Perhydroindan Derivatives. XVI. The Synthesis of Racemic Epiallogibberic Acid[1]

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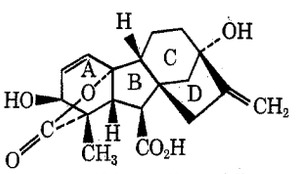
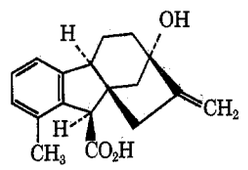
The racemic tetracyclic acetoxy olefin **4a** was subjected to oxymercuration followed by reduction and saponification to form the cis diol **5a**. Successive acetylation, reaction with dihydropyran, and selective saponification afforded the hydroxy tetrahydropyranyl ether **19b**, that was oxidized to the ketone **20**. A subsequent Wittig reaction followed by saponification afforded racemic epiallogibberic acid (**3**). The final product, racemic **3**, as well as the ester **21** and the diol derivatives **5a** and **5b**, were compared with the analogous products (+)-**3**, **12a**, **16a**, and **16b**, obtained from degradation of gibberellic acid (**1**), to establish that the structures of the synthetic and degradation products were the same.

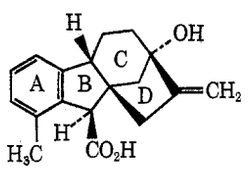
Among the early degradative studies used to establish the structure of gibberellic acid (**1**),[2] reaction of **1** with aqueous hydrazine to form allogibberic acid (**2**) and (+)-epiallogibberic acid (**3**) was especially useful



1 (gibberellic acid)



2 (allogibberic acid)

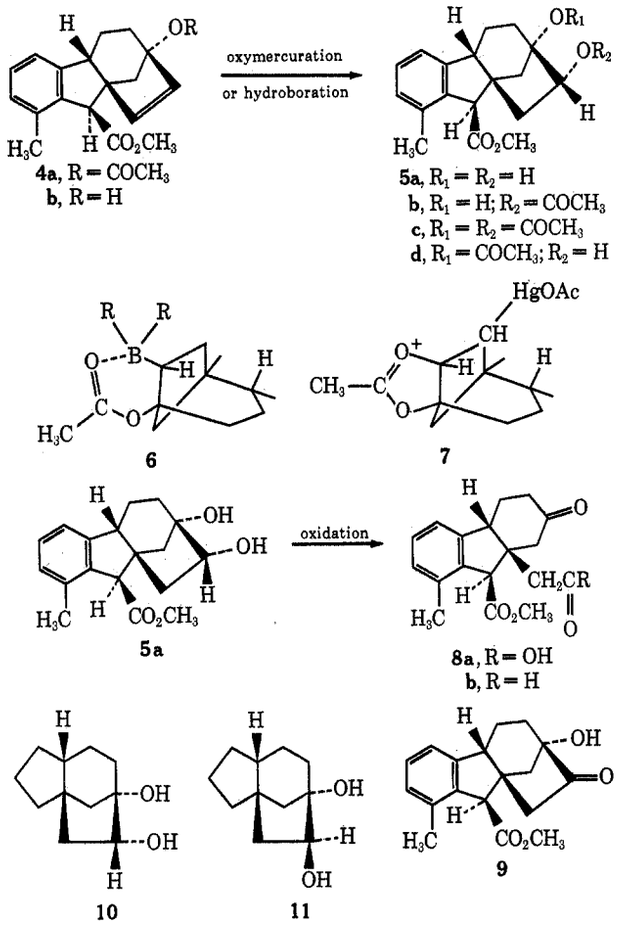


3 (epiallogibberic acid)

in providing intermediates for further structural study.[3] In seeking synthetic routes to the various gibberellins (*e.g.*, **1**) and their analogs, we were also led to consider synthetic routes to epiallogibberic acid (**3**), a substance possessing the same functional groups and stereochemical arrangement in rings B, C, and D that are present in gibberellic acid (**1**). This paper reports our synthesis of racemic epiallogibberic acid (**3**) and its comparison with (+)-epiallogibberic acid (**3**) obtained by degradation of **1**.[4]

For this synthesis, we employed the tetracyclic acetoxy olefin **4a** (Scheme I), whose preparation in synthetically useful amounts has been described in earlier papers in this series.[5] The selective hydration of this olefin **4a** to form a single product, the cis-1,2 diol **5a**, was readily accomplished either by reaction with mercury(II) acetate, followed by reduction, or by hydroboration with bis(2-methyl-2-butyl)borane, followed by oxidation. In each case we believe that the bridgehead acetoxy function plays a key role in this

SCHEME I



selectivity, either by reaction with the olefin–acetoxymercurium ion complex to form an intermediate acetoxonium ion **7** or by solvating, and hence directing, attack of the dialkylborane on the olefin to form the solvated trialkylborane **6**. In the subsequent aqueous basic reduction ($NaBH_4$ + NaOH) or oxidation (H_2O_2 + NaOH), the acetoxyl group was presumably removed by saponification. Additional evidence for the presence of an intermediate such as **7** was obtained by reduction of the organomercury intermediate in neutral aqueous solution to form the cis diol monoacetate **5b**, in which migration of the acetyl group had occurred. This same type of neighboring-group participation by the acetoxyl function has also been observed in the subsequently described degradation of (+)-epiallogibberic acid.

(1) This research has been supported by Public Health Service Grant RO1-CA-12634 from the National Cancer Institute. The execution of this research was also assisted by an Institutional Research Grant from the National Science Foundation for the purchase of a mass spectrometer.

(2) For reviews, see (a) J. F. Grove, *Quart. Rev., Chem. Soc.*, **15**, 56 (1961); (b) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965); (c) G. Schneider, G. Sembdner, and K. Schreiber, *Kulturpflanze*, **13**, 267 (1965).

(3) J. F. Grove and T. P. C. Mulholland, *J. Chem. Soc.*, 3007 (1960).

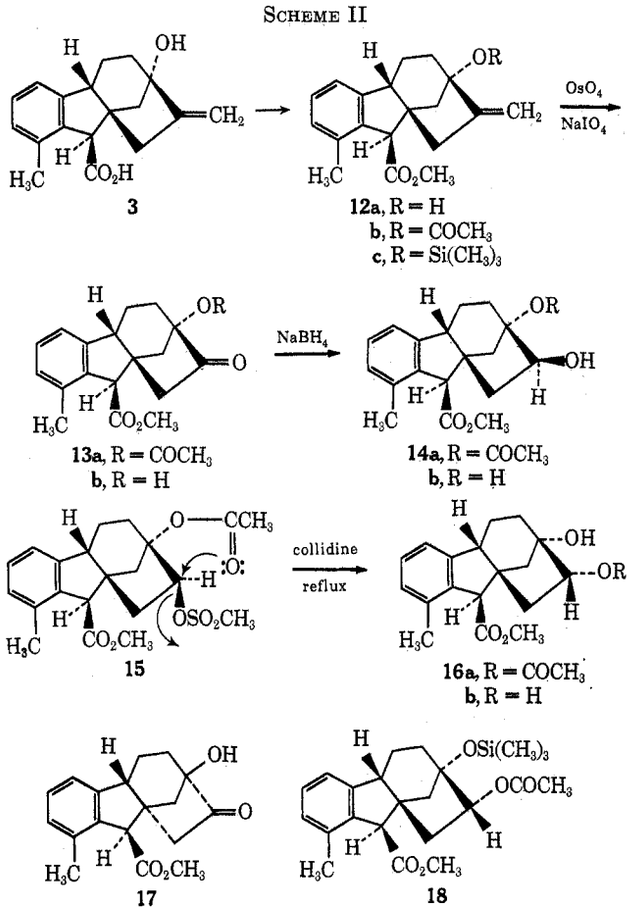
(4) For a recently completed relay synthesis of (−)-epiallogibberic acid, see K. Mori, *Tetrahedron*, **27**, 4907 (1971).

(5) H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, **38**, 741 (1973), and references cited therein.

Our subsequent efforts to oxidize the cis diol **5a** to the ketol **9** with a variety of oxidants (see Experimental Section) were uniformly unsatisfactory because of competing oxidative cleavage to form either the keto acid **8a** (in partially aqueous media) or the keto aldehyde **8b** (in anhydrous media). Although the successful oxidation of an analogous diol to the ketol has been reported,[6] the structurally similar trans diol **11** and, especially, the cis diol **10** have been noted to undergo oxidation cleavage.[7] Our efforts to prepare and selectively oxidize the monoacetylated diol **5b** were also unsatisfactory; a number of experimental observations suggested that the ready transfer of the acetyl group from one oxygen to the other (*i.e.*, **5b** ⇌ **5d**) was the cause of our difficulty with this approach.

At this stage in the synthesis, we concluded that it would be prudent to develop and refine further reaction conditions for the conversion of the racemic diol **5a** to racemic epiallogibberic acid (**3**) with a material that was more readily accessible than the racemic diol **5a**. For this reason, we interrupted our synthetic sequence to examine the degradation of gibberellic acid (**1**) *via* (+)-epiallogibberic acid (**3**, Scheme II) to the optically

SCHEME II

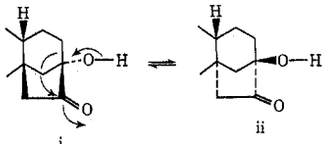


active cis diol **16b**, an ideal "model" compound for the reactions we wished to develop.

The previously reported[3,4] noncrystalline methyl (+)-epiallogibberate (**12a**) was converted to the crystalline acetate **12b** and then oxidized with a mixture of $NaIO_4$ and OsO_4.[8] Although neither the oxidation product, the keto acetate **13a**, nor the subsequent transformation products, **14**, **15**, and **16**, could be induced to crystallize, we were able to obtain satisfactory separation of the various reaction products by a combination of column chromatography and thin layer chromatography. The various spectroscopic properties of these liquid intermediates provided compelling evidence for the structural assignments indicated. Reduction of the intermediate acetoxy ketone **13a** with $NaBH_4$ formed a product believed to be the trans diol derivative **14a**, the product expected[6,9] from attack on the ketone **13a** from the less hindered exo direction. Subsequent reaction of this hydroxy acetate **14a** with methanesulfonyl chloride in pyridine followed by decomposition of the intermediate acetoxy mesylate **15** in collidine and subsequent hydrolysis produced the cis hydroxy acetate **16a**. We conclude that this transformation involves the indicated (structure **15**) displacement of the mesylate anion by the neighboring acetoxyl function and not initial elimination to form the olefin **4a**, because the olefin **4a** is stable under the conditions of this reaction.[5] Saponification of **16a** afforded the cis diol **16b**. Comparison of the ir, nmr, and mass spectra and of the tlc R_f values of both of these cis diol derivatives **16** with the racemic cis diol derivatives **5a** and **5b** provided compelling evidence that these intermediates had the same structures. Consequently, we were able to explore various transformations employing the diol **16b** with confidence that these same transformations would be applicable to the synthetic diol **5a**.

Two obstacles needed to be overcome in completing the synthesis. The first was the conversion of the cis diol **5a** to a suitable derivative of the ketol **9** (or **13b**) without serious competition from oxidative cleavage, and the second was the need to protect the hydroxyl group in the ketol **9** (or **13b**) to prevent base-catalyzed isomerization of the ketol (**13b** ⇌ **17**)[10] during introduction of the methylene group with a Wittig reagent. When the hydroxyl group was not protected in an analogous conversion of the ketol to (−)-epiallogibberic acid, the isolated yield was only 8.6%.[4] A trimethylsilyl group was used to block the ketol hydroxyl function in an analogous synthesis of steviol.[6] In the present case we found that, although a trimethylsilyl group could be selectively removed from the allylic ether **12c** to regenerate alcohol **12a**, all of our efforts to selectively remove the acetyl group from intermediate acetoxy silyl ether **18** resulted either in no reaction or in removal of both groups. Consequently,

(6) I. F. Cook and J. R. Knox, *Tetrahedron Lett.*, **No. 47**, 4091 (1970).
(7) E. J. Corey and R. L. Carney, *J. Amer. Chem. Soc.*, **93**, 7318 (1971).
(8) The use of this mixture of oxidants to cleave olefins has been described by R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
(9) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Amer. Chem. Soc.*, **89**, 1499 (1967).
(10) Examples of this bicyclic ketol isomerization (i → ii) have been

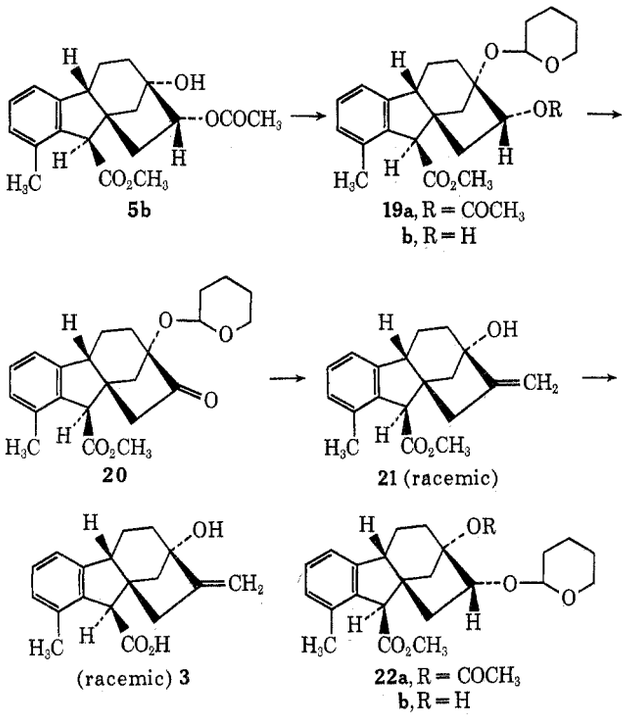


observed with a diastereoisomer of ketol **13b** (ref 4), in analogous derivatives of steviol [ref 6 and E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt, and J. A. Waters, *J. Amer. Chem. Soc.*, **85**, 2305 (1963)], and in simple bicyclo[2.2.1]heptane derivatives [J. V. Paukstelis and D. N. Stephens, *Tetrahedron Lett.*, **No. 38**, 3549 (1971)].

we turned our attention to the tetrahydropyranyl ether blocking group.

The racemic cis diol **5a** could be selectively acetylated at the less hindered secondary hydroxyl function to form the acetoxy alcohol **5b**. Reaction with dihydropyran under carefully controlled conditions (see Experimental Section) afforded primarily the acetoxy ether **19a** (Scheme III) accompanied by a minor by-

SCHEME III



product believed to be **22a** formed by migration of the acetyl group (to form **5d**) during the acid-catalyzed ether formation. In practice, it was simplest to saponify the mixture **19a** + **22a** to the mixture of alcohols **19b** + **22b** and then to oxidize the mixture with the chromium trioxide–pyridine complex.[11] The resulting mixture of the keto ether **20** and the unchanged hydroxy ether **22b** was readily separated by chromatography. In the final stage of the synthesis we found it advantageous to treat the keto ether **20** with salt-free[12] methylenetriphenylphosphorane in order to facilitate decomposition of the intermediate betaine and, hence, minimize the reaction time. Acidic hydrolysis of the crude product cleaved the tetrahydropyranyl ether to form racemic methyl epiallogibberate (**21**), a viscous liquid product with ir, uv, nmr, and mass spectra and tlc R_f values that corresponded to those obtained with methyl (+)-epiallogibberate. Saponification with aqueous alkali afforded racemic epiallogibberic acid, mp 254–255.5° dec. Comparison of the ir, uv, nmr, and mass spectra for this sample and (+)-epiallogibberic acid, mp 243–245° dec, indicated that the two materials have the same structure.

(11) See W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969), and references cited therein.

(12) M. Schlosser, G. Müller, and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 667 (1966).

Experimental Section[13]

Preparation of the Racemic Cis Diol 5a. With $Hg(OAc)_2$.—To a solution of 354 mg (1.09 mmol) of the acetoxy olefin **4a** in 2.5 ml of THF was added a solution of 380 mg (1.19 mmol) of $Hg(OAc)_2$ in 2.5 ml of H_2O. The resulting yellow suspension was stirred at 25° for 10 hr and treated successively with 4 ml of aqueous 10% NaOH and 4 ml of aqueous 10% NaOH containing 2.0 mmol of $NaBH_4$. The resulting gray suspension was stirred at 25° for 30 min and then partitioned between H_2O and $CHCl_3$. The organic layer was washed with H_2O, dried, and concentrated to leave 348 mg of liquid residue. Crystallization from Et_2O separated 87 mg (27%) of the cis diol **5a** as white needles, mp 108.5–110°. Chromatography of the mother liquors on silica gel with Et_2O–hexane mixtures as the eluent separated, in order of elution, 22 mg of the starting acetoxy olefin **4a**, 55 mg of the crude hydroxy olefin **4b**, and an additional 134 mg of the diol **5a**. The hydroxy olefin **4b** crystallized from an Et_2O–hexane mixture as white needles: mp 103–104°; ir ($CHCl_3$) 3590 (OH) and 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.8–7.4 (3 H m, aryl CH), 5.8–6.2 (2 H m, vinyl CH), 3.82 (1 H s, benzylic CH), 3.71 (3 H s, OCH_3), 3.2–3.5 (1 H m, benzylic CH), and 1.5–2.5 (10 H m, OH and aliphatic CH including an aryl CH_3 singlet at δ 2.27); mass spectrum *m/e* (rel intensity), 284 (M^+, 27), 252 (30), 227 (59), 225 (100), 197 (28), 196 (36), 195 (59), 181 (24), and 155 (19). The hydroxy olefin **4b** was reacetylated with 0.50 ml of Ac_2O in 0.75 ml of pyridine and the acetylated product was mixed with the recovered acetoxy olefin **4a** and treated with 91 mg of $Hg(OAc)_2$ in 0.5 ml of THF and 0.5 ml of H_2O. After subsequent treatment with 1.0 ml of aqueous 10% NaOH and 0.7 mmol of $NaBH_4$ in 1.4 ml of aqueous 10% NaOH, the previously described isolation procedure separated 9 mg (3% overall) of the acetoxy olefin **4a**, 29 mg (9% overall) of the hydroxy olefin **4b**, and an additional 41 mg of the cis diol **5a** (total yield 262 mg, 80%). The pure cis diol **5a** crystallized from Et_2O–hexane as white needles: mp 111.5–112.5°; ir ($CHCl_3$) 3400–3600 (broad, associated OH) and 1728 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ε 291) and 273 (206); nmr ($CDCl_3$) δ 6.8–7.3 (3 H m, aryl CH), 3.6–4.0 (5 H m, CHO, benzylic CH, and CH_3O singlet at δ 3.65), 3.2–3.5 (1 H m, benzylic CH), 2.64 (2 H s, OH), and 1.5–2.9 (11 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23); mass spectrum *m/e* (rel intensity), 302 (M^+, 2), 285 (21), 284 (100), 256 (71), 214 (25), 197 (40), 169 (33), 156 (22), 155 (30), 143 (22), 142 (21), 141 (28), 105 (29), and 43 (22).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.70; H, 7.21.

The oxymercuration was repeated without an alkaline isolation procedure with 45 mg (0.14 mmol) of the acetoxy olefin **4a**, 47 mg (0.15 mmol) of $Hg(OAc)_2$, 0.7 ml of THF, and 0.7 ml of H_2O. After a reaction period of 13 hr at 25°, the mixture was partitioned between CH_2Cl_2 and saturated aqueous NaCl and the organic layer was washed with aqueous $NaHCO_3$, dried, and concentrated. A solution of the crude organomercury intermediate (87 mg of colorless liquid) in 1.0 ml of *i*-PrOH was treated with 10 mg (0.27 mmol) of $NaBH_4$, stirred at 25° for 40 min, and then partitioned between $CHCl_3$ and H_2O. The crude product (47 mg) recovered from the organic layer was chromatographed on silica gel with Et_2O–hexane mixtures as eluents to separate 20 mg (42%) of the crude hydroxy acetate **5b**. Crystallization from Et_2O–hexane afforded the pure hydroxy acetate **5b** as white prisms, mp 103–104°, identified with a subsequently described sample by a mixture melting point determination and comparison of ir spectra.

B. With Bis(3-methyl-2-butyl)borane.—To a cold (0°) solution of the dialkylborane, prepared from 2.5 mmol of BH_3 and 366 mg (5.25 mmol) of 2-methyl-2-butene in 4.3 ml of THF, was added 258 mg (0.79 mmol) of the acetoxy olefin **4a**. The re-

(13) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrophotometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

sulting solution was stirred at 0° for 30 min and at 25° for 23 hr and then treated successively with 0.2 ml of H_2O, 4 ml of aqueous 10% NaOH, and 4 ml of aqueous 30% H_2O_2. After the resulting mixture had been stirred at 25° for 1.5 hr, it was partitioned between $CHCl_3$ and aqueous 5% $NaHCO_3$ and the organic layer was washed with H_2O, dried, and concentrated. Chromatography of the residual oil (216 mg) on silica gel with an Et_2O–hexane eluent separated 102 mg (43%) of the crude diol **5a**; recrystallization from Et_2O–hexane separated the pure cis diol **5a** as white needles, mp 109–110°.

Preparation of the Racemic Hydroxy Acetate 5b.—A solution of 290 mg (0.96 mmol) of the cis diol **5a** and 4 ml of Ac_2O in 6 ml of anhydrous pyridine was stirred at 25° for 2 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. The organic layer was washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. Crystallization of the residual liquid (345 mg) from Et_2O–hexane separated 246 mg (74%) of the hydroxy acetate **5b** as white prisms: mp 103–104°; ir (CCl_4) 3590, 3480 (OH), and 1735 cm^{-1} (ester C=O); uv max (95% EtOH) 255 mμ (ε 273) and 273 (189) with intense end absorption at 210 (10,700); nmr ($CDCl_3$) δ 6.8–7.3 (3 H m, aryl CH), 4.92 (1 H d of d, *J* = 3.5 and 7 Hz, CHO), 3.77 (1 H s, benzylic CH), 3.65 (3 H s, OCH_3), 3.2–3.5 (1 H m, benzylic CH), and 1.5–2.7 (15 H m, OH and aliphatic CH including an aryl CH_3 singlet at δ 2.25 and a $COCH_3$ singlet at 2.11); mass spectrum *m/e* (rel intensity) 284 (10), 266 (34), 225 (25), 224 (47), 155 (44), 143 (21), 142 (23), 141 (42), 128 (22), and 43 (100).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.78; H, 7.01.

The mother liquors from this crystallization were chromatographed on silica gel with an Et_2O–hexane eluent to separate 24 mg (6%) of the crude diacetate **5c** and an additional 40 mg of the hydroxy acetate **5b** (total yield 286 mg, 87%). A solution of 26 mg (0.086 mmol) of the cis diol **5a** in 0.4 ml of Ac_2O and 0.6 ml of pyridine was stirred at 25° for 72 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. The organic layer was dried and concentrated to leave 39 mg of yellow liquid that was chromatographed on silica gel with an Et_2O–hexane eluent. The fractions (27 mg, 82%) containing (tlc analysis) the diacetate **5c** were recrystallized from hexane to give the cis diacetate **5c** as white prisms: mp 122.5–123.5°; ir ($CHCl_3$) 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 5.2–5.5 (1 H m, CHO), 3.78 (1 H s, benzylic CH), 3.63 (3 H s, CH_3O), 3.1–3.5 (1 H m, benzylic CH), and 1.1–2.5 (*ca.* 17 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and two CH_3CO singlets at 2.03 and 1.97).

Oxidation of the Racemic Cis Diol 5a. A. With H_2CrO_4.—A cold (0°) solution of 26 mg of the diol **5a** in 1.0 ml of acetone was treated with excess aqueous H_2CrO_4 (Jones reagent),[14] stirred at 0° for 2 min, treated with excess *i*-PrOH, and then partitioned between $CHCl_3$ and aqueous HCl. The organic layer was extracted with aqueous $NaHCO_3$ and the aqueous extract was acidified and extracted with $CHCl_3$. After the $CHCl_3$ extract had been dried and concentrated, the residual crude keto acid (10 mg) was recrystallized from Et_2O–hexane to separate 6 mg of the keto acid **8a**, mp 167–171°. This product and several comparable samples were combined and recrystallized from Et_2O–hexane to afford the pure keto acid **8a** as white needles: mp 166–169°; ir ($CHCl_3$) 2800–3500 (carboxyl OH), 1730 (ester C=O), and 1715 cm^{-1} (carboxyl and ketone C=O); uv max (95% EtOH) 264 mμ (ε 271) and 270 (221) with intense end absorption at 210 (11,900); nmr ($CDCl_3$) δ 7.0–7.8 (4 H m, OH and aryl CH, 1 H exchanged with D_2O), 4.02 (1 H s, benzylic CH), 3.68 (3 H s, OCH_3), 3.6–4.0 (1 H m, benzylic CH), and 2.0–3.1 (11 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.34); mass spectrum *m/e* (rel intensity) 316 (M^+, 3), 257 (43), 256 (100), 197 (37), 169 (29), 155 (48), 141 (20), and 55 (22).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.04; H, 6.29.

An attempt to prevent oxidative cleavage by reaction of the diol **5a** with H_2CrO_4 in aqueous HOAc containing $Mn(NO_3)_2$[15] was not useful in this case, since oxidation of 15 mg of the diol **5a** under these conditions yielded 10 mg of the keto acid **8a**.

B. With CrO_3(pyridine)$_2$.—A solution of 28 mg (0.093 mmol) of the diol **5a** and 201 mg (0.78 mmol) of CrO_3(pyridine)$_2$[11] in 2.0 ml of CH_2Cl_2 was stirred at 25° for 30 min and then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The crude neutral product (52 mg) from the organic layer was chromatographed on silica gel with Et_2O–hexane as an eluent. The partially purified keto aldehyde **8b** was isolated as a colorless liquid with ir and nmr spectra comparable to the spectra of the subsequently described sample obtained from degradation of gibberellic acid. Attempts to oxidize the racemic diol **5a** to a keto alcohol **9** with either *N*-bromosuccinimide or *t*-BuOCl[7] in pyridine–CH_2Cl_2 mixtures or with a modified Pfitzner–Moffatt oxidation (DMSO–pyridine·SO_3–Et_3N)[16] or Ag_2CO_3 on Celite[17] were not satisfactory in our hands.

Preparation and Transformations of (+)-Epiallogibberic Acid (3).—A solution of 18.82 g (54.4 mmol) of gibberellic acid (**1**) in 19 ml of H_2NNH_2 and 10 ml of H_2O was refluxed for 26 hr and then cooled, diluted with H_2O, and acidified with HCl to precipitate 4.18 g (27%) of (+)-epiallogibberic acid (**3**), mp 239–245° dec. Recrystallization from MeOH afforded the pure (+)-acid **3** as white prisms: mp 243–245° dec (lit.[3] mp 244°); ir (KBr pellet) 2700–3500 (OH) and 1680 cm^{-1} (carboxyl C=O); uv max (95% EtOH) 260 mμ (shoulder, ε 254), 265 (296), and 274 (204) with intense end absorption at 210 (18,650); mass spectrum *m/e* (rel intensity) 285 (20), 284 (M^+, 97), 209 (38), 195 (40), 193 (33), 181 (42), 179 (46), 178 (40), 165 (95), 155 (78), 153 (62), 152 (62), 142 (51), 141 (85), 129 (58), 128 (100), 127 (42), 115 (81), 45 (40), 43 (47), and 39 (44); nmr [$(CD_3)_2$NCDO] δ 6.8–7.3 (3 H m, aryl CH), 5.18 (1 H m, vinyl CH), 5.00 (1 H m, vinyl CH), 3.66 (1 H s, benzylic CH), 3.2–3.6 (1 H m, benzylic CH), 2.5–3.1 (*ca.* 2 H m, allylic CH), and 1.1–2.5 (9 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.27).

A cold (0°) Et_2O solution of 1.259 g (4.43 mmol) of the (+)-acid **3** was esterified with excess CH_2N_2 to yield 1.33 g of the ester **12a** as a colorless, viscous liquid (reported[3,4] as a gum): ir ($CHCl_3$) 3590 (OH), 1730 (ester C=O), and 910 cm^{-1} (C=CH_2); uv max (95% EtOH) 265 mμ (ε 317) and 273 (238) with intense end absorption at 210 (9240); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 5.21 (1 H t, *J* = 2.5 Hz, vinyl CH), 5.08 (1 H t, *J* = 2.4 Hz, vinyl CH), 3.67 (4 H s, CH_3O and benzylic CH), 3.3–3.6 (1 H m, benzylic CH), 2.5–2.8 (2 H m, allylic CH_2), 2.25 (3 H s, aryl CH_3), and 1.2–2.2 (7 H m, aliphatic CH and OH at δ 1.82 exchanged with D_2O); mass spectrum *m/e* (rel intensity) 298 (M^+, 20), 239 (36), 238 (68), 155 (36), 141 (21), 119 (24), 105 (100), and 91 (20).

A solution of 980 mg (3.29 mmol) of the hydroxy ester **12a** and 10 ml of Ac_2O in 16 ml of anhydrous pyridine was stirred at 50° for 85 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. The organic layer was washed successively with aqueous 2 *M* HCl, aqueous $NaHCO_3$, and H_2O and then dried and concentrated. The residual yellow liquid (1.12 g) was chromatographed on silica gel with an Et_2O–hexane eluent to separate the crude acetate **12b**. Crystallization from Et_2O–hexane afforded 1.023 g (91%) of the acetate **12b** as white needles: mp 89–91° (recrystallization sharpened the melting point to 90.5–91°); ir ($CHCl_3$) 1730 (ester C=O) and 910 cm^{-1} (C=CH_2); nmr ($CDCl_3$) δ 6.8–7.4 (3 H m, aryl CH), 5.0–5.3 (2 H m, vinyl CH), 3.72 (1 H s, benzylic CH), 3.67 (3 H s, OCH_3), 3.3–3.6 (1 H m, benzylic CH), 2.5–2.9 (2 H m, allylic CH_2), and 1.5–2.5 (12 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and a CH_3CO singlet at 1.98); mass spectrum *m/e* (rel intensity) 340 (M^+, 76), 298 (29), 282 (43), 281 (100), and 221 (28).

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.89; H, 7.10.

After a mixture of 32 mg (0.11 mmol) of the hydroxy ester **12a**, 0.25 ml of Me_3SiCl, and 0.50 ml of pyridine had been stirred at 25° for 55 hr, the mixture was concentrated under reduced pressure and partitioned between $CHCl_3$ and H_2O. The organic layer was dried and concentrated and the residual yellow liquid (36 mg) was chromatographed on silica gel with an Et_2O–hexane eluent to separate 26 mg (65%) of the trimethylsilyl ether **12c** as a colorless liquid: ir (CCl_4) 1735 (ester C=O) and 900 cm^{-1} (C=CH_2); nmr (CCl_3) δ 6.8–7.2 (3 H m, aryl CH), 4.9–5.2 (2 H m, vinyl CH), 3.2–3.7 (5 H m, two benzylic CH and CH_3O singlet at δ 3.62), 2.5–2.8 (2 H m, allylic CH_2), 2.24 (3 H s, aryl CH_3), 1.0–2.4 (6 H m, aliphatic CH), and 0.05 (9 H s, CH_3Si); mass spectrum *m/e* (rel intensity) 370 (M^+, 100), 355 (20), 75 (53), 74 (20), 73 (92), and 59 (25). When a solution of 10 mg of this silyl ether **12c** and 0.05 ml of aqueous 1 *M* HCl in 0.5 ml of

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THF was stirred at 25° for 1.5 hr and then concentrated under reduced pressure, the residue was the alcohol **12a** identified with the previously described sample by comparison of ir spectra and tlc R_f values (silica gel coating).

A solution of 175 mg (0.51 mmol) of the acetoxy olefin **12b** in 6 ml of dioxane (distilled from $LiAlH_4$) and 1.7 ml of H_2O was treated with 1.2 ml of an aqueous solution containing 0.012 mmol of OsO_4. After the resulting black mixture had been stirred at 25° for 10 min, 234 mg (1.09 mmol) of powdered $NaIO_4$ was added during 10 min.[8] The resulting pale yellow solution was stirred at 25° for 17 hr and then partitioned between $CHCl_3$ and H_2O. The organic layer was dried and concentrated to leave 210 mg of yellow liquid, that was chromatographed on silica gel with an Et_2O–hexane eluent to separate 94 mg (53%) of colorless liquid fractions containing (tlc analysis) the keto acetate **13a**: ir ($CHCl_3$) 1760 (C=O in a five-membered ring) and 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 3.83 (1 H s, benzylic CH), 3.68 (3 H s, OCH_3), 3.4–3.7 (1 H m, benzylic CH), and 1.2–3.2 (14 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.27 and a CH_3CO singlet at 2.01); mass spectrum *m/e* (rel intensity) 342 (M^+, 100), 283 (21), 282 (34), 271 (65), 256 (66), 240 (28), 214 (22), 198 (20), 197 (29), 155 (31), 153 (71), 147 (23), 120 (21), and 105 (34); calcd for $C_{20}H_{22}O_5$ 342.146, found 342.14.

A solution of 401 mg (1.17 mmol) of the keto acetate **13a** and 2 ml of aqueous 3 *M* NaOH in 25 ml of MeOH was stirred at 25° for 2.5 hr and then partitioned between $CHCl_3$ and H_2O. The organic solution was dried and concentrated to leave 378 mg of liquid product with ir and nmr absorption indicating the presence of two isomeric ketols, presumably **13b** and **17**.[10]

A cold (0°) solution of 90 mg (0.26 mmol) of the keto acetate **13a** and 24 mg (0.63 mmol) of $NaBH_4$ in 3 ml of THF and 4.5 ml of MeOH was stirred for 1.5 hr and then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with H_2O, dried, and concentrated to leave 90 mg of colorless liquid believed to be the crude hydroxy acetate **14a**: ir ($CHCl_3$) 3490 (OH) and 1720 cm^{-1} (broad, ester C=O); nmr ($CDCl_3$) δ 6.8–7.4 (3 H m, aryl CH), 4.1–4.5 (1 H m, CHO), 3.3–3.8 (5 H m, two benzylic CH and a CH_3O singlet at δ 3.62), and 1.2–2.9 (*ca.* 15 H m, OH and aliphatic CH including an aryl CH_3 singlet at δ 2.23 and a CH_3CO singlet at 2.00). A mixture of 30 mg (0.087 mmol) of this crude hydroxy acetate **14a**, 1 ml of aqueous 3 *M* NaOH, and 1 ml of THF was stirred at 25° for 6 hr and then partitioned between $CHCl_3$ and aqueous 0.5 *M* HCl. The organic layer was washed with H_2O, dried, concentrated, and chromatographed on silica gel. The later fractions, eluted with Et_2O, amounted to 26 mg of a colorless liquid containing (tlc analysis) a compound believed to be the trans diol **14b**: ir ($CHCl_3$) 3590, 3450 (OH), and 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) 6.8–7.3 (3 H m, aryl CH), 4.22 (1 H d of d, J = 5 and 11 Hz, CHO), 3.3–3.8 (5 H m, two benzylic CH and a CH_3O singlet at δ 3.63), and 1.2–2.8 [*ca.* 13 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and OH (exchanged with D_2O)]; mass spectrum *m/e* (rel intensity) 302 (M^+, 2), 284 (100), 256 (50), 214 (45), 197 (51), 169 (37), 155 (46), 141 (33), 129 (30), 97 (30), 83 (31), 71 (30), 57 (37), 43 (36), and 41 (30). Reaction of this trans diol **14b** with excess Ac_2O in pyridine produced (tlc analysis) a new liquid product with ir and nmr spectra suggesting that it was the corresponding diacetate. Saponification of this material formed either the starting diol **14b** (ir and tlc analysis) or, under less vigorous conditions, a mixture (tlc analysis) corresponding in R_f values to the diacetate, the hydroxy acetate **14a**, and the trans diol **14b**.

A solution of 537 mg (1.56 mmol) of the crude hydroxy acetate **14a** and 1.2 ml of CH_3SO_2Cl in 12 ml of anhydrous pyridine was stirred at 25° for 4.5 hr and then partitioned between $CHCl_3$ and cold aqueous 2 *M* HCl. The organic layer was washed successively with aqueous 1 *M* HCl, aqueous $NaHCO_3$, and H_2O and then dried and concentrated to leave 688 mg of the crude mesylate **15**. A 95-mg portion of the crude product was chromatographed on silica gel with an Et_2O–hexane eluent to separate 82 mg of the mesylate **15** as a colorless liquid: ir ($CHCl_3$) 1730 (ester C=O), 1360, and 1180 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 5.30 (1 H d of d, J = 4 and 11 Hz, CHO), 3.3–3.8 (5 H m, two benzylic CH including a singlet at δ 3.71 and a CH_3O singlet at δ 3.65), 3.08 (3 H s, CH_3SO_2), and 1.2–2.9 (14 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and a CH_3CO singlet at 1.98); mass spectrum *m/e* (rel intensity), 326 (1), 266 (70), 224 (35), 197 (21), 155 (41), 141 (29), 84 (31), 83 (29), 79 (56), 55 (21), 43 (100), 42 (22), and 41 (28). A solution of 456 mg (1.08 mmol) of the crude mesylate **15** in 20 ml of collidine was refluxed for 6.5 hr and then partitioned between $CHCl_3$ and cold aqueous 2 *M* HCl. The organic layer was dried and concentrated and the residual yellow liquid (431 mg) was chromatographed on silica gel. The fractions eluted with Et_2O contained (tlc analysis) 326 mg (88%) of the hydroxy acetate **16a** as a colorless, viscous liquid that we could not induce to crystallize. Comparison of the tlc R_f values (silica gel coating), the ir spectra, and the nmr spectra of this sample **16a** and the crystalline racemic hydroxy acetate **5b** (mp 103–104°) indicated that the two samples had the same structure. A solution of 153 mg (0.45 mmol) of the hydroxy acetate **16a** and 1.0 ml of aqueous 10% NaOH in 4 ml of MeOH was stirred at 25° for 15 min and then partitioned between $CHCl_3$ and aqueous 1 *M* HCl. The organic layer was washed with H_2O, dried, and concentrated. The colorless liquid residue (156 mg) was chromatographed on silica gel and the fractions (121 mg or 91%) eluted with Et_2O contained (tlc analysis) the cis diol **16b** as a colorless liquid that again failed to crystallize. Comparison of the tlc R_f values (silica gel coating) and the ir, nmr, and mass spectra of the sample **16b** and the crystalline racemic cis diol **5a** (mp 111.5–112.5°) indicated that the two samples had the same structure.

A solution of 43 mg (0.13 mmol) of the hydroxy acetate **16a** and 0.50 ml of $(CH_3)_3SiCl$ in 1.0 ml of anhydrous pyridine was stirred at 25° for 7 hr and then concentrated under reduced pressure and partitioned between $CHCl_3$ and H_2O. The organic solution was dried, concentrated, and chromatographed on silica gel with an Et_2O–hexane eluent to separate 38 mg (73%) of the trimethylsilyl ether **18** as a colorless liquid: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 6.8–7.3 (3 H m, aryl CH), 4.8–5.2 (1 H m, CHO), 3.62 (4 H s, benzylic CH and CH_3O), 3.2–3.5 (1 H m, benzylic CH), 1.1–2.4 (14 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.25 and a CH_3CO singlet at 2.00), and 0.03 (9 H s, CH_3Si); mass spectrum *m/e* (rel intensity) 416 (M^+, 34), 330 (25), 329 (68), 297 (29), 283 (29), 271 (30), 270 (48), 269 (60), 268 (29), 267 (50), 266 (60), 227 (32), 226 (98), 117 (27), 75 (52), 73 (100), and 43 (63); calcd for $C_{23}H_{32}O_5Si$ 416.208, found 416.209. Attempts to saponify selectively the acetoxy function with NaOH in H_2O–THF resulted in conversion of this intermediate to the diol **16b** (tlc and ir analysis).

A cold (−60°) solution of 47 mg (0.16 mmol) of the diol **16b** and 0.2 ml of pyridine in 1 ml of CH_2Cl_2 was treated with 0.1 ml of *t*-BuOCl[7,18] and the resulting solution was stirred in the dark at −60° for 5 hr and then treated with 0.5 ml of aqueous 10% KI and 0.5 ml of aqueous 15% $Na_2S_2O_3$. After the resulting mixture had been partitioned between $CHCl_3$ and aqueous 1 *M* HCl, the organic layer was washed with H_2O, dried, concentrated, and chromatographed on silica gel. The fractions eluted with Et_2O–hexane (3:2, v/v) contained 33 mg (71%) of the crude keto aldehyde (one epimer of **8b**) as a colorless liquid that crystallized from Et_2O–hexane. Recrystallization from Et_2O–hexane separated 16 mg of the keto aldehyde (one epimer of **8b**) as white prisms: mp 97.5–98.5°; ir (CCl_4), 2820, 2720 (aldehyde CH), 1735 (ester C=O), and 1718 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 4.05 (1 H s, benzylic CH), 3.4–3.8 (4 H m, benzylic CH and CH_3O singlet at δ 3.65), 2.93 (2 H broad, CH_2CO), and 1.1–2.8 (9 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.31); mass spectrum *m/e* (rel intensity) 300 (M^+, 44), 256 (100), 214 (20), 169 (22), 155 (45), and 56 (22); calcd for $C_{18}H_{20}O_4$ 300.140, found 300.14.

Preparation of Racemic Epiallogibberic Acid (Racemic 3).—After considerable experimentation, the following procedure was found most satisfactory for the formation of tetrahydropyranyl ethers. A solution of 71 mg (0.21 mmol) of the hydroxy acetate **5b** and 416 mg (4.95 mmol) of dihydropyran in 4 ml of PhH was dehydrated by distilling the solvents until approximately 1.5 ml of solution remained. The resulting solution was cooled, treated with 2 mg (0.01 mmol) of *p*-TsOH, and then stirred at 25° for 2 hr. Pyridine (0.05 ml) was added to neutralize the TsOH and then the reaction mixture was partitioned between PhH and aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NaCl, treated with several drops of pyridine, and then concentrated under reduced pressure to leave 139 mg of the crude acetoxy ether **19a** as a yellow liquid: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) prominent singlets at δ 3.60 (CH_3O), 2.23 (aryl CH_3), and 2.02 (CH_3CO) attributable to the ether **19a**. A solution of the crude ester **19a** (139 mg) and 1 ml of aqueous 10% NaOH in MeOH was stirred at 25° for 1.5 hr

(18) M. J. Mintz and C. Walling, *Org. Syn.*, **49**, 9 (1969).

and then partitioned between $CHCl_3$ and H_2O. The organic solution was dried over Na_2CO_3 and concentrated to leave 126 mg of the crude hydroxy ether **19b** as a colorless liquid: ir (CCl_4) 3470 (OH) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) prominent singlets at δ 3.59 (CH_3O) and 2.23 (aryl CH_3) attributable to the ether **19b**. To a solution of the crude hydroxy ether **19b** (126 mg) in 2 ml of CH_2Cl_2 was added a solution of 704 mg (2.73 mmol) of CrO_3(pyridine)$_2$ in 7 ml of CH_2Cl_2. The resulting red-brown solution was stirred at 25° for 1 hr and then partitioned between Et_2O and aqueous 5% NaOH. The organic layer was washed with H_2O, dried over Na_2CO_3, and concentrated. Chromatography of the residual yellow liquid (101 mg) on silica gel with Et_2O–hexane (1:3, v/v) separated 52 mg (66% based on the hydroxy acetate **5b**) of early fractions containing (tlc and ir analysis) the keto ether **20** as a colorless liquid: ir (CCl_4) 1765 (C=O in a five-membered ring) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 6.8–7.3 (3 H m, aryl CH), 4.5–5.1 (1 H m, OCHO), 3.3–3.8 (*ca.* 7 H m, CH_2O, two benzylic CH with a singlet at δ 3.74, and a CH_3O singlet at 3.61), and 1.1–2.6 (*ca.* 17 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.26). Later fractions from the chromatography contained (tlc and ir analysis) a second component believed to be the isomeric hydroxy ether **22b**.

A 0.19 *M* solution of "salt-free" $Ph_3P{=}CH_2$ in benzene was prepared from $NaNH_2$ and $Ph_3PCH_3{}^+Br^-$ by the procedure of Schlosser and coworkers.[12] A solution of 52 mg (0.14 mmol) of the keto ether **20** in 0.5 ml of anhydrous PhH was treated with 0.86 ml of the PhH solution containing 0.16 mmol of $Ph_3P{=}CH_2$. After the resulting yellow solution had been refluxed for 6 hr, it was cooled, treated with 0.5 ml of aqueous 1 *M* HCl, and then partitioned between $CHCl_3$ and H_2O. The organic solution was dried and concentrated and a solution of the residual yellow oil (104 mg) in 1.0 ml of THF was treated with 0.5 ml of aqueous 1 *M* HCl and then stirred at 25° for 1 hr. The resulting mixture was again partitioned between $CHCl_3$ and H_2O and the organic layer was dried, concentrated, and chromatographed on silica gel. The early fractions, eluted with Et_2O–hexane (1:3 v/v), contained 29 mg (72%) of the hydroxy olefin **21** as a viscous, colorless liquid. This product was shown to have the same structure as the methyl (+)-epiallogibberate (**12a**) by comparison of ir (CCl_4), uv (95% EtOH), nmr ($CDCl_3$), and mass spectra and tlc R_f values (silica gel coating). The later fractions from the chromatograph, eluted with Et_2O, contained 32 mg (85%) of crystalline Ph_3PO, mp 154–156°.

A solution of 53 mg (0.18 mmol) of the hydroxy ester **21** and 1.0 ml of aqueous 4 *M* NaOH in 1.0 ml of MeOH was refluxed for 1 hr and then partitioned between $CHCl_3$ and aqueous 5% NaOH. The aqueous layer was acidified (HCl) to pH 1 and extracted with EtOAc. After the EtOAc extract had been washed with H_2O, dried, and concentrated, the white solid residue (53 mg) was recrystallized from MeOH–Et_2O to separate 40 mg (80%) of racemic epiallogibberic acid (**3**) as white prisms, mp 253–255° dec. Recrystallization from MeOH sharpened the decomposition point to 254–255.5° dec.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.18; H, 7.11.

This product was shown to have the same structure as a sample of (+)-epiallogibberic acid by comparison of mass spectra, nmr spectra [$(CD_3)_2NCDO$], uv spectra (95% EtOH), and ir spectra ($CHCl_3$ containing 5% Et_3N).

Registry No.—**1**, 77-06-5; (±)-**3**, 28862-60-4; (+)-**3**, 13613-87-1; **4a**, 37741-45-0; **4b**, 38223-11-9; **5a**, 38229-34-4; **5b**, 38229-35-5; **5c**, 38229-36-6; **8a**, 38229-37-7; **8b**, 38229-38-8; **12a**, 34707-34-1; **12b**, 38229-40-2; **12c**, 38229-41-3; **13a**, 38229-42-4; **14a**, 38229-43-5; **14b**, 38229-44-6; **15**, 38229-45-7; **16a**, 38229-46-8; **16b**, 38229-47-9; **18**, 38229-48-0; **19a**, 38229-49-1; **19b**, 38229-50-4; **20**, 38229-51-5; **21**, 38229-52-6.

Reactivities of Polystyrene and Polypropylene toward *tert*-Butoxy Radical

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Di-*tert*-butylperoxy oxalate was decomposed at 45° under vacuum in benzene solutions of polystyrene, polypropylene, and several aromatic and aliphatic hydrocarbons. The relative reactivities of the substrates and the carbon–hydrogen bonds were measured from the ratio of *tert*-butyl alcohol and acetone formed. Both polymers were found to be less reactive than the corresponding simple model hydrocarbons: polypropylene was about one-half as reactive as calculated from 2,4-dimethylpentane and 2,2,4-trimethylpentane, and polystyrene was about one-fifth as reactive as polypropylene.

The autoxidation of polyolefins must proceed by a radical chain mechanism[1] similar to simple hydrocarbons, where hydrogen atom abstractions from the substrate by the peroxy and alkoxy radicals are among the important rate-determining steps.[2]

$$RH + ROO\cdot \longrightarrow R\cdot + ROOH$$

$$RH + RO\cdot \longrightarrow R\cdot + ROH$$

The reactivities of various hydrocarbons toward peroxy[3,4] and alkoxy[5] radicals have been determined by several investigators. Especially, those for *tert*-butoxy radical have been most extensively studied partly because the *tert*-butoxy radical can be produced rather easily from di-*tert*-butyl peroxide,[6] *tert*-butyl hypohalite,[5] di-*tert*-butylperoxy oxalate (DBPO),[7] and *tert*-butyl hyponitrite.[8]

To our knowledge, however, the reactivities of polyolefins toward the radicals have not yet been obtained. In the course of our study on the autoxidations of polyolefins, we measured the reactivities of the polymers toward oxy radicals. The objective of this work is to determine the relative reactivities of polystyrene and polypropylene toward *tert*-butoxy radical and to compare them with the simple, corresponding model hydrocarbons.

Experimental Section

Materials.—Polypropylene, kindly supplied by Mitsui Petrochemical Industries, was first soaked in benzene at room tem-

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