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# An Efficient Route to Steroidal 6α- and 6β-Malonates and Acetates by Alkylation of π-Allylpalladium Complexes*

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*Abstract*

Reaction of the π-allylpalladium compounds derived from some 3-oxo 4-ene steroids with malonate ion gives dialkyl (3-oxo-steroid-4-en-6β-yl)malonates in high yield and with complete stereospecificity. The 6β-malonates can be epimerized to give the more stable 6α-epimers or decarboalkoxylated to give the corresponding acetic acid derivatives.

## Introduction

The importance of 6α- (*6*) and 6β- (*5*) acetic acid derivatives of steroids as compounds with potential in the field of immunochemical investigations has been described.[1] The synthesis of such compounds by a six-stage non-stereospecific route was described and other workers have described the preparation of pregnan-[1–3] and androstan-6-ylacetic acid[4] derivatives by an essentially similar route. In this paper we describe the preparation of the steroid-6-yl acetic acid compounds in high overall yield (up to 57%) from the steroid-4-en-3-ones in a sequence involving the π-allylpalladium compounds of the steroids.

## Discussion

There has been much recent interest in new synthetic reactions based on the reactions of π-allylpalladium complexes with nucleophiles.[5,6] The regiospecific reaction of the π-allylpalladium compounds from α,β-unsaturated carbonyl groups[5] suggested a new and short potential route to 6-substituted steroid-4-en-3-ones. Allylpalladium complexes of steroid-4-en-3-ones have been reported previously.[7,8]

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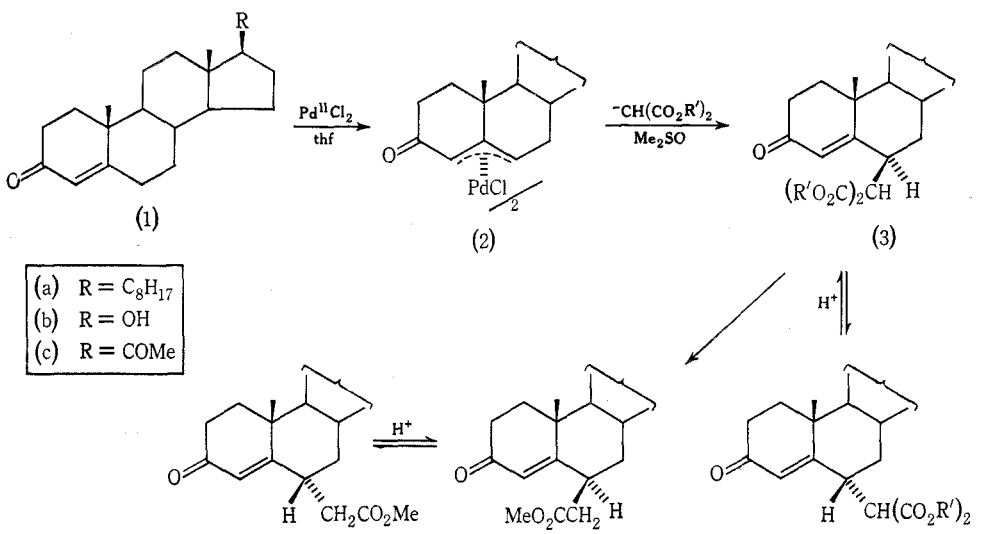
[1] Collins, D. J., Horn, C. M., and Welker, V. J., *Aust. J. Chem.*, 1976, **29**, 2077.
[2] Riley, W. J., Smith, E. R., Robertson, D. M., and Kellie, A. E., *J. Steroid Biochem.*, 1972, **3**, 357.
[3] Jones, C. D., and Mason, N. R., *Steroids*, 1974, **23**, 323.
[4] Jones, C. D., and Mason, N. R., *Steroids*, 1975, **25**, 23.
[5] Jackson, W. R., and Strauss, J. U. G., *Tetrahedron Lett.*, 1975, 2591; Jackson, W. R., and Strauss, J. U. G., *Aust. J. Chem.*, 1977, **30**, 553.
[6] Trost, B. M., and Fullerton, T. J., *J. Am. Chem. Soc.*, 1973, **95**, 292; Trost, B. M., Dietsche, T. J., and Fullerton, T. J., *J. Org. Chem.*, 1974, **39**, 737.
[7] Howsam, R. W., and McQuillin, F. J., *Tetrahedron Lett.*, 1968, 3667.
[8] Harrison, I. T., Kimura, E., Bohme, E., and Fried, J. H., *Tetrahedron Lett.*, 1969, 1589.

However, attempted substitution with both 'hard' (e.g. cyanide ion) and 'soft' (e.g. malonate ion) nucleophiles led predominantly to elimination[8] and formation of 3-oxo 4,6-dienes.

Reaction of cholest-4-en-3-one, testosterone, and progesterone (1a–c) (see Scheme 1) with palladium chloride in refluxing tetrahydrofuran containing sodium chloride gave palladium complexes in yields ranging from 50 to 90%. Yields usually lay in the range 70–80%. The absorption spectra of our samples were in good general agreement with published data and the optical rotations were of the same sign but usually larger than literature values.[7] The complexes in each case appeared to be a single diastereoisomer. Careful examination of t.l.c. plates and of $^{1}H$ and $^{13}C$ n.m.r. spectra produced no evidence for the existence of a second diastereoisomer. Jones and Knox[9] reported that reaction of cholest-5-ene with palladium chloride gave exclusively an $\alpha$-4–6-$\eta$ complex and that cholest-4-ene gave a mixture of $\alpha$- and $\beta$-complexes in which the sterically favoured $\alpha$-complex predominated. The signal due to the C 10 methyl protons in the p.m.r. spectrum was deshielded in the $\beta$-isomer due to the close proximity of the palladium atom. Other examples are known where a proximate palladium atom leads to proton deshielding in the p.m.r. spectra.[10] In the complexes (2) the C 10 methyl signal absorptions were at almost identical chemical shifts to those in the parent enones (1). The relevant chemical shifts were: 1·17 and 1·25 for (1a) and (2a); 1·20 and 1·27 for (1b) and (2b); and 1·18 and 1·27 for (1c) and (2c). In view of these results and other general considerations, including the inspection of molecular models, which exemplify the possibility of adverse steric interactions between the C 10 $\beta$-methyl group and a $\beta$-4–6-$\eta$ palladium, we tentatively assign the $\alpha$-4–6-$\eta$ stereochemistry for complexes (2a–c).




Scheme 1

[9] Jones, D. N., and Knox, S. D., *J. Chem. Soc., Chem. Commun.*, 1975, 165.
[10] Roe, D. M., Bailey, P. M., Moreley, K., and Maitlis, P. M., *J. Chem. Soc., Chem. Commun.*, 1972, 1273; Immirzi, A., and Musco, A., *J. Chem. Soc., Chem. Commun.*, 1974, 400; Matsumoto, M., Yoshioka, H., Nakatsu, K., Yoshioda, T., and Otsuka, S., *J. Am. Chem. Soc.*, 1974, **96**, 3322.

Reaction of the complexes (2) with malonate ion, generated from dialkyl malonate and sodium hydride in dry dimethyl sulphoxide, in dimethyl sulphoxide solution at ambient temperature gave the malonate esters (3) in virtually quantitative yield (Scheme 1). One recrystallization of the crude product gave pure esters (3) in yields frequently greater than 90%. The 6β-stereochemistry of the malonate esters was assigned on the basis of their p.m.r. spectra which showed the 4-proton as a singlet and, in the case of (3a) and (3c), the 6α-proton as a doublet of doublets with $^3J_{6\alpha,6'}$ 12 Hz and $^3J_{6\alpha,7}$ 5 Hz. The coupling constant $^4J_{4,6}$ could not be detected and was less than 0·8 Hz for all compounds (3). The absence of significant allylic coupling and of axial–axial coupling for H 6–H 7 is consistent with the presence of pseudo-equatorial H 6α proton and thus a 6β-pseudoaxial-carbon substituent.[11] In support of this proposed stereochemistry all of the malonate esters (3) were converted into the thermodynamically more stable 6α-isomers (4) on heating with *p*-toluenesulphonic acid in benzene solution. No trace of the 6α-isomers could be found (by chromatographic or spectroscopic methods) in the crude products from reactions of the complexes (2). When the malonate ion was generated in the presence of methanol or ethanol, significant amounts of cholesta-4,6-dien-3-one were formed. If our assignment of α-4–6-η stereochemistry to the palladium complexes (2) is correct, the stereospecific formation of 6β-malonate compounds must involve nucleophilic attack on the open face of the allyl system remote from the metal. Similar stereochemical results were obtained for the reaction of nucleophiles with another π-allylpalladium system.[12] This stereochemistry is consistent with the transition state proposed for these reactions[5] in which an '$S_N2$'-type displacement of a carbon–metal bond occurs in an allylpalladium structure stabilized by σ–π dimethyl sulphoxide.

Decarboalkoxylation of the 6β-malonate esters (3) with lithium iodide in dry dimethylformamide gave the 6β-acetate esters (5). Conditions were not optimized but yields of the methyl testosterone 6β-acetate (5b) of around 50% after one crystallization were obtained. The corresponding methyl acetates from cholestenone and progesterone (5a) and (5c) were purified by preparative t.l.c. and compared with authentic samples.[1] Epimerization of the 6β-methyl acetate from testosterone (5b) with a solution of *p*-toluenesulphonic acid in benzene gave the 6α-epimer (6). The 6α-stereochemistry was demonstrated by the significant value of $^4J_{6\beta,4}$ 1·5 Hz.

Attempts to prepare the 6α-methyl acetates (6) by decarbomethoxylation of the 6α-malonates (4) under a variety of conditions led in all cases to a complicated mixture of products.

## Experimental

Melting points were carried out with a Riechert hot stage microscope apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Microanalyses were carried out by the Australian Microanalytical Service. Ultraviolet spectra were obtained with a Unicam SP800A spectrophotometer and refer to solutions in 95% ethanol unless otherwise stated. Infrared spectra were recorded with a Perkin–Elmer 257 spectrophotometer. Proton magnetic resonance spectra were recorded on Varian HA-100 or Bruker WH-90 instruments in deuterochloroform with tetramethylsilane as internal reference. Carbon magnetic resonance spectra were recorded at 22·62 MHz on a Bruker WH-90 instrument in deuterochloroform with tetramethylsilane as internal reference. Mass spectra were recorded at 70 eV with a Hitachi Perkin–Elmer

[11] Collins, D. J., Hobbs, J. J., and Sternhell, S., *Aust. J. Chem.*, 1963, **16**, 1030.
[12] Trost, B. M., and Weber, L., *J. Am. Chem. Soc.*, 1975, **97**, 1611.

RMU-6E spectrophotometer. Preparative thin-layer chromatography was carried out on Merck type E alumina or Merck type 60 silica gel, $PF_{254}$ adsorbents, and ultraviolet light was used to visualize the components.

*Preparation of the π-Allylpalladium Complexes*

All of the palladium complexes were prepared by the procedure described below for the 3-oxocholest-4-ene complex.

*Di-μ-chloro-bis[4–6-η-(3-oxocholesteryl)palladium*(II)] (*2a*)

A mixture of palladium(II) chloride (0·53 g, 3 mmol) and sodium chloride (0·24 g, 4 mmol) was mildly refluxed for 3–4 h in dry tetrahydrofuran (30 ml), under nitrogen. Cholest-4-en-3-one (1·34 g 3·5 mmol) was added and the mixture was heated under mild reflux for 42 h. The precipitate was removed by filtration through Celite and the filter cake was washed successively with water and chloroform. The aqueous phase of the filtrate was extracted with chloroform which, together with the main chloroform solution, was washed with water (2 × 100 ml), dried ($MgSO_4$) and the solvent evaporated. Crystallization of the residue from light petroleum gave yellow crystals of *di-μ-chloro-bis[4–6-η-(3-oxocholesteryl)palladium*(II)] (1·13 g, 72%). The mother liquors from the recrystallization were chromatographed on basic alumina (activity 2). Elution with chloroform–light petroleum (1 : 19) gave cholestenone. Elution with ethyl acetate gave more of the allylpalladium compound (0·37 g). The total yield of complex was thus 1·50 g (95%), m.p. 166–168°; $[\alpha]_D$ +259°, $[\alpha]_{578}$ +282°, $[\alpha]_{546}$ +370°, $[\alpha]_{436}$ −575°, $[\alpha]_{365}$ −960° (*c*, 0·51 in chloroform) (lit.[7] $[\alpha]_D$ +162°) (Found: C, 61·9; H, 8·3; Cl, 6·7. $C_{54}H_{86}Cl_2O_2Pd_2$ requires C, 61·7; H, 8·3; Cl, 6·8%). $\lambda_{max}$ ($CHCl_3$) 281 nm (ε 9110), 249 (7400); $\lambda_{min}$ 259 nm (7130) [lit.[7] $\lambda_{max}$ ($CHCl_3$): 282 (7360), 244 (6370)]. $\nu_{max}$ (Nujol) 2900sb, 1678s, 1455s, 1430w, 1418w, 1378s, 1354w, 1256w, 1228w, 1205w, 1191m, 1138w, 1022w, 960w, 926w, 887w, 857w, 815w, 730w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·68, s (18-Me); 1·25, s (19-Me); 0·83–0·94, m, 9H (21,26,27-Me); 3·39, s, 1H (H 4, π-allyl); 4·38, d, *J* 6 Hz, 1H (H 6, π-allyl). $^{13}C$ n.m.r. δ ($CDCl_3$): 203·8 (C 3); 134·2 (C 5, π-allyl); 83·6, 65·2 (C 4, C 6, π-allyl).

*Di-μ-chloro-bis[4–6-η-(17β-hydroxy-3-oxoandrostenyl)palladium*(II)] (*2b*)

Treatment of testosterone (1·00 g, 3·5 mmol) as in (2a), and crystallization of the product from benzene afforded yellow crystals of *di-μ-chloro-bis[4–6-η-(17β-hydroxy-3-oxoandrostenyl)palladium*(II)] (1·13 g, 88%), m.p. 188–190°; $[\alpha]_D$ +320°, $[\alpha]_{578}$ +348°, $[\alpha]_{546}$ +446°, $[\alpha]_{436}$ −492°, $[\alpha]_{365}$ −565° (*c*, 0·36 in ethanol) (lit.[7] $[\alpha]_D$ +218°) (Found: C, 52·9; H, 6·4. $C_{38}H_{54}Cl_2O_4Pd_2$ requires C, 53·1; H, 6·3%). $\lambda_{max}$ ($CHCl_3$) 281 nm (ε 7460), 249 (6030); $\lambda_{min}$ 260 (5640) [lit.[7] $\lambda_{max}$ ($CHCl_3$): 282 (6720), 244 (6120)]. $\nu_{max}$ (Nujol) 3370sb, 2870sb, 2840s, 1677s, 1448s, 1369s, 1325w, 1310w, 1246w, 1204w, 1173w, 1135w, 1122w, 1078w, 1055m, 1044m, 1028w, 1018m, 968w, 935w, 930w, 925w, 900w, 897w, 889w, 877w, 860w, 829w, 795w, 718w, 703w, 665s $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·77, s (18-Me); 1·27, s (19-Me); 2·47, s (17-OH); 3·38, s, 1H (H 4, π-allyl); 3·64, m (H 17); 4·34, d, *J* 6·5 Hz, 1H (H 6, π-allyl). $^{13}C$ n.m.r. δ ($CDCl_3$): 203·5 (C 3); 134·1 (C 5, π-allyl); 83·1, 65·3 (C 4, C 6, π-allyl); 81·5 (C 17).

*Di-μ-chloro-bis[4–6-η-(3,20-dioxopregnenyl)palladium*(II)] (*2c*)

Treatment of progesterone (1·10 g, 3·5 mmol) as in (2a) and crystallization of the product from acetone–water at room temperature afforded yellow crystals of *di-μ-chloro-bis[4–6-η-(3,20-dioxopregnenyl)palladium*(II)] (0·72 g, 53%), m.p. 163–165°; $[\alpha]_D$ +328°, $[\alpha]_{578}$ +354°, $[\alpha]_{546}$ +459°, $[\alpha]_{436}$ −1775°, $[\alpha]_{365}$ −1803° (*c*, 0·53 in chloroform) (lit.[7] $[\alpha]_D$ +348°) (Found: C, 55·3; H, 6·5. $C_{42}H_{58}Cl_2O_4Pd_2$ requires C, 55·4; H, 6·4%). $\lambda_{max}$ ($CHCl_3$) 279 nm (ε 8570), 249 (7240); $\lambda_{min}$ 260 (6810) [lit.[7] $\lambda_{max}$ ($CHCl_3$): 282 (7750), 244 (6860)]. $\nu_{max}$ (Nujol) 2885s, 2830s, 1690s, 1680s, 1455s, 1410w, 1370w, 1353w, 1285w, 1250m, 1210m, 1189w, 1177m, 1158w, 1128w, 1105w, 1083w, 1040w, 1015w, 990w, 965w, 940w, 915w, 902w, 882w, 865w, 840w, 731w, 710w, 705w, 675w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·65, s (18-Me); 1·27, s (19-Me); 2·13, s (21-Me); 3·47, s, 1H (H 4, π-allyl); 4·45, d, *J* 6 Hz, 1H (H 6, π-allyl). $^{13}C$ n.m.r. δ ($CDCl_3$): 209·2 (C 20); 203·7 (C 3); 133·9 (C 5, π-allyl); 83·4, 65·3 (C 4, C 6, π-allyl).

*Preparation of 6β-Malonate Esters*

All of the 6β-substituted malonate esters were prepared by the procedure described for dimethyl 3-oxocholest-4-en-6β-ylmalonate.

*Dimethyl 3-Oxocholest-4-en-6β-ylmalonate (3a; R′ = Me)*

A mixture of sodium hydride (0·04 g, 1·5 mmol, 100% pellets) and dimethyl malonate (0·50 g, 3·4 mmol) was stirred, under nitrogen, in dry dimethyl sulphoxide (25 ml) at 35° until the pellets dissolved. Di-μ-chloro-bis[4–6-η-(3-oxocholesteryl)palladium(II)] (2a) (0·53 g, 0·5 mmol) was added, and the mixture was heated at 35° for 8 h. The reaction mixture was added with stirring to a mixture of acidified ice-water (30 ml) and methylene chloride (20 ml). The precipitate was removed by filtration through Celite and the filter cake was washed successively with water and methylene chloride. The aqueous phase of the filtrate was extracted with methylene chloride, which together with the main methylene chloride solution, was washed with water (2 × 100 ml), dried ($MgSO_4$), and the solvent evaporated. Crystallization of the residue from aqueous ethanol gave colourless crystals of *dimethyl 3-oxocholest-4-en-6β-ylmalonate* (0·48 g, 91%), m.p. 105–106°; $[\alpha]_D$ +78·2°, $[\alpha]_{578}$ +82·3°, $[\alpha]_{546}$ +93·7°, $[\alpha]_{436}$ +157°, $[\alpha]_{365}$ +83·1° (*c*, 0·65 in chloroform) (Found: C, 74·4; H, 9·5. $C_{32}H_{50}O_5$ requires C, 74·6; H, 9·8%). $\lambda_{max}$ 240 nm (ε 13540). $\nu_{max}$ (Nujol) 2910sb, 1745s, 1725s, 1675s, 1605m, 1455s, 1440s, 1395m, 1350w, 1310m, 1295w, 1276w, 1266w, 1200m, 1155m, 1055m, 1025w, 975w, 940w, 920w, 875w, 820w, 800w, 725w $cm^{-1}$. P.m.r. (100 MHz, δ, $CDCl_3$): 0·74, s (18-Me); 0·80–0·96, m, 9H (21,26,27-Me); 1·25, s (19-Me); 2·29, m (H2); 3·21, dd, *J* 12 Hz, *J* 5 Hz, 1H (H6α); 3·60, s (OMe); 3·71, s (OMe); 3·80, d, *J* 12 Hz, 1H [$CH(CO_2Me)_2$]; 5·77, s (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·2 (C3); 168·2, 167·7, 167·3 (C5 and ester carbonyls); 128·4 (C4). Mass spectrum: *m/e* 514 (100%), 383 (18).

*Diethyl 3-Oxocholest-4-en-6β-ylmalonate (3a; R′ = Et)*

Treatment of di-μ-chloro-bis[4–6-η-(3-oxocholesteryl)palladium(II)] (2a) with diethyl malonate (0·30 g, 1·9 mmol) as in (3a; R′ = Me), and crystallization of the product from aqueous ethanol afforded colourless crystals of *diethyl 3-oxocholest-4-en-6β-ylmalonate* (0·40 g, 74%), m.p. 87–89°; $[\alpha]_D$ +75·6°, $[\alpha]_{578}$ +79·2°, $[\alpha]_{546}$ +90·5°, $[\alpha]_{436}$ +154°, $[\alpha]_{365}$ +98·8° (*c*, 0·92 in chloroform) (Found: C, 75·5; H, 9·8. $C_{34}H_{54}O_5$ requires C, 75·2; H, 10·0%). $\lambda_{max}$ 240 nm (ε 14070). $\nu_{max}$ (Nujol) 2910sb, 2842s, 1723s, 1670s, 1600m, 1460s, 1412w, 1378m, 1329w, 1303w, 1255m, 1222w, 1205w, 1190w, 1170w, 1156m, 1098w, 1037m, 950w, 883w, 693w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·73, s (18-Me); 0·83–0·95, m, 9H (21,26,27-Me); 1·20, t, *J* 7 Hz, 6H [$CH(CO_2CH_2CH_3)_2$]; 1·28, s (19-Me); 2·47, m (H2); 3·21, dd, *J* 12 Hz, *J* 4·5 Hz, 1H (H6α); 3·79, d, *J* 12·3 Hz, 1H [$CH(CO_2Et)_2$]; 4·11, m, *J* 7 Hz, 2H ($CO_2CH_2CH_3$); 4·22, q, *J* 7 Hz, 2H ($CO_2CH_2CH_3$); 5·83, s (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·2 (C3); 167·4 (C5); 153·7, 154·2 (ester carbonyls); 118·7 (C4). Mass spectrum: *m/e* 542 (100%), 469 (10), 468 (10), 384 (10), 383 (10), 382 (10).

*Reaction in Ethanol–Dimethyl Sulphoxide*

Di-μ-chloro-bis[4–6-η-(3-oxocholesteryl)palladium(II)] (2a) (0·53 g, 0·5 mmol) was dissolved in a mixture of ethanol (4 ml) and dimethyl sulphoxide (6 ml). To this solution was added, in one portion, a solution of sodium metal (0·03 g, 1·3 mmol), diethyl malonate (0·22 g, 1·4 mmol) in ethanol (8 ml) and dimethyl sulphoxide (4 ml). The mixture was stirred at room temperature for 5 h and poured into a mixture of chloroform and acidified ice-water, filtered through Celite and the filter cake was washed with water and chloroform. The water was extracted with chloroform (2 × 100 ml), and the combined extracts were washed with water (2 × 100 ml), dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on a column of acidic alumina of activity 2. Elution with benzene gave cholesta-4,6-dien-3-one as an oil which was crystallized from methanol to give colourless crystals (0·14 g, 36%), m.p. 80–81° (lit.[13] 81°). Elution with chloroform gave diethyl 3-oxocholest-4-en-6β-ylmalonate (3a; R′ = Et) as an oil which was crystallized from aqueous ethanol to give colourless crystals (0·30 g, 55%), m.p. 87–89°.

[13] Sondheimer, F., Amendolla, C., and Rosenkranz, G., *J. Am. Chem. Soc.*, 1953, **75**, 5932.

*Dimethyl 17β-Hydroxy-3-oxoandrost-4-en-6β-ylmalonate (3b; R′ = Me)*

Treatment of di-μ-chloro-bis[4–6-η-(17β-hydroxy-3-oxoandrostenyl)palladium(II)] (2b) (0·43 g, 0·5 mmol) with dimethyl malonate (0·50 g, 3·4 mmol) as in (3a; R′ = Me) and crystallization of the product from aqueous ethanol afforded colourless crystals of *dimethyl 17β-hydroxy-3-oxoandrost-4-en-6β-ylmalonate* (0·42 g, 96%), m.p. 221–223°; $[\alpha]_D$ +86·7°, $[\alpha]_{578}$ +91·0°, $[\alpha]_{546}$ +104°, $[\alpha]_{436}$ +172°, $[\alpha]_{365}$ +37·6° (*c*, 0·49 in chloroform) (Found: C, 68·7; H, 8·4. $C_{24}H_{30}O_6$ requires C, 68·9; H, 8·0%). $\lambda_{max}$ 239 nm (ε 14470). $\nu_{max}$ (Nujol) 3425 sharp, 2900sb, 1750sb, 1660s, 1610m, 1460s, 1436s, 1380m, 1366w, 1350w, 1299m, 1279m, 1237w, 1214w, 1205w, 1182w, 1145m, 1088w, 1075w, 1057w, 1030w, 1006w, 981w, 969w, 945w, 912w, 892w, 845w, 820w, 760w, 731w, 700w $cm^{-1}$. P.m.r. (100 MHz, δ, $CDCl_3$): 0·80, s (18-Me); 1·26, s (19-Me); 2·40, m (H2); 3·20, m, 1H (H6α); 3·61, s (OMe); 3·65, m (H17); 3·70, s (OMe); 3·79, d, *J* 12 Hz, 1H [$CH(CO_2Me)_2$]; 5·77, s (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 191·0 (C3); 178·8, 172·1, 168·1 (C5 and ester carbonyls); 128·4 (C4); 78·5 (C17). Mass spectrum: *m/e* 418 (100%), 359 (15), 327 (10), 326 (10), 287 (25).

*Diethyl 17β-Hydroxy-3-oxoandrost-4-en-6β-ylmalonate (3b; R′ = Et)*

Treatment of di-μ-chloro-bis[4–6-η-(17β-hydroxy-3-oxoandrostenyl)palladium(II)] (2b) (0·43 g, 0·5 mmol) with diethyl malonate (0·30 g, 1·9 mmol) as for (3a; R′ = Me) and crystallization of the product from acetone afforded colourless crystals of *diethyl 17β-hydroxy-3-oxoandrost-4-en-6β-ylmalonate* (0·40 g, 90%), m.p. 192–194°; $[\alpha]_D$ +79·6°, $[\alpha]_{578}$ +83·5°, $[\alpha]_{546}$ +95·0°, $[\alpha]_{436}$ +153°, $[\alpha]_{365}$ −9·1° (*c*, 0·83 in chloroform) (Found: C, 69·8; H, 8·5. $C_{26}H_{38}O_6$ requires C, 69·9; H, 8·6%). $\lambda_{max}$ 239 nm (ε 13990). $\nu_{max}$ (Nujol) 3427 sharp, 2915s, 2865s, 2845s, 1740s, 1653s, 1602w, 1457s, 1416w, 1375m, 1346w, 1295m, 1280s, 1238w, 1213w, 1205w, 1192s, 1142m, 1102w, 1090w, 1075w, 1035w, 1020w, 970w, 950w, 915w, 865w, 840w, 810w, 758w $cm^{-1}$. P.m.r. (100 MHz, δ, $CDCl_3$): 0·79, s (18-Me); 1·18, s (19-Me); 1·25, t, *J* 7 Hz, 3H ($CO_2CH_2CH_3$); 1·27, t, *J* 7 Hz, 3H ($CO_2CH_2CH_3$); 2·31, m (H2); 3·20, m, 1H (H6α); 3·61, t, *J* 8·5 Hz, 1H (H17); 3·75, d, *J* 12 Hz, 1H [$CH(CO_2Et)_2$]; 4·06, m, *J* 7 Hz, 2H ($CO_2CH_2CH_3$); 4·18, q, *J* 7 Hz, 2H ($CO_2CH_2CH_3$); 5·79, s (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·1 (C3); 167·3, 167·0, 154·3 (C5 and ester carbonyls); 119·4 (C4); 81·5 (C17). Mass spectrum: *m/e* 446 (100%), 363 (28), 362 (24), 327 (10), 326 (10), 287 (38), 286 (10).

*Dimethyl 3,20-Dioxopregn-4-en-6β-ylmalonate (3c; R′ = Me)*

Treatment of di-μ-chloro-bis[4–6-η-(3,20-dioxopregnenyl)palladium(II)] (2c) (0·46 g, 0·5 mmol) with dimethyl malonate (0·50 g, 3·4 mmol) as in (3a; R′ = Me), and crystallization of the product from aqueous ethanol afforded colourless crystals of *dimethyl 3,20-dioxopregn-4-en-6β-ylmalonate* (0·32 g, 72%), m.p. 136–138°; $[\alpha]_D$ +141·2°, $[\alpha]_{578}$ +147·8°, $[\alpha]_{546}$ +170·8°, $[\alpha]_{436}$ +314·5°, $[\alpha]_{365}$ +369·0° (*c*, 0·44 in chloroform) (Found: C, 70·5; H, 8·3. $C_{26}H_{36}O_6$ requires C, 70·2; H, 8·2%). $\lambda_{max}$ 240 nm (ε 13990). $\nu_{max}$ (Nujol) 2905s, 2845s, 1736s, 1697s, 1676s, 1610m, 1452s, 1430m, 1413w, 1380s, 1348s, 1322m, 1305s, 1270s, 1260s, 1238m, 1210s, 1190s, 1180m, 1168m, 1150s, 1100w, 1080w, 1067w, 1050w, 1030w, 1012w, 996w, 990w, 976w, 954w, 940w, 920w, 907w, 895w, 878m, 864w, 844w, 825w, 796w, 785w, 765w, 744w, 718w, 700w, 690w, 670w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·69, s (18-Me); 1·28, s (19-Me); 2·12, s (21-Me); 3·25, dd, *J* 12 Hz, *J* 5 Hz, 1H (H6α); 3·65, s (OMe); 3·76, s (OMe); 3·83, d, *J* 12 Hz, 1H [$CH(CO_2Me)_2$]; 5·81, s (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 209·1 (C20); 199·1 (C3); 168·1 (C5); 167·6, 166·8 (ester carbonyls); 128·7 (C4). Mass spectrum: *m/e* 444 (100%), 395 (15), 394 (10), 353 (10), 352 (10), 314 (12), 313 (40), 312 (15).

*Preparation of the 6α-Malonate Esters*

All of the 6α-malonate esters were prepared by the procedure described below for dimethyl 3-oxocholest-4-en-6α-ylmalonate.

*Dimethyl 3-Oxocholest-4-en-6α-ylmalonate (4a; R′ = Me)*

*p*-Toluenesulphonic acid monohydrate (0·04 g, 0·2 mmol) was dissolved in dry benzene (30 ml) and the water was removed by azeotropy. Dimethyl 3-oxo-cholest-4-en-6β-ylmalonate (3a; R′ = Me) (0·40 g, 0·78 mmol) was added, and the mixture was heated under reflux, under nitrogen for 2 h.

The benzene was evaporated and the residue dissolved in methylene chloride. The methylene chloride solution was washed with water (2 × 100 ml), dried ($MgSO_4$), and the solvent evaporated. Crystallization of the residue from aqueous ethanol gave colourless crystals of *dimethyl 3-oxocholest-4-en-6α-ylmalonate* (0·29 g, 73%), m.p. 107–110°; $[\alpha]_D$ +77·0°, $[\alpha]_{578}$ +80·1°, $[\alpha]_{546}$ +90·3°, $[\alpha]_{436}$ +142·0°, $[\alpha]_{365}$ −246·4° (*c*, 0·70 in chloroform) (Found: C, 74·7; H, 9·5. $C_{32}H_{50}O_5$ requires C, 74·6; H, 9·8%). $\lambda_{max}$ 241 nm (ε 13380). $\nu_{max}$ (Nujol) 2910s, 2850s, 1757s, 1734s, 1681s, 1609m, 1463s, 1437m, 1380m, 1345w, 1331w, 1320w, 1305w, 1275w, 1250m, 1228w, 1210m, 1185w, 1175w, 1145m, 1025w, 973w, 958w, 928w, 909w, 880w, 870w, 822w, 792w, 750w, 725w, 690w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·71, s (18-Me); 0·82–0·93, m, 9H (21,26,27-Me); 1·25, s (19-Me); 2·33, m (H2); 3·22, m, 1H (H6β); 3·62, d, *J* 9·4 Hz, 1H [$CH(CO_2Me)_2$]; 3·72, s (OMe); 3·75, s (OMe); 5·52, d, *J* 1·2 Hz (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·2 (C3); 170·7 (C5); 168·9, 168·5 (ester carbonyls); 120·8 (C4). Mass spectrum: *m/e* 514 (100%), 483 (10), 456 (10), 384 (10), 383 (15), 382 (20).

*Diethyl 3-Oxocholest-4-en-6α-ylmalonate (4a; R′ = Et)*

Treatment of diethyl 3-oxocholest-4-en-6β-ylmalonate (3a; R′ = Et) (0·27 g, 0·5 mmol) with *p*-toluenesulphonic acid monohydrate (0·04 g, 0·2 mmol) as in (4a; R′ = Me), and crystallization of the product from aqueous ethanol afforded colourless crystals of *diethyl 3-oxocholest-4-en-6α-ylmalonate* (0·13 g, 48%), m.p. 82·5–83·5°; $[\alpha]_D$ +72·5°, $[\alpha]_{578}$ +75·6°, $[\alpha]_{546}$ +85·4°, $[\alpha]_{436}$ +130·8°, $[\alpha]_{365}$ −25·0° (*c*, 0·65 in chloroform) (Found: C, 75·2; H, 9·8. $C_{34}H_{54}O_5$ requires C, 75·2; H, 10·0%). $\lambda_{max}$ 240 nm (ε 13560). $\nu_{max}$ (KBr) 2950sb, 2850s, 1742s, 1730s, 1697s, 1610m, 1460m, 1370w, 1327w, 1312m, 1268m, 1240w, 1217w, 1201w, 1180m, 1150m, 1100w, 1030w, 980w, 865w, 693w $cm^{-1}$. P.m.r. (100 MHz, δ, $CDCl_3$): 0·68, s (18-Me); 0·80–0·96, m, 9H (21,26,27-Me); 1·21, t, *J* 7 Hz, 3H ($CO_2CH_2CH_3$); 1·22, s (19-Me); 1·25, t, *J* 7 Hz, 3H ($CO_2CH_2CH_3$); 2·24, m (H2); 3·15, m, 1H (H6β); 3·53, d, *J* 10 Hz, 1H [$CH(CO_2Et)_2$]; 4·13, q, *J* 7 Hz, 2H ($CO_2CH_2CH_3$); 4·17, q, *J* 7 Hz, 2H ($CO_2CH_2CH_3$); 5·51, d, *J* 2 Hz (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·1 (C3); 170·8 (C5); 168·6, 168·1 (ester carbonyls); 120·9 (C4). Mass spectrum: *m/e* 542 (100%), 469 (12), 468 (10), 383 (25), 382 (27).

*Dimethyl 17β-Hydroxy-3-oxoandrost-4-en-6α-ylmalonate (4b; R′ = Me)*

Treatment of dimethyl 17β-hydroxy-3-oxoandrost-4-en-6β-ylmalonate (3b; R′ = Me) (0·21 g, 0·5 mmol) with *p*-toluenesulphonic acid monohydrate (0·11 g, 0·6 mmol) as in (4a; R′ = Me), and purification of the product by preparative thin-layer chromatography on silica afforded a colourless foam of *dimethyl 17β-hydroxy-3-oxoandrost-4-en-6α-ylmalonate* (0·15 g, 71%), m.p. 72–74°; $[\alpha]_D$ +91·2°, $[\alpha]_{578}$ +96·0°, $[\alpha]_{546}$ +108·9°, $[\alpha]_{436}$ +174·6°, $[\alpha]_{365}$ +14·0° (*c*, 0·57 in chloroform) (Found: C, 68·4; H, 8·1. $C_{24}H_{30}O_6$ requires C, 68·9; H, 8·0%). $\lambda_{max}$ 241 nm (ε 12080). $\nu_{max}$ (Nujol) 3430sb, 2920s, 2849s, 1732s, 1666s, 1605m, 1454s, 1440w, 1373m, 1360w, 1316m, 1271m, 1234m, 1192m, 1176w, 1160m, 1155w, 1145m, 1061w, 1050w, 1032w, 1015w, 978w, 970w, 957w, 918w, 910w, 879w, 865w, 805w, 775w, 750m, 715w, 672w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·80, s (18-Me); 1·27, s (19-Me); 2·34, m (H2); 3·20, m, 1H (H6β); 3·63, d, *J* 9·4 Hz, 1H [$CH(CO_2Me)_2$]; 3·65, m (H17); 3·73, s (OMe); 3·75, s (OMe); 5·53, d, *J* 1·2 Hz (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·0 (C3); 170·5 (C5); 168·8, 168·4 (ester carbonyls); 120·9 (C4); 81·4 (C17). Mass spectrum: *m/e* 419 (35%), 418 (100), 359 (10), 355 (10), 287 (25), 286 (25).

*Dimethyl 3,20-Dioxopregn-4-en-6α-ylmalonate (4c; R′ = Me)*

Treatment of dimethyl 3,20-dioxopregn-4-en-6β-ylmalonate (3c; R′ = Me) (0·22 g, 0·5 mmol) with *p*-toluenesulphonic acid monohydrate (0·15 g, 0·8 mmol) as in (4a; R′ = Me), and purification of the product by preparative thin-layer chromatography on silica afforded a colourless foam of *dimethyl 3,20-dioxopregn-4-en-6α-ylmalonate* (0·12 g, 55%), m.p. 60–63°; $[\alpha]_D$ +113·0°, $[\alpha]_{578}$ +119·0°, $[\alpha]_{546}$ +136·5°, $[\alpha]_{436}$ +243·0°, $[\alpha]_{365}$ +189·0° (*c*, 0·60 in chloroform) (Found: C, 70·4; H, 8·3. $C_{26}H_{36}O_6$ requires C, 70·2; H, 8·2%). $\lambda_{max}$ 240 nm (ε 13400). $\nu_{max}$ ($CHCl_3$) 2925s, 2840m, 1730s, 1693s, 1665s, 1608m, 1447m, 1433m, 1420w, 1383w, 1358m, 1323w, 1275w, 1165m, 1155m, 1125w, 1083w, 1045w, 1028w, 990w, 970w, 960w, 900w, 880w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·68, s (18-Me); 1·26, s (19-Me); 2·12, s (21-Me); 3·31, m, 1H (H6β); 3·62, d, *J* 5·0 Hz, 1H [$CH(CO_2Me)_2$]; 3·72, s (OMe); 3·76, s (OMe); 5·54, s, $W_{h/2}$ 3 Hz (H4).

$^{13}C$ n.m.r. $\delta$ ($CDCl_3$): 209·1 (C20); 199·0 (C3); 170·1 (C5); 168·8, 168·4 (ester carbonyls); 120·9 (C4). Mass spectrum: *m/e* 444 (100%), 413 (10), 385 (15), 384 (10), 375 (10), 374 (20), 314 (10), 313 (25), 312 (35).

*Preparation of 6β-Acetate Esters*

All of the 6β-acetate esters were prepared by the procedure described below for methyl 3-oxocholest-4-en-6β-ylacetate.

*Methyl 3-Oxocholest-4-en-6β-ylacetate (5a)*

A mixture of anhydrous lithium iodide (0·10 g, 0·75 mmol) and dimethyl 3-oxocholest-4-en-6β-ylmalonate (3a; R′ = Me) (0·26 g, 0·5 mmol) in dry dimethylformamide (30 ml) was stirred in a 50-ml two-necked round bottom flask at gentle reflux for 5 h. The mixture was continuously flushed with nitrogen and a trap was used to prevent volatile products from re-entering the reaction mixture. The mixture was cooled and poured into iced, slightly acidified, chloroform (30 ml) solution. The aqueous phase was extracted with chloroform and the combined chloroform extracts were washed with water (100 ml), 0·1% sodium bicarbonate solution (100 ml), 0·5% sodium thiosulphate solution (100 ml) and water (100 ml), dried ($MgSO_4$), and the solvent evaporated. The crude oil was purified by preparative thin-layer chromatography on alumina to give a mixture of *methyl 3-oxocholest-4-en-6β-ylacetate* (5a) and *methyl 3-oxocholest-4-en-6α-ylacetate* (6a) in the ratio of 2 : 1 as a colourless gum which could not be further separated (0·15 g, 65%). The spectroscopic data for the mixture are consistent with those previously reported.[1] $[\alpha]_D$ +72·8°, $[\alpha]_{578}$ +77·0°, $[\alpha]_{546}$ +86·6°, $[\alpha]_{436}$ +131·5°, $[\alpha]_{365}$ −49·4° (*c*, 0·47 in chloroform). $\lambda_{max}$ 242 nm (ε 12090). $\nu_{max}$ (oil) 2925s, 2847s, 1752s, 1672s, 1609m, 1462m, 1440m, 1420m, 1377m, 1365m, 1348m, 1330m, 1290m, 1260m, 1223m, 1186m, 1166m, 1097w, 1085w, 1065w, 1034w, 1008m, 973w, 961w, 944w, 910w, 867m, 840w, 810w, 780w, 735w, 730w, 711w, 685w $cm^{-1}$. P.m.r. (90 MHz, $\delta$, $CDCl_3$): 0·73, s (18-Me); 0·82–0·94, m, 9H (21,26,27-Me); 1·22, s (19-Me of 6α isomer); 1·25, s (19-Me of 6β isomer); 3·66, s (OMe of 6β isomer); 3·68, s (OMe of 6α isomer); 5·61, d, *J* 1·4 Hz, $W_{h/2}$ 3 Hz (H4 of 6α isomer); 5·79, s, $W_{h/2}$ 2 Hz (H4 of 6β isomer). Mass spectrum: *m/e* 456 (100%), 428 (10), 380 (10), 355 (12), 310 (10), 281 (25).

*Methyl 17β-Hydroxy-3-oxoandrost-4-en-6β-ylacetate (5b)*

Treatment of dimethyl 17β-hydroxy-3-oxoandrost-4-en-6β-ylmalonate (3b; R′ = Me) (0·21 g, 0·5 mmol) with anhydrous lithium iodide (0·10 g, 0·75 mmol), as in (5a), and crystallization of the product from pure benzene afforded colourless crystals of *methyl 17β-hydroxy-3-oxoandrost-4-en-6β-ylacetate* (0·09 g, 50%), m.p. 148–150°; $[\alpha]_D$ +84·8°, $[\alpha]_{578}$ +87·9°, $[\alpha]_{546}$ +99·7°, $[\alpha]_{436}$ +153·3°, $[\alpha]_{365}$ −74·1° (*c*, 0·58 in chloroform) (Found: C, 73·7; H, 9·0. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·7%). $\lambda_{max}$ 242 nm (ε 13090). $\nu_{max}$ (Nujol) 3455s, 2910s, 2845s, 1735s, 1655s, 1610m, 1459s, 1452s, 1437s, 1414m, 1375s, 1330w, 1291m, 1265s, 1254w, 1229w, 1210w, 1187s, 1161s, 1120w, 1077w, 1065m, 1047w, 1016w, 994w, 975w, 958w, 947w, 920w, 905w, 885w, 870w, 861w, 835w, 824w, 806w, 784w, 748w, 732w, 715w, 674w $cm^{-1}$. P.m.r. (90 MHz, $\delta$, $CDCl_3$): 0·82, s (18-Me); 1·27, s (19-Me); 3·00, m, 1H (H6α); 3·65, m, 1H (H17α); 3·67, s (OMe); 5·80, s (H4). $^{13}C$ n.m.r. $\delta$ ($CDCl_3$): 199·5 (C3); 172·0, 171·2 (C5 and ester carbonyl); 126·5 (C4); 81·6 (C17). Mass spectrum: *m/e* 360 (27%), 359 (100), 328 (10), 300 (15), 286 (12).

*Methyl 3,20-Dioxopregn-4-en-6β-ylacetate (5c)*

Treatment of dimethyl 3,20-dioxopregn-4-en-6β-ylmalonate (3c; R′ = Me) (0·22 g, 0·5 mmol) as for (5a) gave an oil, which was purified by preparative thin-layer chromatography on alumina in acetonitrile/carbon tetrachloride (15 : 85). The band at $R_F$ 0·35 was taken and crystallization from aqueous ethanol afforded colourless crystals of *methyl 3,20-dioxopregn-4-en-6β-ylacetate* (0·03 g, 15%), m.p. 138–139°, mixed m.p. with an authentic sample of (5c) 134–137° (lit.[1] 131–134°). $\lambda_{max}$ 241 nm (ε 14610). $\nu_{max}$ (KBr) 2965s, 2930s, 2885s, 2850s, 1735s, 1702s, 1660s, 1607m, 1477w, 1463w, 1445m, 1430m, 1409w, 1384w, 1375w, 1352m, 1330w, 1309w, 1290m, 1275w, 1250s, 1237w, 1227w, 1220w, 1205w, 1175s, 1130m, 1092m, 1062w, 1040w, 1028w, 1010m, 975w, 942w, 912w, 902w, 872m, 840w, 775w, 730w, 682w $cm^{-1}$. P.m.r. (90 MHz, $\delta$, $CDCl_3$): 0·69, s (18-Me); 1·26, s (19-Me); 2·13, s (21-Me); 3·67, s (OMe); 5·79, s, $W_{h/2}$ 2 Hz (H4).

*Epimerization of Monoester*

*Methyl 17β-hydroxy-3-oxoandrost-4-en-6α-ylacetate* (*6b*).—*p*-Toluenesulphonic acid monohydrate (0·14 g, 0·75 mmol) was dissolved in dry benzene (30 ml) and the water was removed by azeotropy. Methyl 17β-hydroxy-3-oxoandrost-4-en-6β-ylacetate (5b) (0·18 g, 0·5 mmol) was added and heated under reflux, under nitrogen, for 2 h. The benzene was removed at reduced pressure and the residue dissolved in diethyl ether, washed with water (2 × 100 ml), dried ($MgSO_4$), and the solvent evaporated. Purification by preparative thin-layer chromatography on alumina gave a colourless foam of *methyl 17β-hydroxy-3-oxoandrost-4-en-6α-ylacetate* (0·10 g, 56%), m.p. 54–56°; $[\alpha]_D$ +83·2°, $[\alpha]_{578}$ +87·9°, $[\alpha]_{546}$ +99·4°, $[\alpha]_{436}$ +155·3°, $[\alpha]_{365}$ −61·3° (*c*, 0·54 in chloroform) (Found: C, 73·0; H, 8·8. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·7%). $\lambda_{max}$ 241 nm (ε 12770). $\nu_{max}$ ($CHCl_3$) 3600 sharp, 3460b, 2950s, 2860m, 2830m, 1720s, 1650s, 1595m, 1430m, 1420m, 1400w, 1360m, 1335m, 1315m, 1260m, 1220m, 1157m, 1115w, 1102w, 1055w, 1035m, 1000w, 970w, 945w, 935w, 895w, 860w, 855w, 812w $cm^{-1}$. P.m.r. (90 MHz, δ, $CDCl_3$): 0·80, s (18-Me); 1·24, s (19-Me); 3·69, s (OMe); 5·63, s, *J* 1·5 Hz, 1H (H4). $^{13}C$ n.m.r. δ ($CDCl_3$): 199·4 (C3); 172·8, 171·8 (C5 and ester carbonyl); 120·9 (C4); 81·5 (C17). Mass spectrum: *m/e* 360 (25%), 279 (20), 167 (30), 150 (100).

*Attempted Decarbomethoxylation of 6α-Malonate*

Treatment of lithium iodide (0·10 g, 0·75 mmol) and dimethyl 3-oxocholest-4-en-6α-ylmalonate (4a; R′ = Me) (0·13 g, 0·25 mmol) in dry dimethylformamide (20 ml) as in (5a) gave a colourless gum (0·07, 61%). Analytical thin-layer chromatography and p.m.r. spectroscopy indicated a mixture of products which were not separated.

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