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Stereochemical Control of Reductions. The Directive Effect of Carbomethoxy *vs.* Hydroxymethyl Groups in Catalytic Hydrogenation

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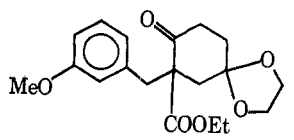
A series of 9a-substituted hexa- and tetrahydrofluorenes has been synthesized from 9a-carbethoxy-7-methoxy-2,2-ethylenedioxy-1,2,3,9a-tetrahydrofluorene (**4**). Catalytic hydrogenation of the carbomethoxy compound **12** gives a cis/trans product ratio of 15:85, while the 9a-hydroxymethyl compound **5** gives a ratio of 95:5. This disparity is discussed in terms of attractive (haptophilic) *vs.* repulsive (steric) interactions between the catalyst surface and the 9a angular group. The stereochemistry of the products is demonstrated by means of intramolecular interactions in the 9a-hydroxymethylhexahydrofluoren-2-ones.

An interest in syntheses leading toward gibberellic acid (**3**)[1] has involved us in the construction and chemistry of model compounds of the type **2**.[2,3] These compounds are readily available by a route involving condensation of *m*-methoxybenzyl chloride[4] with the anion of 2-carbethoxy-4,4-ethylenedioxycyclohexanone.[5] This condensation and the subsequent polyphosphoric acid[6] cyclization of **1** (and reketalization) led to **2** (R = COOEt) in an overall yield of about 33%.



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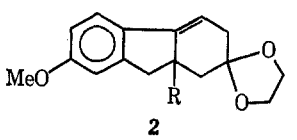

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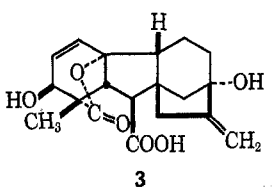


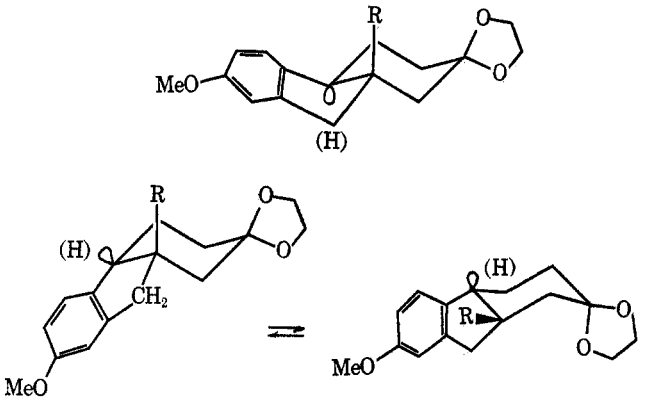
3

Since the B–C ring juncture in gibberellic acid is cis, we wished to introduce this stereochemistry into **2** by reduction of its styrene bond. Of the several routes available, the metal–ammonia reduction of **2** is perhaps the most straightforward in terms of the predictability of its stereochemical outcome. Such a reduction is expected to yield products representing protonation of an equilibrium mixture of the conformers of the anionic reduction intermediate,[7] here, the benzylic anion derived from **2**. The cis and trans forms of this should provide equally good ring overlap with the benzylic anion. However, the cis juncture is known to be more stable in hexahydrofluorenes,[8] and angular substituents apparently increase the relative stability of the cis isomers[9] and may be expected particularly to do so in this case (Scheme I). Hence, if rates of protonation are comparable this equilibrium mixture is expected to yield largely or entirely cis products.

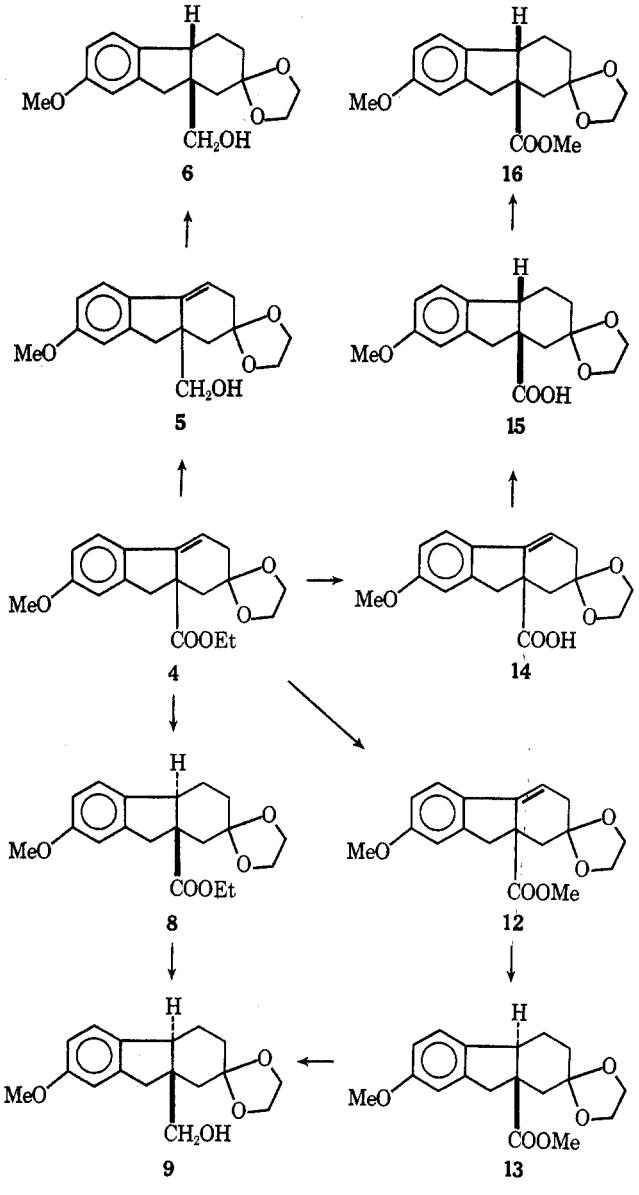
Since at least partial reduction of the ester function by the metal–ammonia system was anticipated, **4** was prereduced with $LiAlH_4$ to give the hydroxymethyl compound (**5**), and this was treated with lithium in liquid ammonia[10] to give what was apparently a single isomer (**6**) of the reduced hydroxymethyl compound.[3] Because the product was liquid, however, we could not be as confident as we wished to be of its stereochemical purity and we decided to convert it into a solid derivative and to synthesize the trans isomer as well for comparison. The latter was easily accomplished, since on catalytic hydrogenation of the original ester (**4**) a single material crystallized from the reaction mixture in high yield, and this reduced ester (**8**), when treated with

(1) R. F. Gould, *Advan. Chem. Ser.*, **28**, 1 (1961).
(2) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, **87**, 1148 (1965).
(3) H. W. Thompson, *J. Org. Chem.*, **32**, 3712 (1967).
(4) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 684 (1942).
(5) (a) S. Rajagopalan and P. V. A. Raman, "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 425; (b) W. S. Emerson and R. I. Longley, Jr., *ibid.*, Collect. Vol. IV, 1963, p 302; (c) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Amer. Chem. Soc.*, **74**, 1401 (1952); (d) P. D. Gardner, L. Rand, and G. R. Haynes, *ibid.*, **78**, 3425 (1956); (e) P. D. Gardner, G. R. Haynes, and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957).
(6) (a) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958); (b) F. Uhlig and H. R. Snyder in "Advances in Organic Chemistry: Methods and Results," Vol. 1, Interscience, New York, N. Y., 1960, pp 35–81.
(7) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).
(8) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *ibid.*, **82**, 1457 (1960).
(9) (a) W. E. Parham and L. J. Czuba, *J. Org. Chem.*, **34**, 1899 (1969); (b) N. L. Allinger, R. B. Hermann, and C. Djerassi, *ibid.*, **25**, 922 (1960); (c) N. L. Allinger and S. Greenberg, *ibid.*, **25**, 1399 (1960).
(10) *Cf.* L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Velarde, and J. A. Edwards, *ibid.*, **30**, 2198 (1965).

SCHEME I



SCHEME II



$LiAlH_4$, provided a crystalline hydroxymethyl compound (**9**) clearly not identical with **6** (Scheme II).

For the solid derivative of **6**, mild acidic hydrolysis in aqueous methanol converted the cis hydroxymethyl ketal entirely to the corresponding crystalline keto alcohol (**7**). However, when the trans isomer was subjected to identical conditions, an elegant confirmation of its stereochemistry was provided by the isolation, in addition to trans hydroxymethyl ketone (**11**), of major quantities of the methyl ketolide **10**. Either **9** or **10** could be converted in high yield to **11** by replacing methanol with THF during the hydrolysis (Scheme III). The fixing of the 9a-hydroxymethyl group in the axial position, which is responsible for formation of **10**, was further confirmed by comparison of the infrared spectra of **7** and **11**. While the carbonyl stretching band of **7** is of normal intensity, that of **11** is severely diminished in CCl_4 solution, indicating not only that **11** exists principally in the hemiketal form (**11b**),[11] but that **7** does not, presumably because its 9a-hydroxymethyl group is mostly or entirely equatorial[2] (*cf.* Scheme I). The KBr spectrum of **11**, however, displays normal carbonyl absorption, indicating that the crystalline material consists entirely of the keto alcohol (**11a**).

With the stereochemistry of both the lithium–ammonia reduction of **5** and the catalytic hydrogenation of **4** firmly established, we were interested to discover that when the sequence catalytic hydrogenation–hydride reduction (**4** → **8** → **9**) was performed on the unsaturated ester **4** in reverse order, the result was a reversal of stereochemistry (**4** → **5** → **6**), the cis ketal alcohol being produced in high yield and purity. Such a result was not entirely unanticipated, a number of cases being known in which a hydroxyl group near a reducible double bond has apparently been responsible for the addition of hydrogen to the olefin cis in relation to the hydroxyl function.[12–19] This outcome contrasts with the more well-known case, presumably applicable to the hydrogenation of **4**, in which the bulk of the neighboring function is the controlling factor and imposes trans stereochemistry by sterically blocking cis approach to the catalyst surface.[20–22]

The present case implies an actual preference for absorption of the compound on the catalyst surface from the same side as the hydroxyl group and suggests that some attraction of this group to the catalyst surface overcomes whatever difficulty to approach its sheer size might otherwise impose. That such affinities should exist and should vary with the nature of the group involved is not surprising, since certain functionalities, notably amines, phosphines, and groups containing divalent sulfur, are known to become so strongly bound to some catalyst surfaces that they constitute poisons.[23,24] This haptophilicity is thought to be associated with the group's ability to donate unshared electron pairs to unfilled surface orbitals of the catalyst metal. From this point of view the hydroxyl function

(11) C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc. C*, 1893 (1970).

(12) L. S. Minckler, A. S. Hussey, and R. H. Baker, *J. Amer. Chem. Soc.*, **78**, 1009 (1956); W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961), and references cited therein.

(13) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(14) T. G. Halsall, W. J. Rodewald, and D. Willis, *ibid.*, 2798 (1959).

(15) N. B. Haynes and C. J. Timmons, *Proc. Chem. Soc.*, 345 (1958).

(16) T. J. Howard, *Chem. Ind. (London)*, 1899 (1963); T. J. Howard, *Recl. Trav. Chim. Pays-Bas*, **83**, 992 (1964).

(17) S. Nishimura and K. Mori, *Bull. Chem. Soc. Jap.*, **36**, 318 (1963).

(18) S. Mitsui, Y. Senda, and H. Saito, *ibid.*, **39**, 694 (1966).

(19) J. E. McMurry, *Tetrahedron Lett.*, 3731 (1970).

(20) R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957).

(21) S. Siegel, *Advan. Catal. Relat. Subj.*, **16**, 123 (1966).

(22) W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. C*, 41 (1966).

(23) G. C. Bond, "Catalysis by Metals," Academic Press, New York, N. Y., 1962, pp 99–100.

(24) E. B. Maxted, *Advan. Catal. Relat. Subj.*, **3**, 129 (1951).

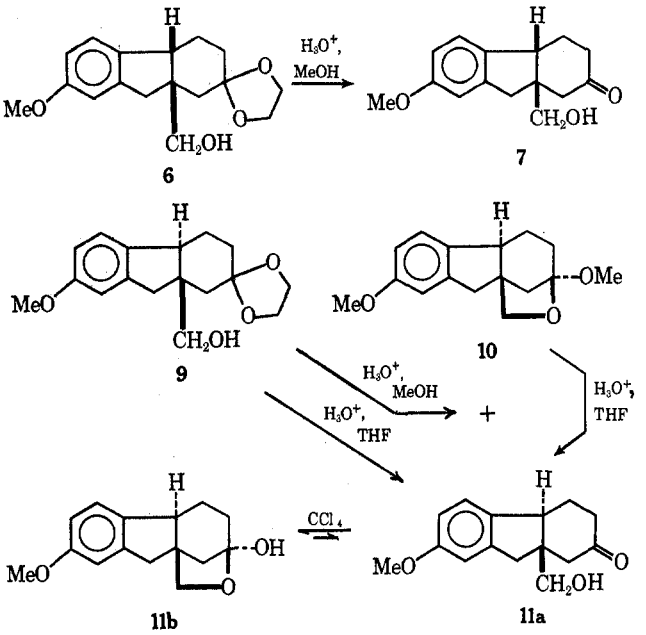
may simply be one whose poisoning action is relatively weak, *i.e.*, reversible; hence it is particularly interesting that the hydrogenations in which we have observed these effects were carried out using alcohols as solvents.[25]

As we became interested in this effect of neighboring functional groups on the stereochemistry of catalytic hydrogenation, we wished to extend our study to include reduction of other compounds in the series represented by **2**. We therefore decided to adapt our procedure to allow the assessment of hydrogenation stereochemistry with as much accuracy and precision as possible for a wide variety of functional groups. (1) All hydrogenations would employ 5% palladium-on-carbon catalyst from the same lot, to avoid batch-to-batch inconsistencies. (2) The ethanol used as solvent in the hydrogenations already described would be replaced by 2-methoxyethanol, whose ability to dissolve polar compounds is considerably greater. (3) Reactions would be run under identical conditions of time, temperature, concentration, etc. (4) Reaction products, freed from catalyst and solvent, would be distilled or sublimed and the entire volatile product assessed by nmr and/or vpc. (5) Control hydrogenations would be carried out on the minority product of each reaction to establish that the preponderance of the majority product was the result of kinetic rather than simply thermodynamic control.

In order to repeat the hydrogenations of **5** and **4** according to the above procedures, we required samples of the trans alcohol and the cis ester for control reductions to establish the absence of product equilibrations. The former was already in hand (**9**); a route to the latter seemed offered by the successful metal–ammonia reduction of the saponification product **14** of the unsaturated ester **4**. This ester itself, as we had anticipated, gave little or no saturated ester, even on careful reduction with insufficiencies of metal in various metal–ammonia systems (the major identifiable products were usually the cis alcohol **6** and the cis aldehyde[3]). The carboxylic acid function, however, in the form of its salt, is known to be almost entirely inert to the conditions of metal–ammonia reductions,[26] and the principles previously cited in predicting stereochemistry in the metal–ammonia reduction of **5** led also to cis stereochemistry[27] in reduction of the unsaturated acid, with, however, no loss of the carboxylic acid function.

Although the esterification of this acid might be accomplished in a number of ways, the hindrance about the acid function and the sensitivity of the ketal made the simplicity, neutrality, and mildness of diazomethane treatment particularly attractive. In addition to this reason for dealing with a carbomethoxy group at R instead of a carbethoxy group, and the advantage of the generally greater crystallinity of methyl esters, the lower bulk of a methyl ester would more closely approximate the size of the hydroxymethyl group we were comparing it with in the catalytic hydrogenation.[28,29] Consequently the cis methyl ester **16** was prepared by diazomethane treatment of the acid **15**, and the unsaturated methyl ester **12** was prepared by (basic) transesterification of **4**.

SCHEME III



Catalytic hydrogenation of the unsaturated methyl ester **12** under the chosen conditions[30] provided a mixture containing 85% trans product **13** and 15% cis material **16**. By contrast, repetition of the hydrogenation of **5** under identical conditions gave 95% cis and 5% trans ketal alcohols. Control hydrogenations of **9** and **16** demonstrated that no detectable equilibration of the products was taking place under our reaction conditions. In addition, our ratio of catalyst to olefin and the large percentage of trans ester **13** produced make it very unlikely that appreciable equilibration can be taking place through the half-hydrogenated state.[31,32]

We believe that these results provide evidence clearly favoring a kinetic stereochemical control effect arising from attractive substrate–catalyst interactions in the hydrogenation of system **2**. This haptophilic effect, which has been observed previously in a number of instances[12-19] but never systematically studied for a wide variety of functional groups, is here documented for a case in which the steric bulks of the groups being compared are reasonably similar,[28,29] and in a system which may readily be extended to include other functional groups of varying bulk, polarity, basicity, etc. We are continuing to examine various aspects of the catalytic hydrogenation of **2** and closely related systems.

Experimental Section[33]

2-Carbethoxy-4,4-ethylenedioxycyclohexanone.—A slurry was prepared of 1.16 mol of NaH (50 g of 56% oil dispersion, washed with hexane) in 230 ml of dry DME under N_2, and to this was

(25) For some recent discussions, with leading references, to the role of solvent in determining stereochemistry, see ref 22 and S. Nishimura, M. Shimahara, and M. Shiota, *J. Org. Chem.*, **31**, 2394 (1966).

(26) M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959).

(27) The trans acid has been prepared and characterized, and will be described in another communication.

(28) O. R. Quayle, *Chem. Rev.*, **53**, 439 (1953).

(29) K. Fajans in "The Technique of Organic Chemistry," Vol. I, part 2, A. Weissberger, Ed., Interscience, New York, N. Y., 1960, pp 1169–1211.

(30) *I.e.*, 33 mg of 5% Pd/C and 16 ml of solvent per 1 mmol of olefin.

(31) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *J. Amer. Chem. Soc.*, **84**, 2614 (1962).

(32) J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961).

(33) Melting points were determined with a Kofler micro hot-stage microscope or a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken using a Beckman IR-10 or a Perkin–Elmer Model 421 spectrometer and, unless otherwise specified, in CCl_4 as solvent. Ultraviolet spectra were determined in 95% EtOH solution with a Cary Model 14 spectro-

(*continued on p 2580*)

added 3.0 ml of absolute EtOH and then, with stirring over a 3-hr period, 158 g (0.58 mol) of diethyl 4,4-ethylenedioxypimelate[5a,b] in 230 ml of DME. After standing for 48 hr, the thick yellow mixture was diluted with 150 ml of benzene, neutralized with aqueous acetic acid, worked up in the usual manner, and distilled to give three colorless fractions boiling between 95 and 112° (*ca.* 0.5 mm), which had identical nmr spectra and were combined: 113 g (86%), n^{18}D 1.4937 [lit.[5d] bp 114° (0.5 mm), n^{25}D 1.4846].

2-Carbethoxy-3-(*m*-methoxybenzyl)-4,4-ethylenedioxycyclohexanone (1).—A slurry was prepared of 55.0 mmol of NaH (2.475 g of 53.5% oil dispersion, washed with hexane) in 60 ml of dry 1:1 DME–DMF. A solution of 12.00 g (52.5 mmol) of keto ester in 60 ml of the same solvent mixture was added under N_2 to the stirred slurry over 45 min. After an additional hour of stirring, a solution of 8.406 g (53.3 mmol) of *m*-methoxybenzyl chloride[4] in 50 ml of the same solvent was added at room temperature and the temperature was then raised to the reflux point. At about 75–80° a precipitate began appearing in the clear greenish brown solution. The mixture was heated with stirring at *ca.* 100° for 3.5 hr and then stirred for another 15 hr at room temperature. The usual work-up by neutralization, extraction, and concentration yielded 1 as a yellow oil, giving a weak $FeCl_3$ test, which was used without purification in the following cyclization: ir 940 (ketal), 1720, 1740 cm^{-1}; nmr δ 1.1 (3 H, t, J = 7 Hz), 1.4–3.1 (8 H, complex), 3.7 (3 H, s), 3.9 (4 H, s), 4.0 (2 H, q, J = 7 Hz), 6.6–7.3 (4 H, complex).

9a-Carbethoxy-7-methoxy-2,2-ethylenedioxy-1,2,3,9a-tetrahydrofluorene (4).—The entire product from the above condensation was mixed thoroughly with 180 g of polyphosphoric acid (76% total P_2O_5 content) and allowed to stand at room temperature for 2 hr. The usual ice–water work-up and extraction provided on concentration an orange oil which had C=O absorption at 1720–1740 cm^{-1} only, and which oxidized readily in air. It was therefore immediately reketalized by refluxing under N_2 in 200 ml of benzene with 6.0 ml (108.5 mmol) of ethylene glycol and 200 mg of *p*-toluenesulfonic acid for 19 hr with continuous separation of water. The usual work-up provided a brownish oil, which solidified and on trituration with ether gave 5.8 g (33.5%) of crude yellow 4. Recrystallization from hexane yielded 5.25 g, which was further purified to give colorless, flat needles: mp 116–117°; ir 940, 1720 cm^{-1}; uv 210 nm (ϵ 21,400), 260 (20,000), 300 (5320); nmr δ 1.1 (3 H, t, J = 7 Hz), 1.8 (1 H, d, J = 13 Hz), 2.8 (1 H, d, J = 13 Hz), 2.5–3.5 (4 H, complex), 3.8 (3 H, s), 4.0 (4 H, m), 4.05 (2 H, q, J = 7 Hz), 5.9 (1 H, t, J = 4 Hz), 6.7–6.9 (2 H, m), 7.4 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.98; H, 6.60.

Lithium Aluminum Hydride Reduction of 4.—A slurry was prepared of 200 mg (5.0 mmol) of $LiAlH_4$ in 40 ml of dry ether. To this stirred mixture was added under N_2 over 1 hr a solution of 660 mg (2.0 mmol) of 4 in 10 ml of dry THF and 40 ml of ether. The resulting mixture was refluxed for 4 hr, allowed to stand overnight, and worked up by titration with saturated aqueous Na_2SO_4 and decantation from the precipitate. The solid resulting from concentration was recrystallized from MeOH–water to give 444 mg (77%) of white needles, mp 120–124°, and an additional 34 mg (6%) of crystalline material was recovered from the liquors. Pure 5 melted at 121–124°: ir 930, 945, 3500, 3620 cm^{-1}; uv 205 nm (ϵ 20,000), 260 (20,000), 300 (5460); nmr δ 1.9 (1 H, d, J = 13.5 Hz), 2.35 (1 H, d, J = 13.5 Hz), 2.4–4.1 (7 H complex), 3.8 (3 H, s), 4.05 (4 H, m), 5.85 (1 H, t, J = 4 Hz), 6.6–6.9 (2 H, m), 7.35 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.98; H, 6.99.

Reduction of 5 with Lithium in Ammonia.—A solution of 910 mg (3.16 mmol) of 5 in 20 ml of dry 1:1 THF–ether was added over 12 min to a stirred solution of 60 mg (8.6 mg-atoms) of Li in 50 ml of liquid NH_3. A few minutes later *ca.* 10 mg more of Li was added to the faded solution, and after 30 min the blue solution was treated with excess solid NH_4Cl and allowed to evaporate. Concentration of the ether-soluble portion gave 970 mg of crude yellow oil 6, showing a single spot on tlc with MeCN–benzene or EtOAc. Material from a similar reaction was purified by chromatography on Al_2O_3 and distilled at 150–160° (0.02 mm) to give a colorless oil: n^{26}D 1.5611; ir 930, 945, 3480, 3550 cm^{-1}; uv 219 nm (ϵ 7190), 227 (6860), 281.5 (2700), 288.5 (2360); nmr δ 1.3–3.3 (12 H, complex), 3.8 (3 H, s), 3.95 (4 H, m), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C 70.24; H, 7.62.

Catalytic Hydrogenation of 5.—A solution of 470 mg (1.63 mmol) of 5 in 20 ml of absolute EtOH containing 40 mg of 5% Pd/C catalyst was hydrogenated with stirring at room temperature and atmospheric pressure. After 1 hr 32 ml of H_2 had been absorbed and the mixture was allowed to stir with H_2 overnight. The filtered solution was concentrated and distilled at *ca.* 175° (0.01 mm), yielding 325 mg (69%) of liquid 6.

Acidic Ketal Hydrolysis of 6.—After 100.5 mg of 5 had been hydrogenated in 5.0 ml of absolute EtOH over 10.3 mg of 10% Pd/C, the isolated product was stirred for 1 hr at room temperature with 15 ml of MeOH, 1.5 ml of water, and 1.5 ml of hydrochloric acid. Neutralization, extraction, and concentration gave crystalline material which was chromatographed on Al_2O_3. Combination of appropriate fractions and recrystallization from ether–hexane gave 66.3 mg (77% overall) of 7 as white needles, mp 82–86°; the mixture melting point with 7 obtained from the Li–NH_3 reduction product of 5 was undepressed. The analytical sample melted at 83.5–85°: ir 1715, 3450, 3650, cm^{-1}; uv 220 nm (ϵ 8100), 282 (2990), 288 (2670); nmr δ 2.0–3.7 (12 H, complex), 3.8 (3 H, s), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.06; H, 7.64.

Catalytic Hydrogenation of 4.—A solution of 268.4 mg (0.814 mmol) of 4 in 13.5 ml of absolute EtOH containing 26 mg of 10% Pd–C catalyst was hydrogenated with stirring at room temperature and atmospheric pressure. After 20 min, uptake of H_2 had stopped (20.1 ml). The filtered solution was concentrated and the resulting solid was recrystallized from hexane to give 223 mg (83.5%) of white crystals (8): mp 88–89°; ir 950, 1715, 1740 cm^{-1}; uv 227 nm (ϵ 7440), 284 (2790), 290 s (2410); nmr δ 1.1 (3 H, t, J = 7 Hz), 1.6–3.2 (9 H, complex), 3.8 (3 H, s), 3.9 (4, H, m), 3.95 (2 H, q, J = 7 Hz), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found: C, 68.60; H, 7.21.

Lithium Aluminum Hydride Reduction of 8.—A solution of 172.3 mg (0.52 mmol) of 8 in 5 ml of 1:1 THF–ether was added over 15 min to a stirred suspension of 100 mg (2.5 mmol) of $LiAlH_4$ in 15 ml of ether under N_2. The mixture was then refluxed for 4 hr and worked up as described for reduction of 4, giving a solid which was recrystallized from ether–pentane to yield 101.5 mg (67.5%) of 9 as prismatic platelets: mp 89–91°; ir 915, 940, 3480, 3640 cm^{-1}; uv 228 nm (ϵ 7600), 282 (2760), 288 s (2350); nmr δ 1.5–4.1 (12 H, complex), 3.8 (3 H, s), 4.0 (4, H, m), 6.5–7.1 (3 H, m).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.71.

Acidic Ketal Hydrolysis of 9.—A solution of 187 mg (0.645 mmol) of 9 in 16.5 ml of MeOH and 1.5 ml of hydrochloric acid was stirred at room temperture for 1 hr, neutralized, and extracted with ether. The concentrated extracts were chromatographed on 10 g of basic Al_2O_3 (deactivated with 5% water). Elution with 10–25% ether in hexane gave 145.5 mg (87%) of 10, recrystallized from hexane to provide 113 mg of needles: mp 77–78.5°; ir no absorption in the OH or C=O regions; uv 227 nm (ϵ 8600), 282 (2900), 288 (2560); nmr δ 1.3–3.9 (11 H, complex), 3.3 (3 H, s), 3.7 (3 H, s), 6.65–7.15 (3 H, complex).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.06; H, 7.88.

Continued elution of the chromatograph with MeOH gave 16 mg (6.5%) of 11. Sulimation at *ca.* 135° (0.02 mm) and recrystallization from benzene–hexane gave small needle clusters: mp 154.5–156°; ir (CCl_4) 1700 (w), 3370 (br), 3600 (sh) cm^{-1}; ir (KBr) 1690 (strong), 3390 (br) cm^{-1}; uv 227 nm (ϵ 7800), 281 (2770), 288 (2420); nmr (CH_2Cl_2) δ 1.6–3.7 (12 H, complex), 3.8 (3 H, s), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.48.

Another hydrolysis performed on the $LiAlH_4$ reduction product from 111 mg (0.334 mmol) of 8 was carried out for 70 min with 10 ml of MeOH, 1 ml of water, and 1 ml of hydrochloric acid, and on chromatography gave 68.5 mg (79%) of 10 and 13.5 mg (5.5%) of 11.

photometer; nmr spectra were taken with a Varian A-60 spectrometer (CH_2Cl_2 and/or TMS internal standard) and, unless otherwise specified, using CCl_4 or $CDCl_3$ as solvent. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. The abbreviations DME, DMF, and THF refer to dimethoxyethane, dimethylformamide, and tetrahydrofuran.

Acidic Ketal Hydrolysis of 10.—A solution of 64.5 mg of **10** in 6 ml of THF, 5 ml of water, and 1 ml of hydrochloric acid was stirred at room temperature for 1.5 hr, neutralized, saturated with NaCl, and extracted. Concentration gave solid which was recrystallized from benzene–hexane, yielding 48.5 mg (79.5%) of **11**, further purified to a melting point of 156–158°. Direct hydrolysis of **9** in the same medium provided only **11**.

Saponification of 4.—A solution of 1.00 g (3.03 mmol) of **4** and 2.03 g of KOH in 80 ml of 1:1 EtOH–water was refluxed under N_2 for 21 hr and worked up by addition of saturated aqueous oxalic acid. Concentration of the ether–CH_2Cl_2 extracts gave 907 mg (99%) of crude yellow solid and recrystallization from absolute EtOH gave 600 mg (65.5%) of prismatic crystals. The analytically pure **14** actually melts at *ca.* 185° when introduced into an already heated apparatus, but usually begins decarboxylating (β,γ-unsaturated acid) and melting at *ca.* 160° under slower heating: ir ($CHCl_3$) 930 1700, 2300–3600 cm^{-1}; uv 209.5 (ϵ 20,500), 259 (19,700), 300 (5270); nmr δ 1.8 (1 H, d, J = 13 Hz), 2.8 (1 H, d, J = 13 Hz), 2.5–3.5 (4 H, complex), 3.8 (3 H, s), 3.95 (4 H, m), 5.95 (1 H, t, J = 3.5 Hz), 6.7–7.0 (2 H, m), 7.4 (1 H, d, J = 9 Hz), 9.0 (1 H, very broad).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C 67.61; H, 6.10.

Reduction of 14 with Lithium in Ammonia.—A solution of 100 mg (0.331 mmol) of **14** in 5.0 ml of THF (freshly distilled from $LiAlH_4$) was added over 30 sec to a stirred solution of 35 mg (5 mg-atoms) of Li in *ca.* 15 ml of liquid NH_3. After 15 min of stirring the blue solution was decolorized with solid NH_4Cl and, allowed to evaporate. Water and ether were added and then aqueous oxalic acid to *ca.* pH 3. Concentration of the organic extracts yielded 105 mg of crude solid, which was sublimed at 155° (0.01 mm) and recrystallized from ether–pentane to give 94 mg (93.5%) of **15** as minute prisms: mp 155.5–157°; ir ($CHCl_3$) 930, 1700, 2300–3600 cm^{-1}; uv 219 nm (ϵ 6930), 227 (7170), 282 (2770), 288.5 (2430); nmr δ 1.3–3.5 (9 H, complex), 3.8 (3 H, s), 3.95 (4 H, s), 6.7–7.3 (3 H, complex), 11.15 (1 H, s, broad).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.10; H, 6.63.

Esterification of 15 with Diazomethane.—A solution of 217 mg (0.715 mmol) of **15** in 25 ml of dry ether was treated with ethereal CH_2N_2 until a definite yellow color persisted. The solution was boiled briefly to remove excess CH_2N_2 and cleared of polymer by passage through a short column of Al_2O_3. The resulting material was chromatographed on 11 g of Al_2O_3 (deactivated with 5% water) and eluted with 20–40% ether in hexane. Recrystallization from pentane gave 182 mg (80%) of **16** as flat plates. Further recrystallization produced material melting at 88.5–89.5°: ir 930, 1735 cm^{-1}; uv 219 nm (ϵ 6920), 228 (7230), 282 (2770), 288.5 (2450); nmr δ 1.2–3.3 (9 H, complex), 3.8 (6 H, 2 s), 3.9 (4 H, s), 6.7–7.2 (3 H, complex).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.13; H, 6.99.

Transesterification of 4 with Sodium Methoxide.—A solution of 991 mg (3.00 mmol) of **4** in methanolic NaOMe prepared from 50 ml of MeOH and 1.01 g (44.0 mmol) of Na was refluxed under N_2 for 21 hr and worked up by addition of aqueous oxalic acid. Concentration of the ether–CH_2Cl_2 extracts gave 889 mg (94%) of crude **12**. Recrystallization from hexane gave 820 mg, which was sublimed at 133° (0.01 mm) and recrystallized further to provide needles: mp 134–135°; ir 940, 1725 cm^{-1}; uv 209 nm (ϵ 22,600), 259 (20,400), 299.5 (5350); nmr δ 1.8 (1 H, d, J = 13 Hz), 2.8 (1 H, d, J = 13 Hz), 2.5–3.5 (4 H, complex), 3.6 (3 H, s), 3.8 (3 H, s), 4.0 (4 H, m), 5.9 (1 H, t, J = 4 Hz), 6.7–6.9 (2 H, m), 7.4 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.52; H, 6.40.

Catalytic Hydrogenation of 12.—A solution of 500 mg (1.58 mmol) of **12** in 25 ml of absolute EtOH containing 50 mg of 5% Pd/C catalyst was hydrogenated with stirring at room temperature and atmospheric pressure. The reaction was complete in 45–50 min (48 ml H_2) and was stopped at 60 min. The filtered solution was concentrated, sublimed at 135–140° (0.02 mm), and recrystallized from ether–pentane to give 440 mg (87.5%) of **13** in two crops Further recrystallization from ether gave diamond-shaped platelets: mp 143.5–145°; ir 940, 950, 1720, 1745 cm^{-1}; uv 219 nm (ϵ 7050), 227.5 (7250), 283.5 (2820), 290 (2450); nmr δ 1.6–3.3 (9 H, complex), 3.55 (3 H, s), 3.8 (3 H, s), 3.95 (4 H, m), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.04; H, 6.88.

Reduction of **13** with $LiAlH_4$ produced material, mp 85–86°, identical with previously described **9**.

Assessment of Cis/Trans Ratio in Hydrogenation of 5.—A solution of 100 mg (0.348 mmol) of **5** in 5.50 ml of solvent[30,34] was hydrogenated with rapid stirring over 11.5 mg of catalyst[30,35] at 25° and atmospheric pressure in a low-pressure hydrogenation apparatus and stopped after 60 min, although it was apparently complete after 20 min (9.1 ml H_2). The filtered mixture was concentrated and distilled in a microsublimation apparatus at 140° (0.01 mm) to give 101 mg (100%) of viscous, colorless liquid. Analysis by vpc[36] of the trimethylsilylated[37] mixture indicated 95 ± 2% cis and 5 ± 2% trans alcohols.

Control Hydrogenation of Trans Alcohol 9.—A solution of 50 mg (0.174 mmol) of **9** in 2.75 ml of solvent[30,34] was hydrogenated with rapid stirring over 5.7 mg of catalyst,[30,35] stopped after 73 min, and isolated as described above to give 50 mg (100%) of crystalline material washed directly from the sublimator cold-finger with $CDCl_3$ and concentrated to give a solution whose nmr spectrum was identical with that of pure **9**.

Assessment of Cis/Trans Ratio in Hydrogenation of 12.—A solution of 100 mg (0.316 mmol) of **12** in 5.0 ml of solvent[30,34] was hydrogenated with rapid stirring over 10.5 mg of catalyst[30,35] at 25° and atmospheric pressure in a low-pressure hydrogenation apparatus and stopped after 60 min, although it was apparently completely reacted after *ca.* 45 min (10.5 ml H_2). The mixture was isolated and purified as described to give 99.5 mg (99%) of colorless, crystalline sublimate. Analysis of the mixture by vpc[36] indicated 85 ± 1% trans and 15 ± 1% cis esters.

Control Hydrogenation of Cis Methyl Ester 16.—A solution of 50 mg (0.158 mmol) of **16** in 2.50 ml of solvent[30,34] was hydrogenated with rapid stirring over 5.2 mg of catalyst,[30,35] stopped after 60 min, and isolated as described to give 49 mg (98%) of material, collected and analyzed as described, whose nmr spectrum was identical with that of pure **16**.

Registry No.—**1**, 30541-60-7; **4**, 30541-61-8; **5**, 30541-62-9; **6**, 30541-63-0; **7**, 30541-64-1; **8**, 30541-65-2; **9**, 30541-66-3; **10**, 30541-67-4; **11**, 30541-68-5; **11b**, 30546-06-6; **12**, 30541-69-6; **13**, 30541-70-9; **14**, 30541-71-0; **15**, 30541-72-1; **16**, 30541-73-2.

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(34) Matheson Coleman and Bell chromatoquality (99.9 mol % pure) 2-methoxyethanol.

(35) 5% palladium–carbon catalyst (Lot No. 11-333) obtained from Engelhard Industries, Inc., Newark, N. J.

(36) We thank R. E. Naipawer for this analysis, which was carried out at 60 psi on a 0.125 in. × 8 ft column packed with 3% OV-1 (dimethylsilicone, obtained from Applied Science Laboratories, Inc., State College, Pa.) on Gas-Chrom Q and programmed from 100 to 250°.

(37) Treated at room temperature with Silyl-8 obtained from Pierce Chemical Co., Rockford, Ill.