.8 (m, 2 H, H-6), 4.2 (m, 1 H, H-5), 5.24 (s, 1 H, H-1); *m/z* 57 (100%), 71 (100), 81 (80), 96 (70), 100 (65), and 142 (4, M^+): high-resolution m.s.: calc. for $C_8H_{14}O_2$: 142.0993 a.m.u.; found: 142.1003.

Compound **7b** had $[\alpha]_D^{23}$ −46.6° (*c* 0.125, pentane); δ_H 0.81 (d, 3 H, *J* 7 Hz, Me-2), 1.17 (d, 3 H, *J* 7 Hz, Me-4), 1.2–2.1 (m, 1 H, H-2,3,4), 3.8 (m, 2 H, H-6), 4.2 (m, 1 H, H-5), and 5.16 (br s, 1 H, H-1); *m/z* 71 (100%), 81 (40), 96 (25), 100 (20), and 142 (3, M^+); high-resolution m.s.: calc. for $C_8H_{14}O_2$: 142.0993 a.m.u.; found: 142.0997.

A solution of the hydrogenated product from 1 g of **6** in diethyl ether was evaporated at atmospheric pressure and the residue redissolved in 50 mL of dichloromethane. The solution was boiled for 5 h with *p*-toluenesulfonic acid (10 mg) under reflux. It was then cooled to room temperature and kept for one week. G.l.c. analysis showed that the ratio **7a**:**7b** had changed to 4.5:95.5. The resulting, dark solution was passed through a short column of silica gel to remove acid and coloring matter, made up to 100 mL with dry dichloromethane and used directly for further conversion.

(2'S,4'S, 5'S)-2-(2,4-Dimethyl-5,6-dihydroxyhex-2-yl)-1,3-dithiane (**8a**) *and its isopropylidene acetal* (**8b**). — To the solution of **7b** from 1 g (7.1 mmol) of **6** was added propanedithiol (860 mg, 8 mmol) and the mixture was then cooled to −10° with stirring. Boron trifluoride etherate (0.5 mL) was then added dropwise and the temperature was allowed to rise during 2 h to 10°. The solution was then diluted with ethyl acetate, washed with aqueous, saturated sodium hydrogencarbonate, dried over magnesium sulfate, and evaporated. The residue was then chromatographed on a column of silica gel. After washing with dichloromethane to remove the unreacted propanedithiol and byproducts, elution with ethyl acetate gave pure **8a** (1.1 g, 62% from **6**); $[\alpha]_D^{23}$ −30.3° (*c* 1.18, chloroform); ν_{max}^{film} 3350, 2960, 2920, 2880, 1460, 1450, 1420, 1380, 1275, 1060, 1020, 910, and 760 cm^{-1}; δ_H 0.88 and

1.08 (2 d, 6 H, *J* 7 Hz, Me-2',4'), 1.4–2.2 (m, 6 H, H-5,2',3',4'), 2.9 (m, 4 H, H-4,6), 3.4–3.8 (m, 5 H, H-5',6', OH), 4.16 (d, 1 H, *J* 5 Hz, H-2); *m/z* 43 (33%), 75 (30), 106 (38), 107 (40), 119 (100), 120 (43), 121 (55), 143 (30), 159 (25), and 250 (15, M^+); high-resolution m.s.: calc. for $C_{11}H_{22}O_2S_2$: 250.1060 a.m.u.; found: 250.1094.

A solution of the glycol **8a** (500 mg) in 2,2-dimethoxypropane (1 mL) was stirred with a catalytic amount of pyridinium *p*-toluenesulfonate for 2 h at room temperature. It was then diluted with dichloromethane (5 mL), washed with aqueous sodium hydrogencarbonate and brine, dried over potassium carbonate, passed through a short column of silica gel, and evaporated to give **8b** (570 mg, 98%); $[\alpha]_D^{23}$ −24.2° (*c* 1.18, chloroform); ν_{max}^{film} 2960, 2940, 2900, 1460, 1420, 1380, 1370, 1250, 1210, 1160, 1065, and 860 cm^{-1}; δ_H 0.84 and 1.08 (2 d, 6 H, *J* 7 Hz, Me-2',4'), 1.34 and 1.40 (s, 6 H, CMe_2), 1.4–2.2 (m, 5 H, H-5,2',3',4'), 2.85 (m, 4 H, H-4,6), 3.5–4.0 (m, 3 H, H-5',6'), and 4.12 (d, 1 H, *J* 6 Hz, H-2); *m/z* 43 (77%), 72 (84), 106 (55), 107 (65), 119 (100), 120 (40), 121 (57), 159 (65), 161 (45), 232 (35), 275 (50), and 290 (45, M^+); high-resolution m.s.: calc. for $C_{14}H_{26}O_2S_2$: 290.1373 a.m.u.; found: 290.1317.

(2'S,4'S,4"S)-2-Ethyl-2-[4-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)pent-2-yl]-1,3-dithiane (**9**). — A solution of butyllithium (1.3M, 1.5 mL) in hexane was added dropwise, at −78° to a solution of **8b** (264.5 mg, 0.912 mmol) and *N,N,N',N'*-tetramethylethylenediamine (500 μL) in dry THF (4 mL), and the temperature was raised to −10° during 2 h and then lowered[10] to −60°. Ethyl iodide (500 μL, 4.8 mmol) was added dropwise at this temperature and the mixture was allowed to warm to 0° with stirring during 16 h. Ice was added and the mixture extracted with diethyl ether. The extract was washed with aq. ammonium chloride, aq. sodium thiosulfite, distilled water, and brine, dried over potassium carbonate, and evaporated. Column chromatography of the residue on silica gel afforded pure **9** (284.5 mg, 98%); $[\alpha]_D^{23}$ −41.6° (*c* 1.05, chloroform); ν_{max}^{film} 2970, 2940, 1450, 1380, 1240, 1210, 1160, 1065, 860, and 800 cm^{-1}; δ_H 0.85 (d, 3 H, *J* 6 Hz, Me-2' or 4'), 1.02 (t, 3 H, *J* 7 Hz, CH_3CH), 1.08 (d, 3 H, *J* 7 Hz, Me-2' or 4'), 1.34 and 1.40 (2 s, 6 H, CMe_2), 1.6–2.0 (m, 5 H, H-5,2',3',4'), 2.1 (q, 2 H, CH_3CH_2-), 2.6–2.9 (m, 4 H, H-4,6), and 3.5–4.1 (m, 3 H, H-2,4',5"); *m/z* 41 (88%), 43 (100), 55 (67), 59 (76), 72 (63), 73 (68), 107 (64), 147 (65), 148 (36), 149 (42), 185 (6), 243 (10), 303 (36), and 318 (16, M^+); high-resolution m.s.: calc. for $C_{16}H_{30}O_2S_2$: 318.1686 a.m.u.; found: 318.1704.

Anal. Calc. for $C_{16}H_{30}O_2S_2$: C, 60.33; H, 9.49. Found: C, 59.89; H, 9.55.

(1S,2S,4S,5R)-2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane [*(−)-δ-multistriatin*, **2**]. — To a stirred suspension of mercuric chloride (96 mg) and calcium carbonate (35 mg) in dry acetonitrile (1 mL) was added a solution of **9** (50 mg, 0.16 mmol) in dry acetonitrile (0.5 mL). The mixture was boiled for 1 h under reflux with stirring under nitrogen. After cooling, the suspension was filtered and the solid washed with 1:1 pentane–dichloromethane. The filtration was washed with 5M ammonium acetate, distilled water and brine, dried over magnesium sul-

fate, passed through a short column of silica gel, and evaporated low volume. G.l.c. indicated almost a single component, with ~5% of the C-4 epimer (β-multistriatin). The analytical sample of **2** was obtained by preparative g.l.c. (7.6 mg); $[\alpha]_D^{23}$ −84.7° (*c* 0.155, pentane); ν_{max}^{film} 2975, 2950, 2880, 1460, 1380, 1245, 1200, 1170, 1135, 1105, 1050, 980, 915, and 895 cm^{-1}; δ_H 0.81 (d, 3 H, *J* 6.6 Hz, Me-4), 0.93 (t, 3 H, *J* 7.3 Hz, CH_3CH_2), 1.16 (d, 3 H, *J* 6.3 Hz, Me-2), 1.2–2.0 (m, 4 H, H-2,3,4), 1.7 (q, 2 H, CH_3CH_2), 3.8 (m, 2 H, H-7), and 4.23 (brs, 1 H, H-1); δ_C 7.08, 16.44, 17.90, 27.38, 32.53, 33.52, 69.97, 78.92, and 111.39; *m/z* 41 (60%), 55 (80), 57 (100), 71 (60), 81 (50), 96 (50), 127 (20), 140 (2), and 170 (2, M^+); high-resolution m.s.: calc. for $C_{10}H_{18}O_2$: 170.1307 a.m.u.; found: 170.1323.

Transglycosylation of **7a**. — The use of platinum oxide (100 mg) as catalyst in the hydrogenation of **6** (3 g) in diethyl ether (200 mL) resulted in **7a** of high diastereomeric purity (**7a**:**7b** = 12.5:1, by g.l.c.). The resulting solution was concentrated at atmospheric pressure to remove most of the solvent, and was used without purification for ethanolysis.

A solution of **7a** (1 g) and trifluoroacetic acid (TFA, 200 μL) in dry ethanol (2 mL) was heated in a sealed tube for 3 h at 120°, and then cooled. Ice-cooled aqueous saturated sodium hydrogencarbonate (5 mL) was added and the mixture was extracted with diethyl ether (5 mL × 2). The extract was washed with distilled water and brine, dried over potassium carbonate, passed through a short column of aluminum oxide, and evaporated. G.l.c. indicated essentially two products, **10a** and **11a**, together with small proportions of their C-2 epimers, which were not separable by t.l.c. under various conditions. The residue was benzylated conventionally to give two major products that were well separated in t.l.c. with toluene as the developing solvent. They could be separated on a column of silica gel with toluene as eluant to afford two benzylated derivatives, **10b** (R_F 0.37, 210 mg, 10.7% from **7a**) and **11b** (R_F 0.15, 185 mg, 9.4%); a considerable proportion of each might have been lost during processing from **7a** because of the high volatilities of **10** and **11**. The high-resolution ^{1}H-n.m.r. data for **10b** and **11b** are listed in Table IV. Compounds **10b** and **11b** had *m/z* 91 (100%), 141 (20), 157 (60), 187 (3, M^+ − Bn), 232 (35, M^+ − EtOH), 233 (15, M^+ − EtO), and 278 (2, M^+).

Ethanolysis of **7a** with other Lewis and protonic acids under various conditions provided similar results.

Transglycosylation of **6**. — The allylic glycoside **6** (1 g) in 0.5% TFA in dry ethanol (2 mL) was heated in a sealed tube for 1 h at 50°, and then cooled. The ratio of the products did not change at longer times of reaction. To this solution was added aqueous sodium hydrogencarbonate (2 mL), and the mixture was extracted twice with diethyl ether (5 mL). The extract was washed with distilled water and brine, dried over potassium carbonate and evaporated. The residue was then chromatographed on a column of silica gel with hexane–diethyl ether as eluant. After washing the column with hexane-ether (1:1) to recover **6** (280 mg), elution with ether gave **12** (690 mg, 52%); $[\alpha]_D^{23}$ +122.5° (*c* 2.58, chloroform) (lit.[7c] +133.6°); ν_{max}^{film} 3450, 2950, 2900, 1100, 1060, 1000, and 900 cm^{-1}; δ_C 15.15, 17.43,

33.40, 36.45, 62.30, 63.24, 74.82, 100.21 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), 110.45, and 143.86; *m/z* 41 (100%), 43 (70), 55 (50), 57 (30), 67 (22), 69 (25), 71 (30), 81 (40), 95 (35), 97 (65), 141 (25), 155 (10), and 185 (1, $M^+ - 1$). The ^{1}H-n.m.r. spectrum was identical to that of the authentic α anomer (**12a**, ethyl 2,3,4-trideoxy-4-*C*-methyl-2-*C*-methylene-α-D-*erythro*-hexopyranoside) provided by Prof. M. Isobe; δ_H 0.9 (d, 3 H, *J* 7 Hz, Me-4), 1.23 (t, 3 H, *J* 7 Hz, CH_3CH_2), 1.76 (m, 1 H, H-4), 2.18 (s, 1 H, OH), 2.3 (m, 2 H, H-3), 3.7 (m, 5 H, CH_3CH_2), 4.9 (m, 2 H, *exo*-alkene), and 5.0 (s, 1 H, H-1). However, g.l.c.–m.s. analysis indicated the presence of the β anomer (**12b**), which exhibited essentially the same fragmentation pattern as **12a**. The ratio **12a**:**12b** was 47:3.

Anal. Calc. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.77. Found: C, 64.19; H, 9.74.

Further elution of the column with ethyl acetate afforded **12c**; δ_H 0.98 (d, 3 H, *J* 7 Hz), 1.2 (t, 3 H, *J* 7 Hz), 1.6–2.3 (4 H), 3.45 (q, 2 H, *J* 7 Hz), 3.5–3.8 (3 H), 3.82 (s, 2 H), and 6.50 (br.s, 1 H); *m/z* 41 (100%), 43 (97), 55 (75), 57 (55), 67 (50), 71 (65), 81 (70), 95 (65), 109 (30), 111 (35), 140 (40), 141 (35), 155 (15), and 186 (20, M^+); high-resolution m.s.: calc. for $C_{10}H_{18}O_3$: 186.1255 a.m.u.; found: 186.1243.

*Ethyl 2,3,4-trideoxy-2,4-di-*C*-methyl-*α*-*D*-ribo-hexopyranoside* (**10a**). — A solution of **12** (600 mg) in diethyl ether (50 mL) was hydrogenated at atmospheric pressure and room temperature with platinum oxide catalyst until g.l.c. indicated complete conversion into **10**; ν_{max}^{film} 3450, 2950, 2900, 1455, 1375, 1200, 1180, 1120, 1060, 1020, 980, and 815 cm^{-1}; δ_H 0.78 and 0.82 (2 d, 6 H, *J* 7 Hz, Me-2,4), 1.12 (t, 3 H, *J* 7 Hz, CH_3CH_2O), 0.9–1.9 (m, 3 H, H-2,3,4), 2.18 (br.s, 1 H, hydroxyl), 3.3–3.8 (m, 5 H, H-5,6, CH_3CH_2O), 4.46 (br.s, 0.2 H, H-1), and 4.58 (d, 0.8 H, *J* 3 Hz, H-1); δ_C 13.98, 14.22, 15.50, 30.30, 33.99 (2 C), 61.60, 62.66, 73.19, and 98.99; *m/z* 41 (55%), 43 (80), 47 (55), 55 (65), 57 (70), 58 (50), 71 (70), 72 (100), 75 (45), 81 (45), 86 (50), 99 (25), 143 (13, $M^+ - EtO$), 157 (40, $M^+ - CH_2OH$). The ^{1}H-n.m.r. spectrum was essentially identical to that provided by Prof. M. Isobe. Capillary g.l.c. indicated the ratio **10a**:**10b** (its C-2 epimer) to be 6:1. The major component (**10a**) was identical with debenzylated **10b**.

(+)-Prelog–Djerassi lactonic acid (**3**). — Compound **10** was converted into **3** by the method of Isobe *et al.* [7c]. Minor diastereomeric impurities could be removed during the transformation steps. Compound **3** had m.p. 124°, $[\alpha]_D^{23}$ +40.3° (*c* 0.24, chloroform); $\nu_{max}^{CHCl_3}$ 2930, 1720, 1455, 1380, 1180, 1125, 1090, 1035, and 990 cm^{-1}; δ_H 1.02 (d, 3 H, *J* 6.3 Hz, Me-4), 1.21 (d, 3 H, *J* 7.1 Hz, Me-2), 1.29 (d, 3 H, *J* 7.1 Hz, Me-6), 1.42 (q, 1 H, *J* 12 Hz), 1.94 (m, 2 H), 2.50 (m, 1 H), 2.73 (m, 1 H), and 4.59 (dd, 1 H, *J* 10.3 and 2.2 Hz, H-3); δ_C 8.42, 16.9, 17.20, 30.95, 36.27, 37.32, 41.07, 86.29, 174.34, and 177.32.

ACKNOWLEDGMENTS

The authors are indebted to Prof. M. Isobe of Nagoya University for kindly providing ^{1}H-n.m.r. spectra of compounds **10a** and **12a** for comparison. We are grateful to Mrs. Y. Naito of the University of Tokyo for elemental analyses.

REFERENCES

1 Y. HALPERN, R. RIFFER, AND A. BROIDO, *J. Org. Chem.*, 38 (1973) 204–209.
2 (*a*) F. SHAFIZADEH AND P. S. CHIN, *Carbohydr. Res.*, 58 (1977) 79–87; (*b*) F. SHAFIZADEH, R. H. FURNEAUX, AND T. T. STEVENSON, *ibid.*, 71 (1979) 169–191.
3 M. MORI, T. CHUMAN, K. KATO, AND K. MORI, *Tetrahedron Lett.*, (1982) 4593–4596.
4 (*a*) G. T. PEARCE W. E. GORE, R. M. SILVERSTEIN, J. W. PEACOCK, R. A. CUTHBERT, G. N. LAINER, AND J. B. SIMEONE, *J. Chem. Ecol.*, 1 (1975) 115–124; (*b*) W. E. GORE, G. T. PEARCE, AND R. M. SILVERSTEIN *J. Org. Chem.*, 41 (1976) 2797–2803; (*c*) G. T. PEARCE, W. E. GORE, AND R. M. SILVERSTEIN, *ibid.*, 41 (1976) 2797–2803.
5 (*a*) B. GERKEN, S. GRUNE, J. P. VITÉ, AND K. MORI, *Naturwissenschaften*, 65 (1978) 110–111; (*b*) K. MORI AND H. IWASAWA, *Tetrahedron*, 36 (1980) 87–90; (*c*) R. W. HOFFMANN AND W. HELBIG, *Chem. Ber.*, 114 (1981) 2802–2807.
6 (*a*) R. ANLIKER, D. DVORNIK, K. GULBLER, H. HEUSSER, AND V. PRELOG, *Helv. Chim. Acta*, 39 (1956) 1785–1790; (*b*) C. DJERASSI AND J. A. ZDERIC, *J. Am. Chem. Soc.*, 78 (1956) 6390–6395.
7 (*a*) R. E. IRELAND AND J. P. DAUB, *J. Am. Chem. Soc.*, 46 (1981) 479–485; (*b*) S. JAROSZ AND B. FRASER-REID, *Tetrahedron Lett.*, (1981) 2533–2534; (*c*) M. ISOBE, Y. ICHIKAWA, AND T. GOTO, *ibid.*, (1981) 4287–4290.
8 D. D. WARD AND F. SHAFIZADEH, *Carbohydr. Res.*, 95 (1981) 155–176.
9 P.-E. SUM AND L. WEILER, *Can. J. Chem.*, 56 (1978) 2700–2702; 60 (1982) 327–334.
10 M. MORI, T. CHUMAN, M. KOHNO, K. KATO, M. NOGUCHI, H. NOMI, AND K. MORI, *Tetrahedron Lett.*, (1982) 667–670.
11 (*a*) R. J. RIFFER AND N. PRASAD, *J. Chem. Soc. C*, (1969) 570–575; (*b*) M. ISOBE, M. KITAMURA, AND T. GOTO, *Tetrahedron Lett.*, (1981) 239–242.
12 P. A. BARTLETT AND J. L. ADAMS, *J. Am. Chem. Soc.*, 102 (1980) 337–342.
13 H. O. HOUSE, C.-Y. CHU, J. M. WILKINS, AND M. J. UMEN, *J. Org. Chem.*, 40 (1975) 1460–1469.