Stereochemical Control in the Acylation of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose. A Route to 1-*O*-Acyl-α- and -β-D-glucopyranoses

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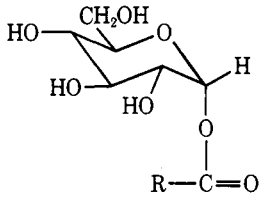
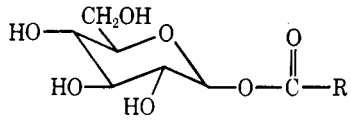
Received March 1, 1976

A recent report[2] has implicated several D-glucosyl fatty acid esters as active plant growth regulating compounds. Although the stereochemistry of these natural products was not rigorously established, they were tentatively assigned the β-D configuration II.[2] To test the validity of this assignment, we

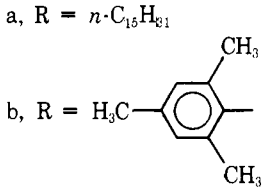


I

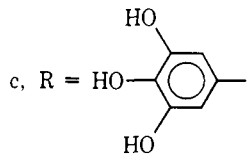


II

a, R = n-$C_{15}H_{31}$



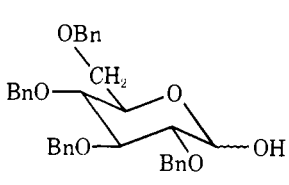
b, R = H_3C



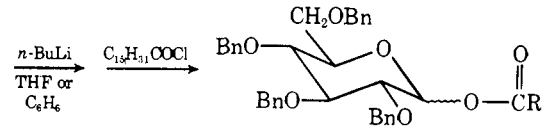
c, R = HO

set out to synthesize anomerically pure derivatives I and II containing long-chain fatty acid ester moieties.

In this paper we report the results of a study in which we have been able to control successfully the stereochemistry of 1-O-acylation of appropriately protected D-glucose to produce, selectively, in high yield (85–90%), α- and β-D-glucose esters Ia and IIa, respectively. Metalation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (TBG), III (5.40 g, 0.01 mol), in 125 ml of tetrahydrofuran (THF) at −30 to −40 °C using 1.1 equiv of n-butyllithium (1.6 M in hexane) followed by acylation with hexadecanoyl chloride produces a mixture of α- and β-D-anomeric esters IVa and IVb (noncrystalline mixture) in a



III



IV

Bn = benzyl

a, α anomer
b, β anomer

Table I. Stereochemical Distribution of Anomeric 1-*O*-Hexadecanoyl-D-TBG as a Function of Temperature and Solvent

Solvent	α	β	Temp, °C	Rotation
THF	90	10 (via ^{1}H NMR)	−30 to −40	+45.9 (CH_2Cl_2)
THF	70	30	25	+39.2
THF	70	30	45	
Benzene	50	50	0–5	+27.8
Benzene	26	74	40–45	+20.6
Benzene	11	89	62	+14.9

Table II. Anomeric Composition and ^{13}C Chemical Shifts, δ (ppm, Me_4Si), of TBG and TBG$^-$Li$^+$ in Benzene and THF at 35 °C

	δ (benzene)		δ (THF)			
	α	β	α	β	% α (benzene)	% α (THF)
TBG	91.3	98.2	91.6	98.6	61	67
TBG$^-$Li$^+$	89.1	95.9	88.8	96.1	50	52

ratio of 9:1, respectively, in chromatographically purified yields exceeding 95%. Other esters which we have prepared include benzoate, acetate, *cis*-9,10-octadecenoate, and octadecanoate; however, in this report we use the hexadecanoate as an illustrative example. Stereochemical assignment and relative amounts of IVa and IVb were readily determined by the measurement of the respective anomeric proton resonances at δ 6.65 (d, J = 2.62 Hz) and 5.85 (d, J = 6.75 Hz) in CCl_4 relative to internal standard Me_4Si.[3] Increasing the temperature in the metalation and acylation reactions in THF changes somewhat the α:β ratio, but the α-D anomer, IVa, still predominates, e.g., at 45 °C the ratio is 2–2.5:1 (Table I). In studying the parameters which influence the stereochemical course of this reaction, we observed that a dramatic inversion in product ratio could be effected by changing the reaction medium. Thus, reaction of III in benzene at 60 °C produces a 1:8 ratio of IVa and IVb, respectively. Compound IVb was isolated from this reaction mixture by crystallization from absolute ethanol, mp 52–53 °C, $[\alpha]^{25}$D +9.1° (c 1.0, CH_2Cl_2). At lower temperatures, intermediate ratios are noted; however, IVb still predominates above 5 °C in benzene (Table I).

At first, interpretation of these data in terms of a solvent and temperature dependent equilibration of metalated anomeric TBG (α-TBG$^+$Li$^-$ and β-TBG$^-$Li$^+$) seemed attractive.[4] Optical rotations of THF and benzene solutions containing TBG$^-$Li$^+$ were +31.6 and +33.4, respectively. These readings were relatively invariant with temperature change from 25 to 56 °C. Rotations obtained for the acetic acid quenched solutions of TBG$^-$Li$^+$ in THF and benzene were +36.8 and +37.0 whereas those of TBG were +46.8 and +53.6, respectively.[5] Presumably, metalation of TBG has only a minor effect on the anomeric equilibrium position seen in a slight shift toward β-D-anomer formation. This is confirmed by ^{13}C NMR spectroscopy which clearly shows the composition of the TBG and TBG$^-$Li$^+$ in benzene and THF. Table II lists the percentage of the α forms for both TBG and TBG$^-$Li$^+$ (generated with an equivalent amount of n-butyllithium) in benzene and THF determined by measurement of the corresponding α and β carbon resonances. Notice that both anomeric carbon shifts

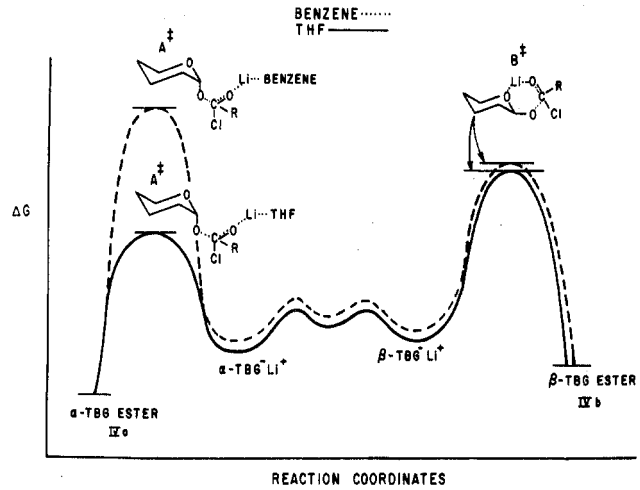


Figure 1. Pathway for the reaction of α and β TBG salts with acid chlorides.

are observed at higher fields in their salt forms, reminiscent of ionization. This result is in sharp contrast with the downfield shifts observed by deWit[4] for D-glucose in D_2O. Furthermore, after metalation and quenching, the anomeric ratios appear to be approximately the same for both solvents (50:50). These findings lead us to believe that the stereochemical control of acylation occurs further along the reaction coordinate, i.e., through the agency of the activated complexes $A^{\ddagger}$ (α form) and $B^{\ddagger}$ (β form) (Figure 1). In THF solution, the lower energy pathway provided by THF-solvated $A^{\ddagger}$ relative to the higher pathway given by intramolecularly bonded $B^{\ddagger}$ leads to a predominance of product IVa. Conversely, in benzene intramolecular coordination in $B^{\ddagger}$ becomes more important since it offers greater stabilization relative to the stabilization imparted to $A^{\ddagger}$ by the relatively nonpolar, poorly solvating benzene. Thus in benzene, product IVb predominates.[6]

Glucosyl esters, especially the α-D anomers, have not been of easy access in the past. Only the gallate, Ic, has been prepared in 5% yield by the procedure of Schmidt[7] and the mesitoate, Ib, in 17% yield by the procedure of Fletcher.[8] Furthermore, Fletcher could not extend either procedure to less hindered systems because of the lack of stereospecificity in the acylation procedure employed[8] and loss of desired product through rapid migration of the unhindered ester function from C-1 to C-2 under the nonneutral deblocking conditions.[9]

Hydrogenolysis of chromatographically purified (90% isomeric purity) IVa and isomerically pure IVb in absolute ethanol containing a catalytic amount of Pd black produced Ia and IIa in yields exceeding 90% (recrystallized from $CHCl_3$).

This synthetic sequence represents the first single pathway to pure, 1-α- and -β-D anomeric esters and the first general, high-yield route to pure unrearranged aliphatic 1-*O*-acyl-α-D-glucopyranoses Ia.

Experimental Section

Melting points are uncorrected. ^{13}C NMR spectra were determined on a Bruker[10] WH-90 spectrometer at 22.63 MHz. ^1H NMR spectra were determined on JEOL C-60H and Varian HA220 spectrometers. All chemical shifts are reported relative to internal Me_4Si. Ir spectra were recorded on a Perkin-Elmer 457 spectrometer. Rotational measurements were made on a Perkin-Elmer Model 141 polarimeter. GLC analyses of all glucose esters were performed on the corresponding trimethylsilyl derivatives prepared from Tri Sil Z reagent. The gas chromatograph used was a Hewlett-Packard Model 5750 equipped with flame ionization detection. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (TBG) was purchased from Pfanstiehl Chemical Co., mp 152–153 °C.

All reported compounds gave satisfactory elemental analyses.

General Procedure for the Preparation of 2,3,4,6-Tetra-*O*-benzyl-1-*O*-acyl-α-D-glucopyranose IVa. For this procedure we have chosen the hexadecanoyl ester as a representative example. Into a dry 250-ml three-neck flask, flushed with N_2, was placed 125 ml of freshly distilled anhydrous THF and 5.40 g (0.010 mol) of dry 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (TBG). The solution was magnetically stirred and the TBG was thoroughly dissolved within a few minutes at room temperature. The solution was then cooled to −30 to −40 °C and 6.8 ml (0.011 mol) of 1.6 M *n*-butyllithium in hexane was added. The homogeneous reaction mixture was stirred at this temperature for 3 min whereupon 3.0 g (0.011 mol) of hexadecanoyl chloride was added and the reaction continued for 20 min. The solution was then allowed to warm to room temperature, quenched with a saturated solution of ammonium chloride, and extracted with methylene chloride. The methylene chloride extracts were dried over sodium sulfate and the solvent removed to yield 7.8 g of crude ester (100%). The crude ester was eluted through an 18 × 0.75 in. column of Florisil with 50:50 methylene chloride–petroleum ether to give 7.7 g (97%) of a glassy solid. Attempts to crystallize this material failed. ^1H NMR in $CDCl_3$ showed the characteristic α and β anomeric proton resonances at δ 6.65 (d, J = 2.62 Hz) and 5.85 (d, J = 6.75 Hz) in the ratio of 9:1, respectively. The ratio of the sum of the α and β anomeric proton resonances to the 2-position methylene resonances of the aliphatic chain at δ 2.5 was 1:2, indicating monoesterification. Ir (neat film) C=O, 1745 cm^{-1}; $[\alpha]^{25}D$ +45.9° (*c* 1.0, CH_2Cl_2).

Preparation of 2,3,4,6-Tetra-*O*-benzyl-1-hexadecanoyl-β-D-glucopyranoses IVb. The preparation of the β-anomeric ester was similar to the above except that the reaction was carried out in anhydrous benzene. Metalation and solubilization of the TBG was carried out at 0 °C. Acylation was then effected at 62 °C for 20 min. Workup was essentially the same as above. Examination of the reaction mixture before crystallization by ^1H NMR indicated a ratio of α:β anomers of 11:89. The yield of crude ester was 95%. Crystallization of the product from absolute ethanol gave pure β anomer, mp 52–53 °C, in 85% yield. ^1H NMR in $CDCl_3$ showed the characteristic β-anomeric proton resonance at δ 5.85 (1 H, d, J = 6.75 Hz), 2.5 (2 H, t, J = 6.75 Hz, the 2 position CH_2 of the fatty acid chain); ir (neat film) C=O 1750 cm^{-1}; $[\alpha]^{25}D$ +9.1° (*c* 1.0, CH_2Cl_2).

Hydrogenolysis of IVa and IVb. IVa (90% α and 10% β) or compound IVb (100% β) (2 g, 0.0025 mol) were dissolved in 20 ml of absolute ethanol containing 75 mg of Pd black. The solutions were shaken on a Parr hydrogenator at room temperature for 8 h at 40 psi. Ia crystallized out of solution following hydrogenolysis of IVa in 92% yield. Recrystallization from $CHCl_3$ gave a solid which rearranged on melting, mp 98–108 °C, $[\alpha]^{25}D$ +66.9° (*c* 0.9, MeOH). ^1H NMR (CD_3OD), taken at 60 °C in a sealed tube because of the compounds' insolubility, showed resonances at δ 6.45 (1 H, d, J = 3.0 Hz, anomeric proton), 2.50 (2 H, t, J = 6.75 Hz, 2-position CH_2 protons of the aliphatic chain); ir (KBr pellet) C=O at 1740 cm^{-1}.

IIa was isolated in 96% yield after recrystallization from ethyl acetate: mp 108, 170–175 °C (double melting point); $[\alpha]^{25}D$ −1.17° (*c* 1.2, MeOH); ^1H NMR (CD_3OD) at 60 °C δ, 5.62 (1 H, d, J = 6.75 Hz, anomeric proton), 2.50 (2 H, t, J = 6.75 Hz, 2-position CH_2 protons of the aliphatic chain); ir (KBr pellet) shows three C=O peaks at 1760, 1750, and 1740 cm^{-1}.

The isomeric purity of Ia and IIa was confirmed by GLC analysis of the corresponding Me_4Si derivatives. Separation of these was made on a 6 ft × 0.25 in. glass column packed with 3% SP2100 and programmed from 180 to 250 °C, 6 °C/min. Under these conditions Ia and IIa have retention times of 12.0 and 12.5 min, respectively.

Acknowledgment. We thank Ms. M. S. Dougherty for her able assistance. ^1H NMR spectra (220 MHz) were taken at the Middle Atlantic Regional NMR facility, which is supported by NIH Grant RR542 at the University of Pennsylvania. Our thanks to G. McDonald for his assistance.

Registry No.—Ia, 59473-41-5; IIa, 39848-71-0; α-III, 6564-72-3; β-III, 59531-24-7; α-III Li, 59473-42-6; β-III Li, 59531-25-8; IVa, 59473-43-7; IVb, 59473-44-8; hexadecanoyl chloride, 112-67-4.

References and Notes

(1) Agricultural Research Service, U.S. Department of Agriculture.
(2) N. Mandava and J. W. Mitchell, *Chem. Ind. (London)*, 930 (1972).
(3) Further verification of assignment of IVa was made through comparison with the material prepared by the alternative route of esterification of TBG in CH_2Cl_2–pyridine. G. P. J. Glaudemans and H. G. Fletcher, Jr., *Methods Carbohydr. Chem.*, **6**, 373 (1972). Structure of IVb was confirmed through its debenzylated product Vb which was identical with the sample obtained

through the 4,6-O-benzylidene-D-glucopyranose acylation, deblocking route. H. G. Fletcher, Jr., *ibid.*, 231 (1963).
(4) A similar anionic equilibration has recently been observed for glucose: G. deWit, A. P. G. Kiekoom, and H. vanBekkum, *Tetrahedron Lett.*, 3943 (1975).
(5) The composition of TBG, e.g., the commercially available mp 149–150 °C material, in both benzene and THF has been determined by 220-MHz ^{1}H NMR to be approximately a 60:40 mixture of α and β anomeric forms. This ratio appears to remain approximately the same in the temperature range 17–56 °C.
(6) Note that addition of 4% HMPA to benzene v/v increases the solvating power of the medium enough to reverse the α:β product ratio to 2.3:1.
(7) O. T. Schmidt and J. Herok, *Justus Liebigs Ann. Chem.*, **587**, 63 (1954).
(8) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).
(9) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 2849 (1956).
(10) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.

A Synthesis of (*Z*)-6-Heneicosen-11-one. The Sex Pheromone of the Douglas Fir Tussock Moth[1]

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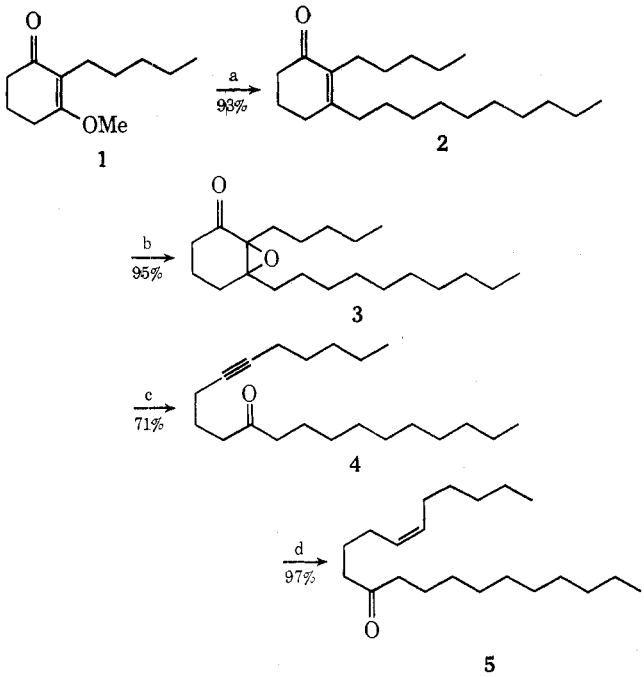
Received March 5, 1976

The sex pheromone of the Douglas fir tussock moth *Orgyia pseudotsugata* (McDunnough) has recently been identified as (*Z*)-6-heneicosen-11-one (**5**),[2] which is unusual in that most lepidopterous sex pheromones thus far identified are monoene or diene fatty alcohols or acetates of C_{12} or C_{14} chain length.[3] The structure and stereochemistry of **5** have been corroborated by unambiguous total synthesis.[4] The Douglas fir tussock moth is a severe defoliator of fir forests in western North America; consequently, considerable interest attends the use of the sex pheromone for purposes of bioassay and population control. Since traps baited with synthetic **5** have been shown to be highly attractive to males in field tests,[2] we have explored an alternate synthesis of **5** which is presented in the scheme below.

The high stereoselectivity and chemical yield anticipated for the reduction of an acetylenic bond to the corresponding *Z* olefin suggested 6-heneicosyn-11-one (**4**) as the primary synthetic goal.[5] The 21-carbon chain with the requisite 1,5 relationship between the ketone and acetylene functions in **4** was introduced in one step by the Eschenmoser cleavage[6] of the epoxy ketone **3** in 71% yield. The synthesis of the epoxy ketone **3** was achieved in two steps from the enol ether **1**[7] as shown in the scheme.



a, n-$C_{10}H_{21}MgBr/Et_2O$, H_3O^+; b, H_2O_2–NaOH/MeOH; c, p-$TsNHNH_2/CH_2Cl_2$–HOAc; d, H_2–$Pd/BaSO_4$, MeOH–pyridine.

To complete the synthesis, the acetylenic bond of **4** was semihydrogenated over Lindlar catalyst poisoned with 5 equiv of pyridine to give the *Z* olefin **5** in 97% yield (60% overall from **1**). The MS, ir, and NMR spectra of synthetic **5** were in complete accord with the published data for the natural pheromone.

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer as ~5% solutions in CCl_4; NMR spectra were obtained with a Varian HA-100 instrument in CCl_4 solution using Me_4Si as an internal standard. Mass spectra were obtained on a Du Pont 29-491B spectrometer. All yields are based on pure, isolated products.

2-*n*-Pentyl-3-*n*-decylcyclohex-2-en-1-one (2). A solution of *n*-decylmagnesium bromide was prepared from 1.77 g (8.00 mmol) of *n*-decyl bromide and 0.19 g (8.25 g-atoms) of Mg in 35 ml of ether. To the magnetically stirred Grignard reagent was added dropwise 1.00 g (5.10 mmol) of 2-*n*-pentyl-3-methoxycyclohex-2-en-1-one (**1**) in 5.0 ml of ether at 0 °C. After addition was complete, the mixture was stirred at 0 °C for 30 min and at ambient temperature for 3 h. The reaction mixture was poured into 15 ml of iced 1 N HCl and the ether layer separated, washed with 2 × 10 ml of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to a pale yellow oil. Kugelrohr distillation afforded 1.40 g (93%) of pure **2** as a colorless oil which crystallized on refrigeration: bp 125 °C (bath, 0.18 mm); ir (CCl_4) 1665, 1618 cm^{-1}; NMR (CCl_4) δ 2.1–2.4 (m, 6 H), 1.8–2.1 (m, 2 H), 1.1–1.8 (m, 24 H), 0.8–1.1 (overlapping distorted triplets, 6 H); mass spectrum (70 eV) *m/e* 306 (60, M^+), 165 [100, $(M - C_{10}H_{21})\cdot^+$]; uv (95% EtOH) 245 nm (ϵ 17 200).

2-*n*-Pentyl-3-*n*-decyl-2,3-epoxycyclohexan-1-one (3). To a solution of 0.590 g (1.93 mmol) of enone **2** in 14 ml of MeOH was added 1.00 ml (11.6 mmol) of 30% H_2O_2 and 0.15 ml of 6 N NaOH. The reaction mixture was allowed to stir at ambient temperature for 24 h after which the MeOH solution was diluted with 35 ml of H_2O and extracted with 2 × 15 ml of ether. The combined ether layers were washed with 2 × 10 ml of H_2O, dried over $MgSO_4$, and concentrated in vacuo to a colorless oil which was distilled via Kugelrohr to afford 0.588 g (95%) of the epoxy ketone **3**: bp 120 °C (bath, 0.15 mm); ir (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 1.8–2.2 (m, 2 H), 1.1–1.8 (m, 30 H), 0.9 (overlapping distorted triplets, 6 H).

6-Heneicosyn-11-one (4).[4] To a magnetically stirred solution of 0.588 g (1.83 mmol) of the epoxy ketone **3** in 4.0 ml of CH_2Cl_2 and 2.0 ml of HOAc at 0 °C was added 0.340 g (1.83 mmol) of *p*-toluenesulfonylhydrazide in one portion. After stirring at 0 °C for 3 h followed by 3 h at ambient temperature, the mixture was poured into 10 ml of water and extracted with 3 × 10 ml of hexane. The combined hexane layers were washed with 3 × 5 ml of water followed by 5 ml of saturated $NaHCO_3$. The mixture was dried over $MgSO_4$ and concentrated in vacuo to give 0.512 g of a pale yellow oil which consisted of two products by TLC on silica gel ($CHCl_3$ eluent, phosphomolybdic acid development). The major component, the desired acetylenic ketone **4** (R_f 0.6), was separated from a single major contaminant of unidentified structure (R_f 0.5) by column chromatography on 15 g of silica gel packed in hexane. The desired product was eluted with 5% ether in hexane to give 0.396 g (71%) of **4** as a colorless oil after distillation via Kugelrohr [bp 125 °C (bath) at 0.35 mm]. The product crystallized on standing: mp 26–27 °C; ir (CCl_4) 1718 cm^{-1}; NMR (CCl_4) δ 2.00–2.20 (m, 4 H), 1.1–1.8 (m, 24 H), 0.8–1.1 (overlapping distorted triplets, 6 H); mass spectrum (70 eV) *m/e* 306 (100, $M\cdot^+$), 169 [74 $(M - C_{10}H_{17})\cdot^+$], 165 [20, $(M - C_{10}H_{21})\cdot^+$], 122 [42, $(C_5H_{11}C{\equiv}C{-}CH{=}CH_2)\cdot^+$].

(*Z*)-6-Heneicosen-11-one (5). A solution of 0.361 g (1.18 mmol) of the acetylene **4** in 5 ml of MeOH containing 100 μl of pyridine was stirred under a slight positive pressure of H_2 over 35 mg of 5% Pd on $BaSO_4$. The progress of the reduction was followed by TLC on silica gel (5% ether in hexane as eluent, phosphomolybdic acid development). When the reaction was complete (~1 h) the catalyst was removed by filtration and the product (0.353 g, 97%) isolated via Kugelrohr distillation as a colorless oil which crystallized on refrigeration: bp 118 °C (bath, 0.4 mm); ir (CCl_4) 1718 cm^{-1}; NMR (CCl_4) δ 5.1–5.5 (m, 2 H), 2.3 (t, 4 H), 1.8–2.2 (m, 4 H), 1.1–1.8 (m, 24 H), 0.8–1.1 (overlapping distorted triplets, 6 H); mass spectrum (70 eV) *m/e* 308