Synthesis of *Z*-Rethrolones and *Z*-Rethrones

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Convenient syntheses of (*Z*)-jasmone {3-methyl-2-[(*Z*)-pent-2-enyl]cyclopent-2-enone} (2c), (*Z*)-cinerone {2-[(*Z*)-but-2-enyl]-3-methylcyclopent-2-enone} (2b), (±)-(*Z*)-jasmololone {(±)-4-hydroxy-3-methyl-2-[(*Z*)-pent-2-enyl]cyclopent-2-enone} (1c), and (±)-(*Z*)-cinerolone {(±)-4-hydroxy-3-methyl-2-[(*Z*)-but-2-enyl]-cyclopent-2-enone} (1b) from readily available allethrolone [4-hydroxy-3-methyl-2-(prop-2-enyl)cyclopent-2-enone] (1a) are described. The route from (1a) to (1b and c) and (2b and c) is especially useful for the introduction of radio-labels into these compounds.

HYDROXYCYCLOPENTENONES (1b—d) (' rethrolones ') are the alcoholic components of the insecticidal ' pyrethrin ' esters found in *Chrysanthemum cinerariaefolium*.[1] The collective name ' rethrones,' is applied to the group of closely related cyclopentenones (2b—d) one member of which, jasmone (2c), occurs in the oil of *Jasminium grandiflorum*. In connection with biosynthetic studies on the natural pyrethrins, we required a synthetic route to compounds (1) and (2) which would allow the convenient introduction of a radio-label into the prop-2-enyl side chains of the molecules. Although several useful and novel routes to (1) and (2) have been described,[2-5] either for reasons of length or convenience none seemed suitable for our particular needs. We now describe syntheses of (1b and c) and (2b and c) starting from the hydroxycyclopentenone (1a) which met our requirements.

Racemic 4-hydroxy-3-methyl-2-(prop-2-enyl)cyclopent-2-enone (1a) (' allethrolone ') is a readily available synthetic rethrolone used in the production of the insecticide ' bioallethrin '.[6] Conversion of (1a) into the methyl ether (3), followed by cleavage of the side chain double bond in (3), by using osmium tetraoxide–sodium

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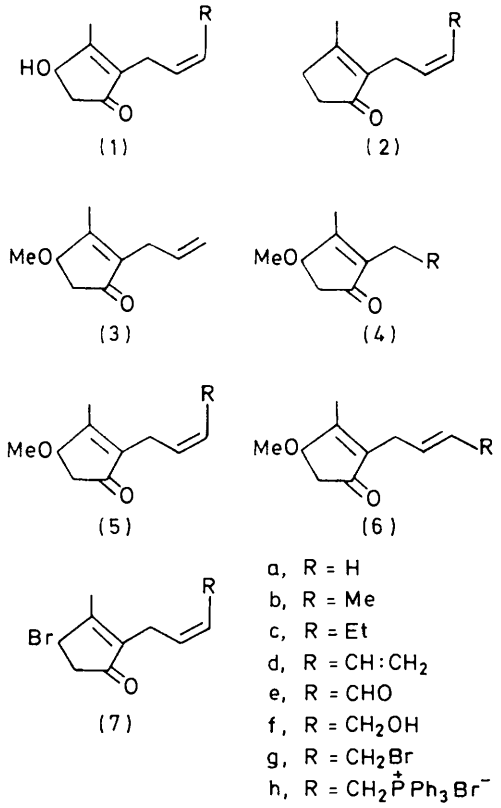
[3] L. Crombie, P. Hemesley, and G. Pattenden, *J. Chem. Soc.* (*C*), 1969, 1024.

[4] For summary of rethrolone and rethrone syntheses see R. A. Ellison, *Synthesis*, 1973, 397.

[5] For more recent rethrolone and rethrone syntheses see J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 3275; K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1973, **95**, 4446; J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367; A. J. Birch, K. S. Keogh, and V. R. Mausdapur, *Austral. J. Chem.*, 1973, **26**, 274; T. Mukaiyama, M. Araki, and T. Takei, *J. Amer. Chem. Soc.*, 1973, **95**, 4763; T. Sakan, Y. Mori, and T. Yamazaki, *Chem. Letters*, 1973, 713; E. Madeleyn and M. Vandewalle, *Bull. Soc. chim. belges*, 1973, **82**, 293.

[6] M. S. Schechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 3165; M. Elliott, *J. Sci. Food Agric.*, 1954, 505.

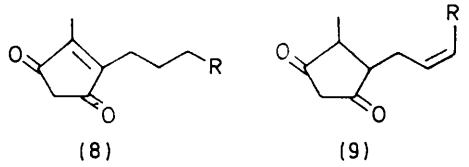
periodate produced the unstable keto-aldehyde (4e). Condensation between (4e) and the ylide derived from n-propyltriphenylphosphonium bromide in dimethyl sulphoxide (DMSO), using methylsulphinylmethanide anion as base, was both regio- and stereo-specific and produced the (*Z*)-olefin (5c) containing less than 10% of the corresponding (*E*)-isomer (6c). Spectral data on the crude product gave no evidence of concomitant condensation at the ketone carbonyl group in (4e). The almost exclusive (*Z*)-olefination in the Wittig reaction with (4e) was surprising, but the observation is consistent with related studies with similar systems.[3,7] The configuration assigned to (5c) followed from chromatographic and spectral comparison with an authentic



a, R = H
b, R = Me
c, R = Et
d, R = CH:CH$_2$
e, R = CHO
f, R = CH$_2$OH
g, R = CH$_2$Br
h, R = CH$_2$$\overset{+}{P}Ph_3Br^-$

sample of the methyl ether prepared from (±)-(*Z*)-jasmololone which was available from an earlier synthesis. In addition, it was found that the major isomer resulting from the Wittig condensation was almost quantitatively converted into the corresponding (*E*)-isomer (6c) upon direct irradiation using a medium pressure mercury lamp. A similar photochemical *Z*—*E* isomerisation was reported previously for the acetate of (1c).[8]

During attempts to demethylate (5c) using boron tribromide, only trace amounts of the expected alcohol (1c) were isolated; the major product isolated was the bromide (7c) (*ca.* 55%). High temperature protic demethylating reagents, such as pyridine hydrochloride,



resulted in the formation of cyclopent-4-ene-1,3-diones (8), whereas use of the fairly neutral ethyl sulphide anion in dimethylformamide as demethylating medium[9] produced the cyclopentane-1,3-diones (9). These unexpected and interesting transformations of (5), and of related compounds, are discussed more fully in the following paper.

The synthesis of (1c) from (5c) was completed by conversion into the corresponding bromide (7c) in one step using boron tribromide,[10] followed by hydrolysis of (7c) by using aqueous calcium carbonate.[11] (*Z*)-Jasmone (2c) was prepared from (7c) by reduction with zinc in acetic acid, Both the (*Z*)-jasmololone (1c) and (*Z*)-jasmone (2c) showed i.r. and n.m.r. spectra closely similar to those of authentic samples obtained by earlier syntheses.[2,3]

By a similar series of transformations but using ethyl- in place of n-propyl-triphenylphosphonium salt, the keto-aldehyde (4e) was converted into (*Z*)-cinerolone methyl ether (5b), which in turn was converted into (*Z*)-cinerolone (1b) and (*Z*)-cinerone (2b) by procedures identical with those described in the synthesis of (1c) and (2c). Since radio-labelled ethyl and n-propyl halides are readily available, syntheses of (1b and c) and (2b and c) containing radio-labels in their prop-2-enyl side chains should be straightforward by the routes outlined above.

In an attempt to prepare the same dienones (5b and c) by use of the ylide from salt (4h) and the appropriate aldehydes, keto-aldehyde (4e) was first reduced to the alcohol (4f). However, we were unable to convert (4f) into (4h) *via* the corresponding bromide in acceptable yields; instead bromide (4g) suffered extensive decomposition upon treatment with triphenylphosphine.

EXPERIMENTAL

N.m.r. spectra were determined with a Perkin-Elmer R10 spectrometer for dilute solutions in deuteriochloroform with Me$_4$Si as internal standard. Coupling constants (*J*) are in Hz. Mass spectra were measured with an A.E.I. MS9 spectrometer. G.l.c. data were obtained on a 10% Apiezon L column. Reactions involving the sensitive aldehyde (4e) and all Wittig reactions were performed under nitrogen. Ethereal solutions were dried over magnesium sulphate prior to evaporation.

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[8] M. J. Bullivant and G. Pattenden, *J.C.S. Chem. Comm.*, 1972, 864, and unpublished work.
[9] G. I. Feutrill and R. N. Millington, *Austral. J. Chem.*, 1972, **25**, 1719.
[10] For similar observations of alkyl bromide formation during BBr$_3$ demethylation of methyl ethers see R. D. Youssefyeh and Y. Mazur, *Chem. and Ind.*, 1963, 609; V. Stehle, M. Brini, and A. Pousse, *Bull. Soc. chim. France*, 1959, 2171; C. Gandolfi, G. Doria, and P. Gaio, *Tetrahedron Letters*, 1972, 2063.
[11] S. B. Soloway and F. B. Laforge, *J. Amer. Chem. Soc.*, 1947, **69**, 979.

4-Methoxy-3-methyl-2-(prop-2-enyl)cyclopent-2-enone (3).—The methyl ether was prepared from allethrolone, *via* the semicarbazone, m.p. 209—211° (lit.,[12] 213—214°) according to the procedure of Katsuda *et al.*,[12] and showed b.p. 90—94° at 2·5 mmHg, n_D^{17} 1·4924 (lit.,[12] b.p. 72—73° at 2 mmHg, n_D^{20} 1·4880), $\lambda_{max.}$ (EtOH) 229 nm (ε 10,900), $\nu_{max.}$ (film) 1713, 1660, and 1640 cm^{-1}, τ (CCl_4) 4·27 (ddt, *J* 18, 10, and 7, C*H*:CH_2), 4·9—5·16 (m, :CH_2), 5·71br (C*H*·OMe), 6·66 (OMe), 7·12 (d, *J* 7, CH_2·CH:), 7·5 (dd, *J* 6 and 18, C*H*H), 7·89 (dd, *J* 2 and 18, CH*H*), and 8·0 (:C*Me*) (Found: M^+, 166. $C_{10}H_{14}O_2$ requires *M*, 166).

2-Formylmethyl-4-methoxy-3-methylcyclopent-2-enone (4e) (*with* S. A. Abou-Donia).—Powdered sodium metaperiodate (22 g) was added to a solution of the cyclopentenone (3) (20 g) and osmium tetraoxide (0·1 g) in dioxan (85 ml) and water (35 ml), and the mixture was stirred at 25° for 36 h, and then extracted with ether (6 × 100 ml). Evaporation of the washed (H_2O) and dried ethereal extracts, *in vacuo*, left the aldehyde (4e) (3·5 g, 34%) as an unstable oil, $\nu_{max.}$ (film) 1713, 1708, and 1650 cm^{-1}, τ 0·33 (t, *J* 1·5, CHO), 5·55 (m, −C*H*·OMe), 6·56 (OMe), 6·66 (d, *J* 1·5, −CH_2CHO), 7·24 (dd, *J* 6 and 19, −C*H*H), 7·72 (dd, *J* 3·5 and 19, CH*H*), and 7·94 (:CMe), which was used in the next stage without further purification. It formed a *bis-2,4-dinitrophenylhydrazone* which crystallised from nitrobenzene–ethanol as orange needles, m.p. 247—250° (Found: C, 47·6; H, 3·9; N, 20·6%; M^+, 528. $C_{21}H_{20}N_8O_9$ requires C, 47·75; H, 3·8; N, 21·2%; *M*, 528).

2-(2-Hydroxyethyl)-4-methoxy-3-methylcyclopent-2-enone (4f).—A solution of sodium borohydride (0·25 g) in ethanol (25 ml) was added over 0·5 h to a stirred solution of the aldehyde (4e) (2·15 g) in ethanol (25 ml) and the mixture was stirred at 25° for 0·5 h, then diluted with water and extracted with ether. The aqueous phase was separated, acidified with concentrated hydrochloric acid, and extracted with chloroform. Evaporation of the dried chloroform extracts left the alcohol (4f) (1·2 g) as an almost colourless oil, $\nu_{max.}$ (film) 3450, 1708, and 1650 cm^{-1}, τ 5·03br (OH), 5·65 (m, C*H*·OMe), 6·39 (t, *J* 7, CH_2CH_2), 6·61 (OMe), 6·71 (t, *J* 7, CH_2CH_2), 7·3—7·7 (m, −CH_2−), and 7·91 (:CMe).

4-Methoxy-3-methyl-2-[(Z)-pent-2-enyl]cyclopent-2-enone (5c).—(a) *From* (Z)-*jasmololone* (1c). A solution of semicarbazide hydrochloride (1 g) in hot water (2 ml) was added to a solution of (*Z*)-jasmololone [2] (1 g) in pyridine (2 ml) and ethanol (5 ml), and the mixture was kept at 25° for 24 h. The solution was diluted with water, and cooled in ice–water. The solid which separated was filtered off, washed with water, and dried to give the crude semicarbazone, m.p. 176—184°, which was used without further purification. A solution of the semicarbazone (0·3 g) in methanol (3 ml) containing sulphuric acid (0·1 ml) was heated under reflux for 2 h, diluted with water, and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts left a residue which was distilled (short-path; free-flame) to give the *ether* (5c) (0·11 g), b.p. *ca.* 70° at 0·10 mmHg, $\nu_{max.}$ ($CHCl_3$) 1700 and 1650 cm^{-1}, τ 4·4—4·9 (m, 2 × :C*H*), 5·7 (d, *J* 6, C*H*·OMe), 6·62 (OMe), 7·04 (d, *J* 6, CH_2·CH:), 7·38 (dd, *J* 6 and 18, C*H*H), 7·78 (dd, *J* 3 and 18, CH*H*), *ca.* 7·9 (CH_2CH_3), 7·94 (Me), and 9·02 (t, *J* 7, CH_2CH_3) (Found: *m/e* 194·1295. $C_{12}H_{18}O_2$ requires *M*, 194·1307). G.l.c. (160°) showed one major band, and a smaller one of shorter retention time corresponding to the (*E*)-isomer (<3%).

(b) *From the aldehyde* (4e). n-Propyltriphenylphosphonium bromide [13] (3·9 g) was added in portions to a solution of dimethyl sulphoxide anion [14] [from NaH (0·27 g)] in dimethyl sulphoxide (30 ml) and the resulting red solution was stirred at 25° for 1 h, and then added over 1 h to the aldehyde (4e) (1·5 g) in dimethyl sulphoxide (10 ml). The mixture was stirred for 0·6 h, diluted with water (1 l), and extracted with ether (5 × 150 ml). Evaporation of the dried ether extracts left a residue which was chromatographed in ether on silica gel to give the olefin (0·4 g, 23%) as an oil; g.l.c. showed the presence of (*Z*)- and (*E*)-isomers in the approximate proportion 88 : 12. Further chromatography gave the (*Z*)-olefin, containing *ca.* 5% (*E*)-isomer, which was both chromatographically and spectrally identical with that obtained in (a).

4-Methoxy-3-methyl-2-[(E)-pent-2-enyl]cyclopent-2-enone (6c) (*with* M. J. Bullivant).—A solution of the (*Z*)-isomer (16 mg) from the preceding experiments in hexane (100 ml) was irradiated for 8 h, and then evaporated to dryness *in vacuo*. The residue was chromatographed in hexane on a short column of silica gel to produce a 7 : 3 mixture (14 mg) of (*E*)- and (*Z*)-isomers of the cyclopentenone, $\nu_{max.}$ (film) 1708, 1650, and 970 cm^{-1}, τ 4·4—4·9 (m, 2 × :C*H*), 5·7 (d, *J* 6, −C*H*·OMe), 6·63 (OMe), 7·10 (d, *J* 6, :C·CH_2C:), 7·38 (dd, *J* 6 and 18, C*H*H), 7·8 (dd, *J* 3 and 18, CH*H*), 7·95 (:CMe), *ca.* 8·0 (CH_2·CH_3), and 9·07 (t, *J* 7, CH_2CH_3) (Found: *m/e*, 194·1300. $C_{12}H_{18}O_2$ requires *M*, 194·1307). Longer periods of irradiation did not alter the (*Z*) : (*E*) ratio (g.l.c. monitoring, 150°).

2-[(Z)-But-2-enyl]-4-methoxy-3-methylcyclopent-2-enone (5b).—The olefin was prepared from ethyltriphenylphosphonium bromide [15] (5·5 g) and the keto-aldehyde (4e) (2 g) in an identical manner to that described for the isomeric pentenylcyclopentenone. Chromatography separated the pure *olefin* (5b) (0·38 g, 18%) as an oil, $\nu_{max.}$ ($CHCl_3$) 1710 and 1654 cm^{-1}, τ 4·5—4·9 (m, 2 × :CH), 5·74 (d, *J* 6, C*H*OMe), 6·63 (OMe), 7·07 (d, *J* 6, CH_2CH:), 7·39 (dd, *J* 6 and 18, C*H*H), 7·78 (dd, *J* 3 and 18, CH*H*), 7·95 (:C*Me*), and 8·31 (d, *J* 7, :CH*Me*) (Found: *m/e* 180·1155. $C_{11}H_{16}O_2$ requires *M*, 180·1150). G.l.c. (160°) showed that less than 12% of the corresponding (*E*)-isomer [eluted before the (*Z*)-isomer] was present.

4-Bromo-2-[(Z)-but-2-enyl]-3-methylcyclopent-2-enone (7b).—A solution of boron tribromide (1·3 g) in methylene chloride (2·5 ml) was added to a solution of the (*Z*)-olefin (5b) (255 mg) in methylene chloride (5 ml) at −78°, and the mixture was stirred at −78° for 0·5 h, and then allowed to warm slowly to 0°. The mixture was diluted with water, and the methylene chloride extract was separated, washed (H_2O), dried, and evaporated *in vacuo*. Chromatography of the residue in benzene on silica gel gave the *bromide* (7b) (179 mg, 54%), as a mobile liquid, $\nu_{max.}$ (film) 1707 and 1645 cm^{-1}, τ 4·4—4·8 (m, CH:CH), 5·04br (−CHBr), 6·9—7·13 (4H, m, 2 × CH_2), 7·84 (:CMe), and 8·3 (d, *J* 6, :CH*Me*) (Found: *m/e* 228·0147/230·0136. $C_{10}H_{13}BrO$ requires *M*, 228·0150/230·0131]. The bromide was chromatographically and spectrally (i.r., n.m.r., and mass) identical with a sample prepared from the alcohol (1b) by reaction with phosphorus tribromide.

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4-*Bromo*-3-*methyl*-2-(*prop*-2-*enyl*)*cyclopent*-2-*enone* (7a).—The bromide was prepared from the corresponding methyl ether and boron tribromide, under identical conditions to those used for (7b). The *bromide* showed $\nu_{max.}$ (film) 1711 and 1645 cm^{-1}, τ 4·38 (ddt, *J* 16, 9, and 6, $CH_2CH{:}CH_2$), 4·8—5·2 (m, ${:}CH_2$ and CHBr), 6·9—7·2 (4H, m), and 7·85 (:CMe) (Found: *m/e* 214/216. $C_9H_{11}BrO$ requires *M*, 214/216).

4-*Bromo*-3-*methyl*-2-[(Z)-*pent*-2-*enyl*]*cyclopent*-2-*enone* (7c).—The bromide, prepared from the corresponding methyl ether in the usual way, showed τ 4·3—4·8 (m, $CH{:}CH$), 5·05 (m, CHBr), 6·9—7·2 (4H, m), *ca.* 7·8 (m, CH_2CH_3), 7·85 (:CMe), and 9·01 (t, *J* 7, CH_2CH_3).

2-[(Z)-*But*-2-*enyl*]-3-*methylcyclopent*-2-*enone* [(Z)-*Cinerone*] (2b).—Zinc dust (0·67 g) was added in portions to a solution of the bromo-compound (7b) (175 mg) in glacial acetic acid (4 ml), and the mixture was kept at 100° for 1 h. Water (25 ml) was added to the cooled mixture, which was then filtered. The filtrate was extracted with ether, and the separated ether extracts were washed with sodium hydrogen carbonate solution and water and then dried. Evaporation of the ether left the ketone (2b) (103 mg, 83%), homogeneous in t.l.c. and showing spectral data (i.r. and n.m.r.) almost identical with those of an authentic sample [containing *ca.* 10% (*E*)-isomer] prepared by an earlier independent route.[3]

3-*Methyl*-2-[(Z)-*pent*-2-*enyl*]*cyclopent*-2-*enone* [(Z)-*Jasmone*] (2c).—The ketone was prepared from the corresponding bromide (150 mg) in an identical manner to that described for (*Z*)-cinerone. It showed spectral data (i.r., n.m.r.) almost identical with those of an authentic sample [containing *ca.* 10% (*E*)-isomer] prepared by an earlier independent route.[3]

3-*Methyl*-2-(*prop*-3-*enyl*)*cyclopent*-2-*enone* (*Allethrone*) (2a).—The ketone was obtained (*ca.* 80%) from the corresponding bromide (310 mg) by reduction with zinc (1 g) in acetic acid (5 ml) in an identical manner to that described for (*Z*)-cinerone. It showed $\nu_{max.}$ (film) 1698 and 1644 cm^{-1}, τ 4·33 (ddt, *J* 16, 9, and 6, $CH_2CH{:}CH_2$), 4·9—5·3 (m, CH_2), 7·11 (d, *J* 6, $CH_2CH{:}$), 7·3—7·8 (4H), and 7·98 (:CMe) (Found: M^+, 136. $C_9H_{12}O$ requires *M*, 136).

(±)-4-*Hydroxy*-3-*methyl*-2-[(Z)-*but*-2-*enyl*]*cyclopent*-2-*enone* [(±)-(Z)-*Cinerolone*] (1b).—The bromo-compound (7b) (200 mg) was added to a suspension of calcium carbonate (2 g) in water (12 ml) and the mixture was heated under reflux for 2 h, cooled, and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts left the alcohol (103 mg, 74%) as an oil, n_D^{21} 1·5132 (Found: M^+, 166. $C_{10}H_{14}O_2$ requires *M*, 166) whose i.r. and n.m.r. spectra were indistinguishable from those of an authentic sample.

(±)-4-*Hydroxy*-3-*methyl*-2-[(Z)-*pent*-2-*enyl*]*cyclopent*-2-*enone* [(±)-(Z)-*Jasmololone*] (1c).—The alcohol was prepared (*ca.* 67%) from the correspondiug bromide in an identical manner to that described for cinerolone. It showed spectral (i.r., n.m.r., mass) data closely identical with those of an authentic spccimen.

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