Conversion of (*Z*)-1,4-dihydroxyalk-2-enes into 2,5-dihydrofurans and of alkane-1,4-diols into tetrahydrofurans *via* acid-catalysed cyclisation of the monoisoureas formed by their copper(I)-mediated reactions with dicyclohexylcarbodiimide †

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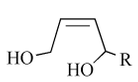
(*Z*)-1,4-Dihydroxyalk-2-enes react with dicyclohexylcarbodiimide in the presence of catalytic amounts of copper(I) chloride to give *O*-alkyl monoisoureas which cyclise to give 2-substituted-2,5-dihydrofurans and dicyclohexylurea when they are treated with trifluoroacetic acid. Alkane-1,4-diols likewise give *O*-alkyl monoisoureas which cyclise to yield tetrahydrofurans.

Introduction

2,5-Dihydrofurans **1** are an important class of compounds, the synthesis of which has received considerable attention. For example, Heck arylation or vinylation of 2,3-dihydrofurans,[1] ring-closing metathesis reactions of diallyl ethers,[2] *retro*-Diels–Alder reactions of modified furan–2,5-dihydrofuran cycloadducts,[3] Wittig cyclo-olefination reactions of suitable β-oxaethylphosphoranes[4] and selenyl halide-induced cyclisations of α-allenic alcohols[5] have all been utilised for this purpose.

The dehydrative cyclisation of (*Z*)-1,4-dihydroxyalk-2-enes **2** to give 2,5-dihydrofurans **1** is, in principle, a simple and attractive synthetic route to these compounds. However, this type of cyclisation is usually effected under relatively harsh acidic conditions. Thus, treatment with sulfuric acid succeeds for some cases[6] but may also lead to the formation of polymers,[7] and it frequently causes acid-catalysed dehydration of the diols **2** so that variable amounts of α,β-unsaturated carbonyl compounds are also produced.[8]

1a R = H
1b R = n-hexyl
1c R = n-nonyl
1d R = CH_2Ph
1e R = CH_2CH_2Ph
1f R = Ph
1g R = 2-MeO-C_6H_4-



2a R = H
2b R = n-hexyl
2c R = n-nonyl
2d R = CH_2Ph
2e R = CH_2CH_2Ph
2f R = Ph
2g R = 2-MeO-C_6H_4-

Reaction of (*Z*)-1,4-dihydroxybut-2-ene **2a** with the diaryldialkoxysulfane **3** has been reported[9] to give 2,5-dihydrofuran in 84% yield, but the reagent is expensive. Diethoxytriphenylphosphorane **4** efficiently cyclises the same diol[10] but this reagent must be prepared from explosive diethyl peroxide. The environmentally toxic butyltrichlorotin reacts with the diol **2a** to give 2,5-dihydrofuran (88%) together with some crotonaldehyde.[11] Barry and Evans have described[12,13] how (*Z*)-1,4-dihydroxybut-2-ene **2a** can be cyclised in the presence of either *tert*-BuOCl–Ph_3P–K_2CO_3 or Ph_3P–CCl_4 to give 2,5-dihydrofuran in >60% yields.

† Electronic supplementary information (ESI) available. Experimental data for compounds **14a–f**, **15a–f**, **7a–f**, **22a–g**, **21a–e** and **2b–e**: See http://www.rsc.org/suppdata/p1/b2/b203389p/

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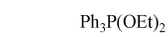

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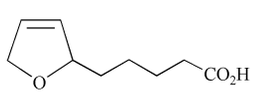
In connection with other work,[14] we needed reliable access to 5-(2′,5′-dihydro-2′-furyl)pentanoic acid **5**, and attempted to make this compound as its methyl ester **6c** *via* cyclodehydration of the (*Z*)-diol **7c** using each of the methodologies described by Barry and Evans. In the event, treatment of **7c** with either of their reagent combinations led to unsatisfactory yields (25–30%) of the dihydrofuran **6c**. Accordingly, we sought to develop a more effective method for this transformation.



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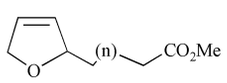
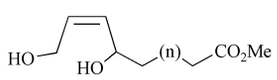


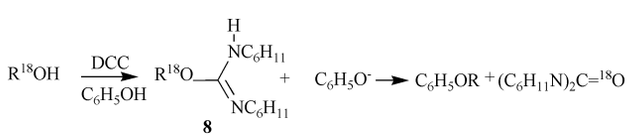
6a n = 1
6b n = 2
6c n = 3
6d n = 4
6e n = 5
6f n = 6



7a n = 1
7b n = 2
7c n = 3
7d n = 4
7e n = 5
7f n = 6

Results and discussion

It has been reported by Vowinkel[15] that phenolic ethers can be synthesised by reaction of an alkanol with a phenol in the presence of dicyclohexylcarbodiimide (DCC), and Bach[16] has demonstrated by ^{18}O labelling experiments (Scheme 1) that this



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Scheme 1

reaction involves protonation of the carbodiimide by the relatively acidic phenol followed by reaction with the alkanol to give an *O*-alkylisourea **8**. This then reacts *in situ* with phenoxide ion to give the product ether together with dicyclohexylurea.

These observations led us to consider the use of DCC for the dehydrative cyclisation of (*Z*)-1,4-dihydroxyalk-2-enes **2** to give

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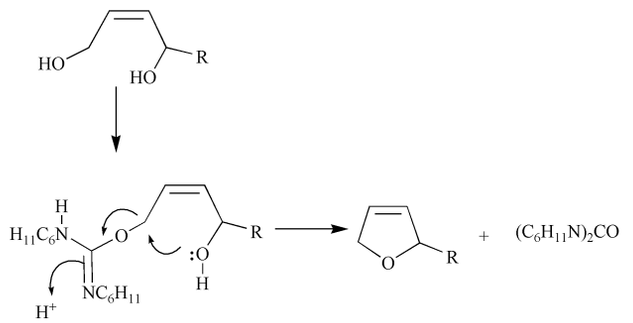
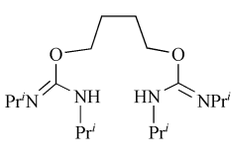


Scheme 2

2,5-dihydrofurans. We reasoned (Scheme 2) that if a (*Z*)-configured unsaturated diol **2** could be converted into a *mono*-isourea *via* reaction with DCC, then treatment of the latter with an acid should lead to a 2,5-dihydrofuran **1**.

Although aliphatic carbodiimides are generally quite inert towards neutral alcohols, the direct synthesis of *O*-alkylisoureas from monohydric alcohols and diisopropyl- or dicyclohexylcarbodiimide has been accomplished by using copper(II) salts, especially copper(II) chloride, as catalysts.[17] Reactions of this type have been reviewed,[18] and Schmidt *et al.* have shown[19] that diisopropylcarbodiimide reacts with, *e.g.*, butane-1,4-diol in the presence of copper(II) chloride to yield the bis-*O,O′*-dialkylisourea **9**.



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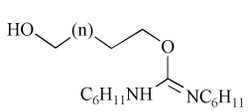
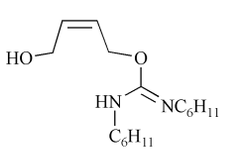
We have found that when the copper(II) chloride used by Schmidt *et al.*[19] is substituted by the *cuprous* salt the monoisourea **10** is efficiently formed from dicyclohexylcarbodiimide and butane-1,4-diol, even in the presence of excess carbodiimide. A similar result was obtained with hexane-1,6-diol which afforded the monoisourea **11**. Each of these compounds showed the expected spectroscopic features, including sharp IR absorptions at *ca.* 1660 cm^{-1} and, in their ^1H NMR spectra, 2H triplets near δ 4.1 ppm which are assigned to the protons of their C-1 methylene groups.



10 n = 1
11 n = 3

Reaction of (*Z*)-but-2-ene-1,4-diol **2a** with dicyclohexylcarbodiimide under similar conditions gave the crystalline monoisourea **12**, mp 87 °C. When a chloroform solution of this compound was treated with catalytic amounts of either methanesulfonic or (better) trifluoroacetic acid it was quantitatively converted (NMR) into a mixture of 2,5-dihydrofuran and dicyclohexylurea, most of the latter crystallising from the solvent. Furthermore, this overall transformation could be accomplished as a one-pot process without isolation of the intermediate isourea **12** by reaction of the diol **2a** with DCC–CuCl followed by the addition of trifluoroacetic acid.



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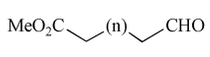
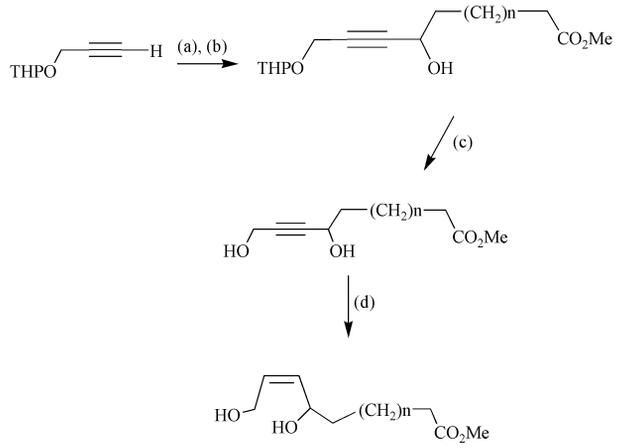
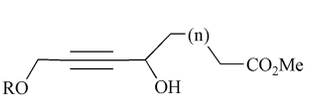


13a n = 1
13b n = 2
13c n = 3
13d n = 4
13e n = 5
13f n = 6

We have successfully applied this cyclodehydration methodology to a series of methyl (*Z*)-dihydroxyalk-2-enoates **7a**–**7f** which yielded the ω-(2′,5′-dihydro-2′-furyl)alkanoic esters **6a**–**6f** under these conditions. The diols **7a**–**7f** were synthesised (Scheme 3) *via* chemoselective reaction of lithiated 3-(tetrahydropyran-2′-yloxy)propyne with each of the appropriate aldehydo-esters **13a**–**13f** to give the hydroxy-esters **14a**–**14f**. Cleavage of the tetrahydropyranyl ether groups of **14a**–**14f** using PPTS–MeOH yielded the acetylenic diols **15a**–**15f** which were then partially hydrogenated over Pd/$BaSO_4$–quinoline to give the (*Z*)-diols **7a**–**7f**. The ^1H NMR spectra of these diols exhibited *J* values for their olefinic protons in the range 5–9 Hz, confirming the expected (*Z*)-configurations. The protons of the methylene groups adjacent to the primary hydroxy functions of each of the diols **7a**–**7f** (and of other related diols described below) exhibited obvious diastereotopicity, appearing as AB systems near δ 4.0 ppm.



Scheme 3 *Reagents*: (a) BuLi; (b) $MeO_2CCH_2(CH_2)_nCH_2CHO$; (c) PPTS–MeOH; (d) H_2–Pd/$BaSO_4$–quinoline.



14a R = THP; n = 1
14b R = THP; n = 2
14c R = THP; n =3
14d R = THP; n = 4
14e R = THP; n =5
14f R = THP; n = 6

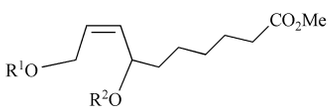
15a R = H; n = 1
15b R = H; n = 2
15c R = H; n = 3
15d R = H; n = 4
15e R = H; n = 5
15f R = H; n = 6

One-pot treatment of chloroform solutions of each of the unsaturated diols **7a**–**7f** with DCC–CuCl, followed by heating at 40 °C in the same solvent with an optimised (13 mol%) amount of trifluoroacetic acid gave the derived 2,5-dihydrofurans **6a**–**6f** in acceptable yields after purification by chromatography (Table 1).

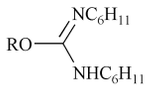
When the diol **7c** was reacted with DCC–CuCl alone and the intermediate isourea was separated, NMR spectroscopy indicated that this was a 75 : 25 mixture of the primary isourea **16** and the isomeric secondary isourea **17**. A competition experiment where one equivalent of each of 1-phenylethanol, 2-phenylethanol and DCC were reacted together in chloroform in the presence of copper(I) chloride afforded a mixture containing 91% of the less hindered primary isourea **18**. Similarly, CuCl-catalysed reaction of one equivalent of each of propan-1-ol, propan-2-ol and DCC gave a 90 : 10 mixture of the derived primary **19** and secondary isoureas. Given that the degree of steric hindrance about the secondary hydroxy function of the diol **7c** is significant compared to that in propan-2-ol, the formation of a 75 : 25 mixture of primary and secondary isoureas from **7c** suggests the possibility that an *O*–*O′*-transfer reaction proceeding *via* the cyclic intermediate **20** cannot be ruled out.

Table 1 Synthesis of methyl ω-(2,5-dihydro-2-furyl)alkanoates from 1,4-dihydroxyalk-2-enes *via* acid-catalysed cyclisation of their monoisoureas

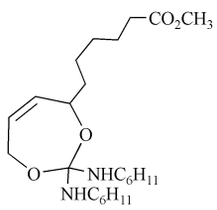
1,4-Diol	2,5-Dihydrofuran	Yield (%)
7a	**6a**	52
7b	**6b**	62
7c	**6c**	57
7d	**6d**	62
7e	**6e**	57
7f	**6f**	56



16 $R^1 = C(NHC_6H_{11})=NC_6H_{11}$, $R^2 = H$
17 $R^2 = H$; $R^1 = C(NHC_6H_{11})=NC_6H_{11}$

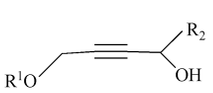


18 $R = PhCH_2CH_2$
19 $R = CH_3CH_2CH_2$



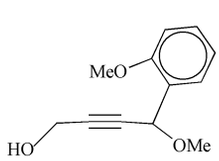
20

A further series of protected acetylenic diols **21a**–**21g** was synthesised in good yields from lithiated 3-(2′-tetrahydropyranyloxy)propyne and the relevant aldehydes. Cleavage of the tetrahydropyranyl ether functions of the product acetals **22a**–**22g** using PPTS–MeOH proceeded normally except in two instances. Thus, the *o*-methoxy compound **22f** yielded the methyl ether **23**, and the enynol **22g** afforded a mixture containing mainly the methyl ether **24** under these conditions. These results are presumably due to the intervention of, respectively, stabilised benzylic or allylic cations. However, for each of the compounds **22f** and **22g** reaction proceeded normally in aqueous tetrahydrofuran to afford the expected products **21f** and **21g** in good yield.



21a $R^1 = H$; R^2 = n-hexyl
21b $R^1 = H$; R^2 = n-nonyl
21c $R^1 = H$; $R^2 = CH_2Ph$
21d $R^1 = H$; $R^2 = CH_2CH_2Ph$
21e $R^1 = H$; $R^2 = Ph$
21f $R^1 = H$; R^2 = 2-MeO-C_6H_4
21g $R^1 = H$; R^2 = (E) HC=CHPh

22a R^1 = THP; R^2 = n-hexyl
22b R^1 = THP; R^2 = n-nonyl
22c R^1 = THP; $R^2 = CH_2Ph$
22d R^1 = THP; $R^2 = CH_2CH_2Ph$
22e R^1 = THP; $R^2 = Ph$
22f R^1 = THP; R^2 = 2-MeO-C_6H_4
22g R^1 = THP; R^2 = (E) HC=CHPh



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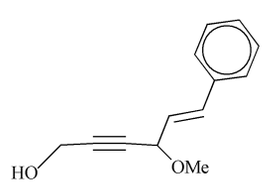

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The acetylenic diols **21a**–**21d** were successfully semi-hydrogenated to the (*Z*)-olefinic diols **2b**–**2e** over Pd/$BaSO_4$ poisoned with quinoline, but use of this catalyst system with the diols **21f** and **21g** led to partial hydrogenolysis of their benzylic secondary hydroxy groups. This problem was overcome by employing the catalyst system Pd/$CaCO_3$–quinoline in the presence of a little triethylamine when reduction proceeded without detectable hydrogenolysis to yield **2f** and **2g**, respectively. However, we were unable to find suitable conditions for the clean semi-hydrogenation of the enynediol **21g**.

Table 2 Synthesis of 2-substituted-2,5-dihydrofurans from alk-2-ene-1,4-diols *via* acid-catalysed cyclisation of their monoisoureas

1,4-Diol	2,5-Dihydrofuran	Yield (%)
2b	**1b**	81
2c	**1c**	90
2d	**1d**	89
2e	**1e**	64
2f	**1f**	79
2g	**1g**	86

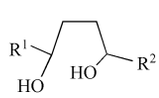
Table 3 Synthesis of 2-substituted tetrahydrofurans from 1,4-diols *via* acid-catalysed cyclisation of their monoisoureas

1,4-Diol	Tetrahydrofuran	Yield (%)
25	**26**	72
27	**28**	85
39[a]	**30**[a]	33

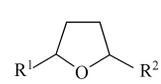
[a] as a mixture of diastereoisomers

Following the general protocol outlined above, each of the unsaturated diols **2b**–**2g** was readily cyclised *via* an intermediate isourea formed by reaction with dicyclohexylcarbodiimide in the presence of catalytic copper(I) chloride to give (Table 2) the derived 2,5-dihydrofurans **1b**–**1g**. These, and the other 2,5-dihydrofurans discussed above must be stored under an inert atmosphere since they undergo rapid oxidation in the presence of air to give the derived furans together with mixtures of more highly oxygenated compounds.

The cyclodehydration process described above is equally applicable to the synthesis of tetrahydrofurans. Thus (Table 3), 1,4-dihydroxy-1-phenylbutane **25** gave 2-phenyltetrahydrofuran **26**, and methyl 6,9-dihydroxynonanoate **27** gave methyl 5-(tetrahydro-2′-furyl)pentanoate **28** in good yield when they were each treated with DCC–CuCl followed by trifluoroacetic acid. Cyclisation of the more hindered methyl 6,9-dihydroxydecanoate **29** was less satisfactory, and methyl 5-(5′-methyltetrahydro-2′-furyl)pentanoate **30** was obtained in only 33% yield.



25 $R^1 = H$; $R^2 = Ph$
27 $R^1 = H$; $R^2 = (CH_2)_4CO_2Me$
29 $R^1 = Me$; $R^2 = (CH_2)_4CO_2Me$



26 $R^1 = H$; $R^2 = Ph$
28 $R^1 = H$; $R^2 = (CH_2)_4CO_2Me$
30 $R^1 = Me$; $R^2 = (CH_2)_4CO_2Me$

Experimental

^{1}H NMR spectra were recorded for solutions in $CDCl_3$ using Bruker WP 80 (with Me_4Si as internal standard), Bruker MSL 300 or Bruker DPX 400 MHz spectrometers. Coupling constants are recorded in Hz. Assignments were verified by appropriate H–H COSY, C–H COSY and DEPT experiments. IR spectra were recorded for Nujol mulls (N) or liquid films (L) between sodium chloride plates using Perkin Elmer 883 or Paragon 1000 spectrometers. High resolution mass spectra were obtained using a Kratos instrument. Melting points (uncorrected) were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus or an Electrothermal IA9100 apparatus. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} 0.2 mm silica gel plates. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) silica gel. All solvents were dried and distilled before use. Ethereal extracts of reaction products were dried over anhydrous magnesium sulfate. Combustion analyses were obtained from the Microanalytical Laboratory, University College, Dublin.

N,N-Dicyclohexyl-*O*-(4′-hydroxybutyl)isourea 10

Butane-1,4-diol (0.45 g), dicyclohexylcarbodiimide (1.03 g) and copper(I) chloride (20 mg) were stirred in chloroform (10 cm^3) for 12 h. Hexane (15 cm^3) was added, and the solution was filtered to remove precipitated dicyclohexylurea and then evaporated to give the *isourea* **10** as a viscous *oil* (1.34 g) which had ν_{max} (L) 3365 and 1664 cm^{-1}; δ_H (80 MHz) 1.25 (10H, m, C*H*$_2$ groups), 1.7 (14H, m, C*H*$_2$ groups), 3.2 (2H, br m, exch. D_2O, N*H* and O*H*), 3.7 (2H, t, *J* 6.2, C*H*$_2$OH) and 4.13 (2H, t, *J* 6.2, C*H*$_2$OC(=NR)NHR) ppm; *m/z* (CI) 297.2554: *calculated for* $[C_{17}H_{32}N_2O_2 + H]^+$ 297.2542 [*Found*: C 68.72, H 10.93, N 9.32%; $C_{17}H_{32}N_2O_2$ *requires* C 68.92, H 10.81, N 9.46%].

N,N-Dicyclohexyl-*O*-(6′-hydroxyhexyl)isourea 11

Hexane-1,6-diol (0.59 g) was reacted with dicyclohexylcarbodiimide (1.03 g) in a similar manner to that described above to yield the *isourea* **11** (1.48 g) as an *oil* which had ν_{max} (L) 3358 and 1667 cm^{-1}; δ_H (80 MHz) 1.25 (9H, m, C*H*$_2$ groups), 1.47 (7H, m, C*H*$_2$ groups), 1.72 (14H, m, C*H*$_2$ groups), 3.2 (2H, br m, exch. D_2O, N*H* and O*H*), 3.71 (2H, dt, *J* 6.5 and 2.0, C*H*$_2$OH) and 4.05 (2H, t, *J* 6.2, C*H*$_2$OC) ppm; *m/z* (CI) 325.2849; *calculated for* $[C_{19}H_{36}N_2O_2 + H]^+$ 325.2855 [*Found*: C 70.52, H 11.26, N 8.76%; $C_{19}H_{36}N_2O_2$ *requires* C 70.37, H 11.11, N 8.64%].

N,N-Dicyclohexyl-*O*-[(2*Z*)-4′-hydroxybut-2-enyl]isourea 12

(*Z*)-But-2-ene-1,4-diol **2a** (0.22 g), dicyclohexylcarbodiimide (0.54 g) and copper(I) chloride (20 mg) in chloroform (3 cm^3) and acetone (2 cm^3) were stirred together during 12 h. Hexane (15 cm^3) was added and the mixture was filtered and evaporated to yield a solid which was recrystallised from 2 : 3 ether–hexane to give the *isourea* **12** (0.45 g; 87%) as colourless crystals, mp 87.3–87.7 °C, which had ν_{max} (N) 3336, 1633 and 1055 cm^{-1}; δ_H (80 MHz) 1.22 (10H, m, C*H*$_2$ groups), 1.7 (10H, m, C*H*$_2$ groups), 2.7 (1H, br m, C*H*NHC–N), 3.4 (1H, br m, C*H*N=C–), 3.55 (1H, exch. D_2O, O*H*), 4.25 (2H, d, *J* 6.8, C*H*$_2$OH), 4.9 (2H, d, *J* 9.5, C*H*$_2$OC), 5.7 (2H, m, olefinic) and 6.8 (1H, br s, exch. D_2O, N*H*) ppm; δ_C (100.6 MHz) 151.9 (*C*=N), 132.8 (C=C), 125.1 (C=C), 60.1 (*C*H$_2$OH), 59.8 (*C*H$_2$OC), 55.3 (CH), 34.3 (CH$_2$), 34.2 (CH$_2$), 34.0 (CH$_2$), 25.6 (CH$_2$) and 24.9 (CH$_2$) ppm; *m/z* (CI): 295.2390; *calculated for* $[C_{17}H_{30}N_2O_2 + H]^+$ 295.2385.

2,5-Dihydrofuran

(*Z*)-But-2-ene-1,4-diol **2a** (88 mg) was dissolved in $CDCl_3$ (3 cm^3) to which was added 1,3-dicyclohexylcarbodiimide (225 mg; 1.1 eq.). Copper(I) chloride (5 mg) was added and the mixture was stirred at room temperature under a nitrogen atmosphere during 12 h. Trifluoroacetic acid (15 mg; 0.13eq.) was then added, and the mixture was heated to 40 °C during 6 h after which time the mixture was cooled and filtered to remove dicyclohexylurea. ^{1}H NMR spectroscopy of a sample which had been diluted with additional $CDCl_3$ revealed that all of the isourea **12** had been consumed and that the solution contained only 2,5-dihydrofuran together with traces of dicyclohexylurea.

Methyl 5-oxopentanoate 13a

δ-Valerolactone (5 g) was dissolved in methanol (100 cm^3) with concentrated sulfuric acid (2 cm^3) and the mixture was refluxed for 12 h. Methanol (60 cm^3) was evaporated under reduced pressure and the product was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate followed by brine, dried and evaporated to give an oil which was distilled, bp 90–93 °C (0.5 mmHg), to give methyl 5-hydroxypentanoate (4.8 g, 73%) as a colourless oil, ν_{max} (L) 3448 and 1736 cm^{-1}; δ_H (300 MHz) 1.55 (2H, m, C*H*$_2$), 1.66 (2H, m, C*H*$_2$), 2.31 (2H, t, *J* 7.3, C*H*$_2$CO$_2$), 2.45 (1H, br s, exch. D_2O, O*H*), 3.58 (2H, t, *J* 6.8, C*H*$_2$OH) and 3.62 (3H, s, CO$_2$C*H*$_3$) ppm. This hydroxyester (3.8 g) was added to a stirred solution of pyridinium chlorochromate (6.2 g) in dichloromethane (40 cm^3) and the resulting suspension was allowed to stir at room temperature during 1.5 h. Ether (40 cm^3) was added and the supernatant liquid decanted from a black gum. The insoluble residue was extracted thoroughly with ether, and the combined extract was filtered, evaporated and distilled to give the aldehydo-ester **13a** as an oil[20] (2.0 g), bp 80–84 °C (14 mmHg), ν_{max} (L) 2955, 1732, 1646, 1438, 1371, 1200, 1167, 1080 and 1006 cm^{-1}; δ_H (300 MHz) 1.93 (2H, m, 3-C*H*$_2$), 2.36 (2H, t, *J* 7.3, C*H*$_2$CO$_2$), 2.52 (2H, dt, *J* 7.3 and 1.3, C*H*$_2$CHO), 3.67 (3H, s, CO$_2$C*H*$_3$) and 9.75 (1H, t, *J* 1.3, C*H*O) ppm.

Methyl 6-oxohexanoate 13b

ε-Caprolactone (25.0 g) in methanol (250 cm^3) with concentrated sulfuric acid (2 cm^3) was left at room temperature during 48 h. Methanol (200 cm^3) was removed at reduced pressure and the product was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate solution followed by brine, dried, evaporated and distilled to give methyl 6-hydroxyhexanoate (27.95 g; 87%) as an oil, bp 92–95 °C (0.5 mmHg); ν_{max} (L) 3416, and 1738 cm^{-1}; δ_H (80 MHz) 1.8 (4H, m, C*H*$_2$ groups), 2.33 (2H, m, C*H*$_2$CO$_2$), 3.25 (1H, br s, exch. D_2O, O*H*), 3.55 (2H, m, C*H*$_2$OH) and 3.65 (3H, s, CO$_2$C*H*$_3$) ppm. This ester (5.11 g), in dichloromethane (10 cm^3), was added to a suspension of pyridinium chlorochromate (8.2 g) in dichloromethane (70 cm^3) and the mixture was stirred at room temperature during 2 h. Ether was added and the supernatant liquid decanted from a black gum. The insoluble residue was thoroughly extracted with ether, and the combined extract was evaporated and distilled to give methyl 6-oxohexanoate **13b** as a colourless oil[21] (3.88 g; 77%), bp 69–71 °C (0.5 mmHg); ν_{max} (L) 1739 cm^{-1}; δ_H (80 MHz) 1.8 (4H, m, C*H*$_2$ groups), 2.45 (4H, m, C*H*$_2$CO$_2$ and C*H*$_2$CHO), 3.7 (3H, s, CO$_2$C*H*$_3$) and 9.4 (1H, s, C*H*O) ppm; *m/z* (EI) 144.0793: *calculated for* $C_7H_{12}O_3$ 144.0787.

Methyl 7-oxoheptanoate 13c

Cycloheptene (7.2 g) was dissolved in a mixture of dichloromethane (250 cm^3) and methanol (50 cm^3) to which was added anhydrous sodium hydrogen carbonate (2 g). The stirred mixture was cooled to −78 °C and a stream of ozone was introduced. The addition of ozone was stopped once the solution had turned blue. The mixture was purged with nitrogen until the blue colour had disappeared, brought to room temperature, and filtered. Benzene (80 cm^3) was added, and the volume was reduced to approximately 50 cm^3 by evaporation at reduced pressure. After dilution with dichloromethane (225 cm^3) the mixture was cooled to 0 °C and triethylamine (16 cm^3) and acetic anhydride (21.25 cm^3) were added slowly with stirring. The solution was allowed to warm up gradually and was left stirring overnight. It was then washed sequentially with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and brine. Evaporation of the solvent followed by short path distillation of the crude product yielded **13c** as a colourless oil[22] (14.6 g; 62%), bp 82–85 °C (0.5 mmHg); ν_{max} (L) 1736 cm^{-1}; δ_H (400 MHz) 1.25 (2H, m, 3-C*H*$_2$), 1.57 (4H, m, 2- and 4-C*H*$_2$ groups), 2.24 (2H, t, *J* 7.5, C*H*$_2$CO$_2$Me), 2.37 (2H, dt, *J* 7.3 and 1.7, C*H*$_2$CHO), 3.59 (3H, s, CO$_2$C*H*$_3$) and 9.75 (1H, t, *J* 1.5, C*H*O) ppm.

Methyl 8-oxooctanoate 13d

Cyclooctene (8.25 g) was ozonized in a manner similar to that described for cycloheptene above to give methyl 8-oxooctanoate **13d** as a colourless oil[23] (10.6 g; 82%), bp 94–97 °C (0.5 mmHg); ν_{max} (L) 1738 cm^{-1}; δ_H (400 MHz) 1.42 (8H, m, C*H*$_2$ groups), 2.39 (4H, m, C*H*$_2$CHO and C*H*$_2$CO$_2$), 3.65 (3H, s, CO$_2$C*H*$_3$)

and 9.68 (1H, t, *J* 1.5, C*H*O) ppm; *m*/*z* (EI) 172.1104: *calculated for* $C_9H_{16}O_3$ 172.1099.

Methyl 9-oxononanoate 13e

Methyl oleate (22.4 g) was ozonised at −78 °C in dichloromethane (250 cm^3) and methanol (50 cm^3) containing anhydrous sodium carbonate (2 g) until the appearance of a blue colour. Nitrogen was then bubbled through the mixture to remove excess ozone and the cold bath was removed. The mixture was filtered and cooled to 0 °C, triethylamine (16 cm^3) was added, and the mixture was allowed to warm to room temperature. After 6 h, the mixture was washed with dilute HCl followed by brine. The extract was dried and evaporated to yield an oil which was fractionally distilled to give nonanal, bp 72–74 °C (17 mmHg) followed by the aldehydo-ester **13e** which was obtained as an oil[24] (6.0 g; 43%), bp 112–116 °C (0.6 mmHg); ν_{max} (L) 1741 cm^{-1}; δ_H (400 MHz) 1.32 (6H, m, CH_2 groups), 1.65 (4H, m, CH_2 groups), 2.36 (4H, m, CH_2CHO and C$H_2$$CO_2$Me), 3.70 (3H, s, CO_2CH_3) and 9.79 (1H, t, *J* 1.9, C*H*O) ppm; *m*/*z* (EI) 186.1249: *calculated for* $C_{10}H_{18}O_3$ 186.1256.

Methyl 10-oxodecanoate 13f

Methyl undec-10-enoate (15 g) was ozonised in a similar manner to that described above for methyl oleate. After work-up the crude product was distilled to yield methyl 10-oxodecanoate **13f** as a colourless oil[25] (9.94 g; 66%), bp 126–130 °C (0.5 mmHg), ν_{max} (L) 1740 cm^{-1}; δ_H (80 MHz) 1.5 (12H, m, CH_2 groups), 2.28 (4H, m, C$H_2$$CO_2$Me and C$H_2$CHO), 3.65 (3H, s, CO_2CH_3) and 9.80 (1H, t, *J* 1.5, C*H*O) ppm; *m*/*z* (EI) 200.1407: *calculated for* $C_{11}H_{20}O_3$ 200.1412.

3-(Tetrahydropyran-2′-yloxy)propyne[26]

Phosphorus oxychloride (180 mg) was added to a stirred mixture of freshly distilled propargyl (prop-2-ynyl) alcohol (14 g) and 2,3-dihydropyran (22.5 g) at 0 °C. The ice-bath was then removed and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with ether, washed with brine, dried and evaporated to yield 3-(tetrahydropyran-2′-yloxy)propyne as a colourless oil (30 g; 80%), bp 39–42 °C (0.5 mmHg), ν_{max} (L) 2122 cm^{-1}; δ_H (80 MHz) 1.55–1.68 (4H, m, CH_2 groups), 1.71–1.89 (2H, m, CH_2 group), 2.3 (1H, t, *J* 3.0, C≡CC*H*), 3.53 (1H, m, 6′-H_a), 3.82 (1H, m, 6′-H_b), 4.15 (2H, d, *J* 3.0, OCH_2–C≡C) and 4.95 (1H, m, 2′-*H*) ppm.

General procedure for the synthesis of methyl ω-(2′,5′-dihydro-2′-furyl)alkanoates 6a–6f

(a) Reaction of lithiated 3-(tetrahydropyran-2′-yloxy)propyne with aldehydo-esters 13a–13f; synthesis of the tetrahydropyranyl ethers 14a–14f. To a solution of 3-(tetrahydro-2′-pyranyloxy)-propyne (10 mmol) in dry THF (20 cm^3) at −78 °C was added *n*-BuLi (2.6 M in hexanes; 10 mmol) dropwise with stirring under an atmosphere of nitrogen. After 10 min one of the aldehydes **13a**–**13f** (10 mmol) in THF (5 cm^3) was added dropwise during 5 min. The reaction mixture was maintained at −78 °C for a further 15 min before being allowed to warm gradually to room temperature. It was then poured on to ice and extracted with ether. The combined extract was washed with brine, dried and evaporated to yield one of the tetrahydropyranyl ethers **14a**–**14f**.

(b) Deprotection of the tetrahydropyranyl ethers 14a–14f; synthesis of the diols 15a–15f. One of the tetrahydropyranyl ethers **14**–**14f** (5 mmol) was dissolved in methanol (70 cm^3) containing pyridinium toluene-*p*-sulfonate (PPTS)[27] (125 mg) and the resulting solution was stirred at 55 °C during 3 h. Ethanol (~50 cm^3) was removed under reduced pressure and the mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to yield one of the acetylenic diols **15a**–**15f**.

(c) Partial hydrogenation of the acetylenic diols 15a–15f; synthesis of the (*Z*)-dihydroxyesters 7a–7f. A solution of one of the acetylenic diols **15a**–**15f** (5 mmol) in methanol (10 cm^3) with quinoline (20 mg) was hydrogenated at 1 atm over Pd/$BaSO_4$ (5%w/w; 20 mg). After absorption of the calculated amount of hydrogen the reaction mixture was filtered through a pad of Celite which was then washed with ether. The combined mixture and washings were extracted with ethyl acetate, and the extract was washed sequentially with dilute HCl, aqueous sodium hydrogen carbonate and brine. The extract was dried and evaporated to yield one of the (*Z*)-olefinic diols **7a**–**7f**.

(d) Cyclodehydration of the (*Z*)-olefinic diols 7a–7f; synthesis of the dihydrofurans 6a–6f. One of the (*Z*)-olefinic diols **7a**–**7f** (1 mmol) was dissolved in chloroform (3 cm^3) with 1,3-dicyclohexylcarbodiimide (1.1 eq.). Copper(I) chloride (5 mg) was added and the mixture was stirred at room temperature under a nitrogen atmosphere during 12 h. Trifluoroacetic acid (0.13 eq.) was then added and the mixture was heated to 40 °C during 6 h. After this time hexane (10 cm^3) was added and the mixture was filtered to remove precipitated dicyclohexylurea. This was washed thoroughly with ethyl acetate and the washings added to the filtrate. Solvents were evaporated and the resulting oil was chromatographed using ethyl acetate–hexane 1 : 5 as eluant to yield one of the dihydrofuran derivatives **6a**–**6f**.

Methyl 5-hydroxy-8-(tetrahydropyran-2′-yloxy)oct-6-ynoate 14a. From 3-(tetrahydropyran-2′-yloxy)propyne and methyl 5-oxopentanoate; an *oil* (2.24 g; 83%).

Methyl 6-hydroxy-9-(tetrahydropyran-2′-yloxy)non-7-ynoate 14b. From 3-(tetrahydropyran-2′-yloxy)propyne and methyl 5-oxohexanoate; an *oil* (2.43 g; 86%).

Methyl 4-hydroxy-1-(tetrahydropyran-2′-yloxy)dec-2-ynoate 14c. From 3-(tetrahydropyran-2′-yloxy)propyne and methyl 5-oxoheptanoate; an *oil* (2.72 g; 87%).

Methyl 8-hydroxy-11-(tetrahydropyran-2′-yloxy)undec-9-ynoate 14d. From 3-(tetrahydropyran-2′-yloxy)propyne and methyl 5-oxooctanoate; an *oil* (2.26 g; 73%).

Methyl 9-hydroxy-12-(tetrahydropyran-2′-yloxy)dodec-10-ynoate 14e. From 3-(tetrahydropyran-2′-yloxy)propyne and methyl 5-oxononanoate; an *oil* (1.92 g; 62%).

Methyl 10-hydroxy-13-(tetrahydropyran-2′-yloxy)tridec-11-ynoate 14f. From 3-(tetrahydropyran-2′-yloxy)propyne and methyl 5-oxodecanoate; an *oil* (2.19 g; 70%).

Methyl 5,8-dihydroxyoct-6-ynoate 15a. From **14a** as an *oil* (0.72 g; 71%).

Methyl 6,9-dihydroxynon-7-ynoate 15b. From **14b** as an *oil* (0.83 g; 83%).

Methyl 7,10-dihydroxydec-8-ynoate 15c. From **14c** as an *oil* (0.99g; 93%).

Methyl 8,11-dihydroxyundec-9-ynoate 15d. From **14d** as an *oil* (1.04 g; 82%).

Methyl 9,12-dihydroxydodec-10-ynoate 15e. From **14e** as an *oil* (2.1 g; 87%).

Methyl 10,13-dihydroxytridec-11-ynoate 15f. From **14f** as an *oil* (0.92 g; 76%).

Methyl (*Z*)-5,8-dihydroxyoct-6-enoate 7a. From **15a** as an *oil* (0.81 g; 86%).

Methyl (*Z*)-6,9-dihydroxynon-7-enoate 7b. From **15b** as an *oil* (0.76 g; 75%).

Methyl (*Z*)-7,10-dihydroxydec-8-enoate 7c. From **15c** as an *oil* (0.95 g; 88%).

Methyl (*Z*)-8,11-dihydroxyundec-9-enoate 7d. From **15d** as an *oil* (1.04 g; 91%).

Methyl (*Z*)-9,12-dihydroxydodec-10-enoate 7e. From **15e** as an *oil* (0.96 g; 79%).

Methyl (*Z*)-10,13-dihydroxytridec-11-enoate 7f. From **15f** as an *oil* (1.11 g; 91%).

Methyl 4-(2′,5′-dihydro-2′-furyl)butanoate 6a. From **7a** as a colourless *oil* (89 mg; 52%), ν_{max} (L) 1737, 1080 and 1020 cm^{-1}; δ_H (300 MHz) 1.58 (2H, m, CH_2), 1.68 (2H, m, CH_2), 2.34 (2H, t, *J* 7.3, CH_2CO_2Me), 3.65 (3H, s, CO_2CH_3), 4.62 (2H, collapsed ABq with long range couplings, 5′-CH_2), 4.84 (1H, m, 2′-C*H*), 5.76 (1H, m, 4′-C*H*) and 5.76 (1H, m, 3′-C*H*) ppm; δ_C (75.5 MHz) 173.9 (*C*=O), 129.3 and 126.6 (–*C*=*C*–), 85.5 (2′-*C*H), 78.7 (5′-*C*H_2), 51.4 (–CO_2CH_3), 33.9 (–*C*H_2), 25.6 (–*C*H_2) and 20.5 (*C*H_2) ppm; *m*/*z* (EI): 170.0943: *calculated for* $C_9H_{14}O_3$ 170.0943.

Methyl 5-(2′,5′-dihydro-2′-furyl)pentanoate 6b. From **7b** as an *oil* (115 mg; 62%), ν_{max} (L) 1749, 1082 and 1020 cm^{-1}; δ_H (300 MHz) 1.5 (6H, m, CH_2 groups), 2.31 (2H, t, *J* 7.3, CH_2CO_2Me), 3.65 (3H, s, CO_2CH_3), 4.61 (2H, collapsed ABq with long range coupling, 5′-CH_2), 4.80 (1H, m, 2′-*H*), 5.76 (1H, m, 4′-*H*) and 5.87 (1H, m, 3′-*H*) ppm; δ_C (75.5 MHz) 174.2 (*C*=O), 129.6 and 126.5 (–*C*=*C*–), 85.8 (2′-*C*H), 75.0 (5′-*C*H_2), 51.5 (CO_2CH_3), 35.6 (*C*H_2), 34.0 (*C*H_2), 25.0 (*C*H_2) and 24.8 (*C*H_2) ppm; *m*/*z* (EI): 184.1100; *calculated for* $C_{10}H_{16}O_3$ 184.1099.

Methyl 6-(2′,5′-dihydro-2′-furyl)hexanoate 6c. From **7c** as an *oil* (0.12 g; 57%), ν_{max} (L) 1740, 1074, 1040 and 1020 cm^{-1}; δ_H (400 MHz) 1.4 (8H, m, CH_2 groups), 2.25 (2H, t, *J* 7.5, CH_2CO_2Me), 3.59 (3H, s, CO_2CH_3), 4.42 (2H, m, 5′-CH_2), 4.65 (1H, m, 2′-C*H*), 5.75 (1H, m, 3′-C*H*) and 5.87 (1H, m, 4′-C*H*) ppm; δ_C (100.6 MHz) 174.2 (*C*=O), 129.7 and 126.3 (–*C*=*C*–), 85.9 (2′-*C*H), 74.9 (5′-*C*H_2), 51.4 (CO_2CH_3), 35.7 (*C*H_2), 33.9 (*C*H_2), 29.1 (*C*H_2), 24.8 (*C*H_2) and 24.8 (*C*H_2) ppm; *m*/*z* (EI): 198.1262: *calculated for* $C_{11}H_{18}O_3$ 198.1256.

Methyl 7-(2′,5′-dihydro-2′-furyl)heptanoate 6d. From **7d** as an *oil* (131 mg; 62%), ν_{max} (L) 1740, 1072 and 1020 cm^{-1}; δ_H (300 MHz) 1.32 (6H, m, CH_2 groups), 1.51 (2H, m, CH_2), 1.61 (2H, m, CH_2), 2.29 (2H, t, *J* 7.4, CH_2CO_2Me), 3.65 (3H, s, CO_2CH_3), 4.60 (2H, collapsed ABq with long range couplings, 5′-CH_2), 4.79 (1H, m, 2′-*H*), 5.76 (1H, m, 4′-*H*) and 5.85 (1H, m, 3′-*H*) ppm; δ_C (75.5 MHz) 174.2 (*C*=O), 129.7 and 126.2 (–*C*=*C*–), 85.9 (2′-*C*H), 74.8 (5′-*C*H_2), 51.3 (CO_2CH_3), 35.8 (*C*H_2), 34.0 (*C*H_2), 29.2 (*C*H_2), 29.0 (*C*H_2), 24.9 (*C*H_2) and 24.8 (*C*H_2) ppm; *m*/*z* (CI): 213.1498 *calculated for* $[C_{12}H_{20}O_3 + H]^+$ 213.1491.

Methyl 8-(2′,5′-dihydro-2′-furyl)octanoate 6e. From **7e** as an *oil* (0.13 g; 57%), ν_{max} (L) 1734, 1076 and 1020 cm^{-1}; δ_H (400 MHz) 1.31–1.75 (12H, m, 6 CH_2 groups), 2.35 (2H, t, *J* 7.5, CH_2CO_2Me), 3.65 (3H, s, CO_2CH_3), 4.52 (2H, collapsed ABq with long range couplings, 5′-CH_2), 4.75 (1H, m, 2′-*H*), 5.74 (1H, m, 4′-*H*) and 5.86 (1H, m, 3′-*H*) ppm; δ_C (100.6 MHz) 173.8 (*C*=O), 129.4 and 125.8 (–*C*=*C*–), 85.6 (2′-*C*H), 74.5 (5′-*C*H_2), 50.9 (CO_2CH_3), 35.5 (*C*H_2), 33.6 (*C*H_2), 29.0 (*C*H_2), 28.7 (*C*H_2), 28.6 (*C*H_2), 24.7 (*C*H_2) and 24.5 (*C*H_2) ppm; *m*/*z* (CI): 227.1652: *calculated for* $[C_9H_{14}O_3 + H]^+$ 227.1647.

Methyl 9-(2′,5′-dihydro-2′-furyl)nonanoate 6f. From **7f** as an *oil* (134 mg; 56%), ν_{max} (L) 1740, 1074 and 1020 cm^{-1}; δ_H (300 MHz) 1.22 (10H, m, CH_2 groups), 1.52 (2H, m, CH_2), 1.89 (2H, m, CH_2), 2.22 (2H, t, *J* 7.3, CH_2CO_2Me), 3.64 (3H, s, CO_2CH_3), 4.60 (2H, collapsed ABq with long range couplings, 5′-CH_2), 4.78 (1H, m, 2′-*H*), 5.76 (1H, m, 4′-*H*) and 5.85 (1H, m, 3′-*H*) ppm; δ_C (100.6 MHz) 184.4 (*C*=O), 130.8 and 129.4 (–*C*=*C*–), 85.6 (2′-*C*H), 74.4 (5′-*C*H_2), 50.9 (CO_2CH_3), 35.6 (*C*H_2), 33.6 (*C*H_2), 29.2 (*C*H_2), 28.9 (*C*H_2), 28.7 (*C*H_2), 24.8 (*C*H_2) and 24.5 (*C*H_2) ppm. [*Found*: C 69.52, H 9.93%; $C_{14}H_{24}O_3$ *requires* C 69.96, H 10.07%].

Reaction of methyl (*Z*)-7,10-dihydroxydec-8-enoate 7c with DCC–CuCl

The (*Z*)-olefinic diol **7c** (1 mmol) was dissolved in $CDCl_3$ (3 cm^3) with 1,3-dicyclohexylcarbodiimide (1.1 eq.). Copper(I) chloride (5 mg) was added and the mixture was stirred at room temperature under a nitrogen atmosphere during 12 h. Hexane (5 cm^3) and ether (5 cm^3) were then added and the mixture was filtered and evaporated to give an oil (184 mg) which contained (NMR) the isourea **16** (75%) [δ_H for 10-CH_2 = 4.81 ppm] and the isourea **17** (25%) [δ_H for 7-C*H* = 5.61 ppm].

Competitive reaction of 1-phenylethanol and 2-phenylethanol with DCC–CuCl: selective formation of *N*,*N*-dicyclohexyl-*O*-(2′-phenylethyl)isourea

1-Phenylethanol (0.49 g; 4 mmol) and 2-phenylethanol (0.49 g; 4 mmol) were added to DCC (0.82 g; 4 mmol) in chloroform (10 cm^3) with copper(I) chloride (30 mg). The reaction mixture was stirred under a nitrogen atmosphere during 6 h. Hexane (5 cm^3) and ether (5 cm^3) were added and the mixture was filtered and evaporated to give an oil (1.54 g) which contained (NMR) *N*,*N*-dicyclohexyl-*O*-(2′-phenylethyl)isourea **18** (91%) [CH_2O–C=N appears at δ_H 4.24 ppm as 2H, t, *J* 6.8] and *N*,*N*-dicyclohexyl-*O*-(1′-phenylethyl)isourea (9%) [PhC*H*O–C=N appears at δ_H 5.95 ppm as 1H, q, *J* 6.5], together with unreacted 1-phenylethanol.

Competitive reaction of propan-1-ol and propan-2-ol with DCC–CuCl

Propan-1-ol (0.22 g; 3.6 mmol) and propan-2-ol (0.22 g; 3.6 mmol) were reacted under nitrogen with DCC (0.75 g; 3.6 mmol) and copper(I) chloride (30 mg) in chloroform 10 cm^3 during 5 h. Hexane (5 cm^3) and ether (5 cm^3) were added and the mixture was filtered and evaporated to yield a viscous oil (1.1 g) which contained (NMR) *N*,*N*-dicyclohexyl-*O*-(propyl)-isourea **19** (90%) [CH_2O–C=N appears at δ_H 3.95 ppm as 2H, t, *J* 6.6] and *N*,*N*-dicyclohexyl-*O*-(2′-methylethyl)isourea (10%) [Me_2C*H*O–C=N appears at δ_H 4.95 ppm as 1H, septet, *J* 6.6], together with unreacted propan-2-ol.

Synthesis of the acetylenic acetals 22a–22g

The general procedure utilised for the synthesis of the tetrahydropyranyl ethers **14a**–**14f** described above was employed.

4-Hydroxy-1-(tetrahydropyran-2′-yloxy)dec-2-yne 22a. From 3-(tetrahydropyran-2′-yloxy)propyne and heptanal; an *oil* (2.24 g; 88%).

4-Hydroxy-1-(tetrahydropyran-2′-yloxy)tridec-2-yne 22b. From 3-(tetrahydropyran-2′-yloxy)propyne and decanal; an *oil* (2.46 g; 83%).

2-Hydroxy-1-phenyl-5-(tetrahydropyran-2′-yloxy)pent-3-yne 22c. From 3-(tetrahydropyran-2′-yloxy)propyne and phenylacetaldehyde; an *oil* (2.36 g; 91%).

4-Hydroxy-6-phenyl-1-(tetrahydropyran-2′-yloxy)hex-2-yne 22d. From 3-(tetrahydropyran-2′-yloxy)propyne and 3-phenylpropanal; an *oil* (2.28 g; 83%).

1-Hydroxy-1-phenyl-4-(tetrahydropyran-2′-yloxy)but-2-yne 22e. From 3-(tetrahydropyran-2′-yloxy)propyne and benzaldehyde; an *oil* (2.33 g; 95%).

1-Hydroxy-1-(2′-methoxyphenyl)-4-(tetrahydropyran-2″-yloxy)but-2-yne 22f. From 3-(tetrahydropyran-2′-yloxy)-propyne and 2-methoxybenzaldehyde; an *oil* (2.5 g; 91%).

(*E*)-3-Hydroxy-1-phenyl-6-(tetrahydropyran-2′-yloxy)hex-1-en-4-yne 22g. From 3-(tetrahydropyran-2′-yloxy)propyne and cinnamaldehyde; an *oil* (2.1 g; 80%).

Hydrolysis of the acetylenic acetals 22a–22g

The general procedure described above which was utilised for the synthesis of the acetylenic diols **15a**–**15f** was employed.

1,4-Dihydroxydec-2-yne 21a. From **22a** as an oil[28] (0.64 g; 75%).

1,4-Dihydroxytridec-2-yne 21b. From **22b** as an *oil* (0.85 g; 80%).

2,5-Dihydroxy-1-phenylpent-3-yne 21c. From **22c** as an oil[29] (0.76g; 86%).

1,4-Dihydroxy-6-phenylhex-2-yne 21d. From **22d** as an oil[30] (0.81 g; 85%).

1,4-Dihydroxy-1-phenylbut-2-yne 21e. From **22e** as needles (0.68 g; 84%), mp 82.0–82.3 °C (*lit.*[31] mp 83–85 °C).

4-Hydroxy-1-methoxy-1-(2′-methoxyphenyl)but-2-yne 23. Obtained from **22f** as an *oil* (0.82 g; 73%), bp 169–172 °C (0.5 mmHg); ν_{max} (L) 3401, 1601, 1590, 1248, 1098 and 765 cm^{-1}; δ_H (80 MHz) 1.8 (1H, br s, exch. D_2O, O*H*), 3.4 (3H, s, OCH_3), 3.8 (3H, s, ArOCH_3), 4.15 (2H, d, *J* 2.2, HOCH_2C≡C), 5.45 (1H, t, *J* 2.2, C*H*OCH$_3$), 6.95 (2H, m, Ar*H*), 7.23 (1H, m, Ar*H*) and 7.62 (1H, m, Ar*H*) ppm; *m*/*z* (EI): 206.0934: *calculated for* $C_{12}H_{14}O_3$ 206.0943. [*Found*: C 69.56, H 6.88%; $C_{12}H_{14}O_3$ *requires* C 69.90, H 6.79%].

1,4-Dihydroxy-1-(2′-methoxyphenyl)but-2-yne 21f. The tetrahydropyranyl ether **22f** (1.38 g) was dissolved in 50% aqueous THF (80 cm^3) containing pyridinium toluene-*p*-sulfonate (0.5 g) and the mixture was stirred at 55 °C during 3 h. The mixture was diluted with water and extracted with ethyl acetate, and the extract was washed, dried and evaporated to yield the *diol* **21f** (0.47 g; 49%), mp 115.9–116.4 °C, ν_{max} (N) 3256, 1601, 1589, 1048, 1023 and 759 cm^{-1}; δ_H (80 MHz) 1.9 (1H, br s, exch. D_2O, O*H*), 3.06 (1H, br s, exch. D_2O, O*H*), 3.9 (3H, s, ArOCH_3), 4.28 (2H, d, *J* 2.0, HOCH_2C≡C), 5.78 (1H, s, C*H*OH), 6.95 (2H, m, Ar*H*), 7.30 (1H, m, Ar*H*) and 7.81 (1H, m, Ar*H*) ppm; *m*/*z* (EI): 192.0779: *calculated for* $C_{11}H_{12}O_3$ 192.0786. [*Found*: C 68.66, H 6.38%; $C_{11}H_{12}O_3$ *requires* C 68.75, H 6.25%].

(*E*)-3,6-Dihydroxy-1-phenylhex-1-en-4-yne 21g. This was obtained as an *oil* (0.7 g; 69%) by hydrolysis of **22g** using PPTS in aqueous THF; ν_{max} (L) 3269, 1620, 1601, 1597, 1078, 1063, 1015, 845, 746 and 687 cm^{-1}; δ_H (80 MHz) 1.50 (2H, br s, exch. D_2O, O*H*), 4.25 (2H, d, *J* 2.1, HOCH_2C≡C), 5.05 (1H, d, *J* 5.6, C*H*OH), 6.24 (1H, dd, *J* 15.2 and 5.7, 3-*H*), 6.68 (1H, d, *J* 15.2, 2-*H*) and 7.34 (5H, m, Ar*H*) ppm; *m*/*z* (EI): 188.0841: *calculated for* $C_{12}H_{12}O_2$ 188.0837. [*Found*: C 76.81, H 6.29%; $C_{12}H_{12}O_2$ *requires* C 76.59, H 6.38%]. Attempted hydrolysis of **22g** using PPTS–methanol led to a mixture containing (NMR) a 66 : 33 mixture of the dimethoxy compound **24** and the acetylenic diol **21g**.

Hydrogenation of the acetylenic diols 21a–21f

The general procedure described above which was utilised for the synthesis of the (*Z*)-olefinic diols **7a**–**7f** was employed.

(*Z*)-1,4-Dihydroxydec-2-ene 2b. From **21a** as an oil[32] (156 mg; 90%).

(*Z*)-1,4-Dihydroxytridec-2-ene 2c. From **21b** as an *oil* (0.9 g; 85%).

(*Z*)-2,5-Dihydroxy-1-phenylpent-3-ene 2d. From **21c** as a solid[33] (0.82 g: 92%), mp 61.8–62.1 °C.

(*Z*)-1,4-Dihydroxy-6-phenylhex-2-ene 2e. From **21d** as an *oil* (0.84 g; 88%).

(*Z*)-1,4-Dihydroxy-1-phenylbut-2-ene 2f. The acetylenic diol **21e** (5 mmol) was hydrogenated at 1 atm in methanol (10 cm^3) containing quinoline (20 mg) and triethylamine (0.5 mg) with Pd/$CaCO_3$ (5%w/w; 20 mg) to give the diol **2f** as needles (0.44 g; 53%), mp 70.9–71.2 °C (*lit.*[31] mp 73–75 °C), ν_{max} (N) 3253, 1040, 1025, 737 and 700 cm^{-1}; δ_H (80 MHz) 1.95 (2H, br s, exch. D_2O, O*H*), 4.30 (2H, collapsed ABq, HOCH_2C≡C), 5.55 (1H, m, C*H*OH), 5.79 (2H, m, olefinic) and 7.36 (5H, m, Ar*H*) ppm.

(*Z*)-1,4-Dihydroxy-1-(2′-methoxyphenyl)but-2-ene 2g. The acetylenic diol **21f** (5 mmol) was hydrogenated as described for **21e** above to give a *solid* (0.15 g; 83%), mp 91.8–92.3 °C, ν_{max} (N) 3249, 1640, 1598, 1038, 699 and 672 cm^{-1}; δ_H (300 MHz) 2.14 (2H, br s, exch. D_2O, O*H*), 3.84 (3H, s, OCH_3), 4.18 (1H, dd, *J* 13.6 and 4.8, HOCH_{2a}C≡C), 4.36 (1H, dd, *J* 13.5 and 6.2, HOCH_{2b}C≡C), 5.75 (3H, m, C*H*OH, *H*-2 and *H*-3), 6.89 (1H, dd, *J* 8.2 and 1.0, Ar 3′-*H*), 6.98 (1H, t, *J* 7.4, Ar 4′-H), 7.27 (1H, dt, *J* 7.4 and 1.8, Ar 5′-*H*) and 7.38 (1H, dd, 7.6 and 1.7, Ar 6′-*H*) ppm; δ_C (75 MHz) 156.1 (quaternary), 133.4 (*C*H), 130.8 (quaternary), 129.7 (*C*H), 129.6 (*C*H), 126.7 (*C*H), 121.0 (C=C), 110.5 (C=C), 65.9 (*C*H), 58.4 (*C*H_2) and 55.3 (*C*H_3) ppm. [Found: C 68.00, H 7.35%; $C_{11}H_{14}O_3$ *requires* C 68.02, H 7.27%].

Cyclisation of the olefinic diols 2b–2g

The general procedure described above for the synthesis of the 2-substituted-2,5-dihydrofurans **6a**–**6f** was employed.

2-Hexyl-2,5-dihydrofuran 1b. From **2b** as an oil[34] (124 mg; 81%), ν_{max} (L) 1077 cm^{-1}; δ_H (300 MHz) 0.87 (3H, t, *J* 6.8, CH_3), 1.2 (8H, m, CH_2 groups), 1.52 (2H, m, CH_2), 4.62 (2H, m, 5-CH_2), 4.81 (1H, m, 2-*H*), 5.77 (1H, m, 4-*H*) and 5.81 (1H, m, 3′-*H*) ppm.

2-Nonyl-2,5-dihydrofuran 1c. From **2c** as an oil[35] (175 mg; 90%), ν_{max} (L) 1071 cm^{-1}; δ_H (300 MHz) 0.87 (3H, t, *J* 6.7, CH_3), 1.25 (12H, m, CH_2 groups), 1.6 (2H, m, CH_2), 4.63 (2H, m, 5-CH_2), 4.8 (1H, m, 2-C*H*), 5.77 (1H, m, 4-*H*) and 5.86 (1H, m, 3-*H*) ppm.

2-Benzyl-2,5-dihydrofuran 1d. From **2d** as an *oil* (142 mg; 89%), ν_{max} (L) 3032, 1071, 746 and 699 cm^{-1}; δ_H (300 MHz) 2.85 (2H, dd, *J* 13.4 and 6.4, CH_{2a}Ph), 2.94 (2H, dd, *J* 13.4 and 6.1, –CH_{2b}Ph), 4.64 (2H, collapsed ABq with long range couplings, 5-CH_2), 5.08 (1H, m, 2-C*H*), 5.79 (1H, m, 4-*H*), 5.88 (1H, m, 3-*H*) and 7.27 (5H, m, Ar*H*) ppm. [Found: C 82.51, H 7.55%; $C_{11}H_{12}O$ *requires* C 82.46, H 7.55%].

2-(2′-Phenylethyl)-2,5-dihydrofuran 1e. From **2e** as an *oil* (112 mg; 64%), ν_{max} (L) 1624, 1603, 1077, 748 and 699 cm^{-1};

δ_H (300 MHz) 1.9 (2H, m, 1′-CH_2), 2.73 (2H, m, 2′-CH_2), 4.68 (2H, m, 5-CH_2), 4.88 (1H, m, 2-*H*), 5.79 (1H, m, 4-*H*), 5.91 (1H, m, 3-*H*) and 7.23 (5H, m, Ar*H*) ppm; *m*/*z* (EI): 174.1037: *calculated for* $C_{12}H_{14}O$ 174.1045. [*Found*: C 82.66, H 8.28%; $C_{12}H_{14}O$ *requires* C 82.76, H 8.05%].

2-Phenyl-2,5-dihydrofuran 1f. From **2f** as an *oil* (115 mg; 79%), ν_{max} (L) 1606, 1073, 699 and 648 cm^{-1}; δ_H (300 MHz) 4.78 (1H, ABq with further coupling, 5-H_a), 4.89 (1H, ABq with further coupling, 5-H_b), 5.80 (1H, m, 2-*H*), 5.89 (1H, m, 3-*H*), 6.04 (1H, m, 4-*H*) and 7.35 (5H, m, Ar*H*) ppm; *m*/*z* (EI): 146.0725: *calculated for* $C_{10}H_{10}O$ 146.0732. [*Found*: C 82.34, H 6.68%; $C_{10}H_{10}O$ *requires* C 82.19, H 6.85%].

2-(2′-Methoxyphenyl)-2,5-dihydrofuran 1g. From **2g** as an *oil* (0.76 g; 86%); ν_{max} (L) 1600, 1589, 1241, 1067, 1048, 1027, 754 and 666 cm^{-1}; δ_H (300 MHz) 3.86 (3H, s, OCH_3), 4.79 (1H, ABq with further coupling, 5-H_a), 4.87 (1H, ABq with further coupling, 5-H_b), 5.97 (2H, m, 3- and 4-*H*), 6.15 (1H, m, 2-*H*), 6.87 (1H, d, *J* 8.1, 3′-*H*), 6.96 (1H, dt, *J* 7.5 and 0.9, 4′-*H*), 7.27 (1H, dt, *J* 7.5 and 1.8, 5′-*H*) and 7.36 (1H, dd, *J* 7.5 and 1.8, 6′-*H*) ppm. [Found: C 75.04, H 7.07%; $C_{11}H_{12}O_2$ *requires* C 74.98, H 6.86%].

1,4-Dihydroxy-1-phenylbutane 25

The olefinic diol **2f** (0.32 g) was hydrogenated at 1 atm in ethyl acetate (10 cm^3) containing triethylamine (0.5 mg) with Pd/C (5%w/w; 20 mg) to give, after recrystallisation from chloroform, a solid, mp 73–74 °C, (*lit.*[36] 75 °C) (167 mg; 51%), which had ν_{max} (N) 3329, 1606, 769 and 704 cm^{-1}; δ_H (300 MHz) 1.65 (2H, m, 3-CH_2), 1.84 (2H, m, 2-CH_2), 2.78 (2H, br s, exch. D_2O, O*H* groups), 3.64 (2H, m, CH_2OH), 4.69 (1H, t, *J* 7.0, C*H*OH) and 7.31 (5H, m, Ar*H*) ppm.

2-Phenyltetrahydrofuran 26

The diol **25** (170 mg) was treated with DCC–CuCl and then with trifluoroacetic acid as described above for the olefinic diols **7a**–**7f** to yield the tetrahydrofuran **26** (106 mg; 72%) as an oil,[37] ν_{max} (L) 1604, 1057, 1028, 757 and 700 cm^{-1}; δ_H (300 MHz) 1.8, 2.02 and 2.3 (1H, 2H and 1H, ms, CH_2 groups), 3.95 (1H, part of ABq, J_{gem} 13.8, 5-CH_{2a}), 4.13 (1H, part of ABq, J_{gem} 13.8, 5-CH_{2b}), 4.9 (1H, t, *J* 7.0, 2-*H*), 7.25 (1H, m, Ar*H*) and 7.34 (4H, m, Ar*H*) ppm.

Methyl 6,9-dihydroxynonanoate 27

Methyl 6,9-dihydroxynon-7-ynoate **15b** (1.2 g) was hydrogenated in ethyl acetate (25 cm^3) over 5% Pd/C (30 mg) until uptake of hydrogen had ceased. The usual work up afforded methyl 6,9-dihydroxynonanoate **27** as an *oil* (1.1 g; 94%), ν_{max} (L) 3247, 1734, 1166 and 1048 cm^{-1}; δ_H (300 MHz) 1.28 (8H, m, CH_2 groups), 1.46 (2H, m, CH_2 group), 2.15 (2H, br s, exch. D_2O, O*H*), 2.29 (2H, t, *J* 6.4, CH_2CO_2Me) and 3.62 (3H, m, CH_2OH and C*H*OH) ppm; δ_C (75.5 MHz) 174 (*C*=O), 72 (*C*H), 63.9 (*C*H_2), 52.4 (*C*H_3), 38.1 (*C*H_2), 34.0 (*C*H_2), 29.4 (*C*H_2), 28.7 (*C*H_2), 25.4 (*C*H_2) and 24.9 (*C*H_2) ppm; *m*/*z* (EI): 204.1369: *calculated for* $C_{10}H_{20}O_4$ 204.1362.

Methyl 5-(tetrahydro-2′-furyl)pentanoate 28

Methyl 6,9-dihydroxynonanoate **27** (0.2 g) was treated with DCC–CuCl and then with trifluoroacetic acid as described above for the saturated diol **25** to yield the tetrahydrofuran **28** as an *oil* (158 mg; 85%), ν_{max} (L) 1741, 1198, 1169 and 1058 cm^{-1}; δ_H (400 MHz) 1.29 (8H, m, CH_2 groups), 1.36–1.49 (2H, m, CH_2 groups), 2.28 (2H, t, *J* 7.3, CH_2CO_2Me), 3.64, (3H, s, CO_2CH_3), 3.69 (1H, m, part of ABq, 5-CH_{2a}), 3.75 (1H, m, part of ABq, 5-CH_{2b}) and 3.84 (1H, m, 2-*H*) ppm; δ_C 173.6 (*C*=O), 78.7 (*C*H), 66.8 (*C*H_2), 51.1 (*C*H_3), 35.3 (*C*H_2), 33.7 (*C*H_2), 30.8 (*C*H_2), 28.6 (*C*H_2), 28.5 (*C*H_2) and 24.5 (*C*H_2) ppm; *m*/*z* (EI): 186.1261: *calculated for* $C_{10}H_{18}O_3$ 186.1256.

Methyl 6,9-dihydroxydecanoate 29

But-1-yn-3-ol was converted into its tetrahydropyranyl ether, bp 50–52 °C at 0.5 mmHg, as described above for the THP derivative of propynol. To this (4.4 g), at −78 °C in dry THF (40 cm^3), was added *n*-BuLi (2.5 M; 11.5 cm^3). After 10 min at −78 °C a solution of methyl 6-oxohexanoate (4.2 g) in THF (20 cm^3) was added dropwise. The mixture was allowed to warm to room temperature and worked up in the usual way to give *methyl 5-hydroxy-2-(tetrahydropyran-2′-yloxy)dec-3-ynoate* as an *oil* (7.8 g), ν_{max} (L) 3448, 1740 and 1020 cm^{-1}; δ_H (400 MHz) (major diastereoisomer) 1.54 (3H, d, *J* 6.6, CH_3), 1.69 (6H, m, CH_2 groups), 2.39 (6H, m, CH_2 groups), 2.58 (2H, t, *J* 6.6, CH_2CO_2Me), 2.87 (1H, br s, exch. D_2O, O*H*), 3.67 (3H, s, OCH_3), 3.70 (2H, m, 6′-CH_2), 4.12 (1H, q, *J* 6.5, 2-*H*), 4.35 (1H, t, *J* 5.4, 5-*H*) and 4.72 (1H, m, 2′-*H*) ppm. The above tetrahydropyranyl ether (7.8 g) was treated during 3 h at 50 °C with PPTS (0.25 g) in methanol (200 cm^3) after which time the usual work up afforded methyl 2,5-dihydroxydec-3-ynoate as an *oil* (4.7 g), ν_{max} (L) 3418 and 1740 cm^{-1}; δ_H (400 MHz) (major diastereoisomer) 1.48 (3H, d, *J* 6.6, CH_3), 1.39–1.51 (6H, m, CH_2 groups), 2.34 (2H, t, *J* 6.5, CH_2CO_2Me), 2.38 (2H, br s, exch. D_2O, OH groups), 3.70 (3H, s, CO_2CH_3) and 4.25–4.48 (2H, m, C*H*OH) ppm. The above acetylenic diol (4.7 g), in methanol (70 cm^3), was hydrogenated at 1 atm over 5% Pd/C (0.3 g) until hydrogen uptake had ceased. Filtration, followed by evaporation of solvent gave *methyl 6,9-dihydroxydecanoate* **29** as an *oil* (4.6 g), ν_{max} (L) 3392 and 1737 cm^{-1}; δ_H (300 MHz) (major diastereoisomer) 1.16 (3H, d, *J* 6.2, CH_3), 1.48 (4H, m, CH_2 groups), 2.16 (6H, m, CH_2 groups), 2.18 (2H, br s, exch. D_2O, O*H* groups), 2.29 (2H, t, *J* 7.4, CH_2CO_2Me), 3.56 (1H, m, 6-*H*), 3.59 (3H, s, CO_2CH_3) and 3.78 (1H, m, 9-*H*) ppm; δ_C (75.5 MHz) (major diastereoisomer) 174.3 (*C*=O), 71.7 (6-*C*H), 68.2 (9-*C*H), 51.4 (CO_2CH_3), 34.8 (7-*C*H_2), 34.5 (8-*C*H_2), 37.2, 35.2, 25.2, 24.9 (*C*H_2 groups) and 23.6 (*C*H_3) ppm; *m*/*z* (CI): 219.1603: *calculated for* $[C_{11}H_{22}O_4 + H]^+$ 219.1596.

Methyl 5-(5′-methyltetrahydro-2′-furyl)pentanoate 30

The diol **29** (1.0 g) and dicyclohexylcarbodiimide (0.97 g), in chloroform (20 cm^3) were stirred with copper(I) chloride (25 mg) during 24 h. Trifluoroacetic acid (68 mg) was then added and the mixture was refluxed for 6 h. The solution was cooled, diluted with hexane (40 cm^3), filtered through Celite and evaporated to give a crude product which was chromatographed over silica gel to yield a 1.4 : 1 mixture of diastereoisomers of *methyl 5-(5′-methyltetrahydro-2′-furyl)pentanoate* **30** as an *oil* (0.38 g; 33%), ν_{max} (L) 1740 cm^{-1}; δ_H (400 MHz) 1.13 (1.75H, d, *J* 6.2, CH_3 {major}), 1.16 (1.25H, d, *J* 6.2, CH_3 {minor}), 1.4 (5H, m, CH_2 groups), 1.58 (3H, m, CH_2 groups), 2.24 (2H, t, *J* 7.5, CH_2CO_2Me), 3.58 (3H, s, CO_2CH_3) and 3.62–4.06 (2H, overlapping ms, 2′-*H* and 5-*H*) ppm; δ_C (100.6 MHz) (major diastereoisomer) 174 (*C*=O), 79.1 (5′-*C*), 75.0 (2′-*C*), 51.3 (CO_2CH_3), 32.7 (*C*H_2), 31.2 (*C*H_2), 35.7 (*C*H_2), 33.9 (*C*H_2), 25.7 (*C*H_2), 24.9 (*C*H_2) and 21.2 (*C*H_3) ppm; *m*/*z* (CI): 201.1491: *calculated for* $[C_{11}H_{20}O_3 + H]^+$ 201.1491.

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