Stereoselective reduction of chiral 2-furoic acid derivatives using group I metals in ammonia

Timothy J. Donohoe,*[a] Andrew A. Calabrese,[a] Clare A. Stevenson[a] and Tamara Ladduwahetty[b]

[a] *Department of Chemistry, The University of Manchester, Oxford Road, Manchester, UK M13 9PL. E-mail: t.j.donohoe@man.ac.uk*
[b] *Merck Sharp and Dohme, Neuroscience Research Centre, Terlings Park, Harlow, Essex, UK CM20 2QR*

Received (in Cambridge, UK) 4th August 2000, Accepted 5th September 2000
First published as an Advance Article on the web 30th October 2000

A series of chiral auxiliaries have been attached to 2-furoic acid and 3-methyl-2-furoic acid. The performance of these auxiliaries in the Birch reduction was assessed and it was found that placing a C-3 methyl group on the heterocycle was essential for good stereoselectivity. Using bis(methoxymethyl)pyrrolidine high levels of diastereoselectivity could be obtained with a range of electrophiles. A model is also presented which explains the sense of stereoselectivity displayed by this auxiliary. After reduction, the auxiliaries could be removed by reaction with acid to furnish dihydrofuran-based carboxylic acids with high enantiomeric excess.

Introduction

The partial reduction of aromatic heterocycles is a useful reaction for the synthesis of stereochemically defined ring systems containing oxygen and nitrogen.[1] Although the Birch reduction has been extensively studied in its application to carbocyclic compounds,[2] the use of this reduction on heterocycles is more limited. We have recently reported the results of a study designed to investigate the partial reduction process (usually–but not always–manifested as the Birch reduction) as applied to heterocycles such as pyrrole,[3] pyridine,[4] and furan.[5]

If we are going to use our methodology in synthesis then it is imperative that we are able to control absolute stereochemistry as well as relative. Perhaps the simplest way of controlling absolute stereochemistry in such reductions is to insert a chiral auxiliary, bound to an acyl group on the heterocycle, prior to reduction. This type of system has been studied extensively by Schultz who reported the stereoselective reductive alkylation of a variety of auxiliary-laden benzoic acid derivatives.[6] In this paper we wish to provide a full account of our studies on chiral derivatives of 2-furoic acid, **1**, Fig. 1.[7] Although the Birch reduction of 2-furoic acid derivatives has been reported before,[8] we are aware of only one (marginally successful) attempt to control the stereoselectivity of this reaction.[9] We initially undertook the sequence described in Fig. 1 as the products **2** and **3** should prove to be useful intermediates in natural product synthesis.

Results and discussion

Following the work of Schultz, we began by attaching (*S*)-methoxymethylpyrrolidine to 2-furoic acid **4** and performing a reductive methylation reaction on the known amide **5**, Scheme 1.[9] Unfortunately, this reaction gave a mixture of diastereoisomers and was characterised by low yields of dihydrofurans (possibly with ring opened products present in the reaction mixture). While we were able to isolate the desired

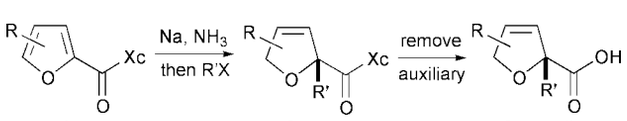
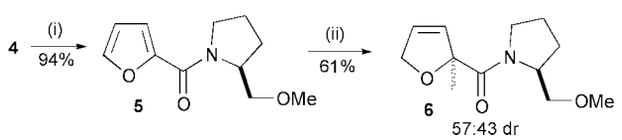


Fig. 1



Scheme 1 *Reagents*: i. $SOCl_2$ then (*S*)-methoxymethylpyrrolidine, CH_2Cl_2, NaOH; ii. Na, NH_3, then MeI.

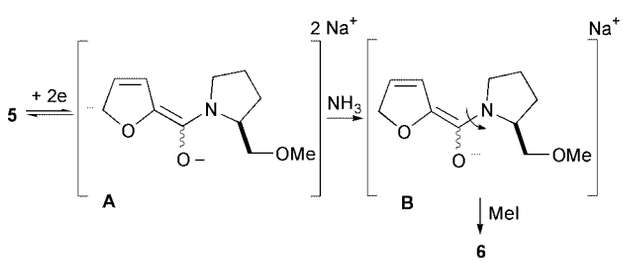


Fig. 2

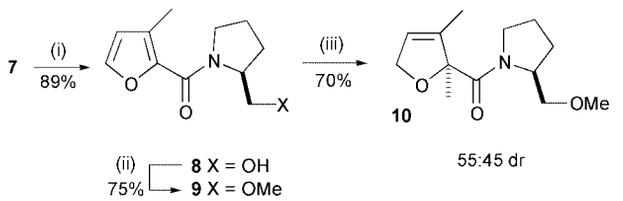
product in 61% yield, it was formed as near to a 1 : 1 mixture of diastereoisomers (as measured by ^{1}H NMR and GC analysis) under all conditions investigated (changing the reducing agent to Li metal gave 61 : 39 dr, 33% yield). This result is close to that reported by Kinoshita who also investigated this auxiliary bound to 2-furoic acid.[9]

The mechanism for the reduction is outlined in Fig. 2 and the salient points are the formation of a reactive dianion by addition of two electrons to the heterocycle; this can then deprotonate ammonia and yield a corresponding enolate **B**. We postulate the formation of a reactive dianion **A** because these Birch reductions proceed without addition of a proton source such as an alcohol and it seems unlikely that a radical anion itself would be basic enough to deprotonate ammonia. Reaction of enolate **B** occurs when an external electrophile is added to the system and like most extended enolates it displays a strong penchant for reaction at the *alpha* position.[10] We reasoned that the lack of selectivity observed in the reduction of **5** had its origins in the formation of a mixture of enolate geometric isomers. Under such circumstances, the auxiliary cannot then be expected to promote the formation of a single diastereoisomer upon reaction with an electrophile.

Our tactic for controlling the enolate geometry within **B** was to introduce a substituent at C-3 as Schultz had shown that an

 DOI: 10.1039/b006390h

ortho-methyl group was sufficient to control enolate geometry in related benzenoid systems.[11] So, 3-methyl-2-furoic acid **7** (commercially available) was coupled (carbonyldiimidazole, CDI) to (*S*)-prolinol and then methylated (NaH, MeI) to give furan **9**. Compound **9** was then subjected to a reductive alkylation reaction as before, Scheme 2. Surprisingly, the outcome

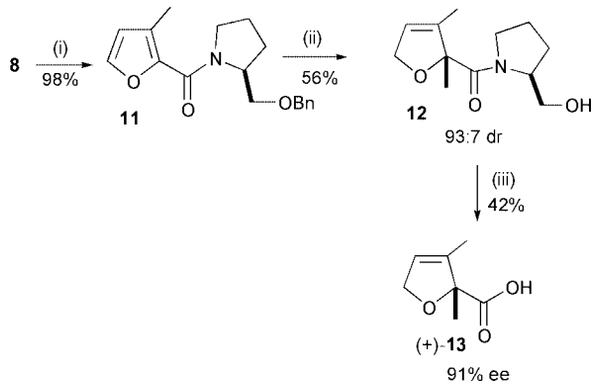


Scheme 2 *Reagents*: i. CDI, (*S*)-prolinol; ii. NaH, MeI; iii. Na, NH_3, then MeI.

was similar to that reported in Scheme 1 and under all conditions tried the product was formed as a less than useful mixture of diastereoisomers. The clearest indication that reductive alkylation had occurred as shown in Scheme 2 was the disappearance of all furyl-H resonances in the ^{1}H NMR spectrum of **10** and the presence of two methyl singlets at δ 1.34 and 1.33 ppm. The alkene resonance in compound **10** was not resolved between the two diastereoisomers and appeared as a broad singlet (1H) at δ 5.41 ppm.

While attempts to reduce compound **8** (X = OH) were complicated by low yields (possibly due to over reduction caused by the presence of an acidic, O–H, proton), any products that we did isolate were formed with significant levels of stereoselectivity. This observation led us to believe that the presence of a methyl group at C-3 was indeed controlling enolate geometry successfully and that the lack of stereoselectivity during reduction of **9** was caused by rotation about the C–N bond in the enolate (see Fig. 2 for an example; this rotation means that the side chain of the auxiliary can shield either face of the enolate in turn and this effect could lead to a 1:1 mixture of diastereoisomers whatever the geometry of the enolate). So, we presumed that reduction of **8** did form a single enolate isomer (as did **9**) but that the alkoxide present in **8** (present on the side chain of the auxiliary after deprotonation of the OH) prevented rotation about the C–N bond, presumably because of chelation. Therefore, we prepared *O*-benzylated derivative **11** in one step from **8** in the hope that the benzyl group would be cleaved under the reductive reaction conditions and that the resulting alkoxide would prevent C–N bond rotation as before and so give rise to high levels of stereoselectivity. Moreover, as there is no acidic proton in the reaction medium the yields of dihydrofuran should be good. In the event, reduction of **11** proceeded smoothly and formed **12** in reasonable yield and with good diastereoselectivity. The stereoselectivity was measured by GC on crude material and against an authentic 1:1 standard and was found to be 93:7 in favour of the isomer shown, Scheme 3. Lithium metal was preferred over sodium as the latter metal also promoted some methylation of the alkoxide on the auxiliary, thus complicating product analysis. Examination of the ^{1}H NMR spectrum of **12** made it clear that both reductive alkylation and debenzylation had occurred. For example, the only olefinic resonance to be found in the spectrum of **12** was a broad singlet (1H) at δ 5.61 ppm; there were no aromatic C–H resonances. Moreover, a methyl singlet at δ 1.53 ppm indicated that reductive methylation had taken place.

The auxiliary was cleaved from **12** with (aq.) HCl in unoptimised 42% yield to give acid **13** with 91% ee (as measured by GC against a racemic standard: the ee measured by optical rotation was lower at 80%, but could easily be due to the inherent inaccuracies in this analytical technique). The enantiomeric excess of (+)-**13** is slightly higher than the diastereoisomeric excess of **12** (86% de), which could easily be due to partial

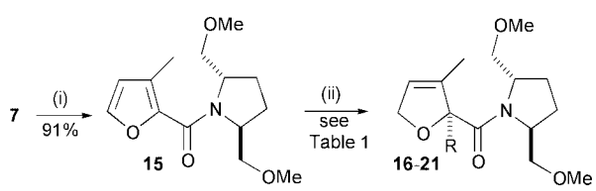


Scheme 3 *Reagents*: i. NaH, BnBr; ii. Li, NH_3, then MeI; iii. 2 M (aq.) HCl, Δ.

separation of the diastereoisomers of **12** on chromatography. The configuration of **13** (and therefore **12**) was assigned from its sign of optical rotation, *vide infra*.

Use of a C_2 symmetrical chiral auxiliary in the Birch reduction

While this route was promising, we did not pursue reduction of **11** further because of exciting developments using the C_2 symmetrical auxiliary bis(methoxymethyl)pyrrolidine, (commercially available as either enantiomer) Scheme 4.[12] Coupling



Scheme 4 *Reagents*: i. $SOCl_2$ then (*S*,*S*)-bis(methoxymethyl)pyrrolidine; ii. Na, NH_3, then RX.

Table 1 Birch reduction of **15**

Entry	RX	R	Yield (%)	Dr	Compound
1	MeI	Me	98	30:1	**16**
2	BnBr	Bn	57	30:1	**17**
3	*i*BuI	*i*Bu	68	30:1	**18**
4	EtI	Et	74	30:1	**19**
5	Allyl Br	Allyl	62	30:1	**20**
6	NH_4Cl	H	65	10:1	**21**

of (*S*,*S*)-(+)-bis(methoxymethyl)pyrrolidine **14** to acid **7** gave the amide **15** in excellent yield. This compound was subsequently reduced with sodium in liquid ammonia and quenched with a variety of electrophiles. In all cases the stereoselectivity of the reaction was excellent and the yields were also better than with any other auxiliary we had previously tested. It is no coincidence that reductive methylation of **15** (Table 1, entry 1), which has been repeated several times, has an excellent yield (98%) while the other entries shown in Table 1 have been performed only once and may be considered unoptimised. In each case the diastereoselectivity was difficult to ascertain by NMR and instead we used GC on the crude reaction mixture and in conjunction with an authentic 1:1 standard prepared by coupling of (*S*,*S*)-(+)-**14** to the corresponding racemic dihydrofuran acid with bis(2-oxooxazolidin-3-yl)phosphinic chloride (BOPCl). Although the level of stereoselectivity cannot be easily determined by ^{1}H NMR spectroscopy, we could obtain a qualitative reading by looking at the region δ 4.0–5.0 ppm where the methine NCH resonances were different for each diastereoisomer. In addition, the ^{13}C NMR spectra of the mixtures clearly showed doubling of many of the peaks. As far as the single isomers were concerned, each could be identified as

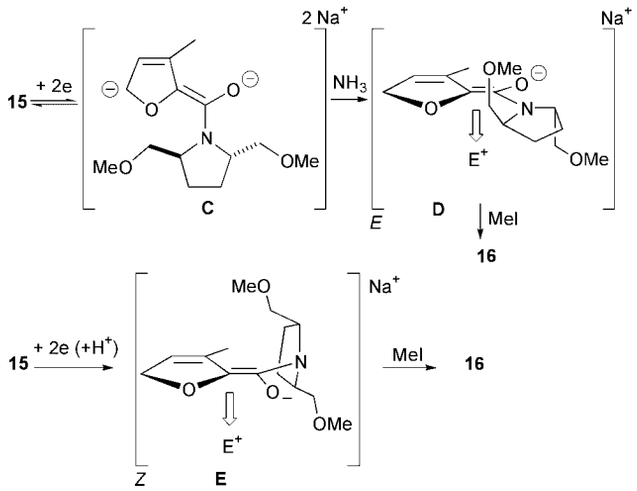


Fig. 3

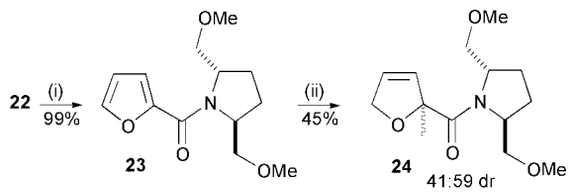
a dihydrofuran by the presence of a (1H) alkene methine resonance around δ 5.5 ppm; this was normally a broad singlet whose fine structure indicated small coupling to the C-5 methylene protons and also possibly to the C-3 methyl group. Moreover, each compound displayed additional peaks in the NMR which were consistent with the introduction of a group R from the electrophile RX used in the Birch reduction. Interestingly, both diastereoisomers of **21** showed a resonance at δ 5.28–5.22 ppm which had fine structure indicative of (allylic) coupling to other protons on the dihydrofuran ring.

We propose that the mechanism of reaction is similar to that described in Fig. 2. The key issue regards the details of how the chiral auxiliary enforces stereoselectivity upon alkylation of enolate **D** or **E**, Fig. 3. It is clear that one enolate geometric isomer is formed in this reaction: however, at present we do not have experimental evidence to indicate which one.

A simple model assumes that the nitrogen in the enolate is planar. We suppose that enolate **D** has the *trans*-geometry (so that the bulky auxiliary can avoid clashing with the methyl group) and also that the electrophile chooses to attack **D** from the lower face as drawn. Although an arm of the auxiliary shields each face of the enolate, one arm is much closer to the enolate α-carbon than the other and this is predicted to be a more efficient block to approach of the electrophile- on the upper face as drawn. However, we must be circumspect because our assumption that the nitrogen atom in the enolate is flat is unsafe. There are X-ray data in the literature to suggest that analogous nitrogen atoms within amide enolates are pyramidalised (in a manner similar to enamines).[13] Fortunately, pyramidalisation of the nitrogen does not create a new stereogenic centre and while reaction of a *trans*-enolate through a variety of different conformations can be envisaged, most do not alter the sense of selectivity predicted by our model as described above with a trigonal nitrogen.

It is more difficult to devise a model whereby a *cis*-enolate shields the correct face of the enolate. In fact we must invoke a pyramidalised nitrogen atom, possibly with some rotation about the C–N axis, see **E**, Fig. 3. While this rotation would reduce allylic strain between the methyl group and the auxiliary, it would also reduce overlap between the nitrogen lone pair and the π-system. Reaction through this conformation would predict the correct face selectivity for the enolate, however, we consider this scenario less likely than the first.

If the first model shown above is correct then use of (*S*,*S*)-**14** as an auxiliary for the reduction of 2-furoic acid will give rise to a mixture of stereoisomers as the enolate will be a mixture of geometric isomers. So, to confirm our hypothesis, compound **23** was prepared from furoyl chloride **22** and subjected to a Birch reductive methylation reaction, Scheme 5. The product **24** was isolated in 45% yield and analysed by GC which showed two

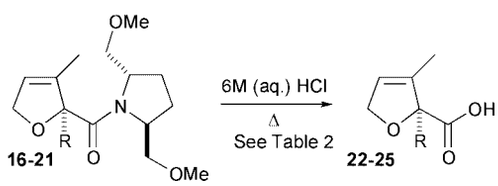


Scheme 5 *Reagents*: i. (*S*,*S*)-bis(methoxymethyl)pyrrolidine, CH_2Cl_2, NaOH; ii. Na, NH_3, then MeI.

peaks in a 41 : 59 ratio. So, this result conforms to our mechanistic model and underscores the importance of substitution at C-3 of the heterocycle to enforce control of stereochemistry. Clearly, chelation between the enolate counterion and the ring oxygen is poor and certainly insufficiently strong to control enolate geometry.

Removal of the chiral auxiliary

For our methodology to become useful we need to be able to remove the auxiliary from the products **16**–**21**. The best way to achieve this was simply to heat the amides in acid. Heating in (aq.) 6 M HCl removed the auxiliary in a few hours and, remarkably, even (aq.) 2 M HCl was sufficient to hydrolyse these amides, as exemplified with **16** and **17**, Scheme 6, Table 2. The



Scheme 6

Table 2 Hydrolysis of **16**–**19**

Entry	R	Yield (%)	% Ee	Compound
1	Me	86[a]	96	**13**
2	Bn	80[a]	>96	**25**
3	Et	74	>96	**26**
4	*i*Bu	68	94	**27**
5	H	—	—	—

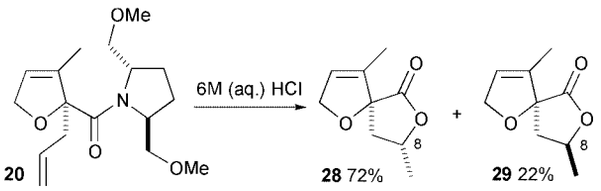
[a] Hydrolysis was carried out in 2 M (aq.) HCl.

enantiomeric excesses of acids **13** and **25**–**27** were high and were measured by GC (on a chiral support) and in comparison with a racemic standard made from 3-methyl-2-furoic acid in three steps (amide formation with pyrrolidine, Birch reduction and amide hydrolysis).

Two of the substrates that were treated with acid did not behave as expected. Compound **21** (R = H) resisted hydrolysis (2–6 M (aq.) HCl) conditions and prolonged exposure to acid eventually led to decomposition. This seems surprising as **21** represents one of the least hindered amides in this sequence and should, therefore, be more reactive to acid hydrolysis.†

Compound **20** was the other amide derivative that did not yield a carboxylic acid upon reaction with (aq.) HCl, and two diastereoisomeric lactones **28** and **29** were produced instead, Scheme 7. Initial experiments showed that while amide **20** could

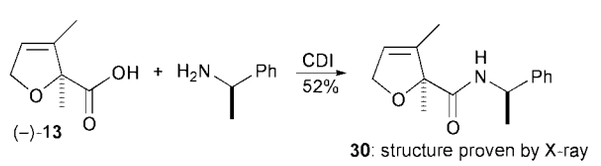
† We tentatively suggest that the reluctance of **21** to be hydrolysed, together with the relative ease of hydrolysis of hindered amides **16**–**20**, can be explained by invoking a mechanism analogous to the $A_{AC}1$ mechanism for hydrolysis of esters. In this scenario, these hindered amides would eventually protonate on nitrogen and ionise to an acylium ion (ionisation may be driven by release of steric strain). Perhaps compound **21** is insufficiently strained to undergo acylium ion formation and yet still too hindered to undergo acid hydrolysis *via* a more conventional mechanism (*i.e.* attack of water on a protonated carbonyl group as the rate determining step).



Scheme 7

be hydrolysed to give some carboxylic acid under mild (2 M (aq.) HCl) conditions, TLC analysis showed that this acid began to convert into the lactones **28** and **29** during the course of the reaction. It was decided, therefore, to convert **20** directly into the two lactones by reaction with strong acid. Gratifyingly, the two diastereoisomers were isolated in 72 and 22% yields. We were able to separate the two isomers by chromatography on silica but we could not assign the relative configuration at C-8 (which is on the lactone ring; the relative stereochemistry shown at C-8 in Scheme 7 is arbitrary). Analysis of the two lactones by GC (on a chiral support) showed that each was of 94% ee which is similar to the diastereoisomeric excess of the starting material. The mechanism of acid-catalysed lactonisation of the intermediate acid seems unremarkable involving protonation of the alkene and cyclisation of the carboxylic acid. It is not clear whether the two lactones are themselves interconverting under the reaction conditions. The five membered lactone structure of **28** and **29** was indicated by IR (C=O at 1769 cm^{-1}) and the presence of a methyl doublet (δ 1.41 ppm, J 6) in the ^1H NMR spectrum.

The configuration of the acids produced in Scheme 6 was determined from an X-ray crystal structure of amide **30**. This was prepared by coupling acid (−)-**13** (94% ee, using CDI) to (*R*)-(+)-α-methylbenzylamine, Scheme 8. The details of this



Scheme 8

X-ray have been reported elsewhere.[5] This structure reveals the configuration at C-2 of the tetrahydrofuran ring.

The structure shown in Scheme 8 can be used to assign stereochemistry to most of the compounds described in this paper. Knowing the configuration at C-2 of **30** means that we know the configuration of acid (−)-**13** from which it came. We can then work out the configuration of amide **16**, assuming that the configuration at C-2 does not change during hydrolysis of the amide, which seems reasonable. We can also assume that the configuration at C-2 is the same for acids **25**–**27** (and therefore for amides **17**–**21**). The basis of this second assumption is that the enolate **D** (Fig. 3) will react with all electrophiles from the same face. This is sensible with the carbon electrophiles used and is only really debatable with a proton electrophile (which may protonate on oxygen and rearrange). Of course, knowing the configuration of (−)-**13** means that the stereochemistry of (+)-**13**, Scheme 3 is also secure.

To conclude, we have investigated a range of chiral auxiliaries for the Birch reduction of 2-furoic acid derivatives. Bis-(methoxymethyl)pyrrolidine is the auxiliary of choice as long as a substituent is present at C-3 of the heterocycle. Using this protocol we prepared dihydrofurans with a range of substituents at the C-2 position and with excellent levels of diastereoselectivity. A model is presented which explains the sense of diastereoselectivity observed in such reductive alkylations. Moreover, the chiral auxiliary could be readily removed by treatment with acid to give carboxylic acid derivatives with very high enantiomeric excess. The use of this methodology in the synthesis of biologically important natural products is currently being investigated.[14]

Experimental

General details

All reactions, except aqueous reactions, were carried out under an atmosphere of dry nitrogen. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Gemini 200 at 200 MHz, a Bruker AC300/Varian XL300 at 300 MHz, a Bruker AM360 at 360 MHz or a Bruker AC250 at 250 MHz. ^{13}C nuclear magnetic resonance spectra were recorded on a Gemini 200 at 50 MHz, a Bruker AC300/Varian XL300 at 75 MHz, or a Bruker AM360 at 90 MHz. Coupling constants (J) are quoted in Hz. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FTIR as evaporated films. Optical rotations were recorded on an Optical Activity Ltd. AA-100 polarimeter and $[\alpha]_D$ values (all reported at 21 °C) are given in units of 10^{-1} deg cm^2 g^{-1}; concentration c in units of g 100 ml^{-1}. Mass spectra were recorded on a Kratos Concept or a Fisson VG Trio 2000. Chemical ionisation (CI) was performed using NH_3. Microanalysis was obtained from the microanalytical section of the University of Manchester's Chemistry Department. Melting points were obtained on a Kofler block and are uncorrected. Thin layer chromatography (TLC) was carried out using Polygram G/UV_{254} pre-coated plastic plates. Flash column chromatography was carried out using the solvent system indicated and Silica Gel 60 230–400 mesh. Gas/liquid chromatography (GC) was carried out using a chiral column; CP-Chirasil DEXCB column (25 m × 0.32 mm, 0.28 μ) controlled by a Shimadzu Chromatopac R4AX unit. All solvents and reagents requiring purification were done so using standard laboratory techniques according to methods published in ref. 15. Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as indicator, under an atmosphere of nitrogen. Dichloromethane (DCM) was distilled over calcium hydride. Petroleum ether (boiling range 40–60 °C) was distilled prior to use. Ammonia was distilled from sodium metal and ferric chloride. Where mentioned, isoprene was added to metal ammonia reductions dropwise until the blue colour of the reaction was dispersed.

(2′*S*)-[2′-(Hydroxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](3-methyl-2-furyl)methanone 8

3-Methyl-2-furoic acid **7** (0.5 g, 3.8 mmol) was stirred in THF (25 ml) at RT and carbonyldiimidazole (0.707 g, 8.7 mmol) was added. The reaction was stirred for 30 min and then (*S*)-prolinol (0.39 ml, 3.8 mmol) was added in one portion. After stirring overnight at RT the THF was removed under reduced pressure and the residue dissolved in dichloromethane (50 ml). The organics were washed with 2 M (aq.) HCl (20 ml) and brine (20 ml) before being dried ($MgSO_4$). Evaporation under reduced pressure gave a brown oil which was purified by chromatography on a silica column, eluting with 30% ethyl acetate–petrol, to afford **8** as a colourless oil (734 mg, 89%) (Found M^+, 209.1052. $C_{11}H_{15}NO_3$ requires M^+, 209.1052); ν_{max} (film)/cm^{-1} 3400, 2957, 2929, 2878, 1609, 1494; δ_H (300 MHz, $CDCl_3$) 7.37 (1H, d, J 1.6), 6.34 (1H, d, J 1.4), 5.31 (1H, br s, OH), 4.44–4.41 (1H, m), 3.98–3.67 (4H, m), 2.35 (3H, s), 2.14–1.79 (4H, m); δ_C (75 MHz, $CDCl_3$) 162.0, 143.0, 142.4, 129.5, 115.0, 67.2, 61.9, 49.2, 27.8, 25.0, 11.8; m/z (CI^+) 210 (M + 1, 100%), 109 (M − 100, 10%); $[\alpha]_D$ −66.5 (c 0.01 in $CHCl_3$).

(2′*S*)-[2′-(Methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](3-methyl-2-furyl)methanone 9

A solution of the amide **8** (1.5 g, 7.2 mmol) in THF (50 ml) was added to sodium hydride (373 mg, 9.3 mmol) at 0 °C under N_2. After 1 hour at 0 °C, methyl iodide (1.4 ml, 21.5 mmol) was

added and the reaction heated at reflux overnight. The THF was then removed under reduced pressure and the residue dissolved in dichloromethane (100 ml). The organics were washed with 2 M (aq.) HCl (20 ml), and brine (20 ml), and dried ($MgSO_4$). Evaporation under reduced pressure gave the crude product as a brown oil (1.4 g, 87%). Purification by flash chromatography gave **9** as an orange oil (1.2 g, 75%) (Found M + H^+, 224.1283. $C_{12}H_{18}NO_3$ requires M + H^+, 224.1287); ν_{max} (film)/cm^{-1} 2974, 2927, 2885, 1611, 1494; δ_H (300 MHz, $CDCl_3$) 7.30 (1H, s), 6.29 (1H, s), 4.58–4.38 (1H, br s), 3.93–3.12 (7H, m), 2.32 (3H, s), 2.11–1.78 (4H, m); δ_C (75 MHz, $CDCl_3$) 159.9, 143.2, 141.9, 128.5, 114.8, 72.4, 59.0, 57.1, 48.4, 27.0, 24.8, 11.7; *m*/*z* (CI^+) 224 (M + 1, 100%), 178 (M − 45, 10%); $[\alpha]_D$ −97.0 (*c* 0.01 in $CHCl_3$).

(2*RS*,2′*S*)-[2′-(Methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2,3-dimethyl-2,5-dihydrofuran-2-yl)methanone 10

Compound **9** (500 mg, 2.2 mmol) was stirred in THF (10 ml) and ammonia (120 ml) at −78 °C. Sodium (144 mg, 6.2 mmol) was added to the reaction and stirred for 1 h, during which time the reaction became blue. Isoprene was then added followed by methyl iodide (948 μl, 6.6 mmol) and the reaction mixture became colourless. Ammonium chloride (0.5 g) was added, and the ammonia then allowed to evaporate. The residual tetrahydrofuran was removed under reduced pressure and the crude product was purified by column chromatography, eluting with 50% ethyl acetate–petrol, affording **10** as a mixture of diastereoisomers (55:45) as a colourless oil (375 mg, 70%). Data for the mixture are shown (Found M + H^+, 240.1599. $C_{13}H_{22}NO_3$ requires M + H^+, 240.1600); ν_{max} (film)/cm^{-1} 2976, 2930, 2889, 2879, 1626; δ_H (300 MHz, $CDCl_3$) 5.41 (1H, s), 4.59–4.31 (2H, m), 4.09–4.27 (1H, m), 3.69–3.06 (4H, m), 3.21, 3.18 (s, 3H), 1.85–1.51 (4H, m), 1.50 (3H, br s), 1.34, 1.33 (3H, s); δ_C (75 MHz, $CDCl_3$) 173.1, 140.5, 139.5, 121.2, 93.3, 73.9, 72.5, 72.2, 59.4, 59.3, 58.6, 58.5, 46.9, 26.9, 26.8, 25.4, 23.4, 12.6, 12.4; *m*/*z* (CI^+) 240 (M + 1, 100%), 97 (M − 142, 10%).

(2′*S*)-{2′-[(Benzyloxy)methyl]-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl}(3-methyl-2-furyl)methanone 11

A solution of amide **8** (1.85 g, 8.8 mmol) in THF (35 ml) was added to a suspension of washed sodium hydride (60% dispersion, 708 mg, 17.7 mmol) in THF (5 ml) at 0 °C. After 1 h at 0 °C, benzyl bromide (1.2 ml, 10.1 mmol) and tetra-*n*-butylammonium iodide (20 mg) were added, and the reaction then stirred overnight at room temperature. The suspension was filtered, the residue washed with THF and the solvent was removed under reduced pressure to give the crude product. Column purification, eluting with 30% ethyl acetate–petrol afforded **11** as a colourless oil (2.6 g, 98%) (Found M + H^+, 300.1598. $C_{18}H_{21}NO_3$ requires M + H^+, 300.1600); ν_{max}/cm^{-1} 2965, 2874, 1617 (C=O); δ_H (200 MHz, $CDCl_3$) 7.38–7.22 (6H, m), 6.30 (1H, d, *J* 1.5), 4.61–4.43 (m, 3H), 3.96–3.45 (m, 4H), 2.35 (3H, s) and 2.17–1.80 (4H, m); δ_C (75 MHz, $CDCl_3$) 159.8, 143.4, 141.8, 139.5, 129.6, 128.2, 127.4, 114.8, 73.1, 70.2, 57.2, 48.5, 27.0, 24.8, 11.7; *m*/*z* (CI) 300 (M + H^+, 100%); $[\alpha]_D$ −154.6 (*c* 0.57 in CH_2Cl_3).

(2*R*,2′*S*)-(2,3-Dimethyl-2,5-dihydrofuran-2-yl)[2′-(hydroxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl]methanone 12

Compound **11** (500 mg, 1.7 mmol) was stirred in THF (10 ml) and ammonia (120 ml) at −78 °C. Lithium (58 mg, 8.4 mmol) was added to the reaction and stirred for 1 h, during which time the reaction became blue. Isoprene was then added followed by methyl iodide (474 μl, 3.3 mmol) and the reaction mixture became colourless. Ammonium chloride (0.5 g) was added, and the ammonia then allowed to evaporate. The residue was extracted into ethyl acetate (4 × 50 ml) and evaporated to dryness under reduced pressure to give a yellow oil. Column purification, eluting with 50% ethyl acetate–petrol, afforded **12** as a mixture of diastereoisomers as a colourless oil (210 mg, 56%). Data for major diastereoisomer shown (Found M + H^+, 226.1442. $C_{12}H_{19}NO_3$ requires M + H^+, 226.1443); ν_{max}/cm^{-1} 3433 (br, O–H), 2974, 2854, 1609 (C=O); δ_H (300 MHz, $CDCl_3$) 5.61 (1H, br s), 4.82 (1H, m), 4.74–4.44 (2H, m), 4.39 (1H, m), 3.99–3.38 (4H, m), 2.02–1.79 (4H, m), 1.81 (3H, br s), 1.53 (3H, s); δ_C (75 MHz, $CDCl_3$) 173.1 (C=O), 139.3, 120.8, 93.0, 73.4, 67.7, 62.4, 46.9, 27.2, 25.2, 23.0, 12.0; *m*/*z* (CI) 226 (M + H^+, 100%).

(2*R*)-2,3-Dimethyl-2,5-dihydrofuran-2-carboxylic acid 13

Compound **12** (200 mg, 0.89 mmol) was heated at reflux in 2 M (aq.) hydrochloric acid (3 ml) for 1.5 h. The reaction mixture was extracted into ethyl acetate (4 × 30 ml) and the combined organics dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography, eluting with 30% ethyl acetate–petrol containing 5% acetic acid to give **13** as a yellow oil (53 mg, 42%) (Found C, 59.06; H, 7.30%; $C_7H_{10}O_3$ requires C, 59.14; H, 7.09%. Found M + NH_4^+, 160.0977. $C_7H_{10}O_3$ requires M + NH_4^+, 160.0973); ν_{max}/cm^{-1} 3400 (br, OH), 1744 (C=O); δ_H (300 MHz, $CDCl_3$) 9.6 (1H, br), 5.52 (1H, br s), 4.69–4.58 (2H, m), 1.79–1.77 (3H, br s), 1.48 (3H, s); δ_C (75 MHz, $CDCl_3$) 174.3, 137.6, 121.7, 91.1, 74.3, 22.3 and 11.9; *m*/*z* (CI) 160 (M^+ + NH_4^+, 100%), 97 (M^+ − CO_2H); $[\alpha]_D$ +63.5 (*c* 0.15 in EtOH).

(2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](3-methyl-2-furyl)methanone 15

Thionyl chloride (12 ml, excess) was added to 3-methyl-2-furoic acid (2.39 g, 19.0 mmol) and the resulting dark mixture refluxed for 3–4 h. Excess thionyl chloride was then removed under reduced pressure, azeotroping with toluene. To the brown liquid was added dichloromethane (10 ml), and this solution was then added dropwise to a stirring mixture of (*S*,*S*)-bis(methoxymethyl)pyrrolidine (3.32 g, 21.0 mmol), 2 M (aq.) sodium hydroxide (40 ml, 80 mmol) and dichloromethane (40 ml) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The dichloromethane was then removed under reduced pressure, and the residue extracted into ethyl acetate (4 × 75 ml). The combined organics were then dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield a brown oil. The crude product was purified by column chromatography, eluting with 25% ethyl acetate–petrol to give **15** as a pale yellow oil (4.6 g, 91%) (Found M^+, 267.1478, $C_{14}H_{21}NO_4$ requires M^+, 267.1471); ν_{max}/cm^{-1} 1617 (C=O); δ_H (300 MHz, $CDCl_3$) 7.25 (1H, d, *J* 1.5), 6.25 (1H, d, *J* 1.5), 4.74–4.64 (1H, m), 4.48–4.37 (1H, m), 3.48 (1H, dd, *J* 9.0 and 3.0), 3.35–3.23 (1H, m), 3.26 (3H, s), 3.12 (3H, s), 3.04–2.88 (2H, m), 2.25 (3H, s), 2.20–1.79 (4H, m); δ_C (75 MHz, $CDCl_3$) 159.5 (C=O), 142.9, 141.5, 128.5, 114.8, 73.7, 71.8, 58.9, 58.8, 57.4, 57.0, 27.3, 23.9, 11.5; *m*/*z* (CI) 268 (M + H^+, 100%); $[\alpha]_D$ −123.8 (*c* 0.64 in EtOH).

(2*S*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2,3-dimethyl-2,5-dihydrofuran-2-yl)methanone 16

A solution of **15** (1.0 g, 3.7 mmol) in THF (15 ml) was added to ammonia (200 ml) at −78 °C under N_2. Freshly cut sodium (258 mg, 11.2 mmol) was then added, and the mixture stirred at −78 °C for 30 min, during which time the solution became blue. Isoprene was then added to disperse the blue colour, followed immediately by methyl iodide (700 μl, 11 mmol), which resulted in the yellow solution becoming colourless. After stirring for a further 40 min, the reaction was quenched by the addition of solid ammonium chloride (0.5 g) and the stoppers removed

from the reaction flask to allow evaporation of ammonia. The residual tetrahydrofuran was removed under reduced pressure and the crude product was purified by column chromatography, eluting with 25% ethyl acetate–petrol, to afford **16** as a yellow oil (1.04 g, 98%) (Found M + H$^+$, 284.1853. $C_{15}H_{25}NO_4$ requires M + H$^+$, 284.1862); ν_{max}/cm^{-1} 1621 (C=O); δ_H (300 MHz, $CDCl_3$) 5.48–5.45 (1H, m), 4.67 (1H, m), 4.57–4.53 (2H, m), 4.23 (1H, m), 3.45 (1H, dd, *J* 9.0 and 3.0), 3.30–3.09 (2H, m), 3.27 (3H, s), 3.21 (3H, s), 2.97 (1H, t, *J* 9.0), 2.12–1.74 (7H, m), 1.44 (3H, s); δ_C (75 MHz, $CDCl_3$) 172.1 (C=O), 140.9, 120.3, 93.3, 74.0, 73.0, 71.3, 58.7, 58.6, 57.9, 57.6, 27.3, 25.9, 23.3, 12.7; *m*/*z* (CI) 284 (M + H$^+$, 100%); $[a]_D$ −107.1 (*c* 2.0 in EtOH).

(2*S*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2-benzyl-3-methyl-2,5-dihydrofuran-2-yl)-methanone 17

To a solution of **15** (200 mg, 0.75 mmol) in THF (8 ml) and ammonia (120 ml) at −78 °C was added sodium (52 mg, 2.3 mmol). The reaction was stirred for 25 min during which time the reaction mixture turned blue. Isoprene was then added until the blue colour was dispersed, followed by addition of benzyl bromide (257 µl, 2.3 mmol). After 1 min the reaction mixture became colourless and after a further 10 min stirring, the reaction was quenched by the addition of saturated (aq.) ammonium chloride solution (1 ml). The ammonia was then allowed to evaporate, and the resulting residue was extracted into ethyl acetate (4 × 50 ml). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. The crude material was purified by column chromatography, eluting with 30% ethyl acetate–petrol to give **17** as a yellow oil (153 mg, 57%) (Found M + H$^+$, 360.2171. $C_{21}H_{29}NO_4$ requires M + H$^+$, 360.2175); ν_{max}/cm^{-1} 2922, 1618 (C=O); δ_H (300 MHz, $CDCl_3$) 7.37–7.15 (5H, m), 5.50 (1H, m), 4.69 (1H, m), 4.51 (1H, m), 4.31–4.24 (2H, m), 3.34–3.20 (10H, m), 3.15 (1H, dd, *J* 8.5, 3.5), 2.85 (1H, t, *J* 8.5), 1.89–1.77 (7H, m); δ_C (75 MHz, $CDCl_3$) 170.1 (C=O), 139.2, 136.7, 130.8, 127.4, 126.2, 122.1, 96.5, 74.2, 73.6, 71.1, 58.7, 58.6, 58.0, 57.5, 44.3, 27.1, 22.9, 13.2; *m*/*z* (CI) 360 (M + H$^+$, 100%), 268 (M − 91), 173 (M − 186); $[a]_D$ −132.5 (*c* 1.5, in EtOH).

(2*S*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2-isobutyl-3-methyl-2,5-dihydrofuran-2-yl)-methanone 18

A solution of **15** (115 mg, 0.43 mmol) in THF (5 ml) and ammonia (50 ml) was stirred at −78 °C. Freshly cut sodium (30 mg, 1.3 mmol) was then added, and the mixture stirred at −78 °C for 30 min, during which time the solution turned from yellow to blue. Isoprene was then added to disperse the blue colour, followed immediately by isobutyl iodide (250 µl, 2.15 mmol). After stirring for 4 h, the pale yellow reaction mixture was quenched by the addition of saturated (aq.) ammonium chloride solution (1 ml) and the ammonia was allowed to evaporate. The residue was extracted with ethyl acetate (4 × 25 ml), and the combined organics washed with brine, then dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield a brown oil. The crude product was purified by column chromatography, eluting with 25% ethyl acetate–petrol, to afford **18** as a yellow oil (95 mg, 68%) (Found M + H$^+$, 326.2336. $C_{18}H_{31}NO_4$ requires M + H$^+$, 326.2331); ν_{max}/cm^{-1} 1619 (C=O); δ_H (300 MHz, $CDCl_3$) 5.47 (1H, dd, *J* 3.0 and 1.5), 4.75 (1H, m), 4.52 (2H, m), 4.25 (1H, m), 3.45 (1H, dd, *J* 9.0 and 3.0), 3.25 (3H, s), 3.20 (3H, s), 3.27–3.17 (1H, m), 3.10 (1H, dd, *J* 8.5 and 2.5), 2.94 (1H, t, *J* 9.0), 2.02 (1H, dd, *J* 14.0 and 5.5), 2.05–1.75 (7H, m), 1.69–1.58 (1H, m), 1.42 (1H, dd, *J* 14.0 and 7.0), 0.87 (3H, d, *J* 6.5), 0.83 (3H, d, *J* 6.5); δ_C (75 MHz, $CDCl_3$) 171.8 (C=O), 140.8, 120.7, 96.9, 74.1, 73.2, 71.3, 58.6, 58.6, 58.0, 57.7, 46.8, 27.3, 24.5, 24.2, 23.7, 23.2, 13.1; *m*/*z* (CI) 326 (M + H$^+$, 100%); $[a]_D$ −131.6 (*c* 1.02 in EtOH).

(2*S*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2-ethyl-3-methyl-2,5-dihydrofuran-2-yl)-methanone 19

Sodium (50 mg, 2.1 mmol) was added to a solution of **15** (240 mg, 0.9 mmol) in THF (10 ml) and ammonia (100 ml) at −78 °C and stirred for 25 min during which time the reaction turned blue. The colour was dispersed with isoprene followed by ethyl iodide (217 µl, 0.27 mmol) and after 30 min stirring at −78 °C the reaction was quenched with saturated (aq.) ammonium chloride (2 ml) and the ammonia allowed to evaporate. The residue was extracted with ethyl acetate (4 × 50 ml) and the combined organics dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the crude product as an orange oil. Column purification, eluting with 25% ethyl acetate–petrol, afforded **19** as a clear oil (197 mg, 74%) (Found M + H$^+$, 298.2015, $C_{16}H_{27}NO_4$ requires M + H$^+$, 298.2018); ν_{max}/cm^{-1} 1619 (C=O); δ_H (300 MHz, $CDCl_3$) 5.50 (1H, dd, *J* 3.0 and 1.5), 4.76 (1H, m), 4.60–4.58 (2H, m), 4.30 (1H, m), 3.49 (1H, dd, *J* 9.0 and 3.0), 3.30 (3H, s), 3.26 (3H, s), 3.24–3.12 (2H, m), 3.00 (1H, t, *J* 9.0), 2.10–1.68 (9H, m), 0.82 (3H, t, *J* 7.5); δ_C (75 MHz, $CDCl_3$) 171.8 (C=O), 139.3, 121.1, 96.5, 74.2, 73.8, 71.4, 60.2, 58.7, 58.0, 57.6, 27.3, 23.2, 14.0, 12.9, 7.5; *m*/*z* (CI) 298 (M + H$^+$, 100%); $[a]_D$ −146.2 (*c* 1.2 in EtOH).

(2*S*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2-allyl-3-methyl-2,5-dihydrofuran-2-yl)-methanone 20

A solution of **15** (500 mg, 1.9 mmol) in THF (8 ml) was added to ammonia (80 ml) at −78 °C. To this was added sodium (130 mg, 5.6 mmol), and the reaction stirred for 40 min. Isoprene was then added to the blue solution until the colour changed to yellow, followed by the immediate addition of allyl bromide (485 µl, 5.6 mmol). The solution then became pink, but after 10 min the yellow colour returned. After 1 h stirring at −78 °C, the reaction was quenched by the addition of saturated (aq.) ammonium chloride (2 ml) and the ammonia allowed to evaporate, and the residue extracted into ethyl acetate (4 × 75 ml). The combined organics were dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield the crude product as a yellow oil. The crude product was purified by column chromatography (25% ethyl acetate–petrol) to give **20** as a pale yellow oil (358 mg, 62%) (Found M + H$^+$, 310.2018. $C_{17}H_{27}NO_4$ requires M + H$^+$, 310.2018); ν_{max}/cm^{-1} 3062, 2976, 2854 and 1619 (C=O); δ_H (300 MHz, $CDCl_3$) 5.77–5.66 (1H, m), 5.58 (1H, m), 5.13–5.02 (2H, m), 4.76 (1H, m), 4.60–4.59 (2H, m), 4.31 (1H, m), 3.48 (1H, dd, *J* 9.0 and 3.0), 3.31 (3H, s), 3.25 (3H, s), 3.31–3.13 (2H, m), 3.00 (1H, t, *J* 9.0), 2.78 (1H, dd, *J* 14.0 and 7.0), 2.53 (1H, dd, *J* 14.0 and 7.0), 2.05–1.70 (7H, m); δ_C (75 MHz, $CDCl_3$) 171.0 (C=O), 139.1, 132.9, 121.4, 118.1, 95.8, 74.1, 73.9, 71.4, 58.7, 58.1, 57.6, 43.3, 27.3, 23.2, 12.8; *m*/*z* (CI) 310 (M + H$^+$, 100%); $[a]_D$ −156.3 (*c* 0.53 in EtOH).

(2*S*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](3-methyl-2,5-dihydrofuran-2-yl)methanone 21

To a solution of **15** (500 mg, 1.9 mmol) in THF (8 ml) and ammonia (100 ml) at −78 °C, was added sodium (130 mg, 5.6 mmol). This mixture was stirred for 20 min to allow dissolution of the metal, then isoprene was added to disperse the blue colour, followed by immediate addition of saturated (aq.) ammonium chloride solution (2 ml). The colourless solution was allowed to warm to room temperature with evaporation of the ammonia, then the residue was extracted into ethyl acetate (4 × 75 ml). The combined organics were dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography, eluting with 25% ethyl acetate–petrol, to afford two compounds as colourless oils, **21** (298 mg, 60%) and its diastereoisomer (29 mg, 5%). Compound **21** (Found

M + H$^+$, 270.1702. $C_{14}H_{23}NO_4$ requires M + H$^+$, 270.1705); ν_{max}/cm^{-1} 2971, 2858, 1655 (C=O); δ_H (360 MHz, $CDCl_3$) 5.61 (1H, br s), 5.29–5.22 (1H, m), 4.83–4.75 (1H, m), 4.63–4.55 (1H, m), 4.18 (1H, m), 4.10 (1H, m), 3.43–3.34 (3H, m), 3.27 (3H, s), 3.22 (3H, s), 3.16 (1H, t, *J* 9.0), 2.12–1.80 (4H, m), 1.66 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.3 (C=O), 135.0, 123.2, 86.1, 76.8, 74.2, 71.5, 59.2, 58.8, 57.5, 57.2, 27.5, 25.0, 11.9; *m*/*z* (CI) 270 (M + H$^+$, 100%); $[\alpha]_D$ −155.4 (*c* 5.4 in EtOH).

Minor diastereoisomer **21** (Found M + H$^+$, 270.1700. $C_{14}H_{23}NO_4$ requires M + H$^+$, 270.1705); ν_{max}/cm^{-1} 2071, 1656 (C=O); δ_H (250 MHz, $CDCl_3$) 5.60–5.58 (1H, m), 5.28–5.22 (1H, m), 4.70–4.60 (2H, m), 4.28–4.10 (2H, m), 3.56 (1H, dd, *J* 9.5 and 3.0), 3.38–3.16 (3H, m), 3.27 (3H, s), 3.26 (3H, s), 2.15–1.70 (7H, m); δ_C (75 MHz, $CDCl_3$) 169.7 (C=O), 135.1, 122.8, 87.2, 75.7, 75.1, 70.9, 59.0, 58.8, 57.2, 56.8, 27.1, 24.9, 12.7; *m*/*z* (CI) 270 (M + H$^+$, 100%).

(2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2-furyl)methanone 23

Furoyl chloride **22** (309 µl, 3.1 mmol) was added dropwise to a stirring mixture of (*S*,*S*)-bis(methoxymethyl)pyrrolidine (500 mg, 3.1 mmol) in 3 M aq. sodium hydroxide (5 ml) and dichloromethane (5 ml) at 0 °C. The reaction was stirred overnight at room temperature, and dichloromethane was then removed under reduced pressure. The residue was extracted into ethyl acetate (4 × 50 ml) and the combined organic layers dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give **23** as a cream solid (784 mg, 99%). Mp 41–43 °C (Found C, 61.56; H, 7.79; N, 5.58%. $C_{13}H_{19}NO_4$ requires C, 61.64; H, 7.56; N, 5.53%; Found M + H$^+$, 254.1389. $C_{13}H_{19}NO_4$ requires M + H$^+$, 254.1392); ν_{max}/cm^{-1} 2978, 1617 (C=O); δ_H (300 MHz, $CDCl_3$) 7.51 (1H, dd, *J* 3.4 and 1.8), 7.15 (1H, dd, *J* 3.4 and 0.8), 6.51 (1H, dd, *J* 3.4 and 1.8), 4.78–4.67 (1H, m), 4.48–4.36 (1H, m), 3.56–3.48 (1H, m), 3.35 (1H, t, *J* 8.0), 3.28 (3H, s), 3.19 (3H, s), 3.14–3.08 (2H, m), 2.22–1.83 (4H, m); δ_C (75 MHz, $CDCl_3$) 158.1 (C=O), 148.7, 143.6, 116.6, 111.5, 73.9, 71.7, 59.0, 58.9, 57.8, 57.3, 27.4, 24.1; *m*/*z* (CI) 254 (M + H$^+$, 100%); $[\alpha]_D$ −103.8 (*c* 0.45 in CH_2Cl_2).

(2*SR*,2′*S*,5′*S*)-[2′,5′-Bis(methoxymethyl)-2′,3′,4′,5′-tetrahydro-1′*H*-pyrrol-1′-yl](2-methyl-2,5-dihydrofuran-2-yl)-methanone 24

To a solution of **23** (500 mg, 1.98 mmol) in THF (8 ml) and ammonia (120 ml) at −78 °C was added sodium (136 mg, 5.9 mmol). The reaction was stirred for 30 min during which time the reaction turned blue. Isoprene was then added until the blue colour was dispersed, followed by addition of methyl iodide (370 µl, 5.9 mmol). After 30 min the reaction mixture was colourless and was quenched by the addition of saturated (aq.) ammonium chloride solution (1 ml). Ammonia was then allowed to evaporate, and the resulting residue was extracted into ethyl acetate (4 × 50 ml). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. The crude material was purified by column chromatography, eluting with 20% ethyl acetate–petrol to give **24** (59 : 41 mixture of diastereoisomers) as a yellow oil (239 mg, 45%) (Found M + H$^+$, 270.1701. $C_{14}H_{23}NO_4$ requires M + H$^+$, 270.1705); ν_{max}/cm^{-1} 2976, 2856, 1621 (C=O); δ_H (300 MHz, $CDCl_3$) 6.07–5.80 (2H, m), 4.74–4.11 (4H, m), 3.57–2.98 (10H, m), 2.07–1.71 (4H, m), 1.50, 1.43 (3H, s); δ_C (75 MHz, $CDCl_3$) 173.2, 172.8 (C=O), 133.5, 132.8, 125.3, 125.1, 93.3, 93.2, 75.4 75.2, 74.7, 74.5, 71.4, 71.1, 58.8, 58.6, 58.6, 58.6, 58.1, 57.6, 57.6, 57.4, 27.3, 27.1, 27.0, 26.0, 23.6, 23.3; *m*/*z* (CI) 270 (M + H$^+$,100%).

(2*S*)-2,3-Dimethyl-2,5-dihydrofuran-2-carboxylic acid 13

Aqueous hydrochloric acid (2 M, 10 ml) was added to **16** (927 mg, 3.3 mmol) and the reaction heated at reflux for 6 h. The mixture was extracted immediately with ethyl acetate (4 × 50 ml), and the combined organics were dried ($MgSO_4$) and evaporated to dryness under reduced pressure, to give the *title compound* as a brown oil (400 mg, 86%); $[\alpha]_D$ −79.1 (*c* 0.21 in EtOH). Other spectroscopic data were as reported above.

(2*S*)-2-Benzyl-3-methyl-2,5-dihydrofuran-2-carboxylic acid 25

Compound **17** (62 mg, 0.17 mmol) was heated at reflux in 2 M (aq.) hydrochloric acid (2 ml, 4 mmol) for 10 h. The reaction mixture was extracted into ethyl acetate (4 × 15 ml) and the combined organics were dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give the crude product as a brown oil. Column purification, eluting with 20% ethyl acetate–petrol containing 5% acetic acid, afforded **25** as an orange oil (30 mg, 80%) (Found M$^+$+H_2O, 236.1045. $C_{13}H_{14}O_3$ requires M$^+$+H_2O, 236.1048); ν_{max}/cm^{-1} 3250–3100 (br, OH), 3031, 2920, 1728; δ_H (250 MHz, $CDCl_3$) 7.31–7.19 (5H, m), 5.52 (1H, dd, *J* 3.0 and 1.5), 4.67–4.58 (1H, m), 4.43–4.32 (1H, m), 3.29 (1H, d, *J* 14.0), 3.07 (1H, d, *J* 14.0), 1.96–1.90 (3H, m); δ_C (75 MHz, $CDCl_3$) 173.0 (C=O), 135.7, 135.1, 130.2, 128.0, 126.8, 123.2, 94.4, 74.8, 40.9, 12.4; *m*/*z* (CI) 236 (M + H_2O^+, 100%), 173 (M − CO_2H).

(2*S*)-2-Ethyl-3-methyl-2,5-dihydrofuran-2-carboxylic acid 26

Compound **19** (82 mg, 0.28 mmol) was refluxed in 6 M (aq.) hydrochloric acid (1 ml) for 4 h. The reaction mixture was extracted into ethyl acetate (4 × 30 ml) and the combined organics were dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a brown oil. Column purification, eluting with 30% ethyl acetate–petrol containing 5% acetic acid, afforded **26** as a yellow oil (32 mg, 74%) (Found M$^+$ − CO_2H, 111.0808. $C_8H_{12}O_3$ requires M$^+$ − CO_2H, 111.0810); ν_{max}/cm^{-1} 3400 (br, OH), 1720 (C=O); δ_H (300 MHz, $CDCl_3$) 5.56 (1H, m), 4.73–4.52 (2H, m), 1.98–1.66 (5H, m), 0.82 (3H, t, *J* 7.5); δ_C (75 MHz, $CDCl_3$) 173.9 (C=O), 135.8, 122.5, 94.6, 74.8, 28.0, 12.1, 7.3; *m*/*z* (CI) 111 (M − CO_2H, 100%); $[\alpha]_D$ −127.3 (*c* 0.59 in EtOH).

(2*S*)-2-Isobutyl-3-methyl-2,5-dihydrofuran-2-carboxylic acid 27

Compound **18** (280 mg, 0.86 mmol) was refluxed in 6 M (aq.) hydrochloric acid (3 ml) for 6 h. The reaction mixture was extracted into ethyl acetate (4 × 50 ml), the combined organics were dried ($MgSO_4$), and evaporated to dryness under reduced pressure to yield a brown oil. Column purification, eluting with 30% ethyl acetate–petrol containing 5% acetic acid, afforded **27** as a yellow oil (105 mg, 68%) (Found M + NH_4^+, 202.1440, $C_{10}H_{16}O_3$ requires M + NH_4^+, 202.1443); ν_{max}/cm^{-1} 3300, (br, OH), 1710 (C=O); δ_H (250 MHz, $CDCl_3$) 5.54 (1H, d, *J* 1.5), 4.70–4.53 (2H, m), 1.75 (3H, d, *J* 2.0), 1.90–1.57 (3H, m), 0.86 (6H, t, *J* 6.5); δ_C (75 MHz, $CDCl_3$) 175.3 (C=O), 137.0, 122.3, 93.9, 74.3, 43.0, 24.3, 23.9, 23.3, 12.2; *m*/*z* (CI) 202 (M + NH_4^+, 100%); $[\alpha]_D$ −53.1 (*c* 0.10 in EtOH).

(5*S*,8*SR*)-4,8–Dimethyl-1,7-dioxaspiro[4.4]non-3-en-6-one 28/29

Compound **20** (60 mg, 0.19 mmol) was heated at reflux in 6 M (aq.) hydrochloric acid for 24 h, followed by a further 48 h at room temperature. The acidic solution was extracted into ethyl acetate (4 × 20 ml) and the combined organics were dried ($MgSO_4$). Evaporation under reduced pressure afforded the two lactones as a brown oil. Column purification, eluting with 20% ethyl acetate–petrol afforded the two diastereoisomers (**28**: 23 mg, 72%) and (**29**: 7 mg, 22%). Compound **28** (Found M + NH_4^+, 186.1132. $C_9H_{12}O_3$ requires M + NH_4^+, 186.1130); ν_{max}/cm^{-1} 1769 (C=O); δ_H (360 MHz, $CDCl_3$) 5.70 (1H, d, *J* 1.5), 4.77–4.71 (1H, m), 4.61–4.51 (2H, m), 2.51 (1H, dd, *J* 13.5 and

7.0), 1.99 (1H, dd, *J* 13.5 and 7.0), 1.71–1.70 (3H, m), 1.41 (3H, d, *J* 6.0); δ_C (90.5 MHz, $CDCl_3$) 175.9 (C=O), 134.8, 125.0, 92.1, 75.6, 73.9, 40.1, 22.1, 11.6; *m*/*z* (CI) 186 (M + NH_4^+, 100%); $[\alpha]_D$ −46.7 (*c* 0.70 in EtOH).

Compound **29** (Found M + NH_4^+, 186.1137. $C_9H_{12}O_3$ requires M + NH_4^+, 186.1130); ν_{max}/cm^{-1} 1771 (C=O); δ_H (360 MHz, $CDCl_3$) 5.85 (1H, dd, *J* 3.0 and 1.5), 4.81–4.60 (3H, m), 2.33 (1H, dd, *J* 14.0 and 5.5), 1.95 (1H, dd, *J* 14.0 and 9.5), 1.75–1.73 (3H, m), 1.45 (3H, d, *J* 6.0); δ_C (90.5 MHz, $CDCl_3$) 174.4 (C=O), 133.4, 125.6, 92.5, 75.0, 74.8, 40.2, 20.7, 11.5; *m*/*z* (CI) 186 (M + NH_4^+, 100%).

(2*S*,1′*R*)-*N*-(1′-Phenylethyl)-2,3-dimethyl-2,5-dihydrofuran-2-carboxamide 30

To a solution of (–)-**13** (100 mg, 0.70 mmol) in THF (5 ml) was added CDI (125 mg, 0.78 mmol) and the mixture stirred for 1 h at room temperature. (*R*)-(+)-α-Methylbenzylamine (100 µl, 0.78 mmol) was then added and the reaction stirred overnight at room temperature. THF was then removed under reduced pressure, and the residue dissolved in ether (30 ml), and washed successively with 2 M (aq.) hydrochloric acid (5 ml), saturated aq. sodium bicarbonate solution (5 ml) and brine (5 ml). The solution was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a brown oil. Column purification, eluting with 30% ethyl acetate–petrol, afforded **30** as a yellow solid (116 mg, 52%), which was further purified by recrystallisation from dichloromethane–pentane to give colourless crystals. Mp 210–211 °C (Found C, 73.18; H, 8.03; N, 5.58%. $C_{15}H_{19}NO_2$ requires C, 73.31; H, 7.79; N, 5.88%. Found M^+, 245.1407. $C_{15}H_{19}NO_2$ requires M^+, 245.1416); ν_{max}/cm^{-1} 2971, 2926, 1667 (C=O); δ_H (360 MHz, $CDCl_3$) 7.26–7.14 (5H, m), 5.38 (1H, m), 4.98 (1H, quintet, *J* 7.0), 4.59–4.85 (2H, m), 1.76–1.74 (3H, m), 1.43–1.41 (6H, m); δ_C (100 MHz, $CDCl_3$) 172.0 (C=O), 143.4, 140.0, 128.8, 127.0, 125.9, 119.9, 91.9, 73.8, 48.0, 22.8, 22.0, 12.3; *m*/*z* (CI) 246 (M + H^+, 100%); $[\alpha]_D$ −131.56 (*c* 1.0 in EtOH).

Acknowledgements

We wish to thank Merck Sharp and Dohme and the EPSRC for funding this project. AstraZeneca Pharmaceuticals (Strategic Research Fund) and Pfizer are also thanked for unrestricted financial support.

References

1 For reviews see: T. J. Donohoe, R. Garg and C. A. Stevenson, *Tetrahedron: Asymmetry*, 1996, **7**, 317; T. J. Donohoe, P. M. Guyo and A. Raoof, *Targets in Heterocyclic Systems*, Italian Society of Chemistry, 1999, **3**, pp. 117–145.
2 For reviews of the Birch reduction see: L. N. Mander, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol. 8; P. W. Rabideau and Z. Marcinow, *Org. React.*, 1992, **42**, 1; P. W. Rabideau, *Tetrahedron*, 1989, **45**, 1579.
3 T. J. Donohoe and P. M. Guyo, *J. Org. Chem.*, 1996, **61**, 7664; T. J. Donohoe, P. M. Guyo, R. L. Beddoes and M. Helliwell, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 667; T. J. Donohoe, R. R. Harji and R. P. C. Cousins, *Tetrahedron Lett.*, 2000, **41**, 1331.
4 T. J. Donohoe, unpublished results.
5 T. Kinoshita and T. Miwa, *Carbohydr. Res.*, 1973, **28**, 175; T. Kinoshita, K. Miyano and T. Miwa, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1865; J. Slobbe, *Aust. J. Chem.*, 1976, **29**, 2553; T. Kinoshita and T. Miwa, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 223: see also reference 8.
6 For recent references see: A. G. Schultz, T. J. Guzi, E. Larsson, R. Rahm, K. Thakkar and J. M. Bidlack, *J. Org. Chem.*, 1998, **63**, 7795; A. G. Schultz, M. A. Holoboski and M. S. Smyth, *J. Am. Chem. Soc.*, 1996, **118**, 6210 and references therein.
7 T. J. Donohoe, M. Helliwell, C. A. Stevenson and T. Ladduwahetty, *Tetrahedron Lett.*, 1998, **39**, 3071.
8 I. M. Coggiola, *Nature* (*London*), 1963, **200**, 954; T. Kinoshita and T. Miwa, *J. Chem. Soc.*, *Chem. Commun.*, 1974, 181; T. Masamune, M. Ono and H. Matsue, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 491; A. J. Birch and J. Slobbe, *Tetrahedron Lett.*, 1975, 627; A. J. Birch and J. Slobbe, *Tetrahedron Lett.*, 1976, 2079; J. E. Semple, P. C. Wang, Z. Lysenko and M. M. Joullie, *J. Am. Chem. Soc.*, 1980, **102**, 7505; Y. Ohta, M. Onoshima, M. Tamura, R. Tanaka, Y. Morimoto, K. Yoshihara and T. Kinoshita, *J. Heterocycl. Chem.*, 1998, **35**, 461.
9 T. Kinoshita, D. Ichinari and J. Sinya, *J. Heterocycl. Chem.*, 1996, **33**, 1313.
10 See: I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York, 1976, p. 45.
11 A. G. Shultz, M. Macielag, P. Sundaraman, A. G. Taveras and M. Welch, *J. Am. Chem. Soc.*, 1988, **110**, 7828.
12 Both enantiomers of this amine can also be prepared on a large scale, see: Y. Yamamoto, J. Hoshino, Y. Fujimoto, J. Ohmoto and S. Sawada, *Synthesis*, 1993, 298.
13 W. Bauer, T. Laube and D. Seebach, *Chem. Ber.*, 1985, **118**, 764; T, Laube, J. D. Dunitz and D. Seebach, *Helv. Chim. Acta*, 1985, **68**, 1373.
14 For examples see: T. J. Donohoe, C. A. Stevenson, M. Helliwell, R. Irshad and T. Ladduwahetty, *Tetrahedron: Asymmetry*, 1999, **10**, 1315; T. J. Donohoe, J.-B. Guillermin, C. Frampton and D. S. Walters, *Chem. Commun.*, 2000, 465.
15 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1966.