

Calciferol and its Relatives. Part XVII.¹ Ring-A Components for Synthetic Work on Vitamin D₃ and on Model Compounds

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Optically active (*S*)-(Z)-2-(5-hydroxy-2-methylenecyclohexylidene)ethanol (6), which is of interest as a ring-A component for a possible synthesis of vitamin D₃, has been prepared from vitamin D₂. Its simpler analogue (Z)-2-(2-methylenecyclohexylidene)ethanol (9) has been synthesised by two routes. In the more efficient, the βγ-unsaturated lactone 3-oxabicyclo[4.4.0]dec-1(6)-en-4-one (14) was converted by treatment with lithium diisopropylamide into (Z)-(2-methylenecyclohexylidene)acetic acid (30), which was then reduced to the dienol (9).

THE dienediol (6) † is of interest as a ring-A component for a possible synthesis of vitamin D₃ (1; R = C₈H₁₇), since both the aldehyde (4) and the phosphonium cation (5) should be available from it, and either of them would be expected to take part in Wittig reactions in which the vitamin is constructed by the formation of its 7,8-double bond. The dienol (9), a simpler analogue of (6), is of similar interest for the construction of model compounds such as the *cis*-triene² (7). The present paper reports the preparation of the dienediol (6) from vitamin D₂ (1; R = C₉H₁₇), and an exploration of some synthetic routes to the model dienol (9).

Wang and his co-workers³ hydroxylated vitamin D₂ with potassium permanganate, and obtained the triol (2). Glycol cleavage of this gave the ketone (3); but the aldehyde (4), which must have been formed simultaneously, was apparently not isolated. We have now treated the glycol cleavage products with sodium bis-(2-methoxyethoxy)aluminium hydride to give a mixture of des-AB-ergost-22-en-8β-ol and the dienediol (6). The crystalline dienediol (6) was separated by virtue of its water-solubility, and was obtained in over 50% yield from the triol (2). Re-oxidation with manganese dioxide in tetrahydrofuran gave the unstable aldehyde (4) (λ_{max} 253 nm), which reacted with cyclohexylidene-triphenylphosphorane⁴ to give the *cis*-triene (8), isolated as the crystalline 3,5-dinitrobenzoate. The racemic compound *rac*-(8) has been obtained by Havinga⁵ by a photochemical route which ensured its *cis*-structure, and the agreement of our u.v. and i.r. data with those

cited for this compound shows that the trisubstituted double bond in the dienediol (6) retains the *cis*-geometry which it possessed originally in vitamin D₂.

As a preliminary to a synthesis of the dienediol (6) we explored some approaches to the simpler dienol (9), in which the *cis*-geometry of the trisubstituted double bond was ensured by its original incorporation in a bicyclic unsaturated lactone. Thus the αβ-unsaturated γ-lactone (10)⁶ provided the starting-point for a relatively brief, although not very efficient, synthesis. The diol (11), formed⁷ by reduction of the lactone, gave a primary monobenzoate which was oxidised by manganese dioxide in acetonitrile to the keto-benzoate (13). A Wittig reaction with methylenetriphenylphosphorane then gave the benzoate of the dienol (9) [*ca.* 10% based on the diol (11)]. The dienol (9), obtained by saponification, was characterised as the crystalline *p*-nitrobenzoate. The corresponding aldehyde reacted with cyclohexylidene-triphenylphosphorane to give the *cis*-triene² (7), λ_{max} 261 nm (ε 17,200), confirming the *cis*-geometry of the dienol (9).

The dienol (9) can also be obtained from the bicyclic βγ-unsaturated δ-lactone (14). This lactone was first⁸ prepared as follows. Reformatsky reaction between 2-acetoxymethylcyclohexanone (18), methyl bromoacetate, and zinc, followed by treatment of the product with hot acetic anhydride, gave the conjugated δ-lactone (15). Heating with 40% aqueous potassium hydroxide, followed by acidification and distillation, gave a liquid isomeric lactone which was free (u.v. and i.r. spectra) from conjugated material; treatment with piperidine in

† The structures (1)–(8) represent absolute configurations and racemates thereof are denoted by the prefix *rac*. The structures (9)–(30) represent racemates.

¹ Part XVI, T. M. Dawson, J. Dixon, P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc. (C)*, 1971, 2960.

² I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 1958, 837.

³ Y. Wang, H.-S. Ting, J. J. Huang, Y.-C. Chow, and Y.-T. Huang, *Acta Chim. Sinica*, 1958, **24**, 126.

⁴ U. Schöllkopf, Doctoral Dissertation, Tübingen, 1956.

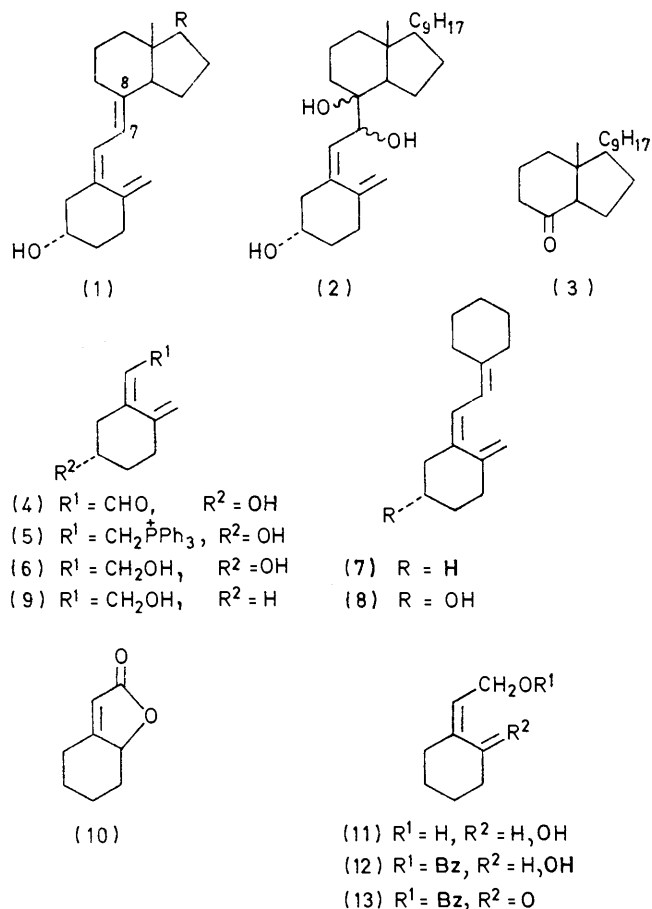
⁵ J. L. M. A. Schlatmann and E. Havinga, *Rec. Trav. chim.*, 1961, **80**, 1101.

⁶ M. S. Newman and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.

⁷ I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 1958, 843.

⁸ I. T. Harrison, Ph.D. Thesis, Leeds, 1958.

hot ethanol re-converted it into the conjugated isomer (15). Kon and Thakur⁹ found that alkaline isomerisation of 2'-methylcyclohexylideneacetic acid (19) gave the

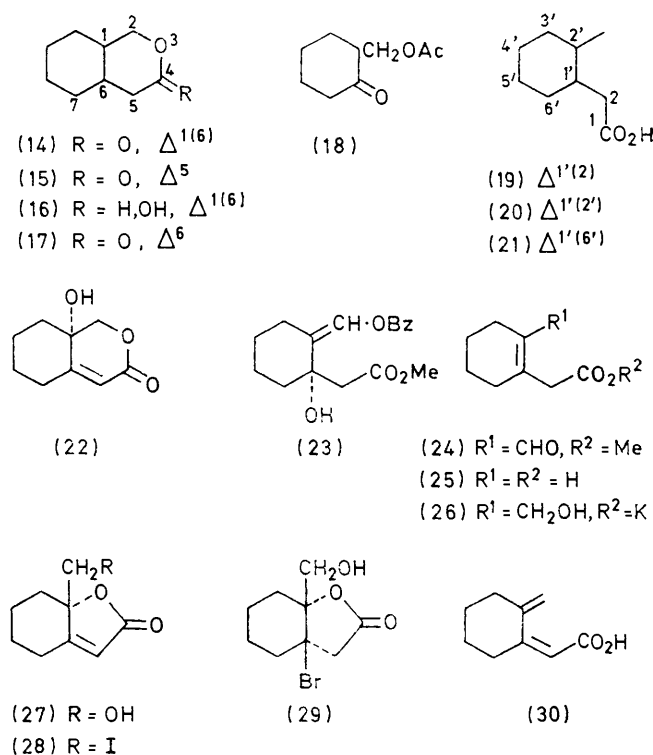


tetrasubstituted olefinic acid (20) rather than the tri-substituted isomer (21); our liquid unconjugated lactone was therefore expected to consist mainly of the isomer (14) rather than (17). That this is the case was shown by its conversion in satisfactory yield into the crystalline hydroxy-lactone (22), a product which was similarly obtained (see below) from an authentic sample of the lactone (14).

Pure lactone (14) was prepared¹⁰ from the enol benzoate¹¹ (23). Acidic hydrolysis of the benzoate gave the conjugated aldehyde (25), λ_{max} 249 nm, which was characterised as its semicarbazone. Reduction of the aldehyde with lithium aluminium hydride at -70° gave a mixture containing the hemiacetal (16) (major product), and the lactone (14) (minor product) from which, no doubt, the hemiacetal was formed. The latter, purified by chromatography, was identified by the signal due to its $-\text{O}-\dot{\text{C}}\text{H}-\text{O}$ group at τ 4.98 (t, J 4.5 Hz). Oxidation of the mixture with sodium dichromate and sulphuric

acid in acetone gave the lactone (14) in good yield. Its n.m.r. spectrum (see Experimental section) confirmed its structure and also its freedom from isomeric lactones.

The structure (14) was ascribed¹² to a liquid lactonic product obtained from a Prins reaction between cyclohex-1-enylacetic acid and 1,3,5-trioxan with trifluoroacetic acid as the solvent and catalyst. The unsaturated alcohols (or their derivatives) which result from Prins reactions are normally¹³ homoallylic, rather than allylic; and the products expected from this particular reaction are the lactones (17) and (15) rather than (14). Indeed, the same reaction, conducted in dioxan with sulphuric acid as the catalyst, gave¹² the lactone (15) in ca. 45% yield. We therefore repeated the trifluoroacetic acid experiment, and investigated the product by g.l.c., t.l.c., and n.m.r. methods. They showed that the product was a mixture of ca. 67% of the conjugated lactone (15), ca. 25% of the unconjugated isomer (17), and <10% of the isomer (14). Although the composition of the product originally obtained in this way may have been different (its homogeneity was not investigated), it seems clear that the method is not reliable as a route to the pure lactone (14).



As the next step towards the dienol (9) we required the $\alpha\beta$ -unsaturated γ -lactone (27). We expected that the potassium salt (26), obtained by mild treatment of the lactone (14) with aqueous potassium hydroxide, would give, on reaction with bromine, the bromolactone (29),

⁹ G. A. R. Kon and R. S. Thakur, *J. Chem. Soc.*, 1930, 2217.

¹⁰ A. K. Saksena, Ph.D. Thesis, Leeds, 1970.

¹¹ A. S. Dreiding and A. J. Tomaszewski, *J. Amer. Chem. Soc.*, 1954, **76**, 6388.

¹² B. Belleau, *Canad. J. Chem.*, 1957, **35**, 673.

¹³ E.g., J. P. Bain, *J. Amer. Chem. Soc.*, 1946, **68**, 641; I. Nazarov and N. V. Kuznetsov, *Doklady Akad. Nauk S.S.S.R.*, 1956, **111**, 358; N. C. Yang, D.-D. H. Yang, and C. B. Ross, *J. Amer. Chem. Soc.*, 1959, **81**, 133; G. Ohloff, *Annalen*, 1959, **627**, 79.

from which the unsaturated lactone (27) would be obtained on dehydrobromination with diethylamine. However, these reactions gave a crystalline product which, although it had the expected composition, was clearly not a γ -lactone; its structure (22) was apparent from the u.v., i.r., and n.m.r. data. Fortunately, this lactone was isomerised by warm dilute alkali, giving the γ -lactone (27). The corresponding iodolactone (28), obtained by reaction with triphenylphosphite methiodide,¹⁴ was treated with zinc dust in methanol to give, after acidification, the crystalline *cis*-dienoic acid (30), λ_{\max} 219 nm (ϵ 7000).

We earlier⁷ attempted, unsuccessfully, to prepare this *cis*-dienoic acid by treating the conjugated lactone (15) with methanolic sodium methoxide. However, use of the sterically hindered base lithium di-isopropylamide in ether gave the acid in moderate yield. Better results were obtained by similar treatment of the unconjugated lactone (14), from which the proton α to the carbonyl group is more readily removed; this gave the acid (30) in ca. 90% yield. From its methyl ester the dienol (9) was conveniently obtained by reduction with sodium bis-(2-methoxyethoxy)aluminium hydride.

EXPERIMENTAL

Unless otherwise specified, u.v. data relate to solutions in EtOH, n.m.r. data to solutions in CDCl_3 , and $[\alpha]_D$ values to solutions in CHCl_3 . T.l.c. was carried out using Kieselgel G or Kieselgel GF₂₅₄.

Preparation of (S)-(Z)-2-(5-Hydroxy-2-methylenecyclohexylidene)ethanol (6).—Lead tetra-acetate (4.4 g) was added in portions to a well-stirred and cooled (20°) suspension of the triol (2) (4 g) in dry benzene (30 cm³). Stirring was continued for 1.5 h, and the mixture was filtered from lead diacetate, which was washed with ether. The combined filtrate and washings were evaporated under reduced pressure at 30° to give a gum (4.3 g) which was dissolved in benzene (30 cm³). A 70% solution of sodium bis-(2-methoxyethoxy)aluminium hydride in benzene (5.35 cm³) was added to the stirred solution dropwise at 5°; stirring was continued for 1 h at 20°, and water was then added dropwise until a granular precipitate separated; it was filtered off, and washed with tetrahydrofuran. The combined filtrates were evaporated under reduced pressure, the residue was dissolved in ether (100 cm³) and light petroleum (b.p. 60–80°; 100 cm³), and the solution was extracted with water (7 × 5 cm³). Evaporation of the dried organic phase gave des-AB-ergost-22-en-8 β -ol as a gum (2.4 g). The aqueous extracts were evaporated under reduced pressure at 40°; crystallisation of the residue from ether gave the *dienediol* (6) as cubes (870 mg), m.p. 101–102°, $[\alpha]_D^{20} + 28^\circ$, λ_{\max} (H₂O) 219 nm (ϵ 6400), ν_{\max} (Nujol) 3250s, 1660w, 1630m, and 920s cm⁻¹, τ 4.5 (1H, t, J_{vic} 7 Hz with further allylic splitting, J 1.3 Hz, =CH-), 5.02 (1H, m, $W_{\frac{1}{2}}$ 4 Hz, =CH₂), 5.37 (1H, d, J 2 Hz, =CH₂), 5.78 (2H, d, J_{vic} 7 Hz, with further homoallylic splitting, -CH₂-O), 6.1 (1H, m, >CH-O), 7.5–8.0 (4H, m, =CH-CH₂-), and 8.05–8.45 (2H, m, -CH₂-) (Found: C, 69.9; H, 8.9. C₉H₁₄O₂ requires C, 70.1; H, 9.1%). The *bis-p-nitrobenzoate* separated from ether as needles, m.p. 104–106°, $[\alpha]_D^{20} + 64.4^\circ$ (Found: C, 60.9; H, 4.7; N, 6.3. C₂₃H₂₀N₂O₈ requires C, 61.1; H, 4.5; N, 6.2%).

(S)-(Z)-3-Cyclohexylidenethylidene-4-methylenecyclohexanol (8).—Reaction of the diol (6) (220 mg) with manganese dioxide (2 g) in tetrahydrofuran (10 cm³) at 20° for 1 h gave, in the usual way, the aldehyde (4) as a gum (202 mg), λ_{\max} 253 nm (ϵ 5400), homogeneous to t.l.c. (in Et₂O). Without delay its solution in dry tetrahydrofuran was added gradually to a stirred solution under nitrogen of cyclohexylidetriphenylphosphorane, prepared from cyclohexyltriphenylphosphonium bromide (2.4 g) and *n*-butyllithium (1 equiv.) in ether (50 cm³). When the mixture had been stirred at 25° for 7 h, water (1 cm³) was added, and the precipitate was filtered off and washed with light petroleum. Evaporation of the filtrates gave a residue which was dissolved in light petroleum (b.p. 40–60°; 20 cm³); the solution was washed with 50% aqueous methanol (2 × 15 cm³) and then dried and evaporated. The gummy product (325 mg) was converted into the *3,5-dinitrobenzoate*, which formed needles (349 mg) (from butan-2-one-ethanol), m.p. 118–120°, $[\alpha]_D^{20} + 108^\circ$ (Found: C, 64.3; H, 5.7; N, 6.7. C₂₂H₄₄N₂O₆ requires C, 64.1; H, 5.9; N, 6.8%). Hydrolysis of this ester gave the trienol (8) as an oil, λ_{\max} (MeOH) 262.5 nm (ϵ 16,800), ν_{\max} (film) 3400s, 1630m, 905s, and 885m cm⁻¹, τ 3.87 (2H, s, =CH-CH=), 4.99 (1H, m, $W_{\frac{1}{2}}$ 4 Hz, =CH₂), 5.2 (1H, d, =CH₂), and 6.15 (1H, m, 7 lines, J 4 Hz and 8 Hz, >CH-O).

(Z)-2-(2-Oxocyclohexylidene)ethyl Benzoate (13).—The diol (11) (58 g) was benzoylated in the normal way with benzoyl chloride (57 g) and pyridine (250 cm³), at first at 0°, then at 20°, during 24 h. Normal work-up gave a crude product, chromatography of which on neutral alumina with light petroleum and then with light petroleum-benzene, gave the *monobenzoate* (53 g), homogeneous on t.l.c. (Found: M^+ , 246.1260. C₁₅H₁₈O₃ requires M , 246.1256). A sample (10.5 g) was stirred with manganese dioxide (100 g) in acetonitrile (400 cm³) for 24 h; filtration, washing the residue with acetone, and evaporation of filtrate and washings, gave the crude keto-benzoate (13) (7.6 g), ν_{\max} (film) 1720s, 1710s, and 1690s cm⁻¹, no OH absorption, τ (CCl₄) 2.00 (2H, m, aromatic H), 2.55 (3H, m, aromatic H), 4.27 (1H, tt, J 6 Hz and 2 Hz, =CH-), and 4.95 (2H, dt, J 6 Hz and 2 Hz, -CH₂-O). The *semicarbazone* had m.p. 150–152° (Found: C, 63.6; H, 6.2; N, 13.8. C₁₆H₁₉N₃O₃ requires C, 63.8; H, 6.4; N, 14.0%).

(Z)-2-(2-Methylenecyclohexylidene)ethanol (9).—To a stirred solution of methylenetriphenylphosphorane, prepared in the usual way from the phosphonium bromide (13.2 g) and *n*-butyllithium (1 equiv.) in tetrahydrofuran (200 cm³) under nitrogen, the keto-benzoate (13) (7.6 g) in tetrahydrofuran (25 cm³) was added during 0.5 h. The mixture was stirred overnight, and a little water was then added. The solvent was evaporated, and the residue dissolved in ether (250 cm³) and washed with water (3 × 25 cm³). The ether was removed, and the residue was extracted with warm light petroleum (b.p. 60–80°; 3 × 100 cm³). Evaporation of the extract gave a yellow oil (7.8 g); t.l.c. showed two components, the dienol (9), and its benzoate. After benzylation in the usual way, chromatography of the product on neutral alumina (Grade III; 500 g) with light petroleum (b.p. 60–80°) as the eluant gave the *benzoate* of the dienol (9) as an oil (2.21 g) (Found: M^+ , 242.1313. C₁₆H₁₈O₂ requires M , 242.1307). The *dienol* (9), obtained by hydrolysis with ethanolic potassium hydroxide, formed an oil, λ_{\max} 218 nm (ϵ 6200), ν_{\max} (film) 3320s, 1630m, 1015s, 995s, and 900s cm⁻¹, τ (CCl₄) 4.65 (1H, t, J 7 Hz,

¹⁴ S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 1953, 2224.

$=\text{CH}-\text{CH}_2-\text{O}$), 5.14 (1H, m, $W_{\frac{1}{2}}$ 4.5 Hz, $=\text{CH}_2$), 5.41 (1H, apparent d, J 2.5 Hz, $=\text{CH}_2$), and 5.92 (2H, d, J 7 Hz, $-\text{CH}_2-\text{O}$) (Found: M^+ , 138.1043. $\text{C}_9\text{H}_{14}\text{O}$ requires M , 138.1004). The *p*-nitrobenzoate formed needles, m.p. 63° (from light petroleum) (Found: C, 66.8; H, 6.0; N, 4.75. $\text{C}_{16}\text{H}_{17}\text{NO}_4$ requires C, 66.9; H, 6.0; N, 4.9%), τ 1.73 (4H, s, aromatic H), 4.47 (1H, t, J 7 Hz, $=\text{CH}-\text{CH}_2$), 4.97 and 5.09 (components of d, J 7 Hz, $-\text{O}-\text{CH}_2-\text{CH}=\text{}$; underlying the low field component, and obscured by it, a signal, 1H, from the $=\text{CH}_2$ group), 5.28 (1H, apparent d, J 2 Hz, $=\text{CH}_2$), 7.73 (4H, m, allylic CH_2), and 8.30 (4H, m, CH_2).

(*Z*)-1-Cyclohexylidenethylidene-2-methylenecyclohexane (7).—The dienol (9) (169 mg) was stirred vigorously with manganese dioxide (2 g) in tetrahydrofuran (10 cm³). The mixture was filtered, the residue was washed with more solvent, and the filtrates were evaporated to give the crude aldehyde (143 mg), λ_{max} 254 nm (ϵ 3400). This was allowed to react with cyclohexylidetriphenylphosphorane as described for the hydroxy-derivative. The product, purified by chromatography on pentane on neutral alumina (Grade II) formed an oil (122 mg), λ_{max} (MeOH) 261 nm (ϵ 17,200) [lit.,^{2,7} 261 nm (ϵ 17,000)], ν_{max} (film) 1635, 1600, 895, and 855 cm⁻¹ (Found: M^+ , 202.1710. Calc. for $\text{C}_{15}\text{H}_{22}$: M , 202.1721). It showed olefinic proton signals closely similar to those of the trienol (8), viz. τ 3.96 (2H, s, $=\text{CH}-\text{CH}=\text{}$), 5.12 (1H, m, $W_{\frac{1}{2}}$ 4 Hz, $=\text{CH}_2$), and 5.32 (1H, apparent d, J 3 Hz, $=\text{CH}_2$).

3-Oxabicyclo[4.4.0]dec-5-en-4-one (15).—A mixture of 2-acetoxymethylcyclohexanone (158 g) and methyl bromoacetate (253 g) was brought into a Reformatsky reaction in the usual way with rasped zinc (140 g) in dry benzene (2 l). When reaction was complete the cooled mixture was acidified with dilute sulphuric acid, the benzene layer was separated, and after being washed and dried it was freed from benzene and methyl bromoacetate by distillation, finally at 100° and 10 mmHg. The residue was heated under reflux with acetic anhydride (400 cm³) for 1.5 h, and the mixture was then distilled. The fraction, b.p. 110—150° at 0.5 mmHg, was redistilled giving the crude lactone (68 g), b.p. 102—105° at 0.4 mmHg. It separated from light petroleum (b.p. 60—80°) as white needles, m.p. 63° (lit.,¹² 59—60°) (Found: C, 71.05; H, 7.8. Calc. for $\text{C}_9\text{H}_{12}\text{O}_2$: C, 71.0; H, 8.0%). On microhydrogenation it absorbed 1.09 mol. equiv. hydrogen (Pd-C). It showed λ_{max} 223 nm (ϵ 12,200) (lit.,¹² ϵ 9000), ν_{max} (film) 1725 cm⁻¹, τ 4.25br (1H, s, $W_{\frac{1}{2}}$ 4.5 Hz, $=\text{CH}-$) and ca. 5.5—6.3 (2H, m; lines at 5.48, 5.57, 5.66, 5.76, 5.90, 6.07, 6.08, and 6.26; $-\text{CH}_2-\text{O}$). The lactone (2.5 g) and 1*N*-potassium hydroxide (25 cm³) were warmed together for 5 min, and the ice-cold solution was treated with 1*N*-sulphuric acid (25 cm³). Thorough ether extraction, and crystallisation of the ether-soluble material from acetone at 0° gave (*Z*)-(2-hydroxymethylcyclohexylidene)acetic acid (0.87 g), m.p. 108.5°, λ_{max} 223 nm (ϵ 12,900).

Interconversion of the Lactones (14) and (15).—The conjugated δ -lactone (15) (20 g) was heated in a sealed glass tube at 130° for 18 h with potassium hydroxide (25 g) in water (40 cm³). The cooled solution was diluted and extracted with carbon tetrachloride, and then acidified with hydrochloric acid and extracted thoroughly with chloroform. Distillation of the product at 100—103° and 0.25 mmHg gave the unconjugated lactone (14) (18.3 g). It showed no λ_{max} above 215 nm; ν_{max} (film) 1740 cm⁻¹. This lactone (100 mg) and piperidine (40 mg) were heated together under reflux in ethanol (20 cm³) for 17 h, and the residue, obtained by evaporation of the ethanol, was dis-

solved in light petroleum, washed with dilute acid and then with water, and dried. Concentration of the solution and cooling gave the δ -lactone (15) as crystals (30 mg), m.p. and mixed m.p. 62°, λ_{max} 223 nm.

Preparation of the Unconjugated δ -Lactone (14) from the Enol Benzoate (23).—A solution of the enol benzoate (9.55 g) in ether (200 cm³) and 50% sulphuric acid (120 cm³) was stirred vigorously for 1 h; the ether layer was then separated, and the acid layer was re-extracted with ether. The combined ether layers were washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give methyl (2-formylcyclohex-1-enyl)acetate (24) as an oil (3.5 g), λ_{max} (MeOH) 249 nm (ϵ 12,200), ν_{max} (film) 1740 and 1670 cm⁻¹, τ (CCl₄) 1.32 (1H, s, CHO). The semicarbazone formed plates, m.p. 172—173° (from methanol) (Found: C, 55.3; H, 7.2; N, 17.6. $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_3$ requires C, 55.2; H, 7.2; N, 17.6%).

A solution of the aldehyde (24) (10.4 g) in dry ether (475 cm³) at -70° was stirred and treated with lithium aluminium hydride (4.2 g) in small portions during 30 min; after stirring at the same temperature for a further 1 h a saturated solution of sodium potassium tartrate was added cautiously. The ether layer was separated, and the aqueous phase re-extracted with ether; the combined ether phases were washed with brine, dried, and evaporated to give an oil (8 g). T.l.c. (chloroform-ether, 1 : 1) showed the presence of the hemiacetal (16) and the δ -lactone (14) (ca. 2 : 1). In one experiment the more polar of these two components, the hemiacetal, was separated by p.l.c., and formed a gum, ν_{max} (film) 3500s, 1730w, 1140s, 1100s, 1020s, 905s, 880s, 840s, and 770m cm⁻¹, τ 4.98 (1H, t, J 4.5 Hz, O-CH-O), and 6.08 (2H, m, $=\text{C}-\text{CH}_2-\text{O}$). A solution of the mixture (8 g) of the lactone and the hemiacetal in acetone (1 l) was cooled to -5° and stirred during the dropwise addition of Jones reagent¹⁵ (42 cm³) (20 min). After a further 10 min the solution was neutralised (sodium hydrogen carbonate), much acetone was removed under reduced pressure, and the residue, diluted with water, was extracted with chloroform. Chromatography on silica gel (100 g) and elution with chloroform gave 3-oxabicyclo[4.4.0]dec-1(6)-en-4-one (14) as an oil (6.3 g) which was homogeneous to t.l.c.; ν_{max} (film) 1745vs, 1407s, 1372s, 1230vs, 1187s, 1065s, 1045s, and 809s cm⁻¹, τ 5.32br (2H, s, $W_{\frac{1}{2}}$ 6 Hz, O-CH₂-C=) and 7.07br (2H, s, $W_{\frac{1}{2}}$ 6.5 Hz, O-CO-CH₂-C=) (Found: M^+ , 152.0831. $\text{C}_9\text{H}_{12}\text{O}_2$ requires M , 152.0837).

Reaction of Cyclohex-1-enylacetic Acid and 1,3,5-Trioxan in Trifluoroacetic Acid.—Cyclohex-1-enylacetic acid (12.6 g), 1,3,5-trioxan (2.85 g), and trifluoroacetic acid (36 cm³) were kept together at 20° for 40 h. Distillation gave two fractions: the first, b.p. 158—165° at 12 mmHg, was taken up in ether and washed with aqueous sodium hydrogen carbonate to remove small amounts of acid; evaporation then gave an oil (fraction 1) (2.63 g), ν_{max} (film) 1680—1750br cm⁻¹; the second fraction (2), had b.p. 165—171° at 12 mmHg (6.11 g), ν_{max} (film) 1700—1750 cm⁻¹. G.l.c. of both fractions on 5% silicone elastomer at 130° showed two main peaks; in fraction (1) the more rapidly eluted (non-conjugated isomers) constituted ca. 55%, the less rapidly eluted (conjugated isomer) 45%; whereas in fraction (2) the non-conjugated isomers constituted ca. 25%, the conjugated isomer 75%. Thus the conjugated lactone (15) formed ca. 67% of the total reaction product. It was isolated by

¹⁵ R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 1953, 457.

preparative g.l.c. (Carbowax at 163°) and identified by its m.p. 63° (from light petroleum).

When fraction (1) material was chromatographed on plates of Kieselgel GF₂₅₄ with 10% ethyl acetate-benzene, two spots were obtained, of which the slower-running, R_F 0.18, corresponded to the conjugated lactone (15). The other spot, R_F 0.26, corresponded to non-conjugated isomers. Column chromatography of fraction (1) material (1.5 g) on Kieselgel GF₂₅₄ with 5–10% ethyl acetate-benzene as the eluant gave non-conjugated material (0.64 g) and the conjugated isomer (15) (0.45 g), m.p. 60°, or, after one recrystallisation from light petroleum (b.p. 60–80°), m.p. 63°.

The liquid non-conjugated material so obtained had ν_{\max} (film) 1750 cm⁻¹ and had the same R_F value (Kieselgel GF₂₅₄, 10% EtOAc-C₆H₆) as the pure δ -lactone (14). The n.m.r. spectrum of the non-conjugated material, contained signals at τ 5.32br(s) and 7.07br(s) due to the CO·O·CH₂· and =C-CH₂-CO groups of the lactone (14) present as 20–25% of the mixture. Signals due to the major component (ca. 75–80%) of the mixture occurred at τ 4.41 (1H, m, $W_{\frac{1}{2}}$ 7.5 Hz, =CH-), 5.52, 5.61, 5.70, 5.78, 5.95, and 6.12 (overlap of two lines), 6.30 (2H, m, -O-CH₂-CH<), and 6.72 (2H, t, J 1.3 Hz, =C-CH₂-CO). These signals, which resemble those observed for the lactone (15), are due to the unconjugated δ -lactone (17). Estimated amounts of the lactone present in the total reaction product are: (15) : (14) = 67 : 25 : 7.

1-Hydroxy-3-oxabicyclo[4.4.0]dec-5-en-4-one (22).—The lactone (14) (1 g) was heated on a steam-bath for 4 min with potassium hydroxide (400 mg) in water (6 cm³). The cooled solution was then saturated with carbon dioxide, and shaken with bromine (1.05 mol. equiv.) in carbon tetrachloride for 5 min, after which the excess of bromine was destroyed by the addition of aqueous sodium thiosulphate. The carbon tetrachloride layer was washed with brine, dried, and evaporated under reduced pressure, giving the crude bromolactone as a gum (1.77 g), ν_{\max} (film) 3550s and 1830s cm⁻¹. To a solution of the gum in dry benzene (6 cm³), diethylamine (1.2 cm³) was added with stirring; after 5 min the mixture was heated to 100° for 2 min, cooled, filtered, and the residue was washed with benzene. Evaporation of the combined filtrates gave a gum, which was chromatographed on silica gel (25 g). Elution with chloroform-ether (1:1) gave the hydroxy- δ -lactone (22) which separated from ether as prisms (654 mg), m.p. 98–100°, λ_{\max} 219 nm (ϵ 13,500), ν_{\max} (CHCl₃) 3500m and 1720s cm⁻¹, τ 4.3 (1H, dd, $W_{\frac{1}{2}}$ 4 Hz, =CH-CO), 5.78 (2H, q, J 13 Hz, >C-CH₂-O) (Found: C, 64.6; H, 7.2. C₉H₁₂O₃ requires C, 64.3; H, 7.2%).

6-Hydroxymethyl-7-oxabicyclo[4.3.0]non-1(9)-en-8-one (27).—The δ -lactone (22) (1.5 g) and 0.3N-aqueous potassium hydroxide (15.7 cm³) were heated on a steam-bath for 4 min, after which water was removed by azeotropic distillation with benzene on a rotary evaporator. Extraction with methylene chloride and evaporation gave the hydroxymethyl- γ -lactone which separated from ether as prisms, m.p. 123–125°, λ_{\max} 215–216 nm (ϵ 13,000), ν_{\max} (Nujol) 3450s and 1750s cm⁻¹, τ 4.25 (1H, d, J 1.5 Hz, =CH-CO), 6.2 (2H; after adding D₂O, q, J 13 Hz, >C-CH₂-O) (Found: C, 64.6; H, 7.3. C₉H₁₂O₃ requires C, 64.3; H, 7.2%). The toluene-*p*-sulphonate formed needles (from ether), m.p. 145–

146°, ν_{\max} (Nujol) 1750 cm⁻¹ (Found: C, 59.2; H, 5.7; S, 10.0. C₁₆H₁₈O₅S requires C, 59.6; H, 5.6; S, 9.9%). It resisted the action of sodium iodide in boiling butan-2-one.

The Iodomethyl- γ -lactone (28).—The lactone (27) (1 g) and triphenylphosphite methiodide (5 g) were heated together under reflux in methyl iodide (40 cm³) for 24 h, after which the solvent was removed under reduced pressure. The residue was passed through silica gel (60 g), which was eluted with chloroform (1 l). Iodine was removed from the eluate by treatment with aqueous sodium thiosulphate, and the washed and dried solution was evaporated. The residual gum (5.3 g) was chromatographed on Kieselgel GF₂₅₄ (100 g), elution with benzene giving the iodolactone in one fraction (1.66 g). Crystallisation from ether gave 6-iodomethyl-7-oxabicyclo[4.3.0]non-1(9)-en-8-one as prisms (1.3 g), m.p. 81–83°, λ_{\max} 215 nm (ϵ 11,600), ν_{\max} (Nujol) 1750s cm⁻¹, τ 4.18 (1H, d, J 1.5 Hz, =CH-CO), 6.45 (2H, q, J 11 Hz, >C-CH₂-I) (Found: C, 39.2; H, 4.0; I, 45.4. C₉H₁₁IO₂ requires C, 38.9; H, 3.9; I, 45.4%).

(Z)-(2-Methylenecyclohexylidene)acetic Acid (30).—(a) The iodolactone (28) (1 g) and freshly activated zinc dust (15.6 g) were stirred together vigorously in dry methanol (120 cm³) which was heated under reflux during 0.5 h. The solution was filtered and evaporated, and the residual zinc salt was suspended in water (20 cm³) and stirred vigorously during the addition of 2N-acetic acid. Extraction with chloroform and crystallisation of the gummy product (350 mg) from pentane gave the dienoic acid (30) as cubes, m.p. 78–79°, λ_{\max} 219 nm (ϵ 7000), ν_{\max} (CCl₄) 2940vs, 2860s, 1695vs, 1643s, 1445s, 1424s, 1295s, 1275s, 1253s, 1222s, 910s, and 898s cm⁻¹, τ 4.40 (1H, s, >C=CH-CO), 5.05br (2H, s, $W_{\frac{1}{2}}$ 5 Hz, =CH₂), 7.67 (4H, m, allylic CH₂), and 8.26 (4H, m, >CH₂) (Found: C, 71.2; H, 7.75. C₉H₁₂O₂ requires C, 71.0; H, 7.9%).

(b) (With J. TIDESWELL). To a stirred solution of lithium di-isopropylamide [from di-isopropylamide (3.17 g) in ether (30 cm³) and 1.975M-butyl-lithium in hexane (15.85 cm³)] at -78°, the δ -lactone (19) (4.75 g) in ether (50 cm³) was added during 45 min; stirring was continued for 2 h, and the solution was then brought to 20° during 40 min. It was then acidified at 0° with N-hydrochloric acid. The aqueous phase was extracted with ether, and the combined organic phases were washed with water, dried, and evaporated. Crystallisation of the residue from light petroleum (b.p. 40–60°) gave the dienoic acid (30) (4.29 g), m.p. 77–78°.

The methyl ester (4.26 g), prepared by treatment of the acid with the calculated amount of diazomethane in ether, was dissolved in benzene (60 cm³) and to the cooled (10°) and stirred solution under nitrogen a solution of sodium bis-(2-methoxyethoxy)aluminium hydride (5.705 g) in benzene (35 cm³) was added during 30 min. Stirring was continued at 20° for a further 1 h, after which saturated aqueous sodium potassium tartrate was added. The benzene layer was washed, dried, and evaporated, giving the crude dienol (9) (3.37 g). The *p*-nitrobenzoate (6.68 g), m.p. 58–62° was recrystallised from light petroleum (b.p. 40–60°), giving pure material, m.p. 62–64° (5.81 g). It showed n.m.r. and i.r. solution (CCl₄) spectra identical with those of material prepared as described above.

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