Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 1111-1118, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00142-1

The Resolution of Tertiary α-Acetylene- Acetate Esters by the Lipase from *Candida Cylindracea*

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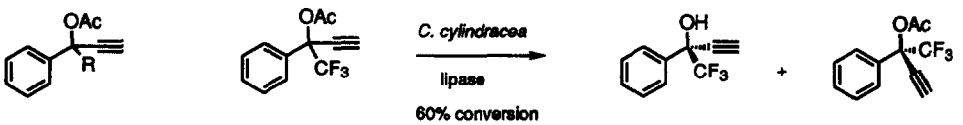
Abstract: The resolution of tertiary alcohols using the *Candida cylindracea* lipase is explored. In particular strategies are deployed to limit nonenzymatic hydrolysis of the tertiary acetate substrates in buffer, such that a full range of the steric requirements and limitations for successful resolutions can be explored.

The preparation of homochiral tertiary alcohols is a challenge in organic chemistry, and only a few synthetic methods exist which offer a general strategy to such systems[1]. This limitation also extends into the arena of biotransformations. There are several reports[2] of lipase resolutions of racemic tertiary carboxylate esters, but few on the resolution of tertiary alcoholic esters[3,4]. This appears principally to be due to adverse steric interactions in bringing such esters into the active site of lipases.



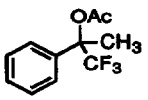
R = CH_3 1
R = Et 2
R = nPr 3

4

R alcohol 5

S acetate 4
>98% ee

We have been interested in this problem for some time and have explored[4] the resolution of a series of α-acetylenic tertiary alcohol acetates (**1-4**) with the lipase from *Candida cylindracea*. A limitation of the substrates (**1-3**) however is that they hydrolyse (*via* alkyl-oxygen cleavage, $B_{AL}1$)[5] to varying degrees in buffered solution, which compromises the enantioselectivity of the resolutions. This was particularly significant for the the α-methyl substrate (**1**), which underwent rapid nonenzymatic hydrolysis. The best substrate of this series was the α-trifluoromethyl-α-acetylenic acetate (**4**). The electron withdrawing power of the CF_3- group arrested the adventitious hydrolytic process. By scaling this reaction up and extending the extent of conversion to 60% we can recover the residual (S)-acetate (**4**) in gramme quantities. This homochiral material has been deployed in various synthesis programmes[7,8].



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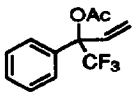

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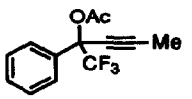

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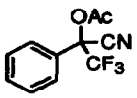

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A feature of these tertiary acetate resolutions is the requirement for an α-acetylene functionality. All attempts at replacing the acetylene with different substituents (eg. compounds **6-9**) have failed. It is not clear why the acetylene is so accommodated and at present we must attribute this to a combination of unique steric and electronic properties which are compatible with this particular lipase. It is noteworthy in the case of (**4**) that the acetylene functionality appears to be located at the same site of the enzyme, occupied by hydrogen during the resolution of secondary α-trifluoromethyl alcohols[9] suggesting that the acetylene is exerting a limited steric influence during these resolutions.

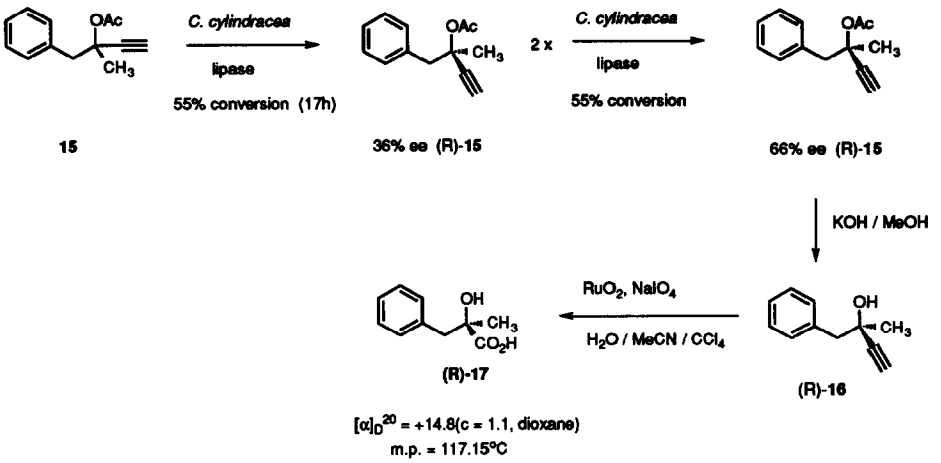
We have now focused our efforts on broadening the substrate range of tertiary acetate esters for the *C. cylindracea* lipase and have been able to extend the substrate range to α-acetylene-α-methyl-, and α-acetylene-α-ethyl- acetate esters. In each case we have attempted to control any adventitious nonenzymatic hydrolysis reactions by placing electron withdrawing groups on the aryl ring of (**1**), or by insulating the aryl ring from the developing carbocation centre by introducing methylene carbons.

Results and Discussion

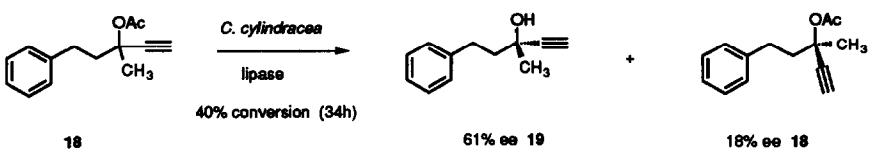
α-Methyl Series of Substrates

R = H	**1**	40% conversion (7h)	0% ee **10**	0% ee **1**
R = CF_3	**11**	55% conversion (120h)	52% ee **12**	60% ee **11**
R = NO_2	**13**	40% conversion (125h)	50% ee **14**	-

Substrate (**1**) underwent rapid nonenzymatic hydrolysis in buffered solution and the resultant alcohol (**10**) and the residual acetate were recovered as racemates after a 40% conversion[4]. However for (**11**) where a *p*CF_3 group was placed on the aromatic ring, then alcohol (**12**) was recovered after 55% conversion in 52%ee and the residual acetate was recovered in 60%ee[10]. Similarly for substrate (**13**) carrying a *p*NO_2 substituent, lipase mediated hydrolysis to 40% conversion gave alcohol (**14**) in 50% ee. It is clear that the deployment of electron withdrawing groups resulted in a significant improvement in the enantioselectivity of these resolutions.



In an effort to establish the enantiomeric preference of the lipase for these α-acetylene-α-methyl- substrates we investigated the resolution of (**15**) such that we could convert it into the known α-hydroxy-acid (**17**)[11] after resolution. Substrate (**15**) carries an insulating methylene group and control experiments demonstrated that it was stable to hydrolysis in buffer. In the event the residual acetate was recovered from the lipase reaction in only 36% ee after 55% conversion. The absolute stereochemistry of the residual (R)-acetate (**14**) was evaluated however, after resubjecting the enantiomerically enriched acetate to the lipase resolution two more times. This afforded a sample of (R)-(**15**) in 66% ee which was then converted to (R)-(**17**) after base hydrolysis and oxidation[12] of the acetylene functionality to a carboxylic acid. After recrystallisation, the acid (**17**) gave identical physical and spectral data to that previously reported for the (R)-enantiomer[11]. It is clear that the optical purity of the prepared acid increased during recrystallisation. The enantiomeric preference of the lipase, deduced from this process, is consistant with that previously evaluated[4] for the α-trifluoromethyl acetate substrate (**4**), if it is assumed that the α-methyl- and α-trifluoromethyl- groups can occupy the same site on the lipase during hydrolysis.

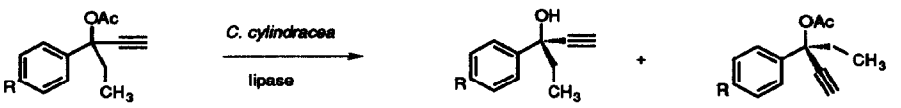


Substrate (**18**), with two insulating methylene groups, was incubated with the lipase to 40% conversion. The lipase displayed an increased selectivity with respect to (**15**), and alcohol (**19**) was recovered in 61% ee. The residual acetate displayed low enantioselectivity (18% ee). By extending the level of conversion to 60% the residual acetate (**18**) was recovered from this hydrolysis in 60% ee. The absolute stereochemistry shown is assumed from the study of (**15**). From the series of α-acetylene-α-methyl substrates studied, it can be concluded that the the *C. cylindracea* lipase will, in a general sense, hydrolytically resolve α-acetylene-α-methyl- acetates in moderate to good enantioselectivity. Clearly improved enantioselectivities can be

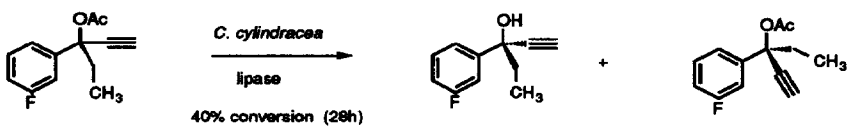
accessed in the usual way by controlling the extents of conversion (eg. for (**20**)) and by employing recycling protocols (eg. for (**15**)).

α-Ethyl Series of Substrates

The programme was then extended to α-acetylene-α-ethyl substrates. We have previously reported that the substrate (**2**) could be resolved in 75%ee after 40% conversion. Control experiments, without enzyme, revealed that this reaction was accompanied by a slow non-enzymatic hydrolysis (3% over 11h)[4,5], and therefore we rationalised that insulation from the aromatic ring by methylene carbons, or strategic placement of fluorine, may improve the selectivity of these resolutions.

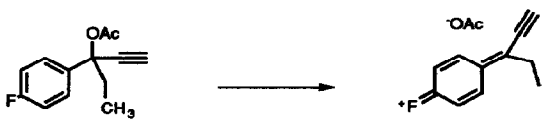


R = H	**2**	40% conversion (11h)	75% ee **19**	31% ee **2**
R = CF_3	**20**	40% conversion (336h)	32% ee **21**	23% ee **20**
R = F	**22**	55% conversion (72h)	36% ee **23**	20% ee **22**



24 77% ee **25** 55% ee **24**

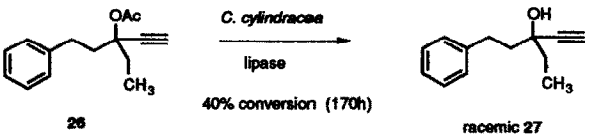
Thus, substrate (**20**), with a *p*CF_3 substituent was subjected to lipase mediated hydrolysis. In the event the hydrolysis was slow and the recovered alcohol (**21**) had a dissapointingly low enantiomeric excess (32% ee). The introduction of the CF_3 group proved deleterious, presumably for steric reasons. The resolution was improved however with substrate (**22**) where the *para*-trifluoromethyl group was replaced with fluorine. Interestingly however (**22**) underwent a slow but significant hydrolysis in buffer, presumably due to stabilisation of an intermediate carbocation by conjugation with the fluorine lone pairs as shown below.



22

This competing non-enzymatic hydrolysis compromises the enantioselectivity of the resolution. Consistant with this analysis, the *m*F-acetate (**24**), which does not have this conguative possibility, emerged as a good substrate and the resultant alcohol (**25**) was recovered in 77%ee after 40% conversion. This is similar to the

resolution of (2), and is consistent with the idea that a single fluorine will have a small steric influence[13], although as illustrated for (22), a single fluorine can have a significant, and in this case a detrimental, electronic influence.



26 racemic 27

Finally substrate (26), with two insulating methylenes, was subjected to the lipase hydrolysis. This substrate was hydrolysed very slowly and only racemic alcohol (27) was recovered after 40% conversion. The poor resolution and slow reaction is analogous to substrate (20), and suggests that these substrates are sterically incompatible with the lipase.

In summary we have been able to extend the range of tertiary acetates which can act as substrates for the *Candida cylindracea* lipase and, with judicious choice, can achieve resolutions up to 77% ee. Our efforts are now focused on extending the range of tertiary acetate substrates and improving the enantioselectivities of these resolutions.

Acknowledgements

We thank the SERC (IPS Initiative) for financial support, Miss Julie A. Cornish for carrying out the resolution of substrate (13) and Dr Alan. M. Kenwright and Mrs Julia M. Say for recording NMR spectra.

Experimental

General Methods

NMR spectra were recorded on either a Varian Gemini 200MHz (^1H at 199.975 MHz, ^{13}C at 50.289 MHz) or a Varian VXR 400S (^1H at 399.952 MHz, ^{13}C at 100.577 MHz) instrument. Chemical shifts are quoted in ppm relative to TMS [$(CH_3)_4Si$] in $CDCl_3$. IR spectra were recorded on Perkin Elmer F.T. 1720X or 1600 spectrometers, neat, between KBr plates. Mass spectra were obtained using a VG Analytical 7070E Organic mass spectrometer operating at 70 eV. Chromatography was carried out using silica gel-60 (35μm) (Fluka) or Sorbsil-C60-H (40-60μm). All solvents were distilled and dried before use. Optical rotations were measured on an Optical Activity Ltd., AA-10 polarimeter.

General Procedures

(a). The synthesis of α-acetylene tertiary alcohols; A solution of the appropriate ketone in tetrahydrofuran (THF) ($20cm^3$) was added to a refluxing solution of ethynylmagnesium bromide (1.2 equiv.) in THF (70cm) and the mixture heated under reflux for 4h, or until all of the ketone had been consumed (t.l.c.). Water ($20cm^3$) was added to the cooled reaction mixture and the product was extracted into ether (3 x $100cm^3$), washed with saturated brine ($100cm^3$), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled to give the alcohol as a colourless oil.

(b). The synthesis of α-acetylene tertiary acetates; A solution of butyllithium (1.1 equiv) in diethylether was added to a solution of the α-acetylene tertiary alcohol (10-35mmol) in THF (50ml) and the mixture stirred for

15 min. Acetyl chloride (1.1 equiv) was then added and the reaction heated under reflux for 1h before being cooled and quenched with water (20ml). The reaction mixture was extracted into ether (2 x 50ml) and the combined organic extracts were washed with saturated brine (100cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residual material was either distilled and/or chromatographed to provide the acetate as a colourless oil.

(c). The lipase hydrolysis were carried out as previously described[4].

3-Acetoxy-(4-trifluoromethylphenyl)but-1-yne (11); 3-(4-Trifluoromethylphenyl)but-1yne-3-ol was prepared by general procedure (a), as a colourless oil (2.7g, 47%), b.p. 43-45°C (0.05mmHg), which solidified on standing (mp. 45-47°C); ν_{max} (neat) 3400 (OH), 3300, 2120 (CCH); δ_H (250 MHz) 1.78 (3H, s, Me), 2.63 (1H, s, OH), 2.71 (1H, s, CCH), 7.6-7.79 (4H, d.d, Ar-H); δ_C (400 MHz) 33.3 (s), 69.55 (s), 73.7 (s), 86.5 (s), 120-128.2 (q), 125.35 (s), 129.5-130.2 (q), 148.8 (s); δ_F 62.56 (s); Ms (m/e) EI (214, 0.5%), (199 (-15), 100%), CI (214, 25.6%); The alcohol (2.6g, 12mmol) was then converted to the acetate by general procedure (b). Purification by chromatography (CH_2Cl_2, 100%) gave the title compound **(11)** as a colourless oil (2.1g, 68%); ν_{max} (neat) 3300, 2120 (CCH) 1752, 1360 (OAc); δ_H (250 MHz) 1.9 (3H, s, Me), 2.11 (3H, s, OAc), 2.87(1H, s, CCH), 7.5-7.8 (4H, d.d, Ar-H); δ_C 21.54, 32.0, 74.78, 76.13, 82.23, 121-128 (q), 125.2, 125.34, 129.8-131.1(q), 146.1, 168.45; δ_F 63.09; Ms (CI) ($M+NH_4^+$) 274.1167 (100%), $C_{13}H_{15}NF_3O_2$ requires 274.1055).

3-Acetoxy-(4-nitrophenyl)but-1-yne (13); 3-(4-nitrophenyl)but-1-yne-3-ol was prepared by general procedure (a) and purified as a coloured oil (10.9g, 57.2%) after distillation (70-75°C (0.01mmHg)); ν_{max} (neat) 3400 (OH), 3300, 2120 (CCH); δ_H (400 MHz) 1.8 (3H, s, Me), 2.78 (1H, s, CCH), 3.35 (1H, s, OH), (7.83 (2H, d, Ar-H), 8.2 (2H, d, Ar-H); δ_C (400MHz) 33.8, 69.8, 74. 63, 86. 5, 124.0, 126.6, 147.8, 152.6. The alcohol (2.6g, 12mmol) was then converted to the acetate by general procedure (b) and chromatography (CH_2Cl_2, 100%) gave the title compound (**13**) as a coloured oil. δ_H (400Mz), 1.9 (3H, s, Me), 2.11 (3H, s, OAc), 2.9 (1H, s, CCH), 7.75 (2H, d, Ar-H), 8.22 (2H, d, Ar-H), δ_C 21.9, 32.4, 74.9, 77.1, 82.2, 124.2, 126.3, 147.9, 149.7, 169.0, Ms (m/e) (M^+ 233.0591 (10.9%), $C_{12}H_{11}NO_4$ requires 233.0688).

3-Acetoxy-3-methyl-4-phenyl-but-1-yne (15); 3-Methyl-4-phenylbut-1-yne-3-ol was prepared by general method (a) as a colourless oil (11g, 77%), b.p. 42-44°C (0.01mmHg); ν_{max} (neat) 3560-3420 (OH), 3300, 2120 (CCH); δ_H (400 MHz) 1.58 (3H, s, Me), 2.4 (1H, b.s, OH), 2.49 (1H, s, CCH), 2.96-3.1 (2H, q, CH_2), 7.3-7.4 (5H, m, Ar-H); δ_C 29.32 (s), 49.16 (s), 67.7 (s), 72.52 (s), 87.13 (s), 126.9 (s), 127.99 (s, 2xCH_2), 130.64 (s, 2xCH_2), 135.89 (s); Ms (m/e) (M^+ 160.0797 (100%), $C_{11}H_{12}O$ requires 160.0888). The alcohol (5.5g, 34mmol) was then converted to the acetate by general procedure (b) and distillation gave the title compound (**15**) as a colourless oil (6.2g, 89%), b.p. 46-50°C (0.01 mmHg); ν_{max} (neat) 3300, 2250 (CCH) 1745, 1230 (OAc); δ_H (250 MHz) 1.63 (3H, s, Me), 2.03 (3H, s, OAc), 2.59 (1H, s, CCH), 3.1-3.3 (2H, q, CH_2), 7.29 (5H, s, Ar-H); δ_C (400MHz) 21.84 (s), 26.11 (s), 46.4 (s), 74.25 (s), 74.33 (s), 83.55 (s), 126.9 (s), 127.86 (s, 2xCH_2), 130.73 (s, 2xCH_2), 135.27 (s), 169.24 (s); Ms (CI) ($M+NH_4^+$) 220.1359 (100%), $C_{13}H_{18}NO_2$ requires 220.1338).

(R)(+)-2-Hydroxy-2-methyl-3-phenylpropanoic acid (17); To a stirred solution of acetylenic alcohol (**16**) (1g, 6.3mmol) in $CCl_4/CH_3CN/H_2O$: 3:2:2 (70ml) was added NaI (7.0g, 33mmol) and RuO_2 (0.03g, 0.2mmol) and the mixture left to stir for 12h. The reaction was then diluted with H_2O (50ml) and extracted into CH_2Cl_2 (2 x 50ml). The combined organic extracts were dried and the solvent removed under reduced pressure. This gave (by ^{1}H-NMR analysis) a mixture of phenylacetone and the acid (**17**) (5:1) as the minor product. Purification by preparative t.l.c (100% CH_2Cl_2) followed by recrystallisation from ether/petrol, gave the title compound (**17**) as colourless crystals (23mg, 2%), m.p. 117.5-118.5°C, $[\alpha]_D^{20}$ = +14.82 (dioxane), for lit. values see ref 11. ν_{max} (KBr) 3430 (OH), 1730 (C=O); δ_H (200 MHz) 1.5 (3H, s, Me), 2.8-3.1 (2H, b.q, CH_2), 7.1-7.3 (7H, m, 5Ar + 2OH).

3-Acetoxy-3-methyl-5-phenylpent-1-yne (18); 3-Methyl-5-phenylpent-1-yne-3-ol was prepared by general procedure (a) as a colourless oil (4g, 68%), b.p. 54-60°C (0.01mmHg); ν_{max} (neat) 3560-3400 (OH), 3300, 2120 (CCH); δ_H (200 MHz) 1.6 (3H, s, Me), 2.0-2.1 (3H, m, CH_2, OH), 2.55 (1H, s, CCH), 2.8-3.0 (2H, m, CH_2), 7.2-7.34 (5H, m, Ar-H); δ_C 30.5 (s), 31.61 (s), 45.73 (s), 68.47 (s), 72.44 (s), 72.45 (s), 126.46 (s), 128.98 (s), 142.31 (s); Ms (m/e) (M^+ 174.0997 (100%), $C_{12}H_{14}O$ requires 174.1045). The alcohol (4g, 23mmol) was then converted to the acetate by general procedure (b) and distillation gave the title compound (**18**) as a colourless oil (3.3g, 67%), b.p. 63°C (0.01 mmHg); ν_{max} (neat) 3300, 2120 (CCH) 1745, 1240 (OAc); δ_H (200 MHz) 1.75 (3H, s, Me), 2.04 (3H, s, OAc), 2.1-2.4 (2H, m, CH_2), 2.65 (1H, s, CCH), 2.8-2.9 (2H, m, CH_2), 7.2-7.4 (4H, m, Ar-H); δ_C (400 MHz) 21.71 (s), 26.37 (s), 30.45 (s), 43.1 (s), 73.59 (s), 74.4 (s), 83.4 (s), 125.85 (s), 128.3 (s), 141.21 (s), 169.2 (s); Ms (m/e) EI (216, .5%), (174 (-42), 14.4%), (157 (-59), 100%), Ms (CI) ($M+NH_4^+$) 234.1491 (100%), $C_{16}H_{20}NO_2$ requires 234.1494).

3-Acetoxy-3-(4-trifluoromethylphenyl)pent-1-yne (20); 3-(4-Trifluoromethylphenyl)pent-1-yne-3-ol was prepared by general procedure (a), as a colourless oil (4.3g, 76%), b.p. 37-42°C (0.01mmHg); ν_{max} (neat) 3400 (OH), 3300, 2120 (CCH); δ_H (200 MHz) 0.96 (3H, t, CH_3), 1.8-2.1 (2H, m, CH_2), 2.67 (1H, bs, OH), 2.7 (1H, s, CCH), 7.6- 7.8 (4H, d.d, Ar-H); δ_C (400 MHz) 8.76 (s), 38.34 (s), 73.48 (s), 74.75 (s), 85.39 (s), 120.1-128.2 (q), 125.13-125.24 (q), 126 (s), 129.55-130.51 (q), 147.88 (s); δ_F 64.6 (s); Ms (m/e) EI (228, 0.8%), (211 (-17), 50.4%), (199 (-29), 100%), CI (228, 85.9%), (211 (-17), 15.6%). The alcohol (4.1g, 18mmol) was then converted to the acetate by general procedure (b) and distillation gave the title compound (**20**) as a colourless oil (3.8g, 78%), b.p. 64-66°C (0.02 mmHg); ν_{max} (neat) 3300, 2120 (CCH) 1752, 1330 (OAc); δ_H (200 MHz) 1.95 (3H, t, CH_3), 1.9-2.3 (2H, m, CH_2), 2.1 (3H, s, OAc), 2.85 (1H, s, CCH), 7.6 (4H, m, Ar-H); δ_C (250 MHz) 8.46 (s), 21.52 (s), 37.45 (s), 77.1 (s), 78.72 (s), 80.94 (s), 120.1-128.2 (q), 125-125.4 (m), 125.5 (s), 129.55-130.26 (q), 144.9 (s), 168.43 (s); δ_F 63.1 (s); Ms (m/e) (M^+ 270.0772 (100%), $C_{14}H_{13}F_3O_2$ requires 270.0868).

3-Acetoxy-3-(4-fluorophenyl)pent-1-yne (22); 3-(4-Fluorophenyl)pent-1-yne-3-ol was prepared by general method(a) as a colourless oil (4.2g, 72%), b.p. 43-45°C (0.05mmHg); ν_{max} (neat) 3400 (OH), 3300, 2100 (CCH); δ_H (400 MHz) 0.93-0.98 (3H, m, Me), 1.85-2.1 (2H, m, CH_2), 2.45 (1H, s, OH), 2.70 (1H, s, CCH), 7.02-7.06 (2H, m, Ar-H), 7.5-7.61 (2H, m, Ar-H); δ_C 8.87 (s), 38.28 (s), 73.35 (s), 74.34 (s), 85.77 (s), 114.8 (s), 115.01 (s), 127.23 (s), 127.31 (s), 139.61 (s), 161.1-163.53 (d); δ_F 115.02-115.09 (m); Ms (m/e) (M^+ 178.0789 (4.2%), $C_{11}H_{11}FO$ requires 178.0794), CI (178, 3.5%), (161 (-17), 100%). The alcohol (2.6g, 34mmol) was then converted to the acetate by general procedure (b) and distillation gave the title compound (**23**) as a colourless oil (2.2g, 69%), b.p. 54-56°C (0.03 mmHg); ν_{max} (neat) 3300, 2250 (CCH) 1745, 1230 (OAc); δ_H (400 MHz) 0.9-0.95 (3H, t, Me), 1.92-2.0 (1H, m, CH), 2.01 (3H, s, OAc), 2.1-2.22 (1H, m, CH), 2.83 (1H, s, CCH), 7.01-7.05 (2H, m, Ar-H), 7.49-7.52 (2H, m, Ar-H); δ_C 8.47 (s), 21.64 (s), 37.36 (s), 76.61 (s), 78.76 (s), 81.34 (s), 114.98 (s), 115.19 (s), 127.02 (s), 127.10 (s), 136.65 (s), 160.99-163.44 (d), 168.57 (s); δ_F 114.74-114.81 (m); Ms (m/e) (M^+ 220.0779 (38.2%), $C_{13}H_{13}FO_2$ requires 220.0899), (Found: C70.59, H5.78, Calc for $C_{13}H_{13}FO_2$: C70.19, H5.91%).

3-Acetoxy-3-(3-fluorophenyl)pent-1-yne (24); 3-(3-Fluorophenyl)pent-1-yne-3-ol was prepared by general method (a) as a colourless oil (4.5g, 79%), b.p. 43-45°C (0.05mmHg); ν_{max} (neat) 3400 (OH), 3300, 2100 (CCH); δ_H (400 MHz) 0.92-0.96 (3H, m, Me), 1.83-2.1 (2H, m, CH_2), 2.69 (1H, s, CCH), 2.83 (1H, b.s, OH), 6.95-7.0 (1H, m, Ar-H), 7.26-7.39 (3H, m, Ar-H); δ_C 8.74 (s), 38.07 (s), 73.31 (s), 74.41 (s), 85.46 (s), 112.65-112.88 (d), 114.42-114.62 (d), 121.09-121.11 (d), 129.53-129.61 (d), 146.52-146.58 (d), 161.36-163.80 (d); δ_F 112.92-112.85 (m); Ms (m/e) (M^+ 178.0804 (9.9%), $C_{11}H_{11}FO$ requires 178.0794). The alcohol (4.5g, 25mmol) was then converted to the acetate by general procedure (b) and distillation gave the title compound (**24**) as a colourless oil (3.5g, 63%), b.p. 56°C (0.05 mmHg); ν_{max} (neat) 3300, 2250 (CCH) 1745, 1230 (OAc); δ_H (400 MHz) 0.88-0.92 (3H, t, Me), 1.92-1.94 (1H, m, CH), 2.04 (3H, s, OAc), 2.09-

2.19 (1H, m, CH), 2.79 (1H, s, CCH), 6.9-6.96 (1H, m, Ar-H), 7.17-7.28 (3H, m, Ar-H); δ_C 8.39 (s), 21.48 (s), 37.31 (s), 76.63 (s), 78.55 (d), 81.05 (s), 112.39-112.62 (d), 114.55-114.76 (d), 120.75 (d), 129.78 (d), 143.58 (d), 161.36-163.80 (d), 168.42 (s); δ_F 112.78-112.72 (m); Ms (m/e) (M^+ 220.0885 (28.3%), $C_{13}H_{13}FO_2$ requires 220.0899).

3-Acetoxy-3-ethyl-5-phenylpent-1-yne (26); 3-Ethyl-5-phenylpent-1-yne-3-ol was prepared by general method (a) as a colourless oil (3.8g, 66%), b.p. 65°C (0.05mmHg); ν_{max} (neat) 3560-3400 (OH), 3300, 2120 (CCH); δ_H (200 MHz) 1.05-1.12 (3H, t, Me), 1.69-1.81 (2H, q, CH_2), 1.91-2.06 (3H, m, CH_2, OH), 2.52 (1H, s, CCH), 2.82-2.93 (2H, m, CH_2), 7.2-7.35 (5H, m, Ar-H); δ_C (400 MHz) 8.41 (s), 30.65 (s), 34.98 (s), 43.17 (s), 71.44 (s), 72.82 (s), 86.17 (s), 125.85 (s), 128.4 (s, 4xCH), 141.91 (s); Ms (m/e) EI (171 (-17), 90.6%), CI (206 (+18), 47.2%), (188, 54.2%), (171 (-17), 100%). The alcohol (2.5g, 13mmol) was then converted to the acetate by general procedure (b) and distillation gave the title compound (**26**) as a colourless oil (1.7g, 56%), b.p. 68-70°C (0.05 mmHg); ν_{max} (neat) 3300, 2120 (CCH) 1745, 1240 (OAc); δ_H (200 MHz) 0.98 (3H, t, Me), 1.9-2.2 (2H, m, CH_2), 2.3-2.5 (2H, m, CH_2), 2.62 (1H, s, CCH), 2.7-2.82 (2H, m, CH_2), 7.2-7.28 (5H, m, Ar-H); δ_C (400 MHz) 8.24 (s), 21.72 (s), 30.37 (s), 31.15 (s), 39.56 (s), 74.42 (s), 78.67 (s), 82.71 (s), 125.83 (s), 128.36 (s), 141.35 (s), 169.25 (s); Ms (m/e) EI (188 (-42), 9.5%), (171 (-59), 1.6%), Ms(CI), ($M+NH_4^+$), 248.1671 (100%), $C_{15}H_{22}NO_2$ requires 248.1651.

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(*Received* 23 *March* 1994)