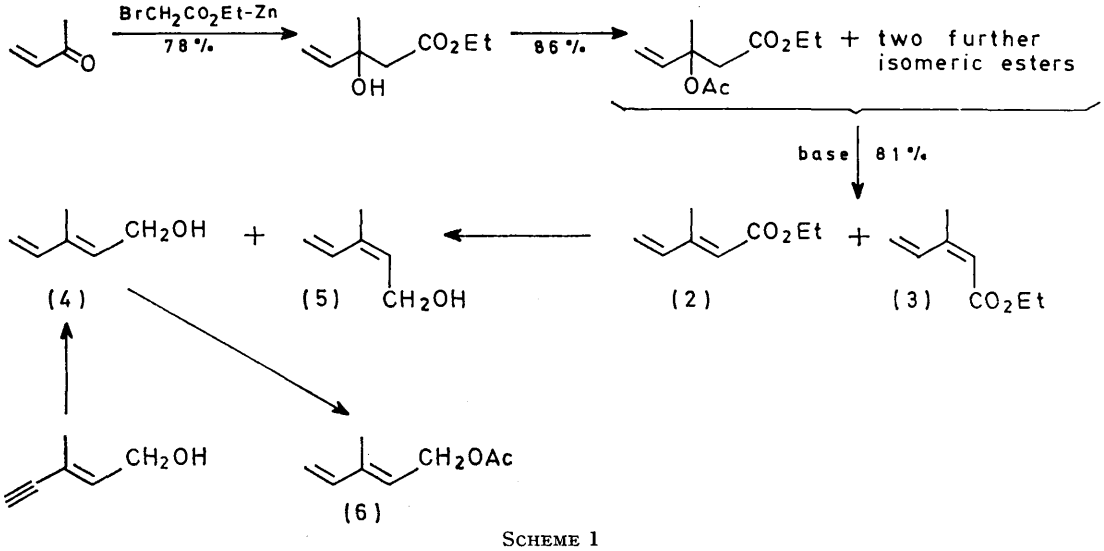
Diels–Alder Reactions. Part II.[1] Condensation of Methyl *trans*-β-Formylcrotonate with Dienols and their Acetates

By **Barend V. Burger, Eberhard du Plessis,** and **Christoph F. Garbers,*** Department of Chemistry, University of Stellenbosch, Republic of South Africa
Klaus G. R. Pachler, N.C.R.L., C.S.I.R., Pretoria, Republic of South Africa

Methyl *trans*-β-formylcrotonate gave Diels–Alder adducts with 3-methylpenta-*trans*-2,4-dien-1-ol and 3-methylpenta-*trans*-2.4-dienyl acetate. The structures of the adducts were determined by their conversion into the corresponding γ- and δ-lactones. A novel rearrangement of a *trans*-γ-lactone to a *cis*-γ-lactone is described.

THE possible use of methyl *trans*-β-formylcrotonate [2] (7) as an intermediate in the synthesis of kitol,[3,4] a dimer of retinol, has been outlined.[1] In this reaction the dienophilic properties of the aldehyde-ester (7) are exploited. In order to obtain more information on the directive effects and relative reactivity of this dienophile in Diels–Alder reactions, its condensation with the model dienol (4) and diene-ester (6) was investigated.

The synthesis of alcohol (4) and its acetate (6) from methyl vinyl ketone and acetylene has been described,[5,6] but yields are poor. The alcohol (4) was also obtained t-butoxide in tetrahydrofuran,[8] yielded a mixture of the *cis*- and *trans*-esters (2) and (3) in an approximate 1 : 1 ratio, which on lithium aluminium hydride reduction gave a mixture of the alcohols (4) and (5). Attempts to separate the higher boiling *trans*-isomer from the *cis*-isomer by fractional distillation failed, as the elevated temperature caused a gradual *trans–cis*-isomerisation, leading to increased yields of the *cis*-isomer in the distillate. The pure *trans*-isomer was finally obtained by preparative g.l.c. Similarly, catalytic reduction of 3-methylpent-*trans*-2-en-4-yn-1-ol gave



SCHEME 1

by reduction of the corresponding diene-ester (2), for which various syntheses have been elaborated.[7] The yield in the procedure whereby methyl vinyl ketone and ethyl bromoacetate are used in a Reformatsky reaction to synthesise the intermediate hydroxy-ester (1), was improved by employing ether as solvent. Similarly, improved yields were obtained in the dehydration of ester (1) by avoiding acidic conditions. Thus acetylation of hydroxy-ester (1) in basic medium, followed by treatment with potassium the pure *trans*-isomer (4). Acetylation of the *trans*-dienol (4) gave the *trans*-acetate (6).

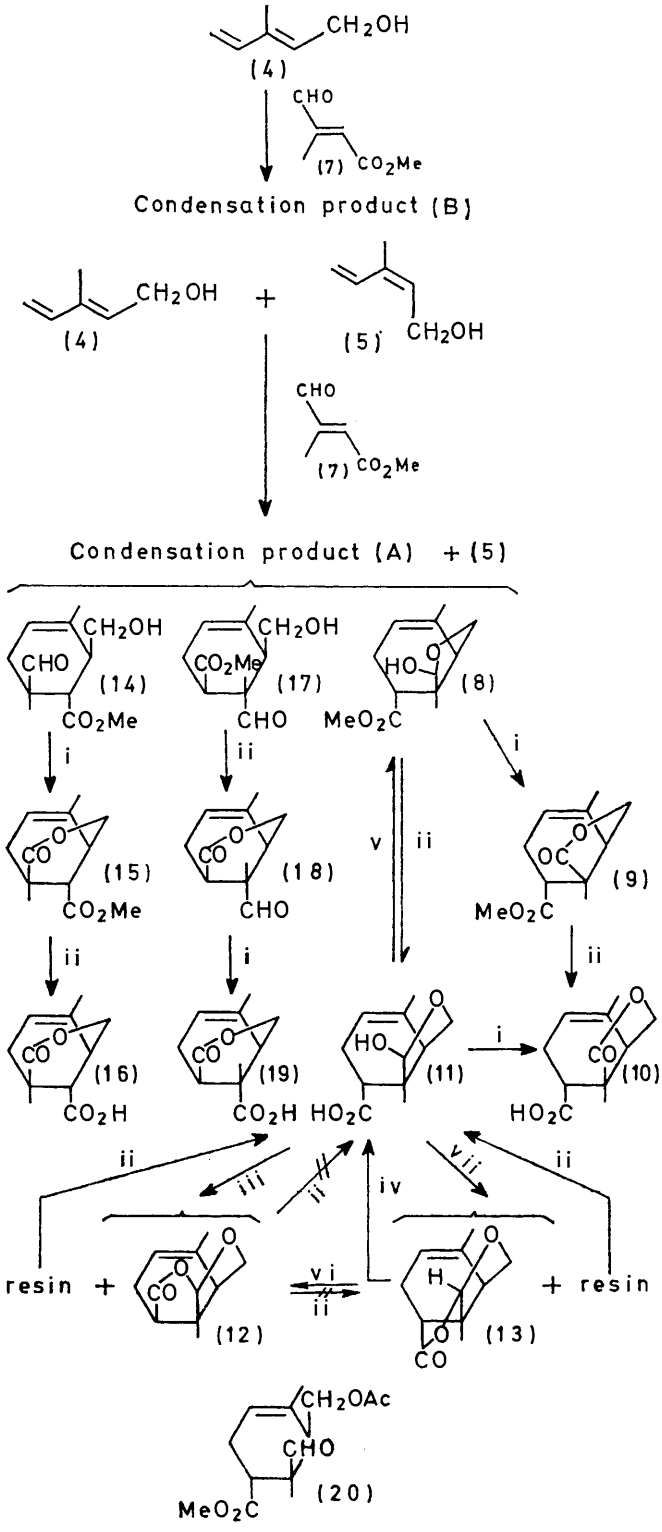
Since the mixture of *cis*- and *trans*-dienols (4) and (5) was more readily available than the pure *trans*-isomer and since it is known that *cis*-1-substituted dienes do not readily yield Diels–Alder adducts,[9] the mixture of dienols (4) and (5) was utilised for the addition. In order to establish whether only the *trans*-diene reacted, an adduct from the *trans*-diene (>96% purity) and the dienophile (7) was prepared for comparison. These

[1] Part I, B. V. Burger, C. F. Garbers, and J. P. van der Merwe, preceding paper.
[2] K. Sisido, K. Kondô, H. Nozaki, M. Tuda, and Y. Udô, *J. Amer. Chem. Soc.*, 1960, **82**, 2286.
[3] B. V. Burger, C. F. Garbers, K. Pachler, R. Bonnett, and B. C. L. Weedon, *Chem. Comm.*, 1965, 588.
[4] C. Giannotti, B. C. Das, and E. Lederer, *Chem. Comm.*, 1966, 28; *Bull. Soc. chim. France*, 1966, 3299.
[5] G. W. H. Cheeseman, I. Heilbron, E. R. H. Jones, F. Sondheimer, and B. C. L. Weedon, *J. Chem. Soc.*, 1949, 2031.
[6] W. Oroshnik, *J. Amer. Chem. Soc.*, 1956, **78**, 2651.
[7] (*a*) I. Heilbron, E. R. H. Jones, M. Julia, and B. C. L. Weedon, *J. Chem. Soc.*, 1949, 1823; (*b*) D. A. van Dorp and J. F. Arens, *Nature*, 1947, **160**, 189; (*c*) L. Crombie and M. Manzoor-i-Khuda, *J. Chem. Soc.*, 1957, 2767; (*d*) J. W. Cornforth, R. H. Cornforth, G. Popjak, and I. Y. Gore, *Biochem. J.*, 1958, **69**, 146; (*e*) W. Stilz and H. Pommer, W.Ger.P. 1,109,671/1958.
[8] K. Eiter, E. Truscheit, and H. Oediger, *Angew. Chem.*, 1960, **72**, 948.
[9] K. Alder, *Annalen*, 1951, **571**, 157.

Diels–Alder reactions gave the addition products (A) and (B) respectively, in high yield. Analysis of the adducts by g.l.c. proved ineffective owing to extensive decomposition of the products. Oxidation of the aldehyde group to yield lactones was considered next, but proceeded unsatisfactorily, either catalytically with oxygen,[10] or with silver oxide [11] in both neutral and basic media. However, oxidation with chromic acid [12] gave lactone-esters in yields in the range 96—99%, which furthermore proved suitable for g.l.c. analysis. According to such analyses both additions gave three products in approximately the same ratios, 93 : 4 : 3. These were separated by g.l.c., and i.r. measurements indicated the presence of two γ-lactone-esters (*ca.* 93 and 3%) and a δ-lactone-ester (*ca.* 4—5%) in both cases. The structures (8),* (14), and (17) for the adducts from the diene synthesis were deduced as follows:

Saponification of the products (A) gave a crystalline acid (11) in >90% yield. Esterification of the acid (11) with diazomethane gave the methyl ester (8), the n.m.r. spectrum of which was identical to that of the major constituent in product (A). The n.m.r. spectrum of product (A) provided evidence that this major constituent (*ca.* 90%) did not contain a free aldehyde group, since only two aldehyde resonances at τ 0·54 and 0·66 were observed, with a total intensity corresponding to *ca.* 10% of the value expected for one proton. Furthermore the resonance at τ 4·45 (s) can be ascribed to a proton on a carbon atom attached to two oxygens and a quaternary carbon atom,[13] leading to the conclusion that the hydroxymethyl and the aldehyde groups had interacted to form a hemiacetal.[14] Further support for this derives from the failure to prepare a dinitrophenylhydrazone and the difficulty in oxidising the compound with silver oxide in neutral or alkaline aqueous medium.

The major product (9) from the oxidation of product (A) exhibited carbonyl absorptions in its i.r. spectrum at 1767 and 1728 cm^{-1}, which were ascribed to the presence of γ-lactone [15] and ester groupings. Since the γ-lactone band appeared at a relatively low frequency in the region where γ-lactones normally absorb, and since on hydrogenation this absorption shifted to 1762 cm^{-1}, this lactone was regarded as a *cis*-γ-lactone.[16] Further work supported this assumption.



SCHEME 2 Reagents: i, CrO_3; ii, OH^- then H^+; iii, *p*-TsOH in C_6H_6; iv, H_2O–Me_2CO; v, CH_2N_2; vi, concentrated OH^- then H^+; vii, heat

* Only one enantiomer shown.

[10] J. R. McNesby and C. A. Heller, jun., *Chem. Rev.*, 1954, **54**, 325.

[11] B. Helferich and T. Malkomes, *Ber.*, 1922, **55**, 702.

[12] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

[13] 'N.m.r. Spectra Catalog,' Varian Associates, Palo Alto, 1963, spectrum 449.

[14] C. D. Hurd and W. H. Saunders, jun., *J. Amer. Chem. Soc.*, 1952, **74**, 5324.

[15] L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Methuen, London, 1958, p. 179.

[16] C. D. Gutsche, D. M. Bailey, C. W. Armbruster, M. W. Wendt, J. L. Kurz, H. H. Strohmayer, and K. L. Seligman, *J. Amer. Chem. Soc.*, 1961, **83**, 1404; W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 1955, 4430; R. A. Clement and Tsu-Chia Shieh, *J. Org. Chem.*, 1960, **25**, 1850; W. G. Dauben, W. K. Hayes, J. S. P. Schwarz, and J. W. McFarland, *J. Amer. Chem. Soc.*, 1960, **82**, 2232; W. Herz and G. Högenauer, *J. Org. Chem.*, 1962, **27**, 905; T. Kanzawa, H. Kamio, M. Sumi, and M. Nishikawa, *J. Amer. Chem. Soc.*, 1958, **80**, 3705; J. H. Brewster and C. H. Kucera, *ibid.*, 1955, **77**, 4564.

Saponification of the ester (9) gave the γ-lactone-acid (10), which could also be prepared from the hemiacetal-acid (11) by chromic acid oxidation. Heating the acid (11) *in vacuo* led to the formation of a glassy solid, with gas evolution. This solid could not be distilled, and on saponification the acid (11) could be recovered. However, rapid heating of the acid (11) *in vacuo* to temperatures just above its m.p. (150°) gave a distillate in 47% yield together with a glassy solid, which could again be saponified to the starting acid (11). The distillate exhibited a strong absorption at 1785 cm^{-1}, but no band due to a hydroxy-group. The n.m.r. spectrum again showed a singlet at τ 4·46, ascribed to a proton on a carbon atom attached to two oxygens and a quaternary carbon atom. The *trans*-γ-lactone structure (13) was assigned to this product.[16,17] Hydrolysis with water or dilute sulphuric acid, or successive treatment with dilute sodium hydroxide and sulphuric acid regenerated the hemiacetal-acid (11). The *trans*-γ-lactone (13) gradually disappeared from a concentrated solution in chloroform, with the formation of a polymeric ester, a reaction probably catalysed by traces of hydrochloric acid in the chloroform.

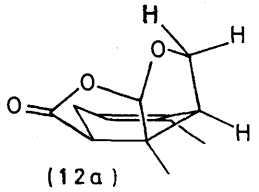
Successive treatment of the *trans*-γ-lactone (13) with more concentrated sodium hydroxide (6N) and 3N-sulphuric acid yielded a new γ-lactone (12) instead of the acid (11). A shift in the carbonyl absorption to 1775 cm^{-1} was observed in the i.r. spectrum and the n.m.r. spectrum again exhibited the singlet at τ 4·21 (1H) ascribed to the proton of the acetal group. This lactone (12) is less strained than the lactone (13) and its formation is best explained by assuming an inversion at C-4 of the *trans*-lactone (13) in the alkaline medium. Such base-induced epimerisations usually proceed to yield *trans*-substituted products. The strain in lactone (13) could be responsible for this isomerisation, where epimerisation apparently proceeds more rapidly than saponification. Base treatment of acid (11) under a variety of conditions did not lead eventually to the formation of lactone (12). The *cis*-γ-lactone (12) could, however, be obtained by treatment of the hydroxy-acid (11) with toluene-*p*-sulphonic acid. Together with lactone (12) a polymeric product was also formed which, on saponification, yielded the hydroxy-acid (11). Treatment of this recovered acid with toluene-*p*-sulphonic acid led to the eventual isolation of the γ-lactone (12) in 83% yield. The n.m.r. data for these lactones and related products are summarised in the Table. The conformation was deduced from the coupling constants of the AMX system (–O–CH_2–CH=) in these products. Dreiding models show two possible conformations (12a) and (12b) for the *cis*-lactone (12). Analysis of the observed coupling constants (J_{AX} 8·8 and J_{MX} 10·5 Hz) and those obtained from the modified Karplus equations [18] (J_{AX} 9·6 and J_{MX} 10·7 Hz) favour structure (12a).

The two minor constituents of the addition products (A) and (B), which on oxidation with chromic acid and g.l.c. separation gave δ- and γ-lactone-esters, were identified as compounds (14) and (17) respectively. By chromatography of this lactone-ester mixture on alumina, the *cis*-γ-lactone-ester (9), originating from the major adduct in (A) and (B), and the δ-lactone-ester (15) could be isolated. The latter on saponification gave the δ-lactone acid (16), m.p. 212°, indicating the preferential formation of the δ-lactone over the *trans*-γ-lactone. Although the n.m.r. spectra of the condensation products (A) and (B) did indeed show the presence of two minor components having free aldehyde groups, it remains an open question whether this adduct (14) should not be represented as the corresponding hemiacetal.

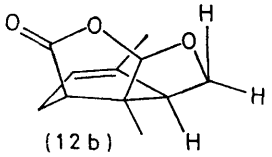
The third component, $\nu_{max.}$ 1766 and 1723 cm^{-1}, obtained by oxidation of the addition products (A) and (B) could not be isolated (preparatively); but from the structure of the *cis*-γ-lactone (9), and since only one further γ-lactone-ester, *viz.* a *trans*-γ-lactone-ester, can be formed by oxidation of the Diels–Alder adducts under discussion, the third component in (A) and (B) must be adduct (17). This assumption was verified by the isolation of the δ-lactone-aldehyde (18)

^{1}H N.m.r. data (τ, *J*/Hz)

Compound	Assignment: OCHO	=CH	CH_2O	OMe	=CMe	–CMe
(8)	4·43 (s)	4·56 (m)	5·58 J_{AM} 8 AMX J_{AX} 9·5 6·41 J_{MX} 9·2	6·27 (s)	8·43 (d, *J ca.* 2)	8·90 (s)
(12)	4·21 (s)	4·45 (m)	5·55 J_{AM} 8·8 AMX J_{AX} 8·8 6·46 J_{MX} 10·5		8·36 (d, *J ca.* 2)	8·60 (s)
(13)	4·46 (s)	4·63 (m)	5·52 J_{AB} 8·7 ABX J_{AX} 8·7 5·89 J_{BX} 8·6		8·30 (d, *J ca.* 2)	8·92 (s)



(12a)



(12b)

[16] W. Cocker, L. O. Hopkins, T. B. H. McMurry, and M. A. Nisbet, *J. Chem. Soc.*, 1961, 4721; J. B. Hendrickson and T. L. Bogard, *ibid.*, 1962, 1678.

[18] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623.

from the saponified products (A) and (B), which on oxidation yielded a δ-lactone acid (19), m.p. 214—215°, mixed m.p. with δ-lactone acid (16) 205—210°.

The preferential formation of the adduct (8) is in agreement with the expected stereochemical course of Diels–Alder reactions as established for other di- and tri-substituted dienophiles. The high yield of adduct (8) may, however, also be due to interaction of the primary hydroxy-group of the diene with the formyl group of the dienophile, either before, or subsequent to the 1,4-addition reaction, thereby favouring the direct formation of compound (8) or shifting the equilibrium in favour of this product. The Diels–Alder addition of the *trans*-dienyl acetate (6) with methyl *trans*-β-formylcrotonate (7) under experimental conditions similar to those employed in the preparation of products (A) and (B) yielded a mixture (C), which contained the adduct (20) as the major component. Hemiacetal formation therefore apparently promoted the formation of adduct (8) in the reaction yielding condensation products (A) and (B). The structure of adduct (20) was established by saponification of product (C) which gave, in addition to the acid (11) (60% isolated yield), an inseparable mixture of γ- and δ-lactone-aldehydes. The n.m.r. spectrum of product (C) indicates the presence of three different components in the approximate ratio of 74 : 19 : 7. The aldehydic proton resonance (total intensity corresponding to 1H) appeared at τ 0·28—0·33.

These results clearly demonstrate the utility of the lactonisation procedure for the determination of the relative stereochemistry of the adducts, and this information was of great value in the structural elucidation of kitol as well as the adducts synthesised from the dienophile (7) and retinol acetate.[19]

EXPERIMENTAL

Combustion analyses were by Dr. F. Pascher, Bonn. I.r. spectra were recorded on a Perkin-Elmer model 21 spectrometer using chloroform as solvent. G.l.c. analyses were performed on a Perkin-Elmer model 116E gas chromatograph, using helium as carrier gas. U.v. spectra were recorded for solutions in 96% ethanol. ^{1}H N.m.r. spectra were recorded with a Varian A-60 spectrometer with tetramethylsilane as internal reference. M.p.s were determined on a Fischer m.p. apparatus.

Ethyl 3-Methyl-3-hydroxypent-4-enoate (1).—A portion of a solution of ethyl bromoacetate (220 g) and methyl vinyl ketone (91 g) in ether (640 ml) was added to activated [20] zinc (153 g) and once the reaction had commenced, the remainder of the solution was added at a rate allowing gentle refluxing. When the addition was complete, the mixture was heated under reflux for 1 h, cooled, and excess of zinc was removed by filtration. The filtrate was treated with 1·7N-AcOH (1 l) and the aqueous layer was saturated with ammonium chloride. The ether layer was separated and the aqueous phase repeatedly extracted with ether. The combined extracts were washed with aqueous sodium bicarbonate and water, and dried. The ether was evaporated and the residue distilled to give the hydroxy-ester (1) (159 g, 78%), b.p. 82° at 15 mmHg, n_D^{20} 1·4341, $\nu_{max.}$ (film) 3490 (OH), 1715 (C=O), 1640, and 923 cm^{-1} (CH=CH$_2$) [lit.,[7c] 57—66° at 4·5 mmHg, n_D^{20} 1·4366—1·4372, $\nu_{max.}$ (film) 3485, 1644, 995, and 924 cm^{-1}].

cis- *and* trans-*Ethyl 3-Methylpenta-2,4-dienoates* (2) *and* (3).—A suspension of *N*-acetylpyridinium chloride [8] was prepared by the gradual addition of acetyl chloride (124 g) in benzene (800 ml) to a solution of pyridine (248 g) in benzene (800 ml). To this stirred suspension the hydroxy-ester (1) (124 g) was added slowly and the resulting mixture was heated at 80° for 12 h and left overnight at room temperature. Solids were removed by filtration and the benzene solution was washed successively with 2N-hydrochloric acid and aqueous sodium carbonate. The extract was dried and the benzene evaporated *in vacuo*. Distillation of the residue yielded a mixture of ethyl 3-methylacetoxy pentenoates (134·5 g, 86%), b.p. 104—105° at 13 mmHg, n_D^{20} 1·4353; $\nu_{max.}$ (film) 1733 (C=O), 1648 (C=C), and 837 cm^{-1} (CH=CH$_2$) (Found: C, 60·4; H, 8·1. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·1%). G.l.c. (2 m; 20% PEGS on 60—80 mesh Chromosorb P) showed the product to be a mixture of three isomeric esters in the ratio 82 : 10 : 8.

t-Butyl alcohol (15·3 g) was slowly added to a suspension of sodamide (8·1 g) in dry tetrahydrofuran, and the ammonia which formed was removed in a stream of nitrogen. The resulting sodium t-butoxide was cooled and added over 15 min to a cold (−3°) solution of the methylacetoxy-pentenoates (39 g) in tetrahydrofuran (130 ml). The temperature was then allowed to rise to 12° (1·5 h), whereupon ice–water was added and the ether layer separated. This was washed, dried, the ether evaporated, and the residue was distilled to yield the *cis–trans* mixture of ethyl 3-methylpenta-2,4-dienoate (22 g, 81%), b.p. 70—74° at 14 mmHg, n_D^{20} 1·4811, $\lambda_{max.}$ 251 nm (ε 21,000), $\nu_{max.}$ (film) 1715 (C=O), 1643 (C=C), 988, and 918 cm^{-1} (CH=CH$_2$) (Found: C, 68·7; H, 8·65. Calc. for $C_8H_{12}O_2$: C, 68·55; H, 8·55%). G.l.c. (2 m; 20% PEGS on 60—80 mesh Chromosorb P) showed the presence of only two components in the ratio 52 : 48.

3-*Methylpenta*-trans-2,4-*dien*-1-*ol* (4).—(a) A solution of the isomeric dienoates (2) and (3) (35·4 g) in ether (500 ml) was added to a solution of lithium aluminium hydride (6·68 g) in ether (500 ml) while the temperature was maintained at −20°. The mixture was subsequently stirred at room temperature for 30 min, excess of reducing agent was decomposed with ethyl acetate (10 ml), and a saturated solution of ammonium chloride (200 ml) added. The ether layer was separated and the aqueous layer extracted with ether. The combined ether layers were washed, dried, the ether evaporated, and the residue was distilled to yield the *cis-* and *trans*-alcohols (4) and (5) (15·5 g, 62%), which still contained unchanged esters (2) and (3) (3%) (g.l.c. analysis). Chromatography on alumina gave a mixture of the pure pentadienols (4) and (5), b.p. 75—76° at 15 mmHg, n_D^{20} 1·4955, $\lambda_{max.}$ 230 nm (ε 23,000). G.l.c. showed the presence of the *trans-* and *cis*-alcohols in a ratio of 58 : 42. This mixture was separated by preparative g.l.c. [2·7 m; Perkin-Elmer preparative column K (Carbowax 1500)], and distilled to give 3-methylpenta-*trans*-2,4-dien-1-ol (4), b.p. 76° at 16 mmHg, n_D^{20} 1·4932, $\lambda_{max.}$ 229·5 nm (ε 24,600) (Found: C, 73·55; H, 10·1. Calc. for $C_6H_{10}O$: C, 73·4; H, 10·2%). Efforts to separate

[19] B. V. Burger and C. F. Garbers, following paper.
[20] E. B. Reid and W. R. Ruby, *J. Amer. Chem. Soc.*, 1951, **73**, 1054.

the *cis*- and *trans*-dienols by fractional distillation under vacuum using a 1 m micro spinning-band fractionating column (E. Haage) led to an enrichment of the *cis*-isomer in the distillate by a gradual isomerisation of the *trans*-isomer. Repeated distillation gave the pure *cis*-dienol (5), b.p. 73° at 13 mmHg, n_D^{25} 1·4891, $\lambda_{max.}$ 230·5 nm (ε 18,500).

(b) 3-Methylpent-*trans*-2-en-4-yn-1-ol * (15·5 g) in dry methanol was hydrogenated in the presence of Lindlar catalyst [21] until no further hydrogen was absorbed (5 days). The catalyst was filtered off and the solvent was evaporated *in vacuo*. Distillation gave the pure *trans*-dienol (4) (15·1 g), b.p. 74° at 14 mmHg, n_D^{25} 1·4930.

3-*Methylpenta*-trans-2,4-*dienyl Acetate* (6).—The *trans*-dienol (4) (12 g) in dry pyridine (11 g) was cooled to 0° and acetic anhydride (12·5 g) was added. After 3 days at room temperature water was added, the product was extracted with ether, and the ether extracts dried. Evaporation of the ether and distillation of the residue gave the *trans*-dienyl acetate (6) (12·5 g), b.p. 73° at 12 mmHg, n_D^{25} 1·4662, $\lambda_{max.}$ 228 nm (ε 22,700), $\nu_{max.}$ (film) 1730 cm^{-1} (C=O) (Found: C, 68·0; H, 8·6. Calc. for $C_8H_{12}O_2$: C, 68·6; H, 8·6%).

Diels–Alder Addition of Methyl trans-β-*Formylcrotonate* (7) *to a Mixture of* cis- *and* trans-3-*Methylpenta*-2,4-*dien*-1-*ols* (4) *and* (5).—A mixture of the dienophile (7) (7·5 g, 0·06 mol), 3-methylpenta-2,4-dien-1-ol (11 g, 0·112 mol; consisting of 58% *trans*- and 42% *cis*-isomer), and hydroquinone was heated in a sealed tube in a nitrogen atmosphere at 90° for 72 h. Unchanged starting material (4·1 g) was recovered by fractional distillation, and further distillation of the residue gave the condensation product (A) (12·5 g, 94%), b.p. 128—129° at 10^{-2} mmHg, n_D^{20} 1·5008, $\nu_{max.}$ (film) 3465 (OH) and 1726 cm^{-1} (C=O) (Found: C, 63·6; H, 8·0. Calc. for $C_{12}H_{18}O_4$: C, 63·7; H, 8·0%). The recovered starting material was treated with a saturated solution of sodium hydrogen sulphite and filtered. The filtrate was extracted with ether, the ether extracts were washed, dried, and the ether evaporated. Distillation of the residue gave 3-methylpenta-2,4-dien-1-ol, b.p. 82—84° at 22 mmHg, $\lambda_{max.}$ 230 nm (ε 21,000) (Found: C, 72·9; H, 10·1%). G.l.c. showed the presence of 75% *cis*- (5) and 25% *trans*-isomer (4).

Composition of Addition Product (*A*).—Chromic acid (0·74 ml of a soln. containing 39·887 g CrO_3 in 200 ml 6N-H_2SO_4) was gradually added to a stirred solution of addition product (A) (500 mg) in acetone (42 ml) at room temperature. Water (100 ml) was added, the mixture was saturated with ammonium chloride, and repeatedly extracted with ether. The combined extracts were washed with water, dried, and the ether evaporated. The resulting oxidation product (476 mg. 96%) was analysed by g.l.c. (2 m Perkin-Elmer column Q; Apiezon L; 20% on 60—100 mesh Celite) and the individual components collected: (i) a γ-lactone-ester (3%), $\nu_{max.}$ ($CHCl_3$) *ca.* 1766 and 1723 cm^{-1}; (ii) a γ-lactone-ester (93%), $\nu_{max.}$ ($CHCl_3$) 1767 and 1728 cm^{-1}; and (iii) a δ-lactone-ester (4%), $\nu_{max.}$ ($CHCl_3$) *ca.* 1725 cm^{-1}.

The components in the oxidation product (466 mg) were also separated by chromatography on acidic alumina (activity I) [22] and the following two components were obtained: (i) a γ-lactone-ester (9) (306 mg). This was eluted with 15—22% ether in light petroleum, and was recrystallised from ether–light petroleum, m.p. 77·5°, $\nu_{max.}$ ($CHCl_3$) 1765 (γ-lactone) and 1728 cm^{-1} (ester) (Found: C, 64·3; H, 7·1. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%); (ii) a δ-lactone-ester (15) which was eluted with 35—45% ether in light petroleum. Evaporation of the solvent and distillation of the residue gave the δ-lactone-ester (15), b.p. (air-bath) 110—115° at 10^{-2} mmHg, $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1} (δ-lactone and ester) (Found: C, 64·8; H, 7·2. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

The third component could not be isolated by column chromatography.

Diels–Alder Addition of Methyl-trans-β-*formylcrotonate* (7) *with* 3-*Methylpenta*-trans-2,4-*dien*-1-*ol* (4).—The ester (7) (8·4 g), alcohol (4) (3·25 g), and a drop of α-tocopherol were mixed and heated in a sealed tube in a nitrogen atmosphere at 90° for 80 h. The reaction product was distilled and gave unchanged starting material (4·4 g), b.p. 75° at 13 mmHg and an addition product (B) (6·1 g, 81%), b.p. 128—129° at 10^{-2} mmHg, n_D^{20} 1·5034 (Found: C, 63·95; H, 8·0%). This product (B) (500 mg) was oxidised with chromic acid as before. Separation of the components of the oxidation product by g.l.c., and i.r. analysis of the individual components again indicated the presence of a γ-lactone-ester (*ca.* 3%), another γ-lactone-ester (93%), and a δ-lactone (*ca.* 5%). By chromatography on acidic alumina (activity I) [22] the γ-lactone-ester (9) and δ-lactone (15) could be isolated and were found to be identical [g.l.c. and i.r., as well as m.p. in the case of lactone-ester (9)] with the components obtained by oxidation of the product (A). The γ-lactone (3%) could not be separated by chromatography.

Saponification of Product (*A*).—Sodium hydroxide (0·4 g) in water (4 ml) was added to a solution of product (A) (1·78 g) in ethanol (4 ml), and after addition of a small amount of hydroquinone, the mixture was stirred under nitrogen at room temperature for 36 h. Water (5 ml) was added and the saponified components were extracted with ether. The aqueous layer was acidified (3N-H_2SO_4), saturated with ammonium chloride, and extracted with ether. The ether extracts were washed, dried, and the ether was evaporated to yield a crystalline product (1·595 g). Recrystallisation from ether or chloroform yielded: (i) hemiacetal-acid (11) (1·487 g, 93%), m.p. 146—147° (with decomp.), $\nu_{max.}$ ($CHCl_3$) 3590 (free OH), 3350 (bonded OH), and 1707 cm^{-1} (acid) (Found: C, 61·65; H, 7·3. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·6%), (ii) an oily fraction (7%). The i.r. spectrum showed the presence of both γ- and δ-lactones as well as acid carbonyl bands. This oily fraction was accumulated from various experiments (498 mg) and chromatographed on silica gel. Two lactones were eluted with 25% petroleum in chloroform, *viz.* (a) a γ-lactone b.p. (air-bath) 85° at 10^{-2} mmHg, $\nu_{max.}$ ($CHCl_3$) 1772 cm^{-1}. No aldehyde bands were observed. The structure of this lactone is uncertain (Found: C, 67·85; H, 7·4. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%) and (b) a δ-lactone (18) which was further purified by chromatography on alumina, b.p. (air-bath) 105—110° at 0·05 mmHg, $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1} (δ-lactone and aldehyde) (Found: C, 68·0; H, 7·45. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

Hydrolysis of Lactone-ester (9).—The ester (9) (100 mg) was saponified with aqueous 2N-sodium hydroxide solution (1 ml) for 2·5 h at room temperature and 0·75 h at 95°. The product was isolated in the usual manner and purified

* Kindly made available by Hoffman–La Roche.

[21] H. Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[22] H. Brockmann and H. Schodder, *Chem. Ber.*, 1941, **74**, 73.

by recrystallisation from ether and vacuum sublimation to yield the γ-lactone-acid (10), m.p. 150—151°, $\nu_{max.}$ ($CHCl_3$) 1769 (γ-lactone) and 1710 cm^{-1} (acid) (Found: C, 62·85; H, 7·0. Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7%).

Oxidation of Hemiacetal-acid (11).—Hemiacetal-acid (11) (23 mg) in acetone (3 ml) was oxidised with chromic acid as described for product (A). The product was isolated and recrystallised from ether to yield the γ-lactone-acid (10), m.p. and mixed m.p. 150—151°.

Pyrolysis of the Hemiacetal-acid (11).—(a) On gradually heating the acid (11) (224 mg) to 120—130° at 10 mmHg in an air-bath and maintaining the product at this temperature for a further 30 min, only a resinous residue was obtained which showed $\nu_{max.}$ ($CHCl_3$) 1730s and 1706w cm^{-1}. Attempted sublimation at 100° (air-bath at 0·3 mmHg) gave only starting material (8 mg).

(b) The hemiacetal-acid (11) (192 mg) was pyrolysed in a glass tube at 0·2 mmHg by placing it in a preheated oven at 145—150°. The γ-lactone (13) which formed distilled. After 15 min no further distillable products formed. The distillate was dissolved in chloroform and cooled and a small quantity of unchanged acid (11) was removed by filtration. The chloroform was evaporated and distillation of the residue yielded the *trans*-γ-lactone (13) (82 mg), b.p. 80° at 0·01 mmHg, which gradually crystallised, m.p. 69—70°, $\nu_{max.}$ ($CHCl_3$) 1785 (γ-lactone) and a strong triplet at 958, 947, and 932 cm^{-1} (Found: C, 68·1; H, 7·4. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%). The glassy residue from the pyrolysis experiment was dissolved in methanol (1 ml) and 3N-sodium hydroxide solution (1·5 ml) was added. The mixture was shaken at room temperature for 24 h. The saponifiable material was isolated and identified as the hemiacetal-acid (11) (m.p. and mixed m.p., i.r. spectrum), which could again be partially converted into *trans*-lactone (13) and a residue.

Hydrolysis of the lactone (13) with aqueous acetone, acidic aqueous acetone, or 2N-sodium hydroxide solution gave the starting hemiacetal-acid (11). The use of more concentrated sodium hydroxide solutions (*e.g.* 4N) led to the formation of the *cis*-γ-lactone (12). However, treatment of the hemiacetal-acid (11) under similar conditions did not give the *cis*-γ-lactone (12).

Synthesis of the cis-γ-*Lactone* (12).—(a) A mixture of the acid (11) (819 mg), toluene-*p*-sulphonic acid (130 mg), and benzene (150 ml) was refluxed for 45 min and the water which formed was removed as an azeotrope. The mixture was treated with anhydrous potassium carbonate, the solid material filtered off, and the benzene was evaporated from the filtrate. Distillation of the residue gave a γ-lactone (130 mg), b.p. 90—110° (air-bath) at 0·01 mmHg, $\nu_{max.}$ ($CHCl_3$) 1775 cm^{-1}, and a residue, $\nu_{max.}$ 1769w, 1728s, and *ca.* 1705w cm^{-1}. The latter was saponified and the saponifiable material treated with toluene-*p*-sulphonic acid in benzene as before. This process was repeated and eventually gave the *cis*-γ-lactone (12) (83%), b.p. 110—112° (air-bath) at 0·01 mmHg, $\nu_{max.}$ 1775 (γ-lactone) and a strong triplet at 963, 947, and 932 cm^{-1} (Found: C, 67·7; H, 7·6. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%). From the product obtained by saponification of the residue the acid (11) was isolated and identified (mixed m.p. and i.r. spectrum).

(b) The *trans*-γ-lactone (13) (18 mg) in ether (5 ml) was shaken with 6N-sodium hydroxide solution (0·5 ml) for 3 min. Water (4·5 ml) was added, the mixture was acidified, the aqueous layer saturated with ammonium chloride, and extracted with ether. The extracts were dried, the ether evaporated, and the residue was distilled to yield the *cis*-γ-lactone (12) (11 mg), b.p. 75° (air-bath) at 0·01 mmHg, $\nu_{max.}$ ($CHCl_3$) 1775 (γ-lactone), and a triplet at 963, 947, and 932 cm^{-1} (Found: C, 67·85; H, 7·4%).

Saponification of δ-*Lactone-ester* (15).—The δ-lactone-ester (15) (26 mg) in ethanol (0·5 ml) was treated with sodium hydroxide (0·05 g) in water (0·5 ml) and the mixture was shaken for 27 h. The product (21 mg) was isolated in the usual manner and was purified by distillation at 130—160° (air-bath) at 0·01 mmHg and recrystallisation from ether. Sublimation gave the acid (16), m.p. 212°, $\nu_{max.}$ 1725—1715 cm^{-1} (δ-lactone and acid) (Found: C, 63·3; H, 6·3. Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7%).

Oxidation of δ-*Lactone* (18).—This δ-lactone (18) (60 mg) in acetone was oxidised with chromic acid and the product was purified as described for acid (16). Final sublimation in vacuum (140—150° at 0·01 mmHg) gave the δ-lactone-acid (19), m.p. 214—215°, $\nu_{max.}$ ($CHCl_3$) 1726—1708 cm^{-1} (δ-lactone and acid). Acids (16) and (19) were not identical (mixed m.p. 205—210°). On cooling, the melt did not crystallise, in contrast to the melts of the individual δ-lactone-acids.

Diels–Alder Addition of Methyl trans-β-*Formylcrotonate* (7) *with* 3-*Methylpenta*-trans-2,4-*dienyl Acetate* (6).—A mixture of the formylcrotonate (7) (9·0 g), the dienyl acetate (6) (10 g), and some hydroquinone was heated in a sealed evacuated tube at 90° for 92 h. Distillation of this mixture gave the product (C) (12·8 g, 67·5%), b.p. 115° at 0·01 mmHg (Found: C, 62·4; H, 7·5. Calc. for $C_{14}H_{20}O_5$: C, 62·7; H, 7·5%).

Composition of Product (*C*).—This product (1·46 g) in ethanol (2 ml) was mixed with sodium hydroxide (0·31 g) in water (3 ml) and the mixture was shaken in a nitrogen atmosphere at room temperature for 52 h. Water (5 ml) was added and the saponifiable material (0·862 g) isolated in the usual way. Repeated crystallisations yielded the hemiacetal-acid (11) (0·455 g), m.p. and mixed m.p. 140°. The mother liquor showed the presence of γ-lactone, δ-lactone, and aldehyde groups, $\nu_{max.}$ ($CHCl_3$) 1760, 1730, and 1715 cm^{-1}. Attempted separation of these components failed.

We thank the South African Council for Scientific and Industrial Research for financial support and for fellowships (to B. V. B. and E. du P.).

[2/2101 *Received*, 6*th September*, 1972]