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SYNTHESIS OF METHYL (±)-7-OXO-8-METHYL-PODOCARP-8-EN-16-OATE

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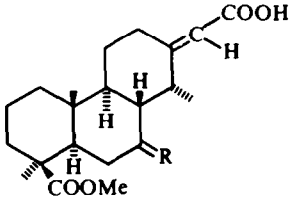
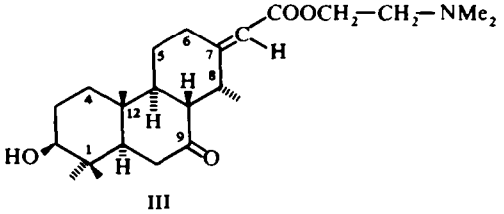
Abstract—The syntheses of methoxy ester IV and the α-β-unsaturated keto ester VI as promising intermediates for diterpenes with the cassane skeleton are reported.

(−)-CASSAMIC acid (I)[1] is a diterpene with the cassane skeleton obtained by hydrolysis of the crystalline alkaloid cassamine isolated from *Erythrophleum guineense* bark. The stereochemistry[2] of cassamic acid (I) has been established by chemical correlation with cassaine (III),[3] but no synthetic evidence has been reported. A fundamental congenor of (−)-cassamic acid (I) is (−)-9-desoxoderivative (II) the stereochemistry of which is known.[4] As the asymmetric centres of the acid I are present also in the (−)-9-desoxocassamic acid (II), we attempted the synthesis of the less difficult (±)-9-desoxo derivative (II) via the key intermediates (IV and VI), followed by transformation of VI into II. The syntheses of the methoxy ester (IV) and the α-β unsaturated ketone (VI) are the subject of this paper.

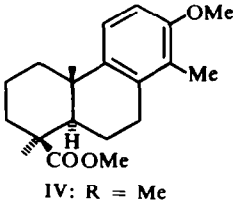
The methyl (±)-7-methoxy-8-methyl desoxypodocarpate (IV)* was previously obtained[5] from ethyl 1,3-dimethylcyclohexan-2-one-1-carboxylate (VIII) and β-(*o*-methylphenyl)ethyl bromide (IX) followed by dehydration and ring-closure of the



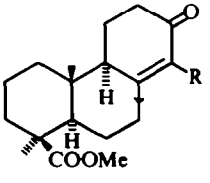
I: R = O
II: R = H



III



IV: R = Me
V: R = H

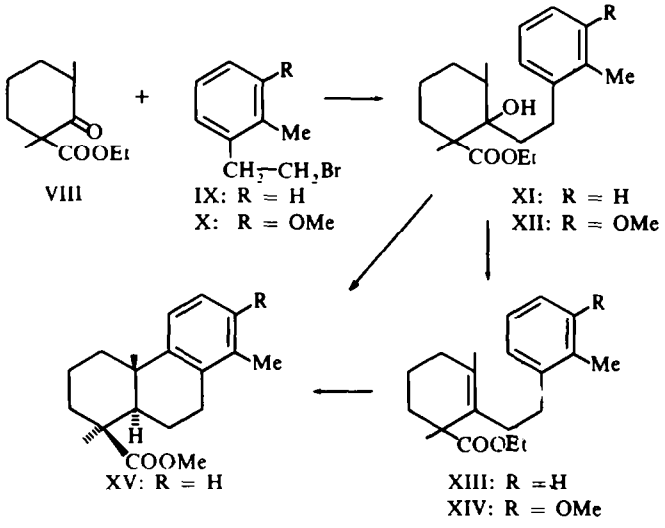


VI: R = Me
VII: R = H

* The nomenclature used is that of W. Klyne, *J. Chem. Soc.* 3072 (1953). The formulae depicted always represent a racemate unless otherwise specified.

unsaturated ester (XIII).[6] The ester (XV) was then converted into methoxy ester (IV) in five steps.

The over-all yield from the keto ester (VIII) was 1·2%. The step IV → VI (see below) causes the greatest difficulty. In order to overcome this and allowing for the importance of IV in the synthesis of the resin acids of the cassane series, we looked for a more suitable route for a large-scale preparation of the ester (IV).

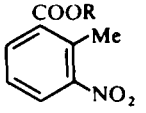


An attempt was made[7] to eliminate the laborious introduction of OMe at C-7 by utilizing direct condensation of the keto ester (VIII) with the Grignard reagent of β-(2-methyl-3-methoxyphenyl) ethyl bromide (X) and then cyclizing the resulting alcohol (XII) or the unsaturated ester (XIV). The yield from VIII, however, was disappointing, 0·5–0·7%. Since the previous investigations[5,7] pointed out that the key-steps VIII + IX → XIII and VIII + X → XII give poor yields, we decided to replace the β-arylethyl bromide with a phenylacetylene derivative as starting material. The condensation reaction of some phenylacetylenes with keto ester (VIII) has been reported[8] for the synthesis of resin acids and good yields were obtained. The suitable phenylacetylene derivative for our purpose is 2-methyl-3-methoxyphenylacetylene (XXIII), unknown in the literature, and consequently its synthesis was necessary.

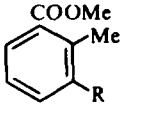
The starting material chosen was the commercial 2-methyl-3-nitro benzoic acid (XVI) which was esterified to give the corresponding methyl ester (XVII); this was further hydrogenated in the presence of C–Pd (10%) and methylcellosolve, to afford methyl 2-methyl-3-aminobenzoate (XVIII). The resulting amino ester (XVIII) was diazotized and hydrolysed to give methyl 2-methyl-3-hydroxybenzoate (XIX) which in a single operation was converted into 2-methyl-3-methoxybenzoic acid (XX)[9] in 60% over-all yield from the acid (XVI).* The methoxy acid (XX) was then converted into 2-methyl-3-methoxy benzoylchloride (XXI) and this substance afforded the 2-

* The acid XX has been prepared[9] from sodium hydrogen-3-aminonaphtalene-1,5-disulphonate and gave a similar over-all yield. Since the commercial naphthalene derivative was difficult to get we decided to synthesize XX as reported above.

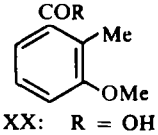
methyl-3-methoxyacetophenone (XXII)[9, 10*] *via* the dimethylcadmium reagent.[11†] Finally, the desired 2-methyl-3-methoxyphenylacetylene (XXIII) was obtained from XXII by reaction, first with phosphorus pentachloride in benzene, and then with sodamide in liquid ammonia.[12] The over-all yield from the starting acid (XVI) was 34%.



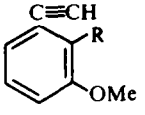
XVI: R = H
XVII: R = Me



XVIII: R = NH_2
XIX: R = OH

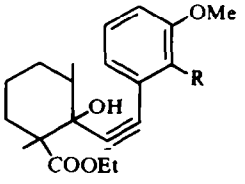


XX: R = OH
XXI: R = Cl
XXII: R = Me

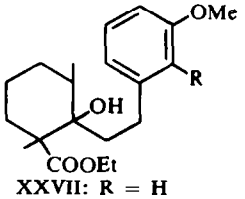


XXIII: R = Me
XXIV: R = H

Condensation of 2-methyl-3-methoxyphenylacetylene (XXIII) with ethyl 1,3-dimethylcyclohexan-2-one-1-carboxylate (VIII) by the Grignard reaction gave a crystalline hydroxy ester (XXV) in 60·5% yield. The latter substance was then hydrogenated over 10% PdC and the resulting alcohol (XII) was treated with sulphuric acid in acetic acid to give (±)-7-methoxy-8-methyldesoxypodocarpic acid (XXVIII) in 23·5% over-all yield from the keto ester (VIII). The methyl ester (IV), obtained by



XXV: R = Me
XXVI: R = H



XXVII: R = H

esterification with diazomethane, was identical in all respects with an authentic sample[5, 7] previously prepared.‡ The condensation reaction *via* the acetylene derivative is therefore a more suitable route for a large scale preparation of the methoxy ester (IV). Comparision with previous reported[5, 7] syntheses shows that the acetylene magnesium bromide derivative is a more selective condensing agent with respect to the

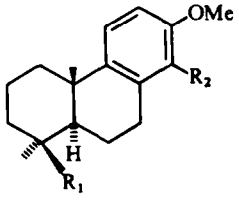
* The acid XX has been converted (in poor yield) into the methoxyacetophenone (XXII) by passing a mixture with acetic acid over thoria.

† The procedure (Experimental) utilizing dimethylcadmium instead of the less practicable methyl zinc iodide.[10] was found preferable.

‡ The good results obtained, suggested a route utilizing the condensation reaction with acetylene magnesium bromide derivatives instead of the phenylethyl magnesium bromide derivatives in order to obtain useful intermediates in the synthesis of non-aromatic resin acids. The results will be published in a subsequent paper.

phenylethyl magnesium bromide derivative and that the better yield in acid cyclization is probably ascribable to the higher purity of the intermediate alcohol (XII). The simplest method for the preparation of the second key compound (VI) appeared to be the Birch reduction of the methoxy ester (IV), followed by mineral acid isomerization of the β-γ unsaturated ketone imtermediate as carried out on analogous compounds (V[13] and XXIX[14]). Unfortunately the reduction of the aromatic ring of IV using the technique of Dryden *et al.*[15] coupled with the "reductive hydrolysis" procedure[16] for converting the ester group into the corresponding acid, was unsuccessful. The only products isolated were the methoxy acid (XXVIII; 80%) and the methoxy alcohol (XXX; 20%) identical (mixture m.p. and IR) with authentic samples. Using t-amyl alcohol-dioxan instead of t-butanol-tetrahydrofuran as proton-donating cosolvent system, the sole isolable product was the methoxy acid (XXVIII). When attempts were made to reduce the methoxy ester (IV) with the most powerful reagent, lithium in ethylamine,[17] in the presence of t-amyl alcohol, a mixture of two or three products was always obtained from which the α-β unsaturated keto ester (VI) could be isolated in only poor yield. From the methoxy ester IV (reaction stopped after 45 min) three products were isolated by chromatography on alumina: the α-β unsaturated keto ester (VI) and two solids of m.p. 104–105° and 130–131°.

The compound, m.p. 104–105° was also obtained as the only isolable product after prolonged (7 hr) reduction of the methoxy alcohol (XXX). On reduction of the acid

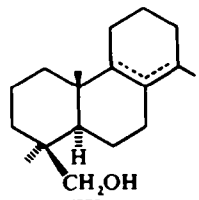


XXVIII: R_1 = COOH; R_2 = Me
XXIX: R_1 = Me; R_2 = Me
XXX: R_1 = CH_2OH; R_2 = Me

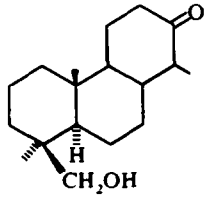
XXVIII for 4 hr, the isolable products were: the desired ketone (VI), the known[5] hydroxy ester (XXXIII) and the above-mentioned solid, m.p. 130–131°.

The structures of compounds, m.p. 104–105° and 130–131° were not further investigated but we assigned the structures XXXI and XXXII, respectively, on the basis of their IR spectra and literature data for similar compounds.[15,18] The lack of reduction of the aromatic ring; the formation of hydrogenolysis products and the demethylation reaction observed during Birch type reductions of the methoxy ester (IV) are also reported for analogous compounds,[15,18] and often represent the principal reactions. The course of the Birch reduction is often taken to support the structures of α-β unsaturated ketones which are obtained after mineral acid isomerization. For the ketone (VI), however, additional proof is necessary because it was always obtained in poor yield, together with unusual by-products. In this connection the known[13] α-β unsaturated ketone (VII)* was treated with methyl iodide in the presence of potassium t-butoxide according to the known procedure.[19] Three products were separated by

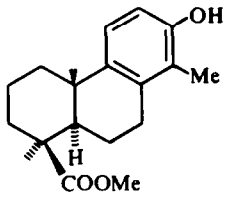
* The ketone VII was prepared from the methoxy ester V.[13] The latter substance was obtained according to known sequence:[8a,13] VIII + XXIV → XXVI → XXVII → V. We obtained a good yield by repeating the procedure described for the cyclization of XXVII. The *m*-methoxyphenylacetylene (XXIV) was prepared (Experimental) from *m*-methoxyacetophenone using a more convenient procedure.



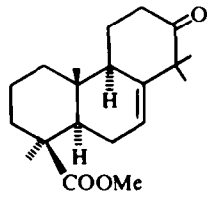
XXXI



XXXII



XXXIII



XXXIV

chromatography on alumina. The least polar material was a saturated ketone which may be represented as XXXIV based on IR spectrum and accepted course of reaction.[19] The second compound eluted (20–25% yield) was identical (mixture m.p., IR spectrum and its 2,4-dinitrophenylhydrazone) with the α-β unsaturated compound (VI) derived from the Birch reduction. The structural features of ketone (VI) are therefore established. The last substance isolated was the starting material (VII).

EXPERIMENTAL

All b.ps and m.ps are uncorrected. IR spectra were measured on a Perkin–Elmer 257 and refer to Nujol mulls for solid samples and films for liquid samples.

Pet ether refers to the fraction b.p. 30–60° and neutral alumina was used for chromatography.

Methyl 2-methyl-3-nitrobenzoate (XVII). The 2-methyl-3-nitrobenzoic acid XVI (100 g), abs MeOH (500 ml) and conc H_2SO_4 (10 ml) were refluxed for 8 hr. The bulk of the MeOH was removed *in vacuo* and after dilution with water, the product was isolated by ether-extraction.

Crystallization from MeOH gave XVII (100 g, 93% yield); m.p. 65–66° (lit.[20] 66°).

Methyl 2-methyl-3-aminobenzoate (XVIII). The nitroester XVII (25·5 g) suspended in 95% EtOH (300 ml) containing methylcellosolve (12 ml) was hydrogenated for 2 hr over 10%Pd–C (1·2 g) at 25–30°, at a press of 2–3 atm.

Hydrogen gas was bubbled into the mixture and the initial temp rose rapidly. The temp was controlled using a cooling bath at 25–30°. After the removal of the catalyst, the soln was concentrated *in vacuo* and the residue, after distillation, gave XVIII (20 g, 92·5%) b.p. 130–131°/2·5 mmHg, $n_D^{26} = 1{\cdot}5688$. The acetate after crystallization had m.p. 108° (lit.[21] 108°).

Methyl 2-methyl-3-hydroxybenzoate (XIX). To an ice-cooled soln of XVIII (21 g) in 5·4% H_2SO_4 (370 g), a soln of $NaNO_2$ (9 g) in water (25 ml) was added slowly. The cooling bath was removed, and after 15 min the mixture was heated to reflux temp for 20 min. After cooling the crystalline phenol was filtered and washed with water. Crystallization of the product from 95% EtOH gave 18 g of XIX (86%); m.p. 75–76° (lit.[22] 74·5–75·5°).

2-Methyl-3-methoxybenzoic acid (XX). To a stirred soln of XIX (58 g) in 15% KOH aq (190 ml) Me_2SO_4 (90·2 g) was added portionwise. The stirring was continued for 1 hr at 60°. The mixture was then heated under reflux for 3 hr, after the addition of 35% KOH aq (130 ml).

The soln was allowed to stand at room temp, diluted with water and then extracted with ether. The aqueous layer was then acidified with dil HCl. The ppt was collected on a Buchner funnel and washed with water. Recrystallization from 75% EtOH afforded 47 g of XX (81·5%); m.p. 152° (lit.[9] 152°).

2-Methyl-3-methoxybenzoyl chloride (XXI). The acid XX (58 g) was added to $SOCl_2$ (200 ml) and the mixture was heated under reflux for 20–25 min. The soln was concentrated *in vacuo* and the residue was distilled to give 57 g of XXI (89%); b.p. 92–93°/0·9 mmHg. m.p. 50–52° (lit.[23] 40°). (Found: C, 59·12; H, 4·93. $C_9H_9O_2Cl$ requires: C, 58·99; H, 4·91%).

2-Methyl-3-methoxyacetophenone (XXII). To a soln of MeMgBr [from 12·4 g Mg and 53 g MeBr] in 230 ml dry ether, a suspension of anhyd powdered $CdCl_2$[24] (51 g) in dry ether (120 ml) was added portionwise. The reaction mixture was stirred for 90 min under N_2 at room temp. Then a soln of XXI (65 g) in dry ether (100 ml) was added in 15 min without cooling and the mixture stirred for 2 hr. After standing overnight at room temp the reaction mixture was heated under reflux for 1 hr and then acidified with cold dil H_2SO_4. The ethereal layer was separated, washed with water, NaOH aq and brine, and then dried (Na_2SO_4). Evaporation of the ether under reduced press, and subsequent distillation of the resulting oil, afforded 49 g of XXII (85%); b.p. 132°/15 mmHg, $n_D^{25} = 1·5359$ (lit.[10] 131–132°/15 mmHg). (Found: C, 73·45; H, 7·40. $C_{10}H_{12}O_2$ requires: C, 73·14; H, 7·37%).

2-Methyl-3-methoxyphenylacetylene (XXIII). To an ice cooled mixture of XXII (31 g) and dry benzene (8 ml) PCl_5 (39·3 g) was added over a period of 45 min, with mechanical stirring. After the addition, stirring was continued for 4 hr and then the mixture was left to stand overnight at room temp. The mixture was poured on to ice and extracted with ether. The organic layer was washed with ice-water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue in dry ether (160 ml) was added slowly to a suspension of sodamide [prepared from Na (10·3 g) and liquid ammonia (600 ml) with a little $FeCl_3$]; stirring was then continued for 2 hr and the mixture was left to stand overnight at room temp. After the addition of NH_4Cl (32·4 g) and water, the ether layer was separated, washed with sat brine, dried (Na_2SO_4) and concentrated *in vacuo*. Distillation of the residue gave 20·2 g of XXIII (73%); b.p. 98–100°/15 mmHg, $n_D^{25} = 1·5562$; ν_{max} 3300 cm^{-1}. (Found: C, 82·35; H, 6·88. $C_{10}H_{10}O$ requires: C, 82·16; H, 6·90%).

m-*Methoxyphenylacetylene* (XXIV). Compound XXIV was prepared according to the procedure described for XXIII, in 73% over-all yield; b.p. 88–90°/15 mmHg, $n_D^{25} = 1,5550$ (lit.[25] b.p. 85°/13 mmHg, $n_D^{25} = 1·5560$).

Ethyl 2-hydroxy-2-(2′-methyl-3′-methoxyphenyl) ethynyl-1,3-dimethylcyclohexanecarboxylate (XXV). To a boiling soln of EtMgBr [from 3·4 g Mg and 16·5 g EtBr] in dry ether (85 ml) and pure THF (85 ml) under N_2, XXIII (20 g) in THF (35 ml) was added during 1 hr with stirring. Boiling was continued for 40 min and then VIII (30 g) in dry THF (40 ml) was added dropwise during 1 hr.

The soln was heated under reflux for 1 hr. After cooling the mixture was treated cautiously with sat NH_4Cl aq (200 ml). The organic layer was separated and the mother liquor extracted with THF. The combined extracts were washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 28·5 g of XXV (60·5%) which recrystallized from EtOAc m.p. 113–114°; ν_{max} 3520, 2292, 1720, 1595, 1577 cm^{-1}. (Found: C, 73·01; H, 8·09. $C_{21}H_{28}O_4$ requires: C, 73·22; H, 8·19%).

Ethyl 2-hydroxy-2-(2′-methyl-3′-methoxyphenyl)ethyl-1,3-dimethylcyclohexanecarboxylate (XII). A mixture of 28·5 g of XXV and 3·3 g 10% Pd–C in EtOAc (130 ml) and THF (65 ml) was hydrogenated at room temp and atm press. After absorbing 2 moles H_2, the catalyst was filtered off and the filtrate was concentrated *in vacuo* to give an oil (27 g); ν_{max} 3560, 1718, 1575 cm^{-1}. This was employed for the next step without further purification.

Methyl (±)-*7-methoxy-8-methyl desoxypodocarpate* (IV). The crude XII (27 g) was dissolved in AcOH (184 ml), conc H_2SO_4 (13 ml) added, and the mixture heated under reflux for 4 hr. After cooling it was poured into 10% EtOH. The above acid was then treated with ethereal diazomethane to give 11·4 g of IV (42%) which was recrystallized from MeOH–benzene 8 : 1; m.p. 159–160°; ν_{max} 1728, 1600, 1595 cm^{-1}.

The ester IV was identical (Mixture m.p. and IR) with an authentic sample.

Attempted reduction of methoxy ester (IV) *in liquid ammonia*. A soln of IV (500 mg) in THF (7 ml) and t-BuOH (7 ml) was added to liquid ammonia (50 ml) cooled in a dry-ice–acetone bath. Na (350 mg) was added to the stirred soln in portions over a period of 30 min. Then Li (350 mg) was added portionwise and the mixture stirred for 4 hr. Li was destroyed using abs EtOH and ammonia evaporated. The residue was dissolved in water and extracted with ether. The ethereal soln afforded 90 mg of XXX (m.p. 132–133° from MeOH aq) identical (mixture m.p. and IR) with an authentic sample. The above aqueous layer was acidified and worked up by a routine procedure to give 350 mg of XXVIII. The corresponding methyl ester was identical with IV by m.m.p. and IR spectrum.

If t-amyl alcohol–dioxan was employed instead of t-butanol–THF, the sole isolable product was XXVIII.

Reduction in ethylamine

(*a*) *from methoxy ester* (IV). Li (300 mg) was added to a well stirred and cooled soln of IV (500 mg) in t-amyl alcohol (7 ml) and $EtNH_2$ (50 ml). A few drops of liquid ammonia were added. After 15 min more Li (200 mg) and t-amyl alcohol (5 ml) were added and the mixture was stirred for 30 min with cooling. Abs EtOH was slowly added to destroy the remaining Li and the solvents were removed *in vacuo*. The residue was dissolved in water, acidified with dil HCl and then extracted with EtOAc. The extract was washed with sat brine, dried (Na_2SO_4) and concentrated.

The semi-crystalline material was dissolved in 95% EtOH (15 ml) containing conc HCl (1·3 ml) and water (1 ml). After refluxing for 45 min, the soln was worked up in the usual way. The residual oil was esterified with ethereal diazomethane and chromatographed over alumina to afford 3 products from pet. ether and eluates of pet. ether–ether solvent gradients. Two products (m.p. 104–105° and 130–131° recrystallized from pet. ether) have been tentatively depicted as XXXI and XXXII, respectively. The third compound (40 mg) was the desired VI; m.p. 113–114° (from pet. ether), ν_{max} 1728, 1670, 1620 cm^{-1}. (Found: C, 75·18; H, 9·33. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%); 2,4-dinitrophenylhydrazone m.p. 240–242° (from EtOAc). (Found: C, 62·12; H, 6·64; N, 11·57. $C_{25}H_{32}O_6N_4$ requires: C, 61·96; H, 6·66; N, 11·56%).

(*b*) *from methoxy alcohol* (XXX). According to the above procedure, XXX (500 mg) was reduced with Li (800 mg) in $EtNH_2$ (60 ml) in presence of t-amyl alcohol (25 ml) for 7 hr. The mixture was then worked up as reported above. After mineral acid isomerization, the mixture was treated with diazomethane and then chromatographed on alumina. The sole isolable product (85 mg) was the probable compound XXXI; m.p. 104–105°, ν_{max} 3450 cm^{-1}.

(*c*) *from methoxy acid* (XXVIII). Li (700 mg) was added to stirred soln of XXVIII (500 mg) in dry dioxan (20 ml). The soln was heated for 6 min and after cooling, $EtNH_2$ (30 ml) and t-amyl alcohol (3 ml) were added. The mixture was stirred for 4 hr with cooling and then worked up as in (*a*). After mineral acid isomerization and subsequent esterification with diazomethane, the residue was chromatographed on alumina.

Elution with pet. ether and pet. ether–ether afforded XXXII (50 mg); m.p. 130–131°, ν_{max} 3450, 1713 cm^{-1}; VI (30 mg), and XXXIII (110 mg); m.p. 203–204°, ν_{max} 3380, 1718, 1690, 1600 cm^{-1}. The identity of XXXIII was proved by m.m.p. and IR comparison.[5]

Repeating the reduction reactions cited above, under identical conditions, in some cases gave different results.

Methyl (±)-7-*Oxo*-8-*methylpodocarp*-8-*en*-16-*oate* (VI) *by methylation of* VII. A soln of VII (2·6 g) in t-BuOH (100 ml) was added under dry N_2 to a boiling soln of K (0·5 g) in t-BuOH (29 ml). After 30 min refluxing, MeI (0·6 ml) in t-BuOH (200 ml) was added dropwise to the boiling soln during 2·5 hr.

After a further 30 min refluxing, the mixture was cooled and concentrated *in vacuo*. Water was then added and the product was isolated with ether in the usual way. The residual material was chromatographed on alumina (200 g) eluting with pet. ether, pet. ether–benzene 1 : 1/1 : 4/1 : 8, benzene, benzene–ether 10 : 1/2 : 1/1 : 1, ether.

The first fractions gave XXXIV (0·150 g) m.p. 88–90° from pet. ether; ν_{max} 1728, 1713 cm^{-1}; 2,4-dinitrophenylhydrazone m.p. 175–176° from MeOH.

The next solid fraction afforded VI (0·750 g) m.p. 112–114° from pet. ether and was identical (m.m.p., IR spectrum and 2,4-dinitrophenylhydrazone) with the compound derived from IV (or XXVIII) *via* the Birch reduction.

The last fractions furnished the starting material VII (0·43 g) with m.p. 96–98° from pet. ether. The IR spectra were identical and no depression in m.p. on admixture was observed.

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