

Synthesis of Tertiary Acyloins using Acyl Anions formed from 1,3-Dithians. Total Synthesis of (\pm)-(2*E*)-1,7-Dihydroxy-3,7,11-trimethyldodeca-2,10-dien-6-one

By Lino Colombo, Cesare Gennari, Carlo Scolastico,* and (in part) M. Grazia Beretta, Istituto di Chimica Organica dell'Università, Centro delle Sostanze Organiche Naturali del C.N.R., Via Saldini 50, 20133 Milano, Italy

An advantageous approach for the synthesis of tertiary acyloins has been studied. The results were used in designing a successful synthesis of (\pm)-(2*E*)-1,7-dihydroxy-3,7,11-trimethyldodeca-2,10-dien-6-one (18). This acyloin was synthesized by alkylation of 2-acyl-1,3-dithians (7a and b) with (2*E*)-5-iodo-3-methylpent-2-en-1-yl tetrahydropyranyl ether (10). The synthesis of the key intermediate (10) is reported. This type of modified farnesol can be used for investigating the biosynthetic intermediates of natural substances.

THE biosynthesis of mycophenolic acid¹ and of cochliquinones² can be examined through the synthesis of intermediates containing farnesyl chains with selective functionalization of the double bond in the 6-position. Such intermediates can be synthesized from (\pm)-(2*E*)-1,7-dihydroxy-3,7,11-trimethyldodeca-2,10-dien-6-one (18) which can also be used for the synthesis of farnesol derivatives containing a 6,7-epoxy group.

Compounds (8) were selected as suitable models for examining the best method of obtaining tertiary acyloins.

¹ L. Canonica, E. Kroszczyński, B. M. Ranzi, B. Rindone, E. Santaniello, and C. Scolastico, *J.C.S. Perkin I*, 1972, 2639; F. Aragazzini, R. Craveri, M. G. Beretta, and C. Scolastico, *Ann. Micr.*, 1974, 24, 257.

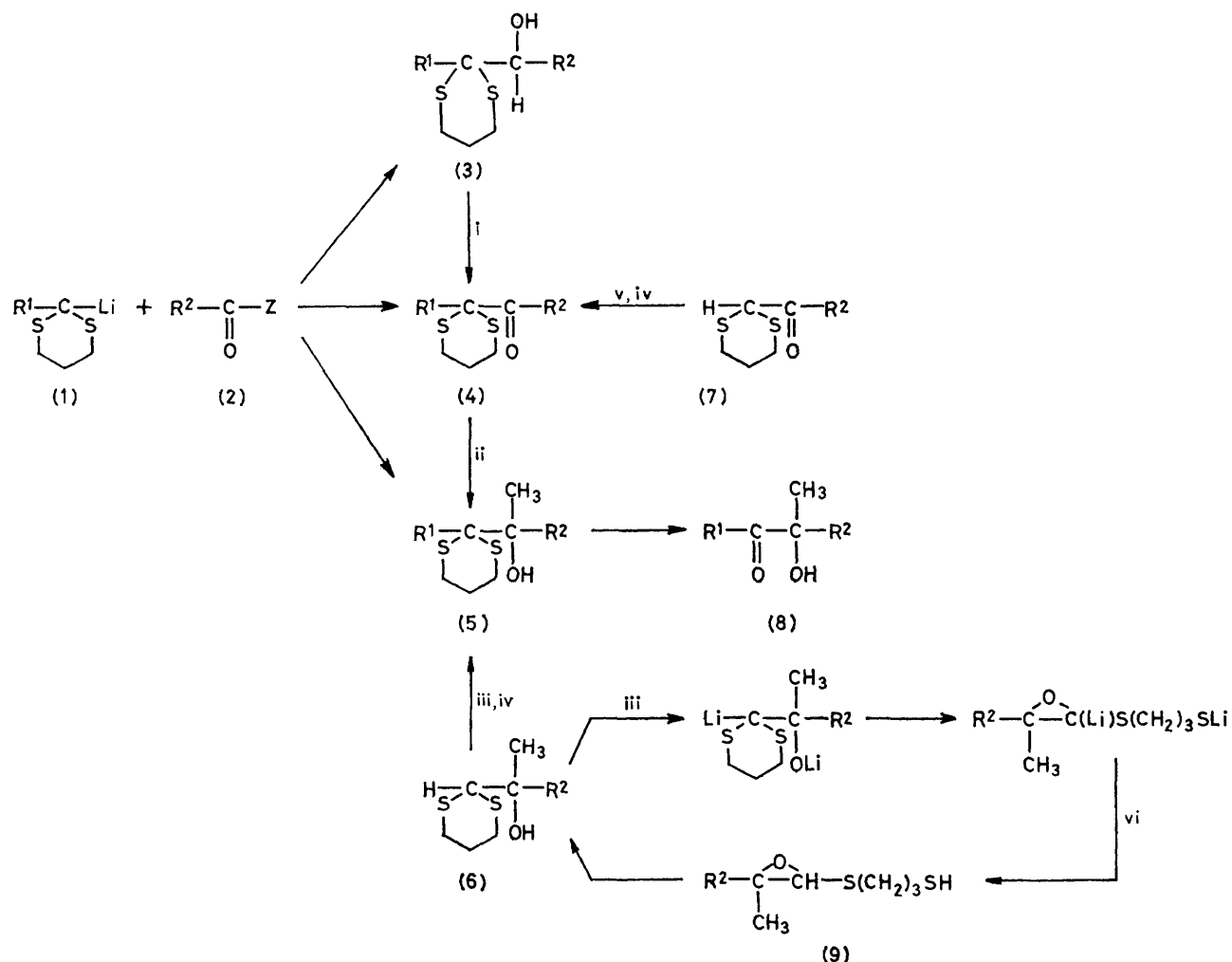
Three different methods of synthesis were adopted employing acyl anions formed from 1,3-dithians³ (Scheme 1). First, the condensation of 2-alkyl-2-lithio-1,3-dithians (1) with carbonyl compounds (2) was investigated. This condensation is markedly influenced both by the nature of R¹ and by the electrophilicity of the reaction centre as well as by its accessibility (Table; experiments 1–8). The reactivity order for Z is H > CH₃ > OCH₃ >> Cl. The yield of the condensation decreases to zero upon increasing the size of the 2-substituent in the dithian.

² L. Canonica, B. M. Ranzi, B. Rindone, A. Scala, and C. Scolastico, *J.C.S. Chem. Comm.*, 1973, 213.

³ O. W. Lever, jun., *Tetrahedron*, 1976, 32, 1943, and references therein.

Only multiunsaturated conjugated aldehydes, among aliphatic carbonyl compounds, condense in high yield with substituted lithiodithians carrying bulky groups.⁴ Also the accessibility of the carbonyl group is important since compounds with a less hindered carbonyl group, such

as 3 β -hydroxypregn-5-en-20-one 3-tetrahydropyranyl ether, form an adduct in 70% yield on condensation with 2-isopentyl-2-lithio-1,3-dithian.⁵ The adduct (3) can be easily converted into (5) on treatment initially with CrO₃ and then with CH₃Li. The hydrolysis of (5) to the corresponding acyloins (8) takes place in high yield when carried out with CH₃I.⁶ This hydrolysis is definitely preferable to that using HgCl₂,⁷ which gives markedly lower yields. The second method was based on the alkylation of 2-(α -hydroxyalkyl)-1,3-dithians (6), as



SCHEME 1 Reagents: i, CrO₃; ii, CH₃Li; iii, 2 equiv. BuⁿLi; iv, R¹I; v, NaH; vi, H₂O

as 3 β -hydroxypregn-5-en-20-one 3-tetrahydropyranyl ether, form an adduct in 70% yield on condensation with 2-isopentyl-2-lithio-1,3-dithian.⁵ The adduct (3) can be easily converted into (5) on treatment initially with CrO₃ and then with CH₃Li. The hydrolysis of (5) to the corresponding acyloins (8) takes place in high yield when carried out with CH₃I.⁶ This hydrolysis is definitely preferable to that using HgCl₂,⁷ which gives markedly lower yields. The second method was based on the alkylation of 2-(α -hydroxyalkyl)-1,3-dithians (6), as

(9), possibly *via* a carbene (Scheme 1). This rearrangement is analogous to known reactions.⁹ The α -epoxy sulphides (9) are extremely labile, tending to close the dithian ring and revert to the starting material.

The best method of synthesizing acyloins (8) in good yield, even with the bulky substituents which make the other routes unattractive, is the alkylation of 2-acyl-1,3-dithians¹⁰ (7) with alkyl iodides (Table, experiments 10–12). The yields were acceptable even for highly hindered primary iodides which engaged side reactions.

We then obtained acyloin (18) by alkylation of the

⁴ E. J. Corey and M. G. Bock, *Tetrahedron Letters*, 1975, 2643.

⁵ M. Koreeda, N. Koizumi, and B. A. Teicher, *Tetrahedron Letters*, 1976, 4565.

⁶ M. Fetizon and M. Jurion, *J.C.S. Chem. Comm.*, 1972, 382; Hsin-Lan Wang Chang, *Tetrahedron Letters*, 1972, 1989.

⁷ E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553.

⁸ J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2429.

⁹ I. Kuwajima and Y. Kurata, *Chem. Letters*, 1972, 291; T. Cohen, D. Kuhn, and J. R. Falck, *J. Amer. Chem. Soc.*, 1975, **97**, 4749.

¹⁰ D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231.

in >90% yield, using CH_3I in aqueous acetone in the presence of CaCO_3 .⁶ Finally the tetrahydropyranyl protecting group was removed by treatment with $\text{AcOH}-\text{H}_2\text{O}-\text{THF}$ (3 : 1 : 1) to give (18) in good yield.

EXPERIMENTAL

Reactions based on the use of lithiodithians were carried out in predried tetrahydrofuran in an inert atmosphere (purified argon). G.l.c. analyses were carried out with a Carlo Erba Fractovap 2400 V (SE 30, 3%; 2 m). Mass spectra were recorded with a LKB 9000 (70 eV) spectrometer, i.r. spectra (CHCl_3) with a Perkin-Elmer 257 spectrophotometer, and n.m.r. spectra (solvent CDCl_3 ; Me_4Si as internal standard) with a Varian A-60 (60 MHz) or XL-100 (100 MHz) instrument. Kieselgel 60 F_{254} (Merck) was used for t.l.c., 70–230 mesh silica gel (Merck) and 60–100 mesh Florisil (B.D.H.) were used for column chromatography.

Synthesis of 2-n-Butyl-1,3-dithian.—A solution of 1,3-dithian (1 g) in tetrahydrofuran (20 ml) at -40°C was treated with 1.68N-n-butyl-lithium in n-hexane (5.178 ml). The mixture was stirred at -15°C for 90 min. The solution, cooled to -70°C , was added to a solution of n-butyl iodide (0.94 ml) in tetrahydrofuran (20 ml). After 90 min at -70°C the mixture was allowed to heat to 0°C , and treated with saturated, aqueous NaCl solution (45 ml). The aqueous phase was extracted with ether (4×40 ml). The organic extracts were dried (K_2CO_3) and evaporated. The crude mixture (1.6 g) was chromatographed on silica gel (160 g). Elution with n-hexane-ethyl acetate (95 : 5) provided an oil which, after distillation (100°C at 0.1 mmHg), gave 2-n-butyl-1,3-dithian (0.963 g, 65%) (Found: C, 55.0; H, 8.9. $\text{C}_8\text{H}_{16}\text{S}_2$ requires C, 54.5; H, 9.1%); m/e 176 (M^+); δ (CDCl_3) 0.9 (3 H, t, CH_3), 2.9 (4 H, m, CH_2S), 4.05 (1 H, t, SCHS). G.l.c. analysis (140°C) showed a single component.

Reactions of 2-n-Butyl-1,3-dithian.—A solution of 2-n-butyl-1,3-dithian (0.2 g) in tetrahydrofuran (5 ml) at -40°C was treated with 1.57N-n-butyl-lithium in n-hexane (0.75 ml). When specified, tetramethylethylenediamine (0.13 g) was added as cosolvent (Table). The mixture was stirred at -15°C for 2 h. To the resulting solution, cooled to -70°C , was added a carbonyl compound (1 equiv.) in tetrahydrofuran (5 ml). After 3 h at -70°C and 18 h at -5°C (Table; experiment 1), 3 h at -70°C (experiment 3), or 1 h at -70°C and 41 h at -5°C (experiment 5), the mixture was treated with saturated brine (10 ml). The aqueous phase was extracted with ether (4×10 ml). The organic extracts were dried and evaporated. The crude mixture was chromatographed on silica gel (experiments 1 and 3) or Florisil (experiment 5). Elution with n-hexane-ethyl acetate (98 : 2) gave the following products: 2-(1-hydroxy-1,5-dimethylhex-4-enyl)-2-n-butyl-1,3-dithian (Found: C, 63.0; H, 10.2. $\text{C}_{16}\text{H}_{30}\text{OS}_2$ requires C, 63.5; H, 9.9%), m/e 302 (M^+), δ (CDCl_3) 1.38 (3 H, s, CH_3CO), 1.69 [6 H, d, (CH_3) $_2\text{C}$], 2.6–3.0 (4 H, m, CH_2S), and 5.2 (1 H, m, CH), ν_{max} 3 500 (OH), 1 380 (OH), and 1 100 cm^{-1} (CO), g.l.c. analysis (200°C) showed a single component; 2-(1-hydroxy-5-methylhex-4-enyl)-2-n-butyl-1,3-dithian (Found: C, 61.9; H, 9.7. $\text{C}_{15}\text{H}_{28}\text{OS}_2$ requires C, 62.5; H, 9.7%), m/e 288 (M^+), g.l.c. analysis (200°C) showed a single component; 2-(5-methyl-1-oxohex-4-enyl)-2-n-butyl-1,3-dithian (Found: C, 62.0; H, 8.5. $\text{C}_{15}\text{H}_{26}\text{OS}_2$ requires C, 62.9; H, 9.0%), m/e 286 (M^+), g.l.c. analysis (200°C) showed a single component, δ (CDCl_3) 1.6br [6 H, s, (CH_3) $_2\text{C}$], 2.7 (4 H, m, CH_2S), 5.1 (1 H, m, CH), ν_{max} 1 705 cm^{-1} (C=O).

Synthesis and Reactions of [1; $\text{R}^1 = E-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CHCH}_2\text{OTHP}$].—A solution of 1,3-dithian (0.28 g) in tetrahydrofuran (4 ml) at -40°C was treated with 1.68N-n-butyl-lithium in n-hexane (1.46 ml). The mixture was stirred at -15°C for 90 min, then cooled to -70°C , and added to a solution of (2E)-5-iodo-3-methylpent-2-en-1-ol tetrahydropyranyl ether (10) (0.483 g) in tetrahydrofuran (4 ml). After 1 h at -70°C the mixture was worked up as usual and chromatographed on silica gel. Elution with n-hexane-ethyl acetate (95 : 5) gave 2-[(3E)-3-methyl-5-tetrahydropyranyloxopent-2-enyl]-1,3-dithian (0.32 g, 68%) (Found: C, 59.8; H, 8.8. $\text{C}_{15}\text{H}_{26}\text{O}_2\text{S}_2$ requires C, 59.6; H, 8.6%); m/e 302 (M^+) and 301 ($M - 1$); δ (CDCl_3) 1.65br (3 H, s, CH_3C), 2.8 (4 H, m, CH_2S), 3.4–3.9 (2 H, m, CH_2O), 3.8–4.2 (2 H, m, $\text{C}(\text{CH}_2\text{O})$), 4.0 (1 H, m, SCHS), 4.6br (1 H, s, OCHO), and 5.4 (1 H, t, $\text{C}(\text{H})$). G.l.c. analysis (175°C) showed a single component. A solution of this compound (0.15 g) in tetrahydrofuran (1.2 ml) at -40°C was treated with 1.62N-n-butyl-lithium in n-hexane (0.32 ml) with stirring at -15°C for 3 h. This solution at -70°C , containing [1; $\text{R}^1 = E-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CHCH}_2\text{OTHP}$] was added to a carbonyl compound (1 equiv.) in tetrahydrofuran (1.2 ml). Tetramethylethylenediamine (0.057 g) was added in the case of 5-methylhex-4-enal and 6-methylhept-5-en-2-one, and not for methyl 5-methylhex-4-enoate. After 65 h, the temperature was slowly raised to -20°C , and the solution was then stored under argon at -20°C for one week. The results are in the Table (experiments 2, 4, and 6).

Oxidation of (3) with CrO_3 .—A solution of [3; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.17 g) in methylene chloride (1 ml) was added in one portion to pyridine (0.582 ml)-chromium(vi) oxide (0.355 g), in methylene chloride (5 ml). After stirring for 4 h at room temperature the solution was decanted from the residue, which was washed with anhydrous ether (4×10 ml). The decanted solutions were evaporated *in vacuo* and the residue was taken up in ether, filtered, washed with saturated brine, dried, and evaporated. The crude mixture (0.165 g) was chromatographed on Florisil (16 g). Elution with n-hexane-ethyl acetate (98 : 2) provided [4; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.143 g, 87%).

Reaction of (4) with CH_3Li .—A solution of [4; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.17 g) in tetrahydrofuran (6 ml) at 0°C was treated with 1N-methyl-lithium in ether (3 ml). Isolation as usual provided [5; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.176 g, 98%).

Hydrolysis of (5).—(i) *With HgCl_2 .* A solution of [5; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.04 g) in aqueous 80% acetonitrile (3 ml) and tetrahydrofuran (1 ml) was treated under nitrogen with CaCO_3 (0.033 g) and HgCl_2 (0.078 g). The mixture was stirred and heated under reflux and under nitrogen for 6 h, cooled, and filtered through Super Cel. The filter cake was washed thoroughly with n-hexane-dichloromethane (1 : 1); the organic phase was washed with 5M aqueous ammonium acetate, water, and saturated brine, dried, and evaporated. Preparative t.l.c. of the crude mixture (0.029 g) with n-hexane-ethyl acetate (9 : 1) as developing agent provided [8; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.014 g, 50%).

(ii) *With CH_3I .* A solution of [5; $\text{R}^1 = \text{Bu}^n$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{CH}(\text{C}(\text{CH}_3)_2)$] (0.04 g) in aqueous 80% acetone (3 ml) was heated at reflux under nitrogen with CaCO_3 (0.033 g) and CH_3I (1.846 g) for 24 h. The mixture was diluted with ethyl ether (10 ml), washed with 5M aqueous ammonium ace-

tate and saturated brine, dried, and evaporated. Preparative t.l.c. of the crude mixture (0.045 g) with n-hexane-ethyl acetate (9:1) as developing solvent afforded 6-hydroxy-6,10-dimethylundec-9-en-5-one [8; $R^1 = \text{Bu}^n$, $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (0.026 g, 94%) (Found: C, 74.0; H, 11.0. $\text{C}_{13}\text{H}_{24}\text{O}_2$ requires C, 73.5; H, 11.3%), m/e 212 (M^+), 169 ($M - \text{C}_3\text{H}_7$), 151 ($M - \text{C}_3\text{H}_9\text{O}$), 130 ($M - \text{C}_6\text{H}_{10}$), and 127 ($M - \text{C}_5\text{H}_9\text{O}$); g.l.c. analysis (150 °C) showed a single component; ν_{max} 3 480 (OH) and 1 705 cm^{-1} (C=O).

Synthesis of (6).—A solution of 1,3-dithian (0.796 g) in tetrahydrofuran (26 ml) at -40°C was treated with 1.58N-n-butyl-lithium in n-hexane (4.19 ml). The mixture was stirred at -15°C for 90 min. A solution of 6-methylhept-5-en-2-one (0.835 g) in tetrahydrofuran (26 ml) was added to the solution cooled to -70°C . After 1 h the mixture was worked up as usual. The crude mixture (1.6 g) was distilled (200 °C at 0.1 mmHg) and provided 2-(1-hydroxy-1,5-dimethylhex-4-enyl)-1,3-dithian [6; $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (1.3 g, 80%) (Found: C, 58.0; H, 9.0. $\text{C}_{12}\text{H}_{22}\text{OS}_2$ requires C, 58.5; H, 8.9%), m/e 246 (M^+), g.l.c. analysis (180 °C) showed a single component; δ (CDCl_3) 1.3 (3 H, s, CH_3CO), 1.6br [6 H, s, $(\text{CH}_3)_2\text{C}:\text{C}$], 2.85 (4 H, m, CH_2S), 4.17 (1 H, s, SCHS), and 5.10 (1 H, m, $\text{CH}:\text{C}$); ν_{max} 3 480 cm^{-1} (OH).

Alkylation of (6).—A solution of [6; $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (0.2 g) in tetrahydrofuran (4 ml), at -40°C , was treated with 1.57N-n-butyl-lithium in n-hexane (1.08 ml) and tetramethylethylenediamine (0.198 g). The mixture was stirred at -15°C for 2 h. This solution was cooled to -70°C and n-butyl iodide (0.149 g) in tetrahydrofuran (4 ml) was added. After 46 h (1 h at -70°C , 4 h at -45°C , 15 h at -35°C , 8 h at -10°C , 18 h at 0°C) the mixture was worked up as usual. Preparative t.l.c. of the crude mixture (0.19 g), with n-hexane-ethyl acetate (9:1) as developing solvent, gave [5; $R^1 = \text{Bu}^n$, $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (0.019 g, 8%).

Rearrangement of (6).—A solution of [6; $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (0.2 g) in tetrahydrofuran (4 ml) at -40°C was treated with 1.57N-n-butyl-lithium in n-hexane (1.08 ml). The mixture was stirred at -30°C for 6 h, and then at -15°C for 12 h. T.l.c. and g.l.c. showed the appearance of two products. These were unstable since they rapidly reverted to the starting alcohol (6). They are assumed to be the two unstable stereoisomeric α -epoxy sulphides [9; $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$]. The mass spectrum is consistent with this structure, m/e 245 ($M - \text{H}$), 139 ($M - \text{C}_3\text{H}_7\text{S}_2$), and 107 ($M - \text{C}_9\text{H}_{15}\text{O}$).

2-Acyl-1,3-dithians (7).—A solution of 1,3-dithian (2 g) in tetrahydrofuran (45 ml) was treated with 1.62N-n-butyl-lithium in n-hexane (10.5 ml). The solution was stirred at -15°C for 90 min, cooled to -70°C , and added to ethyl acetate (0.733 g) in tetrahydrofuran (10 ml). After 1 h the mixture was allowed to heat to 0°C , and treated as before. The crude mixture (2.35 g) was chromatographed on silica gel (118 g). Elution with n-hexane-ethyl acetate (95:5) gave an oil (0.83 g) which, following distillation (120 °C at 0.1 mmHg), provided 2-acetyl-1,3-dithian (7; $R^2 = \text{CH}_3$) (0.7 g, 51%) (Found: C, 44.0; H, 6.0. $\text{C}_6\text{H}_{10}\text{OS}_2$ requires C, 44.4; H, 6.1%); m/e 162 (M^+); δ (CDCl_3) 2.3 (3 H, s, CH_3CO) and 4.25 (1 H, s, CHCO); ν_{max} 1 710 cm^{-1} (C=O); g.l.c. analysis (140 °C) showed a single component.

Similar treatment of 1,3-dithian (1.36 g) with methyl 5-methylhex-4-enoate (0.834 g) gave 2-(5-methyl-1-oxohex-4-enyl)-1,3-dithian [7; $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (0.81 g, 60%) (Found: C, 58.0; H, 7.5. $\text{C}_{11}\text{H}_{18}\text{OS}_2$ requires C,

57.4; H, 7.8%); m/e 230 (M^+); δ (CDCl_3) 1.62br [6 H, s, $(\text{CH}_3)_2\text{C}:\text{C}$], 4.2 (1 H, s, CHCO), and 5.1 (1 H, m, $\text{CH}:\text{C}$); ν_{max} 1 710 cm^{-1} (C=O); g.l.c. analysis (190 °C) showed a single component.

Alkylation of (7).—A suspension of NaH (0.048 g; 50% oil) in anhydrous DME (3 ml) was treated under argon with a solution of (7a) (0.23 g) in DME (1.5 ml). A solution of n-butyl iodide (0.276 g) in DME (1.5 ml) was added to the mixture at 0°C and stirred magnetically. The mixture was heated under reflux with stirring for 1 h, worked up as before, and distilled at 160 °C and 0.1 mmHg to give [4; $R^1 = \text{Bu}^n$, $R^2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$] (0.234 g, 85%).

2-Acyl-2-alkyl-1,3-dithians should be stored under an inert atmosphere to prevent oxidation by air.

Compound (15a).—A suspension of NaH (0.018 g, 50% oil) in anhydrous DME (2 ml) was treated under argon with a solution of (7a) (0.076 g) in DME (1 ml). A solution of iodide (10) (0.102 g) in DME (1 ml) was added at 0°C and stirred magnetically. The mixture was heated under reflux with constant stirring for 96 h, and worked up as before. The crude mixture (0.136 g) was chromatographed on Florisil (15 g). Elution with n-hexane-ethyl acetate (9:1) gave 2-(5-methyl-1-oxohex-4-enyl)-2-(3-methyl-5-tetrahydropyran-2-yl)-1,3-dithian (15a) (0.034 g, 25%), m/e 412 (M^+), 327 ($M - \text{C}_5\text{H}_9\text{O}$), 311 ($M - \text{C}_5\text{H}_9\text{O}_2$), 301 ($M - \text{C}_7\text{H}_{11}\text{O}$), 230 ($M - \text{C}_{11}\text{H}_{19}\text{O}_2$), 199 ($M - \text{C}_{12}\text{H}_{21}\text{O}_3$), and 85 ($M - \text{C}_{17}\text{H}_{27}\text{O}_2\text{S}_2$); δ (CDCl_3) 1.6br (9 H, s, $\text{CH}_3\text{C}:\text{C}$), 2.1 (4 H, s, $\text{CCH}_2\text{CH}_2\text{C}:\text{C}$), 2.4—3.2 (4 H, m, $\text{C}:\text{CCH}_2\text{CH}_2\text{CO}$), 2.4—3.2 (4 H, m, CH_2S), 3.4—4.0 (2 H, m, CH_2O), 4.05 (2 H, m, $\text{C}:\text{CCH}_2\text{O}$), 4.6br (1 H, s, OCHO), 5.1 (1 H, m, $\text{C}:\text{CH}$), and 5.4 (1 H, m, $\text{C}:\text{CHO}$); ν_{max} 1 700 cm^{-1} (C=O).

Compound (15b).—Similar treatment of (7b) gave 2-acetyl-2-(3-methyl-5-tetrahydropyran-2-yl)-1,3-dithian (15b) (50%), m/e 344 (M^+), 301 ($M - \text{C}_2\text{H}_3\text{O}$), 259 ($M - \text{C}_5\text{H}_9\text{O}$), 243 ($M - \text{C}_5\text{H}_9\text{O}_2$), 199 ($M - \text{C}_7\text{H}_{13}\text{O}_3$), and 85 ($M - \text{C}_{12}\text{H}_{19}\text{O}_2\text{S}_2$); δ (CDCl_3) 1.7br (3 H, s, $\text{CH}_3\text{C}:\text{C}$), 2.1 (4 H, s, $\text{CCH}_2\text{CH}_2\text{C}:\text{C}$), 2.3 (3 H, s, CH_3CO), 2.4—3.2 (4 H, m, CH_2S), 3.4—3.9 (2 H, m, CH_2O), 3.8—4.4 (2 H, m, $\text{C}:\text{CCH}_2\text{O}$), 4.6br (1 H, s, OCHO), and 5.4 (1 H, m, $\text{C}:\text{CHCO}$); ν_{max} 1 700 cm^{-1} (C=O).

5-Lithio-2-methylpent-2-ene.—Lithium (0.06 g; freshly cut thin strips) and ether (4 ml) under argon were stirred during the slow addition of 5-bromo-2-methylpent-2-ene¹⁴ (0.698 g) in ether (2 ml); a cooling bath (-30°C) was applied at the start of the reaction. Stirring was continued at -25°C until nearly all the lithium had reacted (5 h). A sample of the solution (0.5 ml) was titrated (0.1N-HCl; phenolphthalein), showing a 0.35N-alkyl-lithium solution.

Compound (16).—A solution of (15b) (0.121 g) in ether (2 ml) at -70°C was treated under argon with 0.35N-5-lithio-2-methylpent-2-ene in ether (3 ml). The mixture was allowed to heat to 0°C , treated with saturated aqueous NH_4Cl solution (5 ml), and extracted with ether (3×5 ml). The extracts were dried and evaporated and the crude mixture (0.24 g) was chromatographed on Florisil (10 g). Elution with n-hexane-ethyl acetate (9:1) gave (16) (0.135 g, 90%). A solution of (15a) (0.03 g) in tetrahydrofuran (1 ml) at 0°C was treated under argon with 1N-methyl-lithium in ether (0.7 ml). Isolation as usual gave 2-(1-hydroxy-1,5-dimethylhex-4-enyl)-2-(3-methyl-5-tetrahydropyran-2-yl)-1,3-dithian (16) (0.031 g, 99%), m/e 428 (M^+), 411 ($M - \text{OH}$), 345 ($M - \text{C}_6\text{H}_{11}$), 343 ($M - \text{C}_5\text{H}_9\text{O}$), 327 ($M - \text{C}_5\text{H}_9\text{O}_2$), 301 ($M - \text{C}_8\text{H}_{15}\text{O}$), 245 ($M - \text{C}_{11}\text{H}_{19}\text{O}_2$), and 85 ($M - \text{C}_{18}\text{H}_{31}\text{O}_2\text{S}_2$); δ (CDCl_3) 1.4 (3 H, s, CH_3CO), 1.64—1.70 (9 H, $\text{CH}_3\text{C}:\text{C}$), 3.4—4.0 (2 H, m, CH_2O), 3.8—4.4 (2 H, m, $\text{C}:$

CH₂O), 4.6br (1 H, s, OCHO), 5.18 (1 H, m, C:CH), and 5.4 (1 H, m, C:CHCO).

Compound (17).—A solution of (16) (0.017 g) in aqueous 80% acetone (2 ml) was heated at reflux under nitrogen with CaCO₃ (0.01 g) and CH₃I (0.564 g) for 24 h. The mixture was diluted with ether (10 ml), washed with 5M aqueous ammonium acetate and saturated brine, dried, and evaporated. Preparative t.l.c. of the crude mixture (0.025 g) with n-hexane-ethyl acetate (8:2) afforded 7-hydroxy-3,7,11-trimethyl-1-tetrahydropyranyloxydodeca-2,10-dien-6-one (17) (0.013 g, 96%). G.l.c. analysis (SE 30, 3%; 1 m; 200 °C) showed a single component; ν_{\max} 1705 cm⁻¹ (C:O); *m/e* 253 (*M* - C₅H₉O), 237 (*M* - C₅H₉O₂), 219 (*M* - C₅H₁₁O₃), 211 (*M* - C₈H₁₅O), 193 (*M* - C₇H₁₃O₃), 154 (*M* - C₁₁H₂₀O₂), 109 (*M* - C₁₂H₂₁O₄), and 85 (*M* - C₁₅H₂₅O₃); δ (CDCl₃) 1.4 (3 H, s, CH₃CO), 1.58—1.70 (9 H, CH₃C:C), 2.63 (2 H, m, CH₂C:O), 3.4—4.0 (2 H, m, CH₂O), 3.8—4.3 (2 H, m, C:CCH₂O), 4.6br (1 H, s, OCHO), 5.05 (1 H, m, C:CH), and 5.4 (1 H, m, C:CHCO).

Compound (18).—A solution of (17) (0.013 g) in AcOH-H₂O-THF (3:1:1; 1.5 ml) was stirred at room temperature for 11 h. The mixture was treated with Na₂CO₃ and extracted with ether (3 × 5 ml). The extracts were washed with saturated aqueous NaHCO₃ (2 × 5 ml) and saturated brine (2 × 5 ml), dried, and evaporated. Preparative t.l.c. of the crude mixture, with n-hexane-ethyl acetate (5:5) as developing agent, gave 1,7-dihydroxy-3,7,11-trimethyldodeca-2,10-dien-6-one (18) (0.009 g, 92%). G.l.c. analysis (SE 30, 3%; 1 m; 160 °C) showed a single component, ν_{\max} 1705 cm⁻¹ (C:O); δ (CDCl₃) 1.32 (3 H, s, CH₃CO), 1.54—1.66 (9 H, CH₃C:C), 2.0 (2 H, m, CH₂C:C), 2.3 (2 H, m, CH₂C:C), 2.63 (2 H, m, CH₂C:O), 3.8br (1 H, s, OH), 4.14 (2 H, d, C:CCH₂O), 5.05 (1 H, m, C:CH), and 5.4 (1 H, m, C:CHCO); *m/e* 236 (*M* - H₂O), 218 (*M* - 2 H₂O), 193 (*M* - C₃H₉O), 154 (*M* - C₆H₁₂O), 127 (*M* - C₇H₁₁O₂; *M* - C₈H₁₅O), 109 (*M* - C₇H₁₃O₃; *M* - C₈H₁₇O₂), and 69 (*M* - C₁₀H₁₇O₃).

(2E)-5-Iodo-3-methylpent-2-en-1-ol Tetrahydropyranyl Ether (10).—(2E)-1,5-Dibromo-3-methylpent-2-ene (11)¹¹ had b.p. 45 °C at 0.005 mmHg (Found: C, 29.8; H, 4.3.

C₆H₁₀Br₂ requires C, 29.75; H, 4.15%); δ (CDCl₃) 1.73 (3 H, s, CH₃C:C), 2.6 (2 H, t, *J* 6 Hz, CH₂C:C), 3.42 (2 H, t, *J* 6 Hz, CH₂Br), 3.96 (2 H, d, *J* 8 Hz, C:CCH₂Br), and 5.6 (1 H, t, *J* 8 Hz, C:CH). G.l.c. analysis (95 °C) showed a single component. A solution of benzyltrimethylammonium dichloroacetate (4.95 g) in anhydrous acetone (12 ml) was treated at 0 °C, under nitrogen, with a solution of dibromide (11) (3.915 g) in anhydrous acetone (24 ml). After 4 h at room temperature, the mixture was filtered and the organic phase evaporated giving dichloroacetate (12) (4.36 g, 93%). G.l.c. analysis (135 °C) showed a single component. A solution of (12) (1.472 g) in tetrahydrofuran (11 ml) was treated at room temperature with 1N-NaOH (5 ml). The solution was evaporated *in vacuo* and the residue extracted with CHCl₃ (4 × 15 ml). The organic phase, dried and evaporated, gave the bromohydrin (13) (0.805 g, 90%). G.l.c. analysis (95 °C) showed a single component. A solution of (13) (4.58 g), in anhydrous dioxan (55 ml) was treated under nitrogen with toluene-*p*-sulphonic acid monohydrate (0.364 g) and anhydrous dihydropyran (7.36 ml). After 30 min triethylamine was added to make the solution slightly basic. The solution was evaporated under vacuum, the residue taken up in methylene chloride (100 ml), washed with saturated brine, dried, and evaporated. The crude mixture (6.14 g) was chromatographed on silica gel (307 g). Elution with CH₂Cl₂ gave (14) (5.72 g, 85%). G.l.c. analysis (145 °C) showed a single component. A solution of bromide (14) (3.54 g) in toluene (2 ml) was treated with an aqueous saturated solution of KI (11.17 g) and C₁₆H₃₃PBu₃Br (0.342 g). After 4 h at 62—65 °C, benzene (50 ml) was added, and the aqueous phase extracted with benzene (3 × 50 ml). The organic extracts were dried and evaporated. The crude mixture (4.26 g) was chromatographed on silica gel (85 g). Elution with n-hexane-ethyl acetate (9:1) provided the iodide (10) (3.55 g, 85%). G.l.c. analysis (160 °C) showed a single component (Found: C, 42.0; H, 6.0. C₁₁H₁₉IO₂ requires C, 42.6; H, 6.1%); *m/e* 310 (*M*⁺), 225 (*M* - C₅H₉O), 209 (*M* - C₅H₉O₂), 183 (*M* - I), 101 (*M* - C₆H₁₀I), 85 (*M* - C₆H₁₀IO).

[7/1616 Received, 12th September, 1977]