Allenes. Part XXVIII.[1] Synthesis of Antibiotic Lactols and an Allenic Ester by Claisen Rearrangement of Prop-2-ynyl Vinyl Ethers

By **Donald K. Black, Zacharias T. Fomum, Phyllis D. Landor,** and **Stephen R. Landor,*** Makerere University, Box 16020, Kampala, Uganda, and Woolwich Polytechnic, London S.E. 18

Naturally occurring 4-hydroxy-2-vinylbut-2-en-4-olide (V), an allenic analogue [4-hydroxy-3,3-dimethyl-2-vinylidenebutan-4-olide (VII)], and the corresponding aldehyde ester [ethyl 2-(1-formyl-1-methylethyl)buta-2,3-dienoate (VIII)] have been synthesised by a Claisen-type sigmatropic rearrangement of 3-carboxyprop-2-ynyl vinyl ethers.

We have reported investigations of the Claisen [2] and the Cope rearrangement [2,3] of prop-2-ynyl vinyl systems. The Claisen rearrangement afforded a general method for the synthesis of β-allenic aldehydes (I) especially in cases where two alkyl substituents (R^1, R^2) in the α-position block the ready rearrangement of the allenic aldehyde to the conjugated dienal.

(I)

We presented evidence supporting a one-electron movement with some radical character in the transition state, for both types of rearrangement; however, in the light of the Woodward–Hoffmann approach [4] the Claisen rearrangement, which shows considerable stereospecificity,[5] is best interpreted as a concerted [3,3] sigmatropic transformation, although it should be noted that both Claisen and Cope transition states are sterically unfavourable for a concerted [3,3] sigmatropic rearrangement.

We now report details [6] of the application of the Claisen rearrangement of a carboxy-substituted prop-2-ynyl vinyl ether to the synthesis of the naturally occurring antibiotic (V) (P.A. 147) first isolated by Els *et al.*[7] from an unidentified Streptomyces strain. As expected, the intermediate skipped allenic aldehyde (III) could not be isolated, but rearranged spontaneously to the conjugated dienal (IV) which then formed the five-membered hydroxy-lactone ring (V). The analogous *gem*-dimethyl allenic compound (VII) and the corresponding *gem*-dimethyl allenic aldehyde ester (VIII) were prepared similarly by Claisen rearrangement of carboxy- and ethoxycarbonyl-prop-2-ynyl 2-methylprop-1-enyl ethers, the prototropic rearrangement being prevented by the blocking *gem*-dimethyl group.

4-Vinyloxybut-2-ynoic acid (II) was prepared from prop-2-ynyl vinyl ether by conversion into the Grignard reagent with ethylmagnesium bromide and treatment with carbon dioxide. Partial rearrangement of the acid (II) was effected by passing it through an electrically heated tube packed with glass wool at 250° in a stream of nitrogen. Careful chromatography gave a 15% yield of the highly unstable hydroxy-lactone (V), together with recovered starting material. The structure was confirmed by the u.v. absorption of the hydroxy-lactone (V) and its sodium and barium salts, which agreed closely with the data reported for the natural product [7] and its salts (see Table). The considerably greater

U.v. data for the hydroxy-lactone (V) and its salts

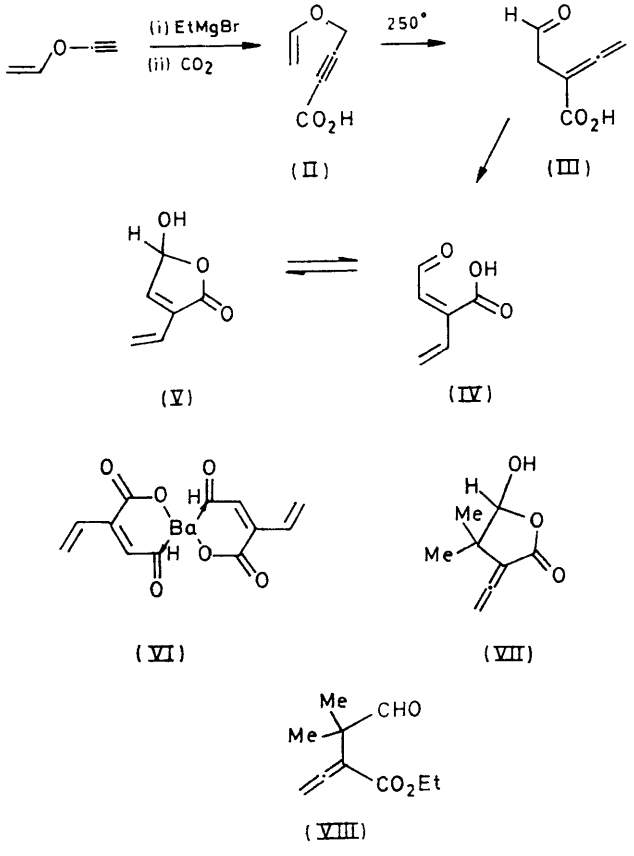
	Natural material From Els *et al.*[7a]		Natural material From Akita *et al.*[7b]		Synthetic material	
Compound	$\lambda_{max.}$/nm	ε	$\lambda_{max.}$/nm	ε	$\lambda_{max.}$/nm	ε
(V)	245	7800	242	7000	245	8800
Na salt	272	20,500			273	19,320
Ca salt			275	31,000		
Ba salt	272	22,000			276	34,000

stability of the barium salt (which gave correct elemental analyses) compared with the sodium salt, which was only obtained in solution, is probably due to the formation of a four-co-ordinate barium complex (VI), which protects the aldehyde groups. The hydroxy-lactone (V) absorbed two equivalents of hydrogen over a palladium catalyst yielding the saturated lactol, which gave the known semicarbazone.[7] The biological activity

[1] Part XXVII, M. Kalli, P. D. Landor, and S. R. Landor, preceding paper.
[2] D. K. Black and S. R. Landor, *J. Chem. Soc.*, 1965, 6784.
[3] S. R. Landor and N. Punja, unpublished work.
[4] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag Chemie and Academic Press, 1971.
[5] E. R. H. Jones, J. D. Loder, and M. C. Whiting, *Proc. Chem. Soc.*, 1960, 180; S. R. Landor and J. P. Regan, *Chem. Comm.*, 1965, 397.
[6] Preliminary report, D. K. Black and S. R. Landor, *Proc. Chem. Soc.*, 1963, 183.
[7] (*a*) H. Els, B. A. Sobin, and W. O. Celmers, *J. Amer. Chem. Soc.*, 1958, **80**, 878; (*b*) E. Akita, Y. Okami, N. Susuki, K. Maeda, T. Takenchi, and H. Umezawa, *J. Antibiotics, Ser. A*, 1962, 183.

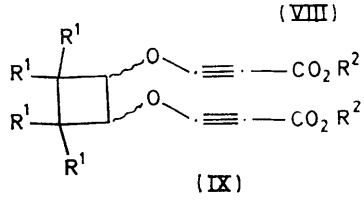
of the synthetic hydroxy-lactone (V) * was lower than that of the natural product but the testing of this unstable lactol under different conditions readily accounts for the reduced activity.

4-(2-Methylprop-1-enyloxy)but-2-ynoic acid was prepared from 2-methylprop-1-enyl prop-2-ynyl ether, ethylmagnesium bromide, and carbon dioxide in ether (41% yield) or tetrahydrofuran (76% yield). Rearrangement of this product, in xylene under reflux, was complete after 6 h, as shown by i.r. spectral monitoring of the reaction, and the hydroxy-lactone (VII) was



isolated by chromatography on silica. The corresponding ethyl ester, ethyl 4-(2-methylprop-1-enyloxy)but-2-ynoate was similarly converted into the comparatively stable dienal (VIII), which distilled unchanged *in vacuo* (10^{-4} mmHg) and gave an orange 2,4-dinitrophenylhydrazone ($\lambda_{max.}$ 361 nm, typical for unconjugated aldehydes).

Both analogues (VII) and (VIII) were biologically inactive, suggesting that the five-membered unsaturated hydroxy-lactone ring is an essential feature for antibiotic activity. The intermediate vinyl ethers, *e.g.* (II), dimerise on heating or keeping for prolonged periods to give the corresponding cyclobutanedicarboxylic acids or esters [probable structures (IX; $R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; and $R^1 = Me$, $R^2 = Et$)] by a [2 + 2] cycloaddition reaction.



EXPERIMENTAL

I.r. spectra were determined for liquid films with Perkin-Elmer Infracord and 257 spectrophotometers. U.v. spectra were obtained for ethanolic solutions with Bausch and Lomb Spectronic 505 and Pye–Unicam 1800 spectrometers. N.m.r. spectra were determined with Perkin-Elmer R10 and Varian T60 spectrometers for solutions in deuteriochloroform with tetramethylsilane as internal standard. G.l.c. was carried out with a Pye 104 instrument on glass columns (5 ft) using nitrogen as carrier gas at a flow rate of 2·5 l h^{-1}. Light petroleum had b.p. 40—60°.

4-Vinyloxybut-2-ynoic Acid.—Prop-2-ynyl vinyl ether (17·6 g, 0·214 mol) in dry ether (50 ml) was added to ethylmagnesium bromide [from magnesium (5·8 g, 0·24 g atom) and ethyl bromide (29·4 g, 0·27 mol) in dry ether (200 ml)]. The mixture was refluxed for 2 h and allowed to cool, and dry carbon dioxide was passed in for 3 h. The product was added to a mixture of ice and dilute sulphuric acid (15%; 300 ml). The ether layer was removed and the aqueous phase was extracted with ether (4 × 30 ml). The combined organic layers were extracted with saturated sodium hydrogen carbonate solution. The extracts were acidified with dilute sulphuric acid (15%), saturated with sodium chloride, and extracted with ether (6 × 50 ml). The aqueous layer was continuously extracted for 3 days and the combined extracts were dried ($MgSO_4$). Ether was removed *in vacuo* giving a red-brown oil (13·8 g) which was chromatographed on silica (100—200 mesh) previously dried at 400° for 3 h. Elution with ether–light petroleum (1 : 9) gave *4-vinyloxybut-2-ynoic acid* (10·1 g, 37%), $\nu_{max.}$ 3400 (OH) 2250 (C≡C), 1680—1740 (C=O and C=C), and 850 cm^{-1} (−HC=CH_2) (Found: C, 56·9; H, 4·6. $C_6H_6O_3$ requires C, 57·1; H, 4·8%). Elution with ether–light petroleum (8 : 2) gave *3,3′-cyclobutane-1,2-diyldioxydiprop-2-ynoic acid* (IX; $R^1 = R^2 = H$) (0·4 g), as needles (from ether–light petroleum, 1 : 1), m.p. 115°, $\nu_{max.}$ 2260 (C≡C), 1720 (C=O), and 1005 cm^{-1} (C–O–C) [Found: C, 56·8; H, 4·4%; *M* (cryoscopic in benzene), 248. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%; *M*, 252).

Ethyl 4-Vinyloxybut-2-ynoate.—A mixture of 4-vinyloxybut-2-ynoic acid (0·3 g, 0·0023 mol), absolute ethanol (20 g, 0·44 mol), and dry benzene (10 ml) in the presence of concentrated sulphuric acid (0·1 ml) was heated in a Dean and Stark apparatus for 3 h. The product on chromatography on silica (100—200 mesh) gave ethyl 4-vinyloxybut-2-ynoate (0·25 g, 57%), $\nu_{max.}$ 2260 (C≡C) and 1730 cm^{-1} (C=O).

Hydrogenation of the ester (0·20 g, 0·0013 mol) in ethyl acetate (20 ml) over Adams catalyst (0·02 g) [uptake 86·9 ml (0·0039 mol requires 87·2 ml)] gave ethyl 4-ethoxybutyrate, identical (spectra) with an authentic sample.[8]

4-Hydroxy-2-vinylbut-2-en-4-olide (V).—4-Vinyloxybut-2-

* M.I.C. against S. aureus in oxoid nutrient broth for 3 days = 500 μg/ml. We are indebted to Professor E. P. Abrahams and the Sir William Dunn School of Pathology at Oxford for microbiological testing.

[8] I. Reppe, *Annalen*, 1955, **596**, 158.

ynoic acid (2·0 g, 0·016 mol) was passed dropwise in a stream of nitrogen through a tube (15 × 2 cm) filled with glass wool and heated electrically to 240°. The product was collected in a trap cooled to −60°. The tube was washed with ether (20 ml), and the washings were added to the trap fraction and dried ($MgSO_4$). Ethyl acetate (15 ml) was added, the ether was removed *in vacuo*, and the residue was chromatographed on deactivated alumina (200 g; Spence grade H; 2 ml 10% acetic acid). Elution with ethyl acetate (50 ml fractions) gave unchanged 4-vinyloxybut-2-ynoic acid (fractions 2—5) (0·9 g) and the hydroxy-lactone (V) (fractions 8 and 9) (0·3 g, 15%), $\nu_{max.}$ 3400 (OH), 1750—1780 (5-membered ring C=O), 1640 cm^{-1} (C=C); $\lambda_{max.}$ 245 nm (ε 8800) [lit.,[7] $\lambda_{max.}$ 245 nm (ε 7800)].

Titration of the hydroxy-lactone (V) (0·015 g) in 50% aqueous ethanol (10 ml) with 0·1N-sodium hydroxide (to pH 7·5) gave a solution of the sodium salt, $\lambda_{max.}$ 273 nm (ε 19,320) [lit.,[7] $\lambda_{max.}$ 272 nm (ε 20,500)]. The hydroxy-lactone (V) (0·2 g) in 50% ethanolic solution (20 ml) was titrated with saturated barium hydroxide solution (to pH 8), ethanol (5 ml) and pentyl acetate (5 ml) were added and the mixture was concentrated *in vacuo* (1 mmHg). Butan-1-ol (10 ml) was added to the residue and the mixture left at −10° for 8 h giving a pale yellow precipitate (20 mg, 8·7%) (Found: C, 36·6; H, 2·5. Calc. for $C_{12}H_{10}BaO_6$: C, 37·2; H, 2·6%), $\nu_{max.}$ 3200—3400 (OH), 1650 (αβγ-unsaturated C=O), and 1575 cm^{-1} (CO_2^-), $\lambda_{max.}$ 276 nm (ε 34,000) [lit.,[7] $\lambda_{max.}$ 272 nm (ε 22,000)].

2-Ethyl-4-hydroxybutan-4-olide.—The hydroxy-lactone (V) (0·1 g, 0·8 mmol) in ethyl acetate (10 ml) was hydrogenated over 10% palladium–carbon (50 mg) [uptake 34·0 ml (1·6 mmol requires 35·8 ml)] to give the *saturated lactone* (0·1 g), $\nu_{max.}$ 3200—3400 (OH), 1770 (5-membered ring lactone), and 1360 cm^{-1} (C–Me); *semicarbazone*, colourless crystals (from dilute ethanol), m.p. 158° (Found: C, 44·8; H, 6·6; N, 22·9. $C_7H_{13}N_3O_3$ requires C, 44·9; H, 6·9; N, 22·5%).

2-Methylprop-1-enyl Prop-2-ynyl Ether.[9]—Dry hydrogen chloride (120 g, 3·6 mol) was passed into a mixture of prop-2-yn-1-ol (89·0 g, 1·5 mol) and isobutyraldehyde (144 g, 2·0 mol) at 0°. On completion, the aqueous phase was separated, diluted with an equal volume of water, and extracted with ether (2 × 50 ml). The extracts were combined with the organic phase and dry nitrogen was passed through the liquid mixture for 40 min. After drying overnight at 0° over molecular sieves (type 4A *ex* B.D.H.), the product was added dropwise with stirring over 1 h to *NN*-diethylaniline (450 g, 3·0 mol) at 75° (most of the ether had evaporated). The mixture was then stirred at 75° for 24 h and allowed to cool, and the solid hydrochlorides were filtered off, and washed with ether. The ethereal solution was dried (over molecular sieves, 70 g) and evaporated. Fractionation through a 1 ft column packed with Fenske rings gave the unsaturated ether [9] (92 g, 48%), b.p. 51—53° at 30 mmHg, $\nu_{max.}$ 3300 (C≡CH), 2120 (C≡CH), 1690 (C=CH–O), and 1145 cm^{-1} (C–O–C), g.l.c. gave one peak t_R 6 min (dinonyl phthalate; 45°), τ 8·40 (3H, d, CH_3), 8·42 (3H, d, CH_3), 6·70 (1H, t, $CH_2{\cdot}C{\equiv}CH$), 5·70 (2H, d, $CH_2{\cdot}C$), and 4·05 (1H, m, =CH).

Ethyl 4-(2-Methylprop-1-enyloxy)but-2-ynoate.—(*a*) 2-Methylprop-1-enyl prop-2-ynyl ether (22 g, 0·2 mol) in ether (100 ml) was added dropwise with stirring to ethylmagnesium bromide [from magnesium (6·1 g, 0·25 g atom) and ethyl bromide (27·3 g, 0·25 mol)] in ether (400 ml) over 1 h. The mixture was then stirred under reflux for 90 min and cooled to room temperature, and freshly distilled ethyl chloroformate (b.p. 93—94° at 760 mmHg) (26·8 g, 0·25 mol) in absolute ether (50 ml) was added dropwise with stirring. The mixture was refluxed for 2 h with stirring, kept overnight at room temperature, decomposed with ammonium chloride, and extracted with ether (4 × 200 ml). The extracts were dried ($MgSO_4$), and the ether was distilled off. The residue (16·4 g, 45%) was distilled yielding *ethyl 4-(2-methylprop-1-enyloxy)but-2-ynoate* (3·4 g), b.p. 50° at 2·27 × 10^{-5} mmHg (Found: C, 65·7; H, 7·8. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%), $\nu_{max.}$ 2220 (–C≡C–), 1720 (C=O), 1690 (C=C), 1250 (C–O), and 1140 cm^{-1} (C–O–C), $\lambda_{max.}$ 208 nm (ε 7000); τ 8·42 (3H, t, $CH_3{\cdot}CH_2$), 8·42 (6H, d, $CH_3{\cdot}CH{\cdot}CH_3$), 5·80 (2H, q, $CH_2{\cdot}CH_3$), 5·56 (2H, s, CH_2), and 4·10 (1H, m, =CH).

(*b*) Similarly 2-methylprop-1-enyl prop-2-ynyl ether (11 g, 0·1 mol) in tetrahydrofuran (100 ml), ethylmagnesium bromide [from magnesium (3·1 g, 0·13 g atom) and ethyl bromide (13·8 g, 0·13 mol)] in tetrahydrofuran (200 ml), and ethyl chloroformate (13·4 g, 0·13 mol) in tetrahydrofuran gave a crude product (14·2 g, 78%) spectroscopically identical with the product from (*a*).

Ethyl 2-(1-Formyl-1-methylethyl)buta-2,3-dienoate (VIII).—Pure ethyl 4-(2-methylprop-1-enyloxy)but-2-ynoate (2·5 g, 0·0136 mol) was refluxed in dry *o*-xylene and the reaction was monitored by i.r. spectroscopy. After 6 h the bands at 2220 (–C≡C–) and 1140 cm^{-1} (C–O–C) had disappeared. The *o*-xylene was removed *in vacuo* to give the crude product, which was distilled yielding pure *ester* (1·72 g, 68·9%), b.p. 49° at 5·67 × 10^{-4} mmHg (Found: C, 65·9; H, 7·8. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%), $\nu_{max.}$ 2960 (C–H), 1960, 1940 (C=C=C), 1730 (CO_2Et), 1710 (CHO), 1390, 1370 (–CMe_2), and 1260 cm^{-1} (C–O–Et), $\lambda_{max.}$ 206 nm (ε 6200), τ 8·60—9·00 (3H, t, $CH_3{\cdot}CH_2$), 8·73 (6H, s, $CH_3{\cdot}C{\cdot}CH_3$), 5·77 (2H, q, $CH_2{\cdot}CH_3$), 4·65 (2H, s, CH_2=), and 0·53 (1H, s, CHO); *2,4-dinitrophenylhydrazone* (63% yield), m.p. 112—113° (Found: C, 53·4; H, 5·1; N, 15·4. $C_{16}H_{18}N_4O_6$ requires C, 53·1; H, 5·0; N, 15·5%), $\lambda_{max.}$ 361 nm.

4-(2-Methylprop-1-enyloxy)but-2-ynoic Acid.—(*a*) 2-Methylprop-1-enyl prop-2-ynyl ether (22 g, 0·2 mol) in ether (150 ml) was added dropwise with stirring over 1·5 h to ethylmagnesium bromide [from magnesium (6·1 g, 0·25 g atom) and ethyl bromide (27·25 g, 0·025 mol)] in ether (600 ml). The mixture was then stirred under reflux for 1·5 h and cooled to −10°, and dry carbon dioxide was passed in for 6 h. The product was added to a mixture of ice and dilute sulphuric acid (15%; 100 ml), the ethereal layer was removed, and the aqueous layer was extracted with ether (5 × 100 ml). The combined organic layers were then extracted with saturated sodium hydrogen carbonate solution. The neutral residue gave unchanged starting ether (0·4 g). The alkaline extracts were acidified and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was removed to give crude product (12·8 g, 41%), which was purified by column chromatography on silica (70—325 mesh, dried at 400° for 2 h); elution with ether–light petroleum (3 : 7) gave the pure *acid* (4·2 g) (Found: C, 63·9; H, 6·3. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%), $\nu_{max.}$ 3600—2700 (OH), 2230 (–C≡C–), 1720 (C=O), 1690 (C=CH–O), 1380, 1360 (C–Me_2), 1245 (C–O), and 1140 cm^{-1} (C–O–C), $\lambda_{max.}$ 205 nm (ε 5900),

[9] Previously prepared by D. K. Black and S. R. Landor (*J. Chem. Soc.*, 1965, 5225). The modified method used here is due to T. L. Jacobs, R. Macomber, and O. Zunker, *J. Amer. Chem. Soc.*, 1967, **89**, 7001.

τ 8·35 (6H, d, CH_3·CH·CH_3), 5·58 (2H, s, CH_2), 4·03 (1H, m, =CH), and 0·45 (1H, s, CO_2H).

(*b*) Ethylmagnesium bromide [from magnesium (1·85 g, 0·08 mol) and ethyl bromide (8·8 g, 0·08 mol)] in dry tetrahydrofuran (100 ml) and 2-methylprop-1-enyl prop-2-ynyl ether (6·93 g, 0·063 mol) in tetrahydrofuran (50 ml) gave the crude acid (7·67 g, 75·6%), identical with the product obtained from (*a*).

4-*Hydroxy*-3,3-*dimethyl*-2-*vinylidenebutan*-4-*olide* (VII).—4-(2-Methylprop-1-enyloxy)but-2-ynoic acid (2·5 g, 0·016 mol) was dissolved in *o*-xylene (100 ml) and refluxed gently, the reaction being followed by i.r. spectroscopy. After 6 h the bands at 2230 (−C≡C−) and 1140 cm^{-1} (C−O−C) had disappeared. The solvent was removed at 0·5 mmHg and the crude product chromatographed on silica gel (70—325 mesh; 200 g; preheated at 400° for 2 h). Elution with ether–light petroleum (1 : 4) gave the hydroxy-lactone (VII) (0·24 g), $\nu_{max.}$ 3600—3100 (OH), 1955 (C=C=C), 1770 (C=C), 1730 (C=O), and 1380 and 1360 cm^{-1} (C−Me_2), $\lambda_{max.}$ 209 (ε 2600), 231 (2100), and 260infl nm (1400). Elution with ether–light petroleum (2 : 3) gave an oil of unknown structure, $\nu_{max.}$ 3600—3100 (OH), 1770 (C=O, lactone), 1730 (C=O), 1640 (C=C), and 1365 and 1340 cm^{-1} (C−Me_2), $\lambda_{max.}$ 220 (ε 3100) and 260infl nm (1600).

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