Degradation Studies under Neutral and Basic Conditions on Ciprofibrate, an Orally Active Hypolipidemic Agent Containing a (4-Alkoxyaryl)-1,1-dichlorocyclopropane Unit

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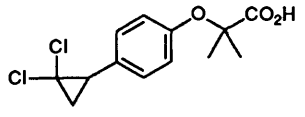
The major product of degradation of ciprofibrate (**1**), 2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid, in aqueous sodium hydroxide under reflux is 2-[4-(3-hydroxypropynyl)-phenoxy]-2-methylpropanoic acid (**11**). A further product, 2-(4-ethynylphenoxy)-2-methylpropanoic acid (**12**) is derived from **11** under the reaction conditions. A third degradant is identified as 2-[4-(2-carboxyethyl)phenoxy]-2-methylpropanoic acid (**13**). Under similar conditions, but at pH 7, the products of degradation were found to be 2-[4-(2-chloro-1-hydroxyprop-2-en-1-yl)phenoxy]-2-methylpropanoic acid (**9**) and (*Z*)-2-[4-(2-chloro-1-hydroxyprop-2-en-3-yl)-phenoxy]-2-methylpropanoic acid (**10**). Treatment of **10** with aqueous sodium hydroxide under reflux afforded a mixture of products in which **11** and **12** predominated, whereas similar treatment of **9** led to compound **13** among other products. A labelling study indicates that the acid **21** derived from base treatment of **17** is labelled only at C-2 of the propanoic acid side chain; the same labelling pattern is observed in the acid **21** derived by base treatment of the labelled allylic alcohol **18**. Mechanisms are suggested which may explain these observations.

Ciprofibrate (**1**; 2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid) is a potent, long-acting hypolipidemic agent. It is effective in type IIa, IIb, III and IV hyperlipoproteinemias and produces a beneficial elevation of the anti-atherogenic high density lipoprotein.[1–3]



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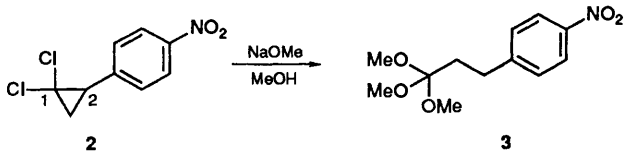
In the course of a development programme involving this compound its stability to aqueous sodium hydroxide under reflux was examined. Treatment of (2,2-dichlorocyclopropyl)-benzenes with strong base has been reported to lead to the corresponding 1-chlorocyclopropene, and reactions of these with nucleophiles have been studied by various groups.[4–7] When the base used is alkoxide, the chlorocyclopropene is not isolated, addition of the reagent leading either to cyclopropanone ketals or to ring-opened orthoesters. The intermediacy of the cyclopropene is demonstrated by incorporation of deuterium at the benzylic position *via* consecutive elimination and addition steps.[4] Novokreshchennykh *et al.* prepared the orthoester **3** in almost quantitative yield by treatment of the dichloro(4-nitrophenyl)cyclopropane **2** with sodium methoxide in methanol, as in Scheme 1.[4] The orthoester

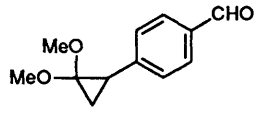


2 **3**

Scheme 1

afforded the corresponding ester in similarly high yield on chromatography.

In a related reaction, Tishchenko and Kulinkovich isolated the corresponding orthoester and the ketal **4** from 4-(2,2-



4

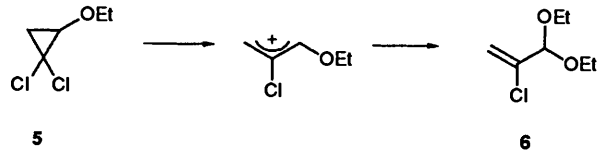
dichlorocyclopropyl)benzaldehyde.[6] In the above reactions ring-opening of the cyclopropane occurs by breaking of the 1,2-bond, the halogens being on C-1 and the substituent on C-2.

Although there are a number of reports of the preparation of 2-aryl-1,1-dichlorocyclopropanes in which the aryl ring bears an electron-releasing substituent,† the reactions of these with bases such as hydroxide or alkoxide do not appear to have been reported widely. It is, however, known that dihalocyclopropanes bearing electron-releasing substituents can react, under conditions similar to those above, by cyclopropyl–allyl ring-opening with loss of halide ion, rather than by elimination–addition. Thus the ether **5** is converted into **6** in high yield by reaction with ethoxide in ethanol, as in Scheme 2.[8] The acetal **6** to some extent reacts further under the reaction conditions, leading to the corresponding alkyne **7**.[8]

A related alkyne has been obtained by reaction of the cyclopropyl phenyl sulfide **8** with potassium *tert*-butoxide in *tert*-butyl alcohol, as in Scheme 3,[9,10] although it is not clear

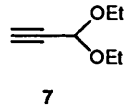
† See, *e.g.*, H. Oelschlaeger, H. J. Peters, T. Stanek, *Arch. Pharm.*, 1988, **321**, 934; R.R. Kostikov, A. P. Molchanov, G. V. Golovanova and I. G. Zenhevich, *Zh. Org. Khim.*, 1977, **13**, 1846; O. G. Kulinkovich, I. G. Tishchenko, I. V. Rezinkov and A. A. Pap, *Zh. Org. Khim.*, 1981, **17**, 473.

what the mechanism is in this case. In both the above cases ring-opening has occurred by overall cleavage of the 2,3-bond, the 'reactive' substituent being on C-2.



5 6

Scheme 2



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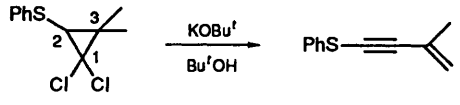

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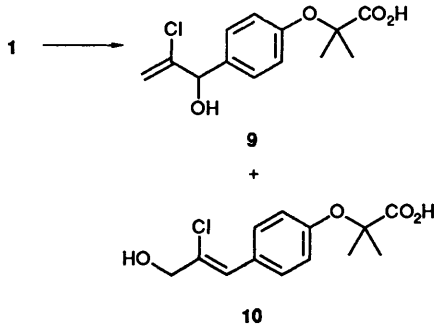
Scheme 3

Results

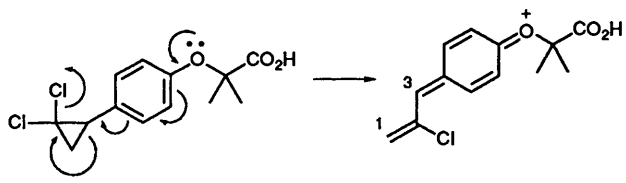
When ciprofibrate (**1**) was dissolved in aqueous sodium dihydrogen orthophosphate buffer at pH 7 and heated under reflux for 96 h, two products were obtained in the ratio *ca.* 2:1. These could be separated from a small amount of unchanged starting material by column chromatography and then from each other by fractional crystallisation. The first product was the alcohol **9**, as in Scheme 4.



9 + 10

Scheme 4

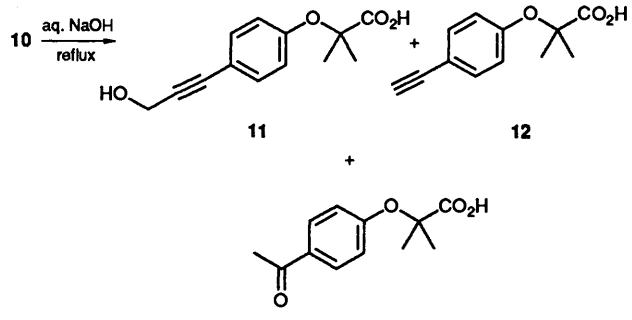
The ^{1}H NMR spectrum of this included three singlets at δ 5.85, 5.55 and 5.34 corresponding to the two alkene hydrogens and the benzylic hydrogen, respectively. The ^{13}C NMR spectrum included two alkene carbon signals at δ 120.7 and 129.3, as well as the benzylic carbon at δ 80.6. The second product was the isomeric alcohol **10**. In this case the ^{1}H NMR spectrum included a broad alkene singlet at δ 6.97 (1 H) and a narrow doublet at 4.41 for the allylic methylene group, and the ^{13}C NMR spectrum again showed two alkene carbons, together with an allylic carbon signal at δ 80.7. The stereochemistry was assigned as *Z*- on the basis of an NOE enhancement between the alkene signal and the hydrogens of the allylic methylene group. Upon pre-irradiation at a frequency corresponding to the allylic methylene group, an enhancement of 12.5% was observed in the signal for the alkene hydrogen. A similar Overhauser effect was observed on pre-irradiation at the frequency of this alkene hydrogen, giving enhancements of 3.2 and 6.15% in the signals at δ 4.3 and 7.7, respectively. The formation of the alcohols **9** and **10** may be explained in terms of loss of chloride ion from **1** with cyclopropyl–allyl rearrangement promoted by the electron-rich aryl substituent, the 2,3-bond breaking, as in Scheme 5, followed by trapping by water at C-1 or C-3 of the allylic group.



Scheme 5

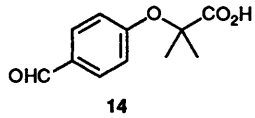
When ciprofibrate **1** was refluxed with aqueous sodium hydroxide for 56 h, the product profile was very different. The major product was the propargylic alcohol **11**, isolated in 42% yield after chromatography. The ^{1}H NMR spectrum of this included a singlet at δ 4.50 for the hydrogens of the methylene group; the ^{13}C NMR spectrum included alkyne carbons at δ 85.4 and 86.5. A second product was the alkyne **12** (7%), which could be characterised on the basis of a ^{1}H NMR singlet at δ 3.04 and an alkyne group in the ^{13}C NMR spectrum at δ 76.6 and 83.3, the former of which was shown to be a methine carbon. A third isolated product was the diacid **13**; this was characterised on the basis of an aliphatic AA'BB' system in the ^{1}H NMR spectrum at δ 2.05–3.05, and two methylene carbons in the ^{13}C NMR spectrum at δ 30.6 and 36.0. In addition, HPLC–MS analysis showed the presence of a number of minor components including the aldehyde **14**, the acid **15** and the methyl ketone **16**. Small amounts of the two allylic alcohols **9** and **10** were also detected by HPLC and ^{1}H NMR spectroscopy.

Although the diacid **13** could be derived by the same overall sequence as the formation of **3** from **2**, the two major products **11** and **12** appeared to be derived instead by further reaction of



11 + 12 + 16

Scheme 6

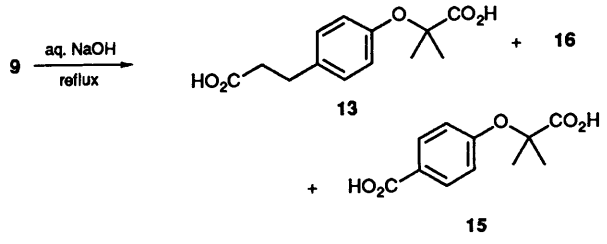


14

the allylic alcohol **10**. In order to support this contention, the alcohol **10** was treated with aqueous sodium hydroxide at reflux for 8 days. As summarised in Scheme 6, work-up gave one major product, the alkyne **11**, together with a minor one, **12**. Also present, in the ratio *ca.* 1:5 compared with **11** was the ketone **16**. On HPLC the peak for this compound appeared as a shoulder on that for **11**, but the structure was established by HPLC–MS; signals that could be assigned to **16** were also present in the NMR spectrum.

It seemed likely therefore that a major pathway in the reaction of **1** with refluxing sodium hydroxide was thermally induced ring-opening as in the reaction of **1** at reflux under neutral conditions to produce **9** and **10**, followed by further reactions of these under the basic conditions. If this mechanism

were correct, the second product of that reaction, **9**, or the products of its further reaction with base should also be observed in the direct reaction of **1** with base. Compound **9** was therefore treated with base at reflux under the same conditions as those used for **1**. As summarised in Scheme 7, work-up gave

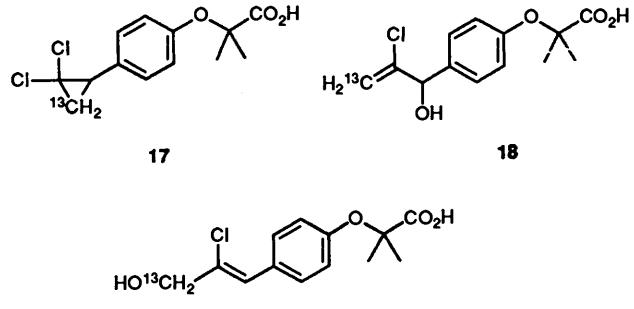


Scheme 7

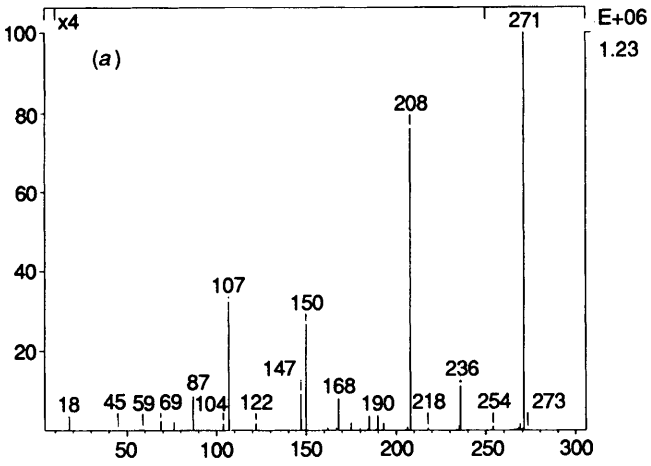
the diacid **13** together with a mixture of two other products which could not be separated by column chromatography but were identified by HPLC–MS as the acid **15** and ketone **16**.

The reactions of the alcohols **9** and **10** with base therefore lead to the same products as those observed on treatment of ciprofibrate with base under similar conditions. Because of the complex series of reactions involved, it was not easy to compare directly the ratios of products in each case, but it seems possible that all the products of the reaction of ciprofibrate are derived by initial ring-opening to the alcohols **9** and **10**.

The mode of formation of the diacid **13** by reaction of **9** with sodium hydroxide at reflux was not obvious. In order to probe the mechanism, the ^{13}C-labelled ciprofibrate **17** was prepared by reaction of ethyl 2-(4-formylphenoxy)-2-methylpropanoate with (^{13}C)-methylenetriphenylphosphorane and then dichlorocarbene, generated from chloroform by reaction with aqueous sodium hydroxide under phase-transfer conditions. The ^1H NMR spectrum of the labelled compound showed signals for the hydrogens of the methylene group each with a large coupling to carbon (162.5 and 160 Hz, respectively), while the benzylic hydrogen signal included a 2.5 Hz coupling to carbon. Treatment of **17** with sodium dihydrogen orthophosphate buffer at reflux as before gave the labelled allylic alcohols **18** and **19**.



Because of the scale of the reaction these alcohols were not separated, and the mixture was treated directly with aqueous sodium hydroxide at reflux as before. The result is summarised in Scheme 8. The crude mixture of products was compared directly by ^1H and ^{13}C NMR and HPLC–MS with the products from the unlabelled alcohols. The HPLC–MS analysis showed the presence of both of the alkynes **20** and **12**; in the latter case the ^{13}C-label had been lost. In addition the acid **21** was present, in this case containing the ^{13}C-label at C-2 of the propanoic acid side chain. Thus the HPLC–MS of the product showed a peak corresponding to **21** with an adduct ion at *m/z* 271



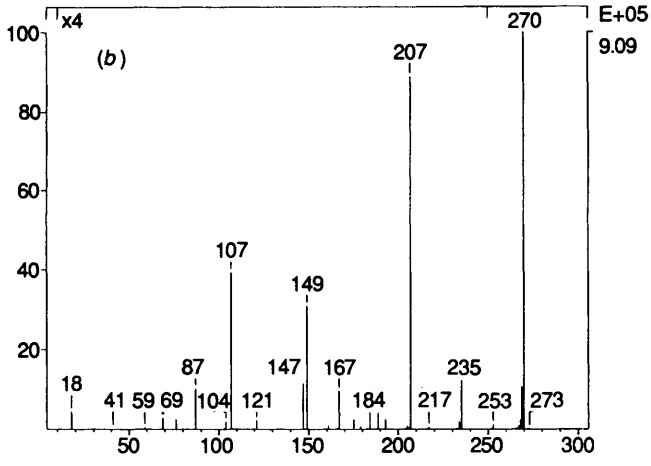
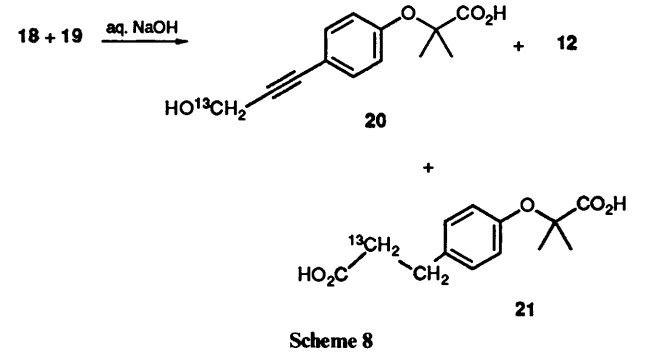


Fig. 1(*a*) Daughter-ion spectrum of **21** where *m/z* is 271 [M + NH_4^+]; (*b*) daughter-ion spectrum of **13** where *m/z* is 270 [M + NH_4^+]

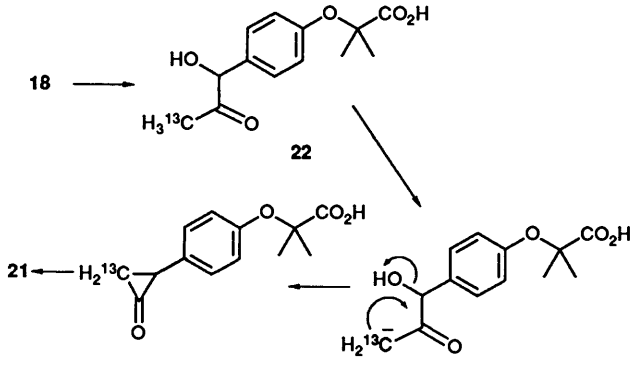


Scheme 8

$[M + NH_4]^+$ [Fig. 1(*a*)], compared with 270 in the unlabelled compound [Fig. 1(*b*)]; peaks at 254 $[M + H]^+$, 236 $[M + H - H_2O]^+$, 208 $[M + H - HCO_2H]^+$, 150 [$^+OC(CH_2)_2C_6H_4$·OH] and 122 [$^+CH_2CH_2C_6H_4$·OH] were all at *m/z* values one higher than those for the unlabelled compound. However, the peak at *m/z* 107 corresponding to the hydroxytropylium ion was identical in labelled and unlabelled compounds. This is consistent with the label being at C-2 of the propyl chain. In agreement with this, the signal at δ 2.7 in the ^1H NMR spectrum which appeared as a triplet in the unlabelled compound was split into a doublet of triplets (*J* 128 Hz), one of which overlapped the triplet at δ 2.9, which was also broadened. The signal for the methylene group of the alcohol **20**, which was a singlet at δ 4.53 in the unlabelled compound was entirely split into a doublet (*J* 148.5 Hz) in the product from the

labelled mixture of alcohols. The ^{13}C spectrum of the product mixture showed just two major signals at δ 51.45 and 35.3, corresponding to the methylene group of **20** and the C-2 methylene group of the propanoic acid chain of **21**.

The formation of **21** from **18** may involve initial conversion of the vinylic halide into the ketone **22** by reaction with the strong base, followed by a Favorskii-type rearrangement in which the benzylic hydroxy-group is lost, as summarised in Scheme 9. Such Favorskii-type reactions of α-hydroxy ketones are known.[11]



Scheme 9

Direct reaction of the labelled ciprofibrate **17** with aqueous sodium hydroxide under the same conditions as those used for the unlabelled compound led to a mixture containing **20**, **21** and **12** as well as **14**, **15** and **16**, as in Scheme 10. The last four

17 ⟶ 20 + 21 + 12 + 14 + 15 + 16

Scheme 10

products were shown by HPLC–MS and NMR spectroscopy to be unlabelled. Compounds **20** and **21** were labelled as in the previous reaction, *i.e.*, the former entirely at the methylene group and the latter at C-2 of the propanoic acid chain.

Experimental

Elemental analyses were performed on a Carlo-Erba Instrumentazione 1106 analyser. Infrared spectra were recorded on a Nicolet 20 SX-B Fourier transform spectrometer. NMR spectra were recorded at 80, 200, 250 or 300 MHz for protons on Bruker AC80, WP200, WP250 or WP300-WB spectrometers; carbon spectra were run at the corresponding frequencies on the same instruments. Electron impact mass spectra were obtained on an AEI MS-9 or a Kratos MS80 instrument and Thermospray liquid chromatography–mass spectrometry (HPLC–MS) data were acquired on a Finnigan TSQ-700 triple stage quadrupole equipped with a TSP II interface (source temperature 220 °C, ammonium acetate (0.5%) buffer assisted ionisation). Collision-induced daughter spectra (MS–MS) were accomplished with argon gas at 66.6 mPa and a collision energy of 30 eV. Petrol refers to the portion of petroleum of boiling point 40–60 °C.

Reaction of Ciprofibrate with Buffer.—Ciprofibrate (5.0 g) was dissolved in aqueous sodium hydroxide (1 mol dm^{-3}; 25 cm^3). Orthophosphoric acid was added to adjust the pH to 7, and the solution was made up to 500 cm^3 by addition of pH 7 sodium dihydrogen orthophosphate buffer. The mixture was refluxed for 96 h, acidified to pH 1 by addition of hydrochloric acid and extracted with chloroform. Evaporation gave a semi-solid (3.9 g) which was shown by NMR spectroscopy to contain two products in the ratio ca. 2:1.

Recrystallisation from chloroform gave an initial batch of crystals that consisted of pure **10**, m.p. 145–147 °C (Found: C, 57.25; H, 5.75. $C_{13}H_{15}ClO_4$ requires: C, 57.67; H, 5.58%). Continued crystallisation gave a mixture of **10** and **9** in which the latter predominated; recrystallisation of this mixture from chloroform gave compound **9**, m.p. 105–107 °C (Found: C, 57.7; H, 5.80).

Compound **10** showed $\delta_H(CD_3OD)$ 1.78 (6 H, s), 4.41 (2 H, d, *J* 1.1 Hz), 6.97 (1 H, br s), 7.04–7.09 and 7.76–7.80 (4 H, AA'BB' system); $\delta_C(CD_3OD)$ 26.1, 68.2, 80.7, 120.35, 124.9, 130.2, 131.5, 133.25, 156.9 and 177.9. Upon pre-irradiation at H_A an enhancement of 12.5% was observed at the frequency of the vinylic hydrogen H_B. A similar Overhauser effect was observed upon pre-irradiation of the frequency of H_B giving enhancements of 3.2 and 6.15% to signals of protons H_A and H_C respectively.

Compound **9** showed $\delta_H(CD_3OD)$ 1.75 (6 H, s), 5.09 (2 H, br s, exchangeable), 5.34 (1 H, s), 5.55 (1 H, s), 5.85 (1 H, s), 7.05 (2 H, br d, *J* 8.6 Hz) and 7.48 (2 H, br d, *J* 8.6 Hz); $\delta_C(CD_3OD)$ 26.05, 77.5, 80.6, 112.95, 120.7, 129.3, 136.1, 145.9, 157.0 and 177.9.

Reaction of Ciprofibrate with Base.—Ciprofibrate (2.5 g) was refluxed for 56 h with sodium hydroxide (1 mol dm^{-3}; 250 cm^3). The products were acidified to pH 1 and extracted with ether. Removal of the solvent gave a brown oil (2.2 g) which was separated by column chromatography.

The first product was 2-[4-(3-hydroxypropynyl)phenoxy]-2-methylpropanoic acid (**11**) (42%), m.p. 103–110 °C (Found: C, 66.35; H, 6.05. $C_{13}H_{14}O_4$ requires: C, 66.66; H, 6.02%) which showed $\delta_H(CDCl_3)$ 1.64 (6 H, s), 4.50 (2 H, s), 5.51 (1 H, br s), 6.75–7.05 (2 H, m) and 7.2–7.45 (2 H, m); δ_C 25.2 (q), 51.6 (t), 85.4 (s), 86.5 (s), 116.9 (s), 119.8 (d), 132.9 (d) and 155.2 (s); *m/z* 234, 148 ($M - C_4H_6O_2$) and 119.

The second was 2-(4-ethynylphenoxy)-2-methylpropanoic acid (**12**) (7%) m.p. 97–110 °C (Found: M^+ 204.0769) which showed $\delta_H(CDCl_3)$ 1.64 (6 H, s), 3.04 (1 H, s), 6.7–7.05 (2 H, m), 7.2–7.55 (2 H, m) and 10.41 (1 H, br s); δ_C 25.3 (CH_3), 34.9 (C), 76.6 (CH), 83.3 (C), 116.5, 119.7, 133.3 and 155.5; ν_{max}/cm^{-1} 2400–3350v br, 2110m and 1705s.

The third was 2-[4-(2-carboxyethyl)phenoxy]-2-methylpropanoic acid (**13**) (4%) m.p. 173–182.5 °C (Found: C, 61.80; H, 6.4. $C_{13}H_{16}O_5$ requires: C, 61.90; H, 6.39%) which showed $\delta_H(CD_3COCD_3)$ 1.55 (6 H, s), 2.05–3.05 (4 H, AA'BB'), 4.90 (2 H, v br s), 6.83 (2 H, br d, *J* 8.5 Hz) and 7.14 (2 H, br d, *J* 8.5 Hz); δ_C 25.6, 30.6, 120.3, 129.6, 135.5, 154.8, 174.0 and 175.6; ν_{max}/cm^{-1} 3600–2400v br, 1700s and 1616m; *m/z* 252, 166 ($M - C_4H_6O_2$) and 107 ($M - C_6H_9O_4$).

HPLC showed the presence of **14**, **15** and **16** identical with known samples by HPLC, MS and UV.

Reaction of the Alcohol **9** *with Base.*—The alcohol **9** (0.23 g) was refluxed for 96 h with aqueous sodium hydroxide as described for the reaction of **1**. Work-up gave an oil, the ^1H NMR spectrum of which showed signals corresponding to **13** (*ca.* 50% of total), together with several other components; column chromatography gave three fractions in which partial separation had occurred. The first (44 mg) contained two components in ratio *ca.* 2.5:1 according to ^1H NMR spectroscopy and two components by HPLC. The major product was the propanoic acid **13**; the minor product was the corresponding benzoic acid **15**. The dicarboxylic acid **15** showed a pair of two-hydrogen double doublets at δ 8.12 and 7.09 and a singlet at δ 1.82 (6 H). The second fraction (94 mg) was very similar by HPLC, although the ^1H NMR spectrum showed additional singlets at δ 2.75 and 1.825 and an additional pair of double doublets at δ 8.11 and 7.07 in an approximate 3:6:2:2 ratio, apparently corresponding to **16**. The presence of this compound was also confirmed by HPLC–MS analysis. The third fraction (15 mg) gave a much more complicated HPLC

trace which included the two acids above, **13** and **15**, together with small amounts of the aldehyde **14**, the acetyl-derivative **16** and two apparent dimers at longer retention time, the proportion of which increased with the time the sample was kept before analysis.

Reaction of the Alcohol **10** *with Base.*—The alcohol **10** (0.23 g) was refluxed as above with aqueous sodium hydroxide for 8 days. Work-up as before gave a crude product which was analysed directly (0.18 g). HPLC coupled to LC–UV and LC–MS showed the presence of one major and one minor component, the acetylenic alcohol **11** and the alkyne **12**, respectively, together with a trace of the acid **15** and the ketone **16** which eluted very close to the alcohol **11**. The ^{1}H NMR spectrum showed the presence of two AA'BB' patterns in the aromatic region in the ratio *ca.* 5:1. The first was centred at δ 7.3 and 6.8 and the second at 7.9 and 6.9. The first of these was of about the correct size to match a peak at δ 4.35 for the alcohol **11**. The second integrated to a total of *ca.* four hydrogens relative to a sharp singlet at δ 2.55 and probably corresponded to **16**; the alkyne signal for **12** was masked by this last singlet.

Ethyl 2-(4-*Formylphenoxy*)-2-*methylpropanoate.*—To 4-hydroxybenzaldehyde (10 g) in DMF (130 cm^3) was added K_2CO_3 (11.3 g) and the solution was heated to 100 °C. To this was added ethyl 2-bromo-2-methylpropanoate (14.4 cm^3) and the heating was continued for 1 h. After this time further K_2CO_3 (11.3 g) and ethyl 2-bromo-2-methylpropanoate (14 cm^3) were added, and the heating was continued for a further 4 h. The reaction mixture was poured into distilled water and extracted three times with ether. The organic layer was washed with further distilled water before being dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a gum which was chromatographed on silica eluting with CH_2Cl_2 and petrol (5:2) to give ethyl 2-(4-formylphenoxy)-2-methylpropanoate as a colourless oil (12.6 g, 65%), which showed δ_H 1.20 (3 H, t, *J* 7.2 Hz), 1.66 (6 H, s), 4.22 (2 H, q, *J* 7.2 Hz), 6.88 (2 H, d, *J* 8.7 Hz) and 7.78 (2 H, d, *J* 8.7 Hz).

Ethyl 2-{4-[(2-^{13}C)*Ethenyl*]*phenoxy*}-2-*methylpropanoate.*—Sodium hydride (0.26 g) in anhydrous dimethyl sulfoxide (3 cm^3) was heated to 75–80 °C for 45 min, then cooled in an ice bath. A solution of (^{13}C)methyltriphenylphosphonium iodide (3.08 g) in dimethyl sulfoxide (7 cm^3) was then added, the mixture stirred for 15 min and then treated with a solution of ethyl 2-(4-formylphenoxy)-2-methylpropanoate (1.5 g) in dimethyl sulfoxide (1.5 cm^3). The reaction mixture was stirred for 16 h at room temperature and then poured into water. The organic layer was extracted with ether (3 × 20 cm^3), washed with water and saturated aqueous sodium chloride and dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica eluting with CH_2Cl_2–petrol (5:2) to give ethyl 2-{4-[(2-^{13}C)ethenyl]-phenoxy}-2-methylpropanoate (0.71, 48%), which was identical by ^{1}H NMR spectroscopy with the unlabelled compound except that the signal at δ 5.61 was a double doublet (*J* 17.6 and 156 Hz), that at δ 5.13 was a double doublet (*J* 10.8 and 160 Hz) and that the signal at δ 112.8 in the ^{13}C spectrum was considerably enhanced relative to the others (it showed side bands, *J* 7 Hz, *ca.* equal in height to the signal at δ 79.8) and the signal at δ 136.73 was split into a doublet (*J* 7 Hz).

2-{4-[(3-^{13}C)-2,2-*Dichlorocyclopropyl*]*phenoxy*}-2-*methylpropanoic Acid.*—Ethyl 2-{4-[(2-^{13}C)ethenyl]phenoxy}-2-methylpropanoate (0.5 g) was dissolved in $CHCl_3$ (10 cm^3) and benzyltriethylammonium chloride (0.35 g) was added, and the mixture was stirred vigorously and warmed to 40 °C with aqueous sodium hydroxide (1 g) in water (1 cm^3) added over 2 h. After 12 h at room temperature, the mixture was diluted with water (10 cm^3) and acidified with conc. HCl (3 cm^3). The mixture was extracted with $CHCl_3$ (3 × 10 cm^3) and the organic phase dried over $MgSO_4$, and then the solvent was removed *in vacuo*. The residue was dissolved in methanol (25 cm^3) and treated with potassium hydroxide (1.0 g) in water (25 cm^3) and stirred overnight at room temperature. The methanol was removed under vacuum and the aqueous phase extracted with diethyl ether (2 × 50 cm^3); the aqueous phase was then acidified with conc. HCl and extracted with $CHCl_3$ (2 × 50 cm^3). The combined $CHCl_3$ phases were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica eluting with toluene and acetic acid (9:1) to give 2-{4-[(3-^{13}C)-2,2-dichlorocyclopropyl]phenoxy}-2-methylpropanoic acid (0.45 g, 73.7%). The ^{1}H NMR spectrum of this was essentially identical with that of the unlabelled compound except that the cyclopropane signals appeared as δ 1.82 (ddd, *J* 162.5, 10.5, 7.4 Hz) and 2.0 (ddd, *J ca.* 160, 8.5, 7.4 Hz), and that at 2.84 was a multiplet which included an additional coupling of *ca.* 2.5 Hz compared with the unlabelled compound.

Reaction of 2-{4-[(3-^{13}C)-2,2-*Dichlorocyclopropyl*]*phenoxy*}-2-*methylpropanoic Acid with Buffer solution.*—2-{4-[(3-^{13}C)-2,2-Dichlorocyclopropyl]phenoxy}-2-methylpropanoic acid (0.4 g) was dissolved in aqueous sodium hydroxide (1 mol dm^{-3}; 2 cm^3). Orthophosphoric acid was added to adjust to pH 7, and then the solution was made up to a volume of 40 cm^3 using pH 7 sodium dihydrogen orthophosphate buffer. The mixture was refluxed for 96 h, when GLC showed that no starting material remained; the solution was acidified to pH 1 using conc. HCl, and was extracted with $CHCl_3$ (3 × 10 cm^3). The combined organic layers were dried, and the solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica, eluting with toluene and acetic acid (85:15) to give a mixture of labelled 2-[4-(2-chloro-1-hydroxyprop-2-enyl)phenoxy]-2-methylpropanoic acid (**18**) and labelled 2-[4-(2-chloro-3-hydroxyprop-1-enyl)phenoxy]-2-methylpropanoic acid (**19**) in the ratio *ca.* 1:1 (0.21 g, 56%). The ^{1}H NMR spectrum of this was identical with that of the product mixture from unlabelled ciprofibrate except that the alkene-hydrogen signals for **18** were each split into doublets (*J* 161 Hz) and the benzylic hydrogen appeared as a doublet (*J ca.* 4.7 Hz) at δ 6.96 while the alkene hydrogen for **19** appeared as a doublet (*J* 3.1 Hz) and the methylene group as a doublet (*J* 145 Hz). In the ^{13}C NMR spectrum ($CDCl_3$), the signals at δ 113 and 67.8 were enhanced considerably relative to all other peaks.

Reaction of the ^{13}C-*Labelled Alcohols* **18** *and* **19** *with Base.*—The mixture of **18** and **19** (0.15 g) obtained above was refluxed for 40 h with 1 mol dm^{-3} sodium hydroxide, using the same conditions and work-up as before to give an oil (0.115 g). The ^{1}H NMR spectrum showed the presence of the alkyne **20** labelled with ^{13}C at the methylene group; thus the signal at δ 4.53 was split into a doublet (*J* 148.5 Hz). Also split into a doublet (*J ca.* 128 Hz) was the triplet at δ 2.7 corresponding to one of the methylene groups of **13**. The other methylene signal for this compound, δ 2.9, remained largely unchanged from the unlabelled compound although some small broadening was apparently observed; there was no evidence of one-bond coupling to the carbon label. The signal at δ 2.56 corresponding to the acetyl methyl of **16** and the terminal alkyne hydrogen of **12** appeared to show evidence of *ca.* 10% coupling to carbon, side bands appearing with *J* 127.5 Hz; an aldehyde signal at δ 9.9 corresponding to **14** showed no splitting by carbon. The ^{13}C spectrum, however, showed only two major signals, at δ 51.45 and 35.3, corresponding to one of the methylene carbons of **21**

and the methylene group of **20**, respectively. HPLC–MS showed the presence of the acid **15** and the aldehyde **14**, containing no ^{13}C label, the propanoic acid **21** and the alkynol **20** containing one ^{13}C-atom. An MS–MS spectrum of **21** confirmed that the label was at C-2 of the acid chain [Fig. 1(*b*)].

Reaction of ^{13}C*-Labelled Ciprofibrate with Base.*—2-{4-[(3-^{13}C)-2,2-Dichlorocyclopropyl]phenoxy}-2-methylpropanoic acid (100 mg) was refluxed with sodium hydroxide (0.6 g) in water (14 cm^3) for 69 h. The solution was then acidified with conc. HCl to pH 7 and then extracted with ether (3 × 10 cm^3). The combined organic phases were dried, and the solvent removed *in vacuo*. The residue was subjected to column chromatography on silica eluting with toluene and acetic acid to give a number of fractions, each of which was a mixture (0.07 g total). HPLC showed the presence of the diacid **15**, the propanoic acid **21**, the aldehyde **14**, the alkyne **20** and the allylic alcohols **18** and **19**; the acetophenone **16** was present as a shoulder on the peak corresponding to **20**. The ^1H NMR spectrum included a doublet at 4.53 (*J* 148.5 Hz). The triplet at δ 2.7 corresponding to the methylene group of **21** was also split into a double triplet (*J* 128 Hz), the downfield part appearing underneath the signal at δ 2.9. The ^{13}C NMR spectrum included a large singlet at δ 52.0 corresponding to the methylene carbon of **20** and a smaller singlet at δ 36.2 corresponding to C-2 of **21**; no signal was visible for C-3 of **21** at δ 30.6.

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