# Partial reduction of 3-heteroatom substituted 2-furoic acids: the role of an *ortho* group in viability and stereoselectivity

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The synthesis of 2-furoic acid derivatives containing both 3-methoxy and 3-TMS groups is described. Reductive alkylation proceeded well to give us access to a series of highly functionalised dihydrofurans with potential for further elaboration. Of the two groups tested at C-3, the TMS derivative was found to be the more useful and gave rise to high levels of stereoselectivity when attached to a furan bearing a chiral auxiliary at C-2. A modification of the reaction conditions was made which enabled the TMS group to be cleaved during the reduction reaction without loss of stereoselectivity. Finally, it was also shown that the chiral auxiliary could be removed under acidic conditions to form 2-alkyl-3-TMS substituted dihydrofurans with excellent levels of enantiomeric purity.

## Introduction

We have recently shown that the partial reduction reaction, as applied to aromatic heterocycles, is a useful methodology for producing highly functionalised and stereochemically defined heterocyclic substrates with considerable potential for use in organic synthesis.[1]

Investigations into the partial reduction of electron-deficient pyrroles also showed that the conditions typically used for reductive alkylation (*i.e.* the Birch reduction, Na, $NH_3$, then add electrophile) could be replaced successfully with an ammonia-free variant that utilised lithium, naphthalene and bis(methoxyethyl)amine (BMEA) in THF.[2] These reaction conditions add greatly to the basic methodology because, for the first time, they allow reactive electrophiles to be used as partners in reductive alkylation reactions.

Studies into the partial reduction of electron-deficient furoic acid derivatives[3] have enabled us to develop a system which gives very high levels of diastereoselectivity during reductive alkylation reactions.[4] Two different chiral auxiliaries have been shown to give good stereoselectivity, *provided* that an *ortho* substituent is present (*i.e.* C-3 must not be substituted with a hydrogen).[5] In these cases we presume that the requirement for such a substituent at C-3 is in fact a matter of controlling enolate geometry (Fig. 1).

Although 3-methyl and other 3-alkyl substituted furans[6] are good substrates for partial reduction, we wanted to expand the range of groups at C-3 and in particular to develop heteroatom replacements that may prove to be more versatile in organic synthesis. We have previously communicated the stereoselective partial reduction of 3-silyl-2-furoic acids[7] and in this paper we wish to discuss our results in full.

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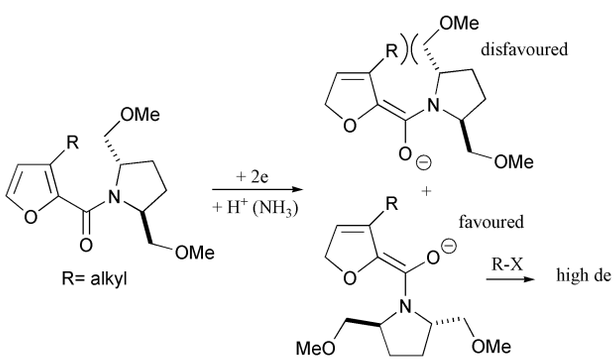


**Fig. 1**

## Results and discussion

### Synthesis and reduction of 3-methoxy-2-furoic acids

Initially, we investigated the role of a methoxy group at C-3 on the furan nucleus; the type of substitution pattern expected after reduction bears clear similarities to that obtained from anisic acid,[8] and the enol ethers that should be produced *via* a reductive alkylation will have plenty of scope for elaboration. We prepared 3-methoxyfuran *via* a literature route[9] and then performed a mono-acylation at C-2 with trichloroacetyl chloride. The activated carbonyl compound **2** thus produced was immediately treated with *i*-PrOH–NaH to give the requisite ester **3** in good (60%) overall yield. This compound was used as a model system for reduction, designed to investigate the viability of this type of substitution pattern under reducing conditions (Scheme 1).

The main part of our work utilised ammonia-free reducing conditions to accomplish the reductive alkylation of these derivatives; this study did give some useful alkylated dihydrofurans containing enol ethers (Scheme 2). However, this reaction was complicated by the persistent formation of minor amounts

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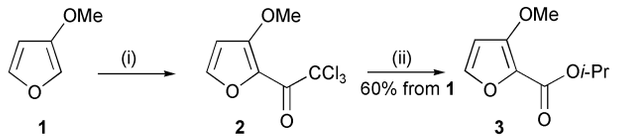
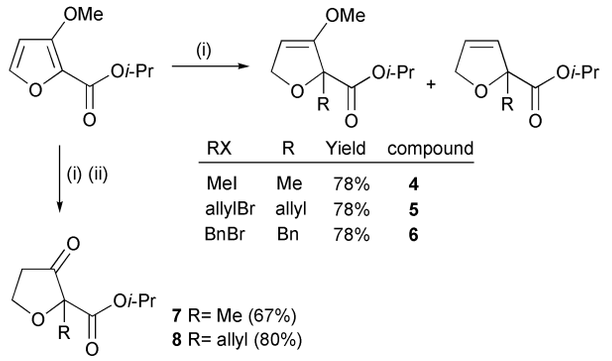



**Scheme 1** *Reagents and conditions*: i. $Cl_3CCOCl$, $Et_3N$, $CH_2Cl_2$, 0 °C, 1.5 h; ii. NaH, *i*-PrOH, rt, 2 h.




| RX | R | Yield | compound |
|---|---|---|---|
| MeI | Me | 78% | **4** |
| allylBr | allyl | 78% | **5** |
| BnBr | Bn | 78% | **6** |

**Scheme 2** *Reagents and conditions*: i. Li, naphthalene, BMEA, −78 °C, 1 h, then *t*-BuBr followed by RX; ii. (aq.) HCl.

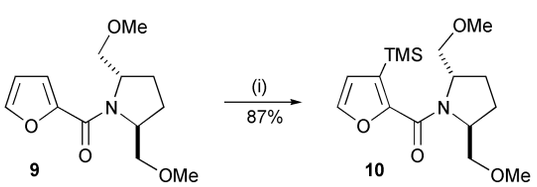
of the C-3 demethoxy reduced compounds (typically 4–6 : 1 mixtures) which proved difficult to separate from their enol ether counterparts. This type of reductive cleavage has been noted before with benzenoid systems.[10] In line with literature precedent, substantial modifications were made to the reducing system (change of metal to Na and K; use of various solvents and use of different electron carriers, *etc.*) to try and reduce this side-reaction, but without success. The yields quoted in Scheme 2 represent those for the mixtures. The enol ethers **4**–**6** each showed a band in the IR spectrum at 1667 $cm^{-1}$, clearly indicative of an enol ether functional group.

Eventually, we found that reaction of the crude reaction mixtures with dilute HCl promoted hydrolysis of the enol ethers and enabled isolation of the C-3 keto compounds in 67–80% yield. We did find, however, that, once formed, the keto compounds **7** and **8** were rather unstable and tended to decompose.

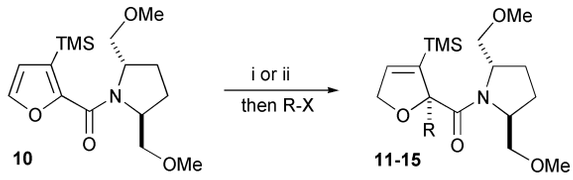
Although the synthesis and partial reduction of this 3-methoxy-2-furoic acid derivative were successful, we did not pursue this line of research further because of the following problems: i. the synthesis of 3-methoxyfuran on a large scale is laborious; ii. the demethoxy dihydrofurans that are produced *via* this sequence were difficult to remove from the corresponding enol ethers; iii. the 3-keto compounds formed by acidic hydrolysis of the reaction mixture were unstable.

### Introduction of a silyl group at C-3

Given the difficulties encountered during the formation of 3-methoxyfuran, we decided to attempt lithiation of the readily available 2-furoic acid nucleus hoping that the presence of an *ortho*-metallating group at C-2 should aid lithiation at C-3 rather than deprotonation at C-5.[11] Encouraged by some literature precedent,[12] we decided to introduce an amide at C-2. In fact, this suited our longer terms goals perfectly as it enabled us to use the chiral auxiliary based compound **9**, which was made from the corresponding amine and furoyl chloride in 99% yield (Scheme 3). This amide proved to be an ideal *ortho*-directing




**Scheme 3** *Reagents and conditions*: i. TMSCl, BuLi, THF, −78 °C.




| Entry | RX | R | Yield (%) | de (%) | Compound |
|---|---|---|---|---|---|
| 1 | MeI | Me | 90 | 94 | **11** |
| 2[a] | MeI | Me | 68 | 94 | **11** |
| 3 | BnBr | Bn | 86 | 94 | **12** |
| 4 | *i*BuI | *i*Bu | 70 | 94 | **13** |
| 5[b] | $I(CH_2)_3Cl$ | $(CH_2)_3Cl$ | 80 | 94 | **14** |
| 6[b] | MOMCl | $CH_2OMe$ | 92 | 94 | **15** |

**Scheme 4** *Reagents and conditions*: i. Na, $NH_3$, −78 °C; ii. [a]Li, naphthalene, $(MeOCH_2CH_2)_2NH$, THF, −78 °C. [b] The de of amides **14** and **15** is assigned by analogy.

group and we were able to isolate the C-3 silylated compound **10** in excellent yield. The $^1H$ NMR spectrum of **10** showed two aryl protons at $\delta$ 6.18 and 7.17 ppm which is consistent with substitution at C-3 (*vide infra*). We suspect that this particular amide has a favourable combination of both steric hindrance and chelating ability that makes it ideal for *ortho*-lithiation. Further work showed that other amide derivatives were not as effective at promoting C-3 lithiation and gave nucleophilic attack at the amide carbonyl or C-5 lithiation (with dialkyl or prolinol-derived amides) as side reactions.

Next, we investigated the Birch reductive alkylation reaction on amide **10**, and found that the furan nucleus could indeed be partially reduced and a range of electrophiles incorporated at C-2 (Scheme 4). Gratifyingly, reduction of **10** under 'ammonia-free' conditions [Li, naphthalene, $(MeOCH_2CH_2)_2NH$] also gave good yields and high stereoselectivity (see entry 2). In each case, examination of the $^1H$ NMR spectrum of the reduced products indicated that the furan ring had been transformed: typically, we could observe a triplet at $\delta$ 5.9 ppm corresponding to the C-4 vinyl proton and a range of signals attributed to the alkyl portion of the electrophile.

The NMR spectra of the crude reaction mixtures also revealed the presence of a single compound. Because the *ortho*-lithiation only worked well when the chiral auxiliary was installed, we could not easily prepare an authentic 1 : 1 diastereoisomeric mixture with which to compare the reduction reactions. In order to assess the diastereoselectivity of the reduction, we decided to analyse the enantiomeric excess of the acids formed after hydrolysis of the amide auxiliary; clearly, no scrambling of the stereochemistry at C-2 can have occurred during hydrolysis.[4,5] The carboxylic acids formed after removal of the auxiliary were shown to have ≥94% ee, *vide infra*, and the de of compounds **11**–**15** is therefore assigned by logical extrapolation. It should also be noted that the material which was subjected to the reduction, then hydrolysis and enantiomeric excess analysis was not subject to purification by chromatography at any stage thus ensuring the validity of the correlation between ee and de.

The relative stereochemistry of the compounds shown in Scheme 4 was assigned by X-ray crystallography ‡ on a derivative

‡ Crystal data: [(*S*)-2-hydroxymethylpyrrolidin-1-yl][(*R*)-2-methyl-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]methanone **16**, $C_{14}H_{25}NO_3Si$, $M$ = 283.44, orthorhombic, space group $P2_12_12_1$, crystal dimensions 0.40 × 0.37 × 0.20 mm, colourless prismatic crystal, $a$ = 9.1439(11), $b$ = 11.6771(15), $c$ = 15.438(2) Å, $U$ = 1648.4(4) Å$^3$, $T$ = 123 K, $Z$ = 4, $\mu$(Mo-K$\alpha$) = 0.7107 Å, 15940 reflections collected, 4186 unique [$R$(int) = 0.0149]. Final $R$ indices [$I > 2\sigma(I)$], $R_1$ = 0.0335, $\omega R^2$ = 0.0931. CCDC reference number 183703. See http://www.rsc.org/suppdata/p1/b2/b203437a/ for crystallographic files in .cif or other electronic format.

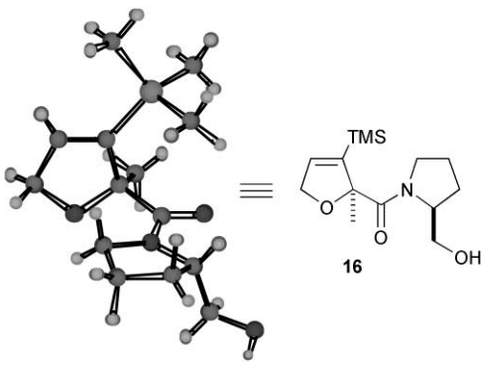
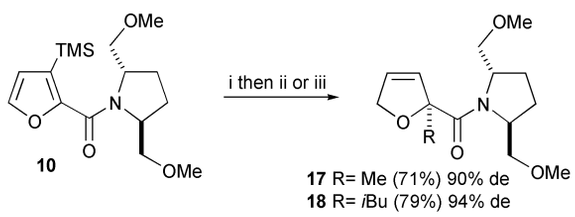



**Fig. 2** X-Ray structure of **16**.

made with (*S*)-prolinol **16** (Fig. 2). Hydrolysis of this compound produced an acid with the same absolute configuration as that released from **11** under acidic conditions.

Further investigation of the reductive alkylation revealed that the TMS group need not be retained during the Birch reduction (Scheme 5). After addition of the substrate to




**Scheme 5** *Reagents and conditions*: i. Na, $NH_3$, −78 °C, then warm to −40 °C; ii. MeI, −78 °C; iii. *i*-BuI, −78 °C.

the reducing medium, the reaction was warmed from −78 to −40 °C, and then recooled to −78 °C, before addition of an electrophile. This procedure gave the two de-trimethylsilyl compounds **17** and **18** in good yield and with good stereoselectivity (again measured *via* the ee of acids formed after hydrolysis). This is a significant result as it removes the straitjacket imposed by the requirement for an *ortho*-substituent on the furan and this in itself greatly expands the scope of our methodology.

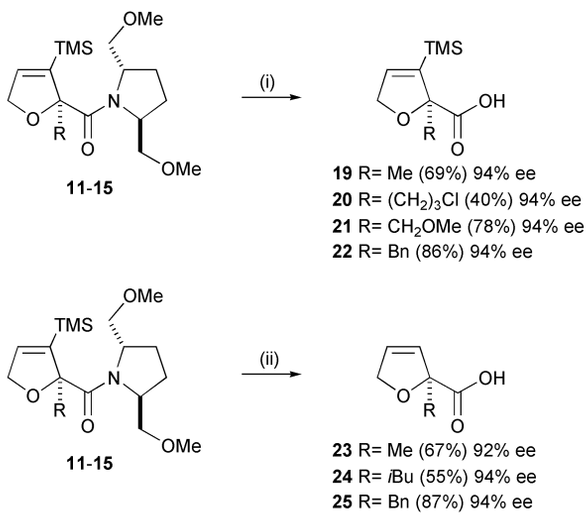
## Mechanism

The formation of the partially reduced products and the sense of stereoselectivity observed during alkylation is consistent with our previous model (Fig. 1), which needs little modification. We believe that addition of two electrons and then a proton (from ammonia) to the furan generates an extended enolate **A** that reacts (stereoselectively) at the α position (Fig. 3). The C-3 TMS group simply sets the enolate geometry (*E*) to minimise steric interactions and possibly to allow an attractive O⟶Si coordination. The relative stereochemistry of the products can be explained from this (*E*)-enolate if we assume that the auxiliary shields the upper face more effectively than the lower. Of course, we have made the reasonable assumption that this (*E*)-enolate reacts with the same sense of selectivity with each electrophile that it encounters.

The desilylation reaction that is encountered at −40 °C is possibly derived from silyl migration from carbon to oxygen of the enolate[13] [this also fits with (*E*)-enolate geometry] followed by protonation of the incipient carbanion by ammonia, **B⟶C** (Fig. 4). The TMS silyl enol ether product **C** could then be destroyed by sodamide (generated as part of our mechanism) to furnish a sodium enolate **D** similar to the one described above. This enolate will then react with the same sense of diastereoselectivity as its predecessor (Fig. 4).

## Hydrolysis of the auxiliary and formation of enantiopure acids

We have already noted the relative ease with which the methoxymethylpyrrolidine auxiliary can be hydrolysed under acidic conditions without affecting stereochemical integrity at C-2.[4,5] The dihydrofurans **11**–**15** described above proved to be no exception and the respective carboxylic acids were liberated after reaction with (aq.) 3 M HCl (Scheme 6). With some of the




**Scheme 6** *Reagents and conditions*: i. (aq.) 3 M HCl, Δ; ii. (aq.) 5 M HCl, Δ.

more bulky groups at C-2 (*e.g.* **13**, R = *i*-Bu) we found that more forcing conditions were required; reaction with (aq.) 5 M HCl cleaved both the auxiliary and the TMS group by *ipso* desilylation.[14] This leads us to report two exciting possibilities for hydrolysis that can either retain or remove the TMS group simply depending on the strength of acid used.

## Measurement of enantiomeric excesses

Note must be made here of the methods used to determine the enantiomeric excesses of the acids shown in Scheme 6, because this information was crucial to our determination of the diastereoselectivity of the Birch reduction. In each case, we

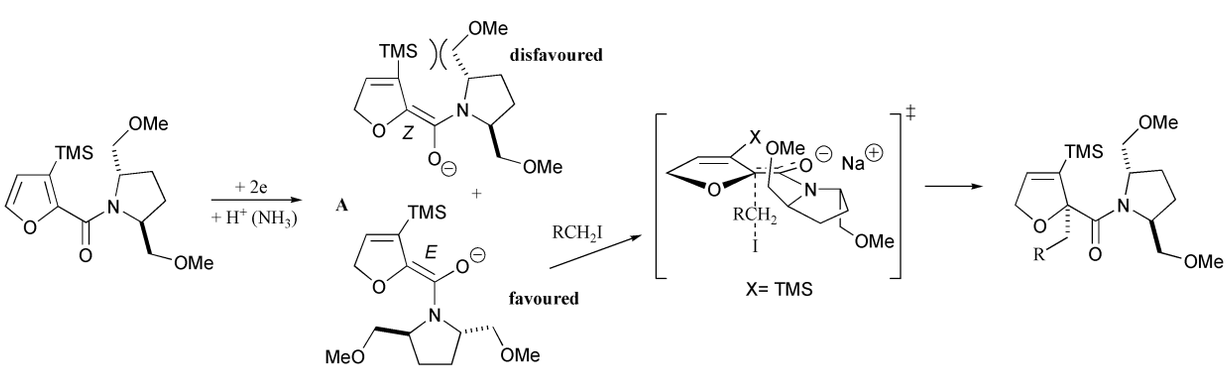



**Fig. 3**

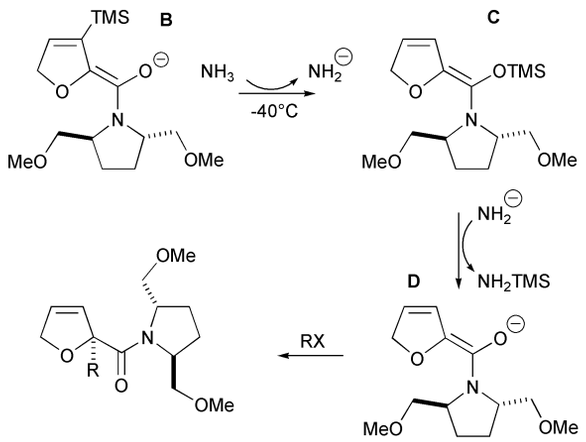
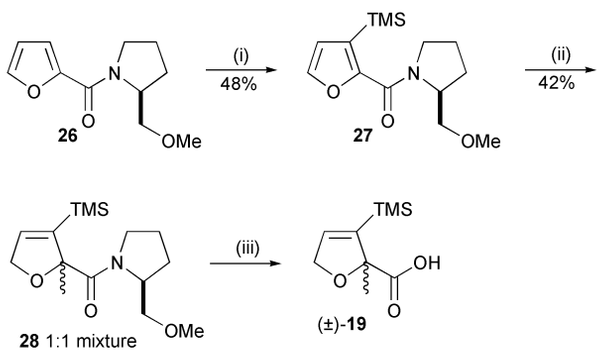



**Fig. 4**

made a racemic standard with which to compare (by GC) the material produced through our methodology. Making the racemic acids with a TMS at C-3 was difficult and eventually we used methylprolinol-derived amide **26** because it (a) lithiated at C-3 with reasonable efficiency and (b) was *not* stereoselective under reductive alkylation conditions[15] (Scheme 7). After




**Scheme 7** *Reagents and conditions*: i. BuLi, TMSCl, THF; ii. Na, $NH_3$, then MeI, −78 °C; iii. (aq.) HCl, Δ.

hydrolysis of the 1 : 1 mixtures we obtained our racemic TMS-containing acids. Synthesis of the racemic acids which lacked the C-3 TMS group was straightforward from the *i*-Pr ester of furoic acid (reduction followed by hydrolysis).[3,16] We attempted to assess the enantiomeric excess of either the 3-TMS (or the de-TMS) acid for each electrophile that was used in the Birch reduction. Using GC with a chiral column, this was achieved for compounds **19**, **20** and **25**. However, we were not able to split the enantiomers of acids **20** or **21**: the enantiomeric excesses quoted in these cases (and therefore the diastereoisomeric excesses quoted in entries 5 and 6, Scheme 4) are made by analogy as it seems unlikely that the enolate **A** would react with MOMCl and $I(CH_2)_3Cl$ with very different levels of selectivity to those observed for the other alkylating agents.

## Conclusions

Our work has defined two *ortho* substituents that can be successfully utilised during the Birch reduction of 2-furoic acid derivatives. Of these two, the 3-TMS group was the easiest to introduce and also to remove. Moreover, the TMS group was efficient at controlling enolate geometry during the reductive alkylation and, therefore, led to high levels of stereoselectivity under Birch and ammonia-free conditions. Our ability to either retain or remove the TMS group during the Birch reduction is noteworthy as it greatly increases the scope and application of this methodology.

## Experimental

### General

All reactions, except aqueous reactions, were carried out under an atmosphere of argon. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Gemini 200 at 200 MHz, a Varian Unity Inova 300 at 300 MHz, a Varian Unity Inova 400 at 400 MHz and a Varian Unity Inova 500 at 500 MHz. $^{13}C$ nuclear magnetic resonance spectra were recorded on a Varian Unity Inova 300 at 75 MHz, a Varian Unity Inova 400 at 100 MHz and a Varian Unity Inova 500 at 125 MHz. Chemical shifts ($\delta$) are quoted in parts per million (ppm), downfield from tetramethylsilane. Coupling constants ($J$) are quoted in Hz. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FTIR as evaporated films (EF). 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 per 100 mL. Mass spectra were recorded on a Kratos Concept or a Fisson VG Trio 2000 using electron impact or chemical ionisation (CI). Melting points were obtained on a Kofler block and are uncorrected.

Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as indicator, under an atmosphere of argon. Dichloromethane (DCM) was distilled over calcium hydride. Petroleum ether (boiling range 40–60 °C) was distilled prior to use and ammonia was distilled from sodium metal and ferric chloride.

### 3-Methoxyfuran-2-carboxylic acid isopropyl ester 3

To a stirred solution of 3-methoxyfuran (1.92 g, 19.6 mmol) in DCM (25 mL) at 0 °C was added $Et_3N$ (5.50 mL, 39.2 mmol) followed by trichloroacetyl chloride (4.37 mL, 39.2 mmol) dropwise over 1 min. The resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched ($H_2O$, 100 mL) then extracted with EtOAc (3 × 50 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was dissolved in *i*-PrOH (200 mL) and NaH (60% disp. in oil, 599 mg, 15.0 mmol) was added in a single portion. The resulting mixture was stirred at rt for 2 h. The reaction was quenched ($H_2O$, 50 mL) then extracted with EtOAc (3 × 25 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (1 : 10 EtOAc–petrol) to afford the title compound as a colourless oil (2.16 g, 60%) (Found $M^+$ 184.0738, $C_9H_{12}O_4$ requires 184.0736, deviation 1.09 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2980, 1703, 1602, 1274, 1090; $\delta_H$ (300 MHz, $CDCl_3$) 1.28 (6H, d, $J$ 6.5), 3.92 (3H, s), 5.24 (1H, q, $J$ 6.5), 6.38 (1H, d, $J$ 2.0), 7.36 (1H, d, $J$ 2.0); $\delta_C$ (75 MHz, $CDCl_3$) 21.88, 58.81, 67.74, 102.33, 144.7, 155.0, 158.3, 172.6; $m/z$ (CI) 184 (M + 1, 100%).

### 3-Methoxy-2-methyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester 4

A solution of lithium (20 mg, 2.8 mmol) and naphthalene (358 mg, 2.80 mmol) in THF (30 mL) was sonicated for 2 h. To this deep green solution cooled to −78 °C was added bis(2-methoxyethyl)amine (0.41 mL, 2.80 mmol) followed by the substrate **3** (103 mg, 0.56 mmol) in THF (20 mL) dropwise over 2 min. After 45 minutes at −78 °C *t*-BuBr (0.40 mL, 2.80 mmol) was added followed by methyl iodide (0.17 mL, 2.80 mmol). The reaction was quenched after a further 15 minutes by addition of solid ammonium chloride (approx. 1 g). The solvents were evaporated *in vacuo* and the crude material was purified by column chromatography (neat petrol then 1 : 10 EtOAc–petrol) to afford the title compound as a colourless oil (87 mg, 78%) and as an inseparable, approx. 4 : 1 mixture with 2-methyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester.

**Compound 4.** (Found M + $H^+$ 201.1122, $C_{10}H_{17}O_4$ requires 201.1127, deviation 2.46 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2981, 1735, 1667, 1266, 1250, 1133, 1103; $\delta_H$ (300 MHz, $CDCl_3$) 1.29 (6H, 2 × d, *J* 6.0), 1.55 (3H, s), 3.71 (3H, s), 4.75 (1H, dd, *J* 1.5, 10.0), 4.78 (2H, m), 5.05 (1H, q, *J* 6.0); $\delta_C$ (75 MHz, $CDCl_3$) 21.50, 29.61, 57.91, 68.59, 72.37, 85.30, 91.29, 157.3, 171.7; *m*/*z* (CI) 218 (M + 18, 90%), 201 (M + 1, 100).

Several NMR peaks were detected for 2-methyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester: $\delta_H$ (300 MHz, $CDCl_3$) 1.56 (3H, s), 5.85, (1H, dt, *J* 2.5, 6.0), 5.99 (1H, app. dt, *J* 6.0); $\delta_C$ (75 MHz, $CDCl_3$) 21.53, 21.58, 24.01, 68.42, 75.67, 90.02, 128.02, 130.11.

### 3-Methoxy-2-allyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester 5

A solution of lithium (19 mg, 2.7 mmol) and naphthalene (352 mg, 2.74 mmol) in THF (30 mL) was sonicated for 1.5 h. To this deep green solution cooled to −78 °C was added bis(2-methoxyethyl)amine (0.40 mL, 2.74 mmol) followed by the substrate **3** (101 mg, 0.55 mmol) in THF (20 mL) dropwise over 1 min. After 45 minutes at −78 °C *t*-BuBr (0.32 mL, 2.74 mmol) was added followed by allyl bromide (0.24 mL, 2.74 mmol). The reaction was quenched after a further 15 minutes by addition of solid ammonium chloride (approx. 1 g). The solvents were removed *in vacuo* and the crude material was purified by column chromatography (neat petrol then 1 : 10 EtOAc–petrol) to afford the title compound as a colourless oil (97 mg, 78%) (Found $M^+$ 227.1282, $C_{12}H_{19}O_4$ requires 227.1283, deviation 0.44 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2981, 1735, 1667; $\delta_H$ (300 MHz, $CDCl_3$) 1.26 (6H, 2 × d, *J* 6.0), 2.60 (1H, ddt, *J* 1.0, 7.0, 14.5), 2.72 (1H, dd, *J* 7.0, 14.5), 3.68 (3H, s), 4.63 (1H, dd, *J* 2.0, 11.0), 4.77 (2H, app. dd, *J* 2.0), 5.10 (3H, m), 5.76 (1H, m); $\delta_C$ (75 MHz, $CDCl_3$) 21.72, 21.79, 38.89, 57.98, 68.77, 72.96, 87.81, 92.44, 118.4, 132.1, 155.4, 170.9; *m*/*z* (CI) 244 (M + 18, 100%), 227 (M + 1, 40).

### 3-Methoxy-2-benzyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester 6

A solution of lithium (19 mg, 2.7 mmol) and naphthalene (341 mg, 2.65 mmol) in THF (30 mL) was sonicated for 1.5 h. To this deep green solution cooled to −78 °C was added bis-(2-methoxyethyl)amine (0.39 mL, 2.7 mmol) followed by the substrate **3** (98 mg, 0.53 mmol) in THF (20 mL) dropwise over 1 min. After 1 h at −78 °C *t*-BuBr (0.31 mL, 2.7 mmol) was added followed by benzyl bromide (0.32 mL, 2.7 mmol). The reaction was quenched after a further 15 minutes by addition of solid ammonium chloride (approx. 1 g). The solvents were removed *in vacuo* and the crude material was purified by column chromatography (neat petrol then 1 : 10 EtOAc–petrol) to afford the title compound as a colourless oil (97 mg, 78%) and as an inseparable, approx. 5 : 1 mixture with 2-benzyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester.

**Compound 6.** (Found $M^+$ 276.1358, $C_{16}H_{20}O_4$ requires 276.1362, deviation 0.44 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2978, 1732, 1668, 1248; $\delta_H$ (300 MHz, $CDCl_3$) 1.02 (6H, 2 × d, *J* 6.0), 3.09 (3H, s), 3.49 (1H, d, *J* 14.5), 3.54 (1H, d, *J* 14.5), 4.03 (1H, app. t, *J* 1.5), 4.21 (1H, dd, *J* 1.5, 10.0), 4.67 (1H, dd, *J* 1.5, 10.0), 5.02 (1H, q, *J* 6.0), 7.10–7.40 (5H, m); $\delta_C$ (75 MHz, $CDCl_3$) 21.58, 21.62, 40.65, 57.16, 68.46, 73.21, 89.27, 93.39, 127.9, 128.0, 129.92, 137.0, 155.5, 170.9; *m*/*z* (CI) 277 (M + 1, 10%), 264 (10), 245 (50), 189 (100).

Several NMR peaks were detected for 2-benzyl-2,5-dihydrofuran-2-carboxylic acid isopropyl ester: $\delta_H$ (300 MHz, $CDCl_3$) 0.96 (1H, d, *J* 6.5), 3.16 (1H, d, *J* 13.5), 3.30 (1H, d, *J* 13.5), 4.52 (1H, dt, *J* 6.5, 13.5), 4.95 (1H, appdt, *J* 1.5, 6.5), 5.65 1H, dt, *J* 2.5, 6.5); $\delta_C$ (75 MHz, $CDCl_3$) 21.62, 43.01, 76.19, 126.6, 127.8, 128.2, 129.1, 130.9, 131.0.

### 2-Methyl-3-oxotetrahydrofuran-2-carboxylic acid isopropyl ester 7

A solution of lithium (16 mg, 2.3 mmol) and naphthalene (296 mg, 2.31 mmol) in THF (30 mL) was sonicated for 2 h. To this deep green solution cooled to −78 °C was added bis-(2-methoxyethyl)amine (0.34 mL, 2.3 mmol) followed by the substrate **3** (85 mg, 0.46 mmol) in THF (20 mL) dropwise over 1 min. After 45 minutes at −78 °C *t*-BuBr (0.33 mL, 2.3 mmol) was added followed by methyl iodide (0.14 mL, 2.3 mmol). The reaction was quenched after a further 15 minutes by addition of solid ammonium chloride (approx. 1 g). The mixture was diluted with $Et_2O$ (50 mL) and washed with 2 M aq. HCl (50 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (neat petrol then 1 : 10 EtOAc–petrol) to afford the title compound as a colourless oil (58 mg, 67%) (Found M + $NH_4^+$ 204.1234, $C_9H_{18}NO_4$ requires 204.1236, deviation 0.98 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2982, 1769, 1738, 1262, 1104, 1084; $\delta_H$ (300 MHz, $CDCl_3$) 1.28 (6H, 2 × d, *J* 5.0), 1.48 (3H, s), 2.63 (2H, app. t, *J* 6.0), 4.36 (2H, app. t, *J* 6.0), 5.05 (1H, q, *J* 5.0); $\delta_C$ (75 MHz, $CDCl_3$) 19.58, 21.63, 35.53, 64.20, 69.85, 82.66, 168.3, 210.8; *m*/*z* (CI) 204 (M + 18, 100%).

### 2-Allyl-3-oxotetrahydrofuran-2-carboxylic acid isopropyl ester 8

A solution of lithium (21 mg, 3.0 mmol) and naphthalene (390 mg, 3.04 mmol), in THF (30 mL) was sonicated for 1.5 h. To this deep green solution cooled to −78 °C was added bis-(2-methoxyethyl)amine (0.45 mL, 3.0 mmol) followed by the substrate **3** (112 mg, 0.61 mmol) in THF (20 mL) dropwise over 1 min. After 45 minutes at −78 °C *t*-BuBr (0.35 mL, 3.0 mmol) was added followed by allyl bromide (0.26 mL, 3.0 mmol). The reaction was quenched after a further 15 minutes by addition of solid ammonium chloride (approx. 1 g). The mixture was diluted with $Et_2O$ (50 mL) and washed with 2 M aq. HCl (50 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (neat petrol then 1 : 10 EtOAc–petrol) to afford the title compound as a colourless oil (103 mg, 80%) (Found M + $H^+$ 213.1125, $C_{11}H_{17}O_4$ requires 213.1127, deviation 0.93 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2980, 1765, 1736, 1105; $\delta_H$ (300 MHz, $CDCl_3$) 1.28 (6H, 2 × d, *J* 6.5), 2.55 (2H, m), 2.78 (2H, ddt, *J* 1.0, 7.0, 14.5), 4.38 (2H, m), 5.06 (1H, q, *J* 6.5), 5.16 (2H, m), 5.74, (1H, m); $\delta_C$ (75 MHz, $CDCl_3$) 21.62, 21.66, 36.15, 38.21, 54.51, 69.95, 85.49, 119.9, 130.9, 167.4, 209.7; *m*/*z* (CI) 230 (M + 18, 100%).

### [(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]furan-2-yl-methanone 9

A solution of (2*S*,5*S*)-bis(methoxymethyl)pyrrolidine (1.01 g, 6.33 mmol) in DCM (10 mL) and 2 M sodium hydroxide (10 mL) was cooled to 0 °C. To this solution was added slowly 2-furoyl chloride (0.75 mL, 7.59 mmol) dropwise over 2 min and the resulting mixture was stirred vigorously at rt for 24 h. The reaction mixture was then extracted with DCM (3 × 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (40 : 60 ethyl acetate–petrol) to afford the title compound as a white solid (1.59 g, 6.27 mmol, 99%) (Found M + $H^+$ 254.1392, $C_{13}H_{20}NO_4$ requires 254.1389, deviation 1.2 ppm); mp 41–43 °C; $[\alpha]_D$ = −103.7 (*c* 0.28 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 2968, 1613; $\delta_H$ (300 MHz; $CDCl_3$) 1.92–2.08 (3H, m), 2.14–2.28 (1H, m), 3.08–3.22 (2H, m), 3.16 (3H, s), 3.26 (3H, s), 3.40 (1H, t, *J* 8.0), 3.60 (1H, dd, *J* 8.5 and 2.0), 4.42–4.58 (1H, m), 4.72–4.85 (1H, m), 6.51 (1H, dd, *J* 3.5 and 2.0), 7.15 (1H, dd, *J* 3.5 and 1.0), 7.50 (1H, dd, *J* 2.0 and 1.0); $\delta_C$ (75 MHz; $CDCl_3$) 24.08, 27.41, 57.25, 57.87, 58.88, 58.97, 71.71, 73.88, 111.5, 116.5, 143.6, 148.7, 158.1; *m*/*z* (CI) 254 (M + 1, 100%), 255 (31), 95 (28), 208 (16).

**[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][3-(trimethylsilyl)furan-2-yl]methanone 10**

To a solution of **9** (0.33 g, 2.1 mmol) in THF (20 mL) containing chlorotrimethylsilane (0.40 mL, 3.16 mmol) at −78 °C was added dropwise *n*-BuLi (2.0 M, 1.25 mL, 2.50 mmol). The resulting solution was stirred at −78 °C for 30 min before being allowed to warm up to room temperature over 1 h. The reaction was quenched by the addition of brine (50 mL) and then extracted (DCM, 3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (20 : 80 diethyl ether–petrol) to afford the title compound as colourless crystals (595 mg, 1.83 mmol, 87%) (Found M + $H^+$ 326.1780, $C_{16}H_{28}NO_4Si$ requires 326.1787, deviation 2.1 ppm); mp 39–40 °C; $[a]_D$ = −105.1 (*c* 0.41 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 2951, 1615; $\delta_H$ (300 MHz; $CDCl_3$) −0.01 (9H, s), 1.60–1.78 (3H, m), 1.82–2.00 (1H, m), 2.76 (2H, d, *J* 6.5), 2.92 (3H, s), 3.04 (3H, s), 3.14 (1H, dd, *J* 9.0 and 7.0), 3.28 (1H, dd, *J* 9.0 and 3.0), 4.14–4.24 (1H, m), 4.42–4.52 (1H, m), 6.18 (1H, d, *J* 1.5), 7.17 (1H, d, *J* 1.5); $\delta_C$ (75 MHz; $CDCl_3$) −0.93, 24.23, 27.47, 57.25, 57.88, 58.90 (×2), 71.88, 73.89, 116.4, 126.2, 141.9, 152.3, 159.4; *m*/*z* (CI) 326 (M + 1, 100%), 327 (15), 208 (12).

**[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*R*)-2-methyl-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]methanone 11**

**Method 1.** To a blue solution of sodium (28 mg, 1.2 mmol) in freshly distilled liquid ammonia (30 mL) at −78 °C was added a solution of substrate **10** (100 mg, 0.31 mmol) in dry THF (10 mL). After 30 minutes, isoprene was added dropwise (until the blue colour dispersed) followed by addition of iodomethane (1.00 mL, 16.05 mmol) to give a yellow solution. After a further 30 minutes, the solution was quenched by saturated ammonium chloride (5 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (40 : 60 diethyl ether–petrol) to afford the title compound as a pale yellow oil (94 mg, 0.28 mmol, 90%).

**Method 2.** A solution of lithium (26 mg, 3.7 mmol) and naphthalene (473 mg, 3.69 mmol) in THF (20 mL) was sonicated for 30 minutes. To this deep green solution cooled to −78 °C was added bis(2-methoxyethyl)amine (0.55 mL, 3.7 mmol) followed by the substrate **10** (120 mg, 0.37 mmol). After 30 minutes at −78 °C methyl iodide (0.23 mL, 3.7 mmol) was added. The solution was quenched after a further 30 minutes by addition of solid ammonium chloride (approx. 1 g). The solvents were evaporated *in vacuo* and the crude material was purified by column chromatography (40 : 60 diethyl ether–petrol) to afford the title compound as a colourless oil (86 mg, 0.25 mmol, 68%) (Found M + $H^+$ 342.2108, $C_{17}H_{32}NO_4Si$ requires 342.2100, deviation 0.6 ppm); $[a]_D$ = −171.0 (*c* 3.48 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 2926, 1621; $\delta_H$ (300 MHz; $CDCl_3$) 0.00 (9H, s), 1.35 (3H, s), 1.66–1.94 (4H, m), 2.82 (1H, t, *J* 9.0), 3.00–3.12 (2H, m), 3.12 (3H, s), 3.18 (3H, s), 3.39 (1H, dd, *J* 9.0 and 3.0), 4.06–4.16 (1H, m), 4.46–4.64 (3H, m), 5.93 (1H, t, *J* 1.5); $\delta_C$ (75 MHz; $CDCl_3$) −0.749, 23.08, 27.25, 27.87, 57.62, 58.20, 58.61, 58.81, 71.50, 73.88, 74.92, 97.86, 136.3, 147.4, 172.6; *m*/*z* (CI) 342 (M + 1, 100%), 343 (18), 90 (17).

**[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*R*)-2-benzyl-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]methanone 12**

To a blue solution of sodium (71 mg, 3.1 mmol) in freshly distilled liquid ammonia (30 mL) at −78 °C was added a solution of substrate **10** (200 mg, 0.62 mmol) in dry THF (20 mL). After 30 minutes, isoprene was added dropwise (until the blue colour dispersed) followed by benzyl bromide (0.40 mL, 3.20 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by the addition of saturated ammonium chloride (50 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (10 : 90 ethyl acetate–petrol) to afford the title compound as a colourless oil (225 mg, 0.54 mmol, 87%) (Found M + $H^+$ 418.2418, $C_{23}H_{36}NO_4Si$ requires 418.2413, deviation 1.2 ppm); $[a]_D$ = −150.9 (*c* 0.32 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 2953, 1619; $\delta_H$ (300 MHz; $CDCl_3$) 0.00 (9H, s), 1.48–1.62 (4H, m), 2.51 (1H, t, *J* 8.5), 2.62 (1H, d, *J* 13.5), 2.66 (1H, t, *J* 9.5), 2.86 (1H, dd, *J* 8.5 and 3.5), 2.96 (3H, s), 2.99 (3H, s), 3.02 (1H, dd, *J* 3.5 and 9.5), 3.12 (1H, d, *J* 13.5), 3.94–4.02 (1H, m), 4.18 (1H, dd, *J* 1.0 and 14.0), 4.34 (1H, dd, *J* 1.5 and 14.0), 4.36–4.43 (1H, m), 5.87 (1H, t, *J* 1.5), 6.90–7.06 (5H, m); $\delta_C$ (75 MHz; $CDCl_3$) −0.47, 22.94, 27.06, 46.03, 57.48, 58.24, 58.66 (×2), 71.21, 74.12, 75.36, 100.9, 126.0, 127.4 (×2), 131.0 (×2), 137.8, 137.1, 146.6, 171.1; *m*/*z* (CI) 418 (M + 1, 100%), 419 (25), 90 (20).

**[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*R*)-2-isobutyl-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]methanone 13**

To a blue solution of sodium (28 mg, 1.2 mmol) in freshly distilled liquid ammonia (20 mL) at −78 °C was added a solution of substrate **10** (100 mg, 0.31 mmol) in dry THF (10 mL). After 30 minutes, isoprene was added dropwise (until the blue colour dispersed) followed by isobutyl iodide (1.0 mL, 8.7 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by addition of saturated ammonium chloride. The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (20 : 80 diethyl ether–petrol) to afford the title compound as a pale yellow oil (82 mg, 0.21 mmol, 70%) (Found M + $H^+$ 384.2571, $C_{20}H_{38}NO_4Si$ requires 384.2570, deviation 0.26 ppm); $[a]_D$ = −173.6 (*c* 3.30 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 2953, 1617; $\delta_H$ (300 MHz; $CDCl_3$) −0.00 (9H, s), 0.73 (3H, d, *J* 7.0), 0.76 (3H, d, *J* 7.0), 1.25 (1H, dd, *J* 6.0 and 13.5), 1.54 (1H, sept, *J* 6.5), 1.66–1.95 (4H, m), 1.98 (1H, dd, *J* 6.0 and 14.0), 2.80 (1H, t, *J* 9.5), 3.00 (1H, dd, *J* 3.0 and 9.0), 3.11 (3H, s), 3.08–3.12 (1H, m), 3.15 (3H, s), 3.38 (1H, dd, *J* 3.0 and 9.0), 4.10–4.18 (1H, m), 4.49 (2H, d, *J* 1.5), 4.62–4.69 (1H, m), 5.95 (1H, t, *J* 1.5); $\delta_C$ (75 MHz; $CDCl_3$) −0.579, 23.30, 23.90, 24.91, 27.38, 27.87, 48.43, 57.71, 58.36, 58.62, 58.67, 71.52, 73.99, 75.05, 100.9, 136.6, 147.8, 172.3; *m*/*z* (CI) 384 (M + 1, 100%), 90 (22).

**[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*R*)-2-(3-chloropropyl)-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]-methanone 14**

To a blue solution of sodium (28 mg, 1.2 mmol) in freshly distilled liquid ammonia (20 mL) at −78 °C was added a solution of substrate **10** (100 mg, 0.31 mmol) in dry THF (10 mL). After 30 minutes, isoprene was added dropwise (until the blue colour dispersed) followed by 1-chloro-3-iodopropane (1.0 mL, 9.3 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by the addition of saturated ammonium chloride (5 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (40 : 60 diethyl ether–petrol) to afford the title compound as a colourless oil (99 mg, 0.25 mol, 80%) (Found M + $H^+$ 404.2020, $C_{19}H_{35}NO_4SiCl$ requires 404.2024, deviation 0.99 ppm); $[a]_D$ = −119.7 (*c* 1.6 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 2953, 1618; $\delta_H$ (300 MHz, $CDCl_3$) −0.00 (9H, s), 1.50–2.10 (8H, m), 2.78 (1H, t,

*J* 9.0), 2.96 (1H, dd, *J* 3.5 and 8.5), 3.09 (3H, s), 3.10–3.14 (1H, m), 3.15 (3H, s), 3.30–3.32 (3H, m), 4.10–4.18 (1H, m), 4.50 (2H, d, *J* 1.5), 4.56–4.64 (1H, m), 5.98 (1H, s); $\delta_C$ (75 MHz; $CDCl_3$) −0.70, 23.40, 27.39, 27.45, 38.15, 45.19, 57.74, 58.44, 58.69, 58.84, 71.67, 74.05, 75.68, 100.5, 137.3, 146.1, 171.8; *m*/*z* (CI), 404 (M + 1, 100%), 406 (45), 90 (28).

### [(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*R*)-2-methoxymethyl-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]methanone 15

To a blue solution of sodium (28 mg, 1.2 mmol) in freshly distilled liquid ammonia (30 mL) at −78 °C was added a solution of substrate **10** (101 mg, 0.31 mmol) in dry THF (10 mL). After 30 minutes, isoprene was added dropwise (until the blue colour dispersed) followed by chloromethyl methyl ether (1.00 mL, 13.16 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by addition of saturated ammonium chloride (2 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 5 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (50 : 50 diethyl ether–petrol) to afford the title compound as a colourless oil (106 mg, 0.29 mmol, 92%) (Found M + $H^+$ 372.2209, $C_{18}H_{34}NO_5Si$ requires 372.2206, deviation 0.8 ppm); $[\alpha]_D$ = −181.6 (*c* 1.3 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 2892, 1621; $\delta_H$ (300 MHz; $CDCl_3$) −0.10 (9H, s), 1.76–2.05 (4H, m), 2.88 (1H, t, *J* 9.0), 3.06 (1H, dd, *J* 2.5 and 9.0), 3.18 (3H, s), 3.10–3.18 (1H, m), 3.28 (3H, s), 3.30 (3H, s), 3.40 (1H, d, *J* 9.5), 3.49 (1H, dd, *J* 3.0 and 9.0), 3.80 (1H, d, *J* 9.5), 4.20–4.30 (1H, m), 4.63 (1H, dd, *J* 1.5 and 14.0), 4.70 (1H, dd, *J* 1.5 and 14.0), 4.75–4.83 (1H, m), 6.18 (1H, t, *J* 1.5); $\delta_C$ (75 MHz; $CDCl_3$) −0.86, 23.23, 27.31, 57.25, 58.50, 58.67, 58.87, 59.52, 71.58, 74.02, 75.91, 78.14, 100.6, 139.3, 143.1, 170.3; *m*/*z* (CI) 372 (M + 1, 100%), 373 (20), 90 (15).

### [(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*S*)-2-methyl-2,5-dihydrofuran-2-yl]methanone 17

To a blue solution of sodium (28 mg, 1.2 mmol) in freshly distilled liquid ammonia (30 mL) at −78 °C was added a solution of substrate **10** (80 g, 0.25 mmol) in dry THF (10 mL). The solution was stirred at −40 °C for a further 2 h before being cooled to −78 °C. Isoprene was then added dropwise (until the blue colour dispersed) followed by iodomethane (1.00 mL, 16.05 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by addition of saturated ammonium chloride (5 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (60 : 40 diethyl ether–petrol) to afford the title compound as a pale yellow oil (47 mg, 0.17 mmol, 71%); $[\alpha]_D$ = −82.3 (*c* 1.23 in EtOH) (Found M + $H^+$ 270.1712, $C_{14}H_{24}NO_4$ requires 270.1705, deviation 2.6 ppm); $\nu_{max}$(film)/$cm^{-1}$ 2925, 1623; $\delta_H$ (300 MHz; $CDCl_3$) 1.36 (3H, s), 1.72–1.94 (4H, m), 2.95 (1H, t, *J* 9.0), 3.08–3.24 (2H, m), 3.17 (3H, s), 3.18 (3H, s), 3.40 (1H, dd, *J* 9.0 and 2.0), 4.04–4.12 (1H, m), 4.44–4.51 (1H, m), 4.58 (2H, 2dt, *J* 13.0 and 1.5), 5.75 (1H, d, *J* 6.0), 5.97 (1H, td, *J* 2.5 and 6.0); $\delta_C$ (75 MHz; $CDCl_3$) 23.73, 27.11, 27.19, 57.68, 57.72, 58.72, 58.79, 71.23, 74.56, 75.46, 93.45, 125.2, 132.9, 173.0; *m*/*z* (CI) 270 (M + 1, 100%), 271 (8).

### [(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl][(*S*)-2-isobutyl-2,5-dihydrofuran-2-yl]methanone 18

To a blue solution of sodium (44 mg, 1.9 mmol) in freshly distilled liquid ammonia (30 mL) at −78 °C was added a solution of substrate **10** (105 mg, 0.32 mmol) in dry THF (10 mL). The solution was stirred at −40 °C for a further 3 h before being cooled to −78 °C. Isoprene was then added dropwise (until the blue colour dispersed) followed isobutyl iodide (1.00 mL, 8.66 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by the addition of saturated ammonium chloride (5 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 10 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by flash column chromatography (40 : 60 diethyl ether–petrol) to afford the title compound as a pale yellow oil (79 mg, 0.25 mmol, 79%); (Found M + $H^+$ 312.2178, $C_{17}H_{30}NO_4$ requires 312.2175, deviation 0.96 ppm); $[\alpha]_D$ = −71.75 (*c* 0.97 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 2953, 1620; $\delta_H$ (300 MHz; $CDCl_3$) 0.76 (6H, t, *J* 6.5), 1.42 (1H, dd, *J* 6.5 and 13.5), 1.55 (1H, sept, *J* 6.5), 1.70–1.96 (4H, m), 1.77 (1H, dd, *J* 6.5 and 13.5), 2.93 (1H, t, *J* 9.0), 3.08 (1H, dd, *J* 3.5 and 8.5), 3.12–3.22 (1H, m), 3.16 (6H, 2 × s), 3.40 (1H, dd, *J* 3.0 and 9.0), 4.05–4.14 (1H, m), 4.48–4.65 (1H, m), 4.55 (2H, 2dt, *J* 1.5 and 9.0), 5.76 (1H, dt, *J* 1.5 and 6.0), 5.90 (1H, dt, *J* 2.5 and 6.0); $\delta_C$ (75 MHz; $CDCl_3$) 23.57, 23.94, 24.24, 24.38, 27.17, 48.26, 57.78, 57.89, 58.65, 58.71, 71.22, 74.54, 75.73, 96.85, 125.4, 132.7, 172.8; *m*/*z* (CI) 312 (M + 1, 100%).

### (*R*)-2-Methyl-3-trimethylsilyl-2,5-dihydrofuran-2-carboxylic acid 19

A solution of **11** (58 mg, 0.18 mmol) in 3 M HCl (10 mL) was heated at reflux for 150 minutes before cooling to room temperature. The solution was then extracted with DCM (3 × 5 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (100% diethyl ether) to afford the title compound as a white solid (24 mg, 0.12 mmol, 69%) (Found M + $NH_4^+$ 218.1210, $C_9H_{20}NO_3Si$ requires 218.1212, deviation 0.9 ppm); mp 76–78 °C; $[\alpha]_D$ = −148.1 (*c* 0.74 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 3100, 2957, 1711; $\delta_H$ (300 MHz; $CDCl_3$) 0.00 (9H, s), 1.37 (3H, s), 4.52–4.64 (2H, 2dd, *J* 13.5 and 1.5), 5.90 (1H, t, *J* 1.5); $\delta_C$ (75 MHz; $CDCl_3$) −0.806, 24.38, 76.08, 95.10, 138.5, 143.9, 176.0; *m*/*z* (CI) 218 (M + 18, 100%), 90 (92), 138 (38).

### (*R*)-2-(3-Chloropropyl)-3-(trimethylsilyl)-2,5-dihydrofuran-2-carboxylic acid 20

A solution of **14** (88 mg, 0.22 mmol) in 3 M HCl (10 mL) was heated at reflux for 3 h before cooling to room temperature. The solution was then basified to pH ≈ 14 with 2 M NaOH and extracted with DCM (5 mL). The resulting aqueous layer was collected and acidified with concentrated HCl solution to pH ≈ 1 and extracted with DCM (3 × 5 mL). The combined organics from the second extraction were dried over magnesium sulfate, filtered, and evaporated *in vacuo* to afford the title compound as a colourless oil (23 mg, 0.09 mmol, 40%) (Found M + $NH_4^+$ 280.1140, $C_{11}H_{23}NO_3SiCl$ requires 280.1136, deviation 1.4 ppm); $[\alpha]_D$ = −104.2 (*c* 0.96 in EtOH); $\nu_{max}$(film)/$cm^{-1}$ 3258, 2955, 1720; $\delta_H$ (300 MHz; $CDCl_3$) 0.00 (9H, s), 1.34–2.00 (4H, m), 3.28–3.50 (2H, m), 4.50–4.66 (2H, 2dd, *J* 14.0 and 1.5), 6.04 (1H, s); $\delta_C$ (75 MHz; $CDCl_3$) −0.77, 26.93, 34.58, 44.66, 76.74, 98.11, 139.0, 142.4, 173.8; *m*/*z* (CI) 280 (M + 18, 100%), 90 (50), 244 (48), 227 (40).

### (*R*)-2-Methoxymethyl-3-trimethylsilyl-2,5-dihydrofuran-2-carboxylic acid 21

A solution of **15** (30 mg, 0.08 mmol) in 3 M HCl (5 mL) was heated at reflux for 150 minutes before being cooled to room temperature. The solution was basified to pH ≈ 14 with 2 M NaOH and extracted with DCM (5 mL). The aqueous layer was then acidified to pH ≈ 1 with concentrated HCl and extracted with DCM (3 × 10 mL). The combined organics from the

second extraction were dried over magnesium sulfate, filtered and evaporated *in vacuo* to afford the title compound as a pale yellow oil (15 mg, 0.07 mmol, 78%) (Found $M^+$ 230.0970, $C_{10}H_{18}O_4Si$ requires 230.0974, deviation 1.74 ppm); $[\alpha]_D$ = −127.58 (*c* 1.2 in EtOH); $\nu_{max}$(film)/cm$^{-1}$ 3222, 2953, 1734; $\delta_H$ (300 MHz; $CDCl_3$) 0.00 (9H, s), 3.20 (3H, s), 3.37 (1H, d, *J* 10.0), 3.63 (1H, d, *J* 10.0), 4.59 (1H, dd, *J* 14.0 and 1.5), 4.65 (1H, dd, *J* 14.0 and 1.5), 6.05 (1H, s); $\delta_C$ (75 MHz; $CDCl_3$) 0.83, 59.57, 75.10, 77.36, 98.40, 139.9, 140.4, 172.6; *m*/*z* (CI) 185 (M − 45, 100%), 248 (72), 73 (68), 95 (60), 231 (M + 1, 55).

### (*R*)-2-Benzyl-3-trimethylsilyl-2,5-dihydrofuran-2-carboxylic acid 22

A solution of **12** (107 mg, 0.26 mmol) in 2 M HCl (20 mL) was heated at reflux for 6 h before cooling to room temperature. The solution was then extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (30 : 70 ethyl acetate–petrol) to afford the title compound as a clear oil (61 mg, 0.22 mmol, 86%) (Found M + $NH_4^+$ 294.1523, $C_{15}H_{24}NO_3Si$ requires 294.1525, deviation 0.68 ppm); $[\alpha]_D$ = −104 (*c* 0.18 in DCM); $\nu_{max}$(film)/cm$^{-1}$ 3567, 2923, 1723; $\delta_H$ (300 MHz; $CDCl_3$) 0.00 (9H, s), 2.67 (1H, d, *J* 13.5), 3.12 (1H, d, *J* 13.5), 4.19 (1H, dd, *J* 14.0 and 1.5), 4.42 (1H, dd, *J* 14.0 and 1.5), 5.87 (1H, t, *J* 1.5), 6.92–7.04 (5H, m); $\delta_C$ (75 MHz; $CDCl_3$) −0.51, 43.26, 76.38, 98.76, 126.7, 127.9 (×2), 130.4 (×2), 138.8, 135.3, 143.0, 172.6; *m*/*z* (CI) 231 (M − 45, 100%), 90 (70), 294 (M + 18, 30).

### (*S*)-2-Methyl-2,5-dihydrofuran-2-carboxylic acid 23

A solution of **11** (88 mg, 0.26 mmol) in 6 M HCl (10 mL) was heated at reflux for 3 h before cooling to room temperature. The solution was then basified to pH ≈ 14 with 2 M NaOH and extracted with DCM (5 mL). The resulting aqueous layer was acidified with concentrated HCl to pH ≈ 1 and extracted with DCM (3 × 5 mL). The combined organics of the second extraction were dried over magnesium sulfate, filtered and evaporated *in vacuo* to afford the title compound as a colourless oil (22 mg, 0.17 mol, 67%) (Found M + $NH_4^+$ 146.0812, $C_6H_{12}NO_3$ requires 146.0817, deviation 3.4 ppm); $[\alpha]_D$ = −141.5 (*c* 0.54 in EtOH); $\nu_{max}$(film)/cm$^{-1}$ 3465, 2872, 1735; $\delta_H$ (300 MHz; $CDCl_3$) 1.51 (3H, s), 4.74 (2H, 2td, *J* 1.5 and 13.5), 5.84 (1H, td, *J* 2.5 and 6.0); 5.94 (1H, dt, *J* 1.5 and 6.0); $\delta_C$ (75 MHz; $CDCl_3$) 23.82, 75.95, 90.58, 127.7, 129.5, 175.2; *m*/*z* (CI) 146 (M + 18, 100%), 83 (52).

### (*S*)-2-Isobutyl-2,5-dihydrofuran-2-carboxylic acid 24

A solution of **13** (117 mg, 0.31 mmol) in 5 M HCl (10 mL) was heated at reflux for 3 h before being cooled to room temperature. The solution was then basified to pH ≈ 14 using 2 M NaOH and then extracted with DCM. The aqueous layer was then acidified with concentrated HCl solution to pH ≈ 1 and extracted several times with DCM. The combined organics from the second extraction were dried over magnesium sulfate, filtered and evaporated *in vacuo* to afford the title compound as a colourless oil (28 mg, 0.16 mmol, 55%) (Found M + $NH_4^+$ 188.1282, $C_9H_{18}NO_3$ requires 188.1287, deviation 2.6 ppm); $[\alpha]_D$ = −117.9 (*c* 0.97 in EtOH); $\nu_{max}$(film)/cm$^{-1}$ 3166, 2955, 1721; $\delta_H$ (300 MHz; $CDCl_3$) 0.85, 0.87 (6H, 2d, *J* 6.5), 1.64 (1H, dd, *J* 6.0 and 13.5), 1.72 (1H, m), 1.86 (1H, dd, *J* 6.0 and 13.5), 4.74 (2H, 2td, *J* 13.5 and 2.5), 5.78 (1H, td, *J* 2.5 and 6.0); 5.94 (1H, dt, *J* 1.5 and 6.0); $\delta_C$ (75 MHz; $CDCl_3$) 23.43, 23.48, 24.47, 44.99, 76.09, 93.92, 127.6, 129.2, 175.2; *m*/*z* (CI) 188 (M + 18, 100%), 125 (66), 189 (50).

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

A solution of **12** (224 mg, 0.54 mmol) in 3 M HCl (200 mL) was heated at reflux for 30 h before cooling to room temperature. The solution was then extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by flash column chromatography (100% ethyl acetate) to afford the title compound an oil (97 mg, 0.47 mol, 87%) (Found M + $NH_4^+$ 222.1134, $C_{12}H_{16}NO_3$ requires 222.1130, deviation 1.8 ppm); $[\alpha]_D$ = −74.4 (*c* 0.18 in DCM); $\nu_{max}$(film)/cm$^{-1}$ 3256, 2952, 1722; $\delta_H$ (300 MHz; $CDCl_3$) 3.04 (1H, d, *J* 14.0), 3.20 (1H, d, *J* 14.0), 4.40 (1H, d, *J* 14.0), 4.66 (1H, d, *J* 14.0), 5.83 (2H, s), 7.09–7.25 (5H, m); $\delta_C$ (75 MHz; $CDCl_3$) 42.74, 76.51, 94.22, 126.8, 127.9, 127.9 (×2), 130.4 (×2) 128.6. 134.9, 173.5; *m*/*z* (CI) 222 (M + 18, 100%), 159 (15).

### [(*S*)-2-Methoxymethylpyrrolidin-1-yl][3-(trimethylsilyl)furan-2-yl]methanone 27

To a solution of **26** (930 mg, 4.43 mmol) in THF (70 mL) containing chlorotrimethylsilane (724 mg, 6.67 mmol) at −78 °C was added dropwise *n*-BuLi (1.3 M, 4.1 mL, 5.3 mmol). The resulting solution was stirred at −78 °C for 30 minutes before being allowed to warm to room temperature. The reaction was quenched by addition of brine (10 mL) and then then extracted with DCM (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (5 : 95 diethyl ether–petrol) to afford the title compound as a pale yellow oil (597 mg, 2.12 mmol, 48%) (Found M + $H^+$ 282.1522, $C_{14}H_{24}NO_3Si$ requires 282.1525, deviation 1.06 ppm); $[\alpha]_D$ = −81.75 (*c* 6.39 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 2953, 1619; $\delta_H$ (300 MHz; $CDCl_3$) −0.00 (9H, s), 1.54–1.84 (4H, m), 2.88–3.62 (4H, m), 3.02 (3H, s), 4.09–4.22 and 4.38–4.50 (1H, 2 × m), 6.18 (1H, s), 7.18 (1H, s); $\delta_C$ (75 MHz; $CDCl_3$) −1.25, −0.89, 20.99, 24.69, 26.89, 28.93, 47.12, 48.44, 56.76, 57.39, 58.98, 72.25, 73.88, 116.2, 116.5, 125.7, 126.0, 142.2, 152.7, 159.3. Some resonances were doubled owing to the presence of amide rotamers; *m*/*z* (CI) 282 (M + 1, 100%).

### [(*S*)-2-Methoxymethylpyrrolidin-1-yl][2-methyl-3-(trimethylsilyl)-2,5-dihydrofuran-2-yl]methanone 28

To a blue solution of sodium (33 mg, 1.4 mmol) in freshly distilled liquid ammonia (30 mL) at −78 °C was added a solution of substrate **27** (100 mg, 0.35 mmol) in dry THF (20 mL). After 30 minutes, isoprene was added dropwise (until the blue colour dispersed) followed by iodomethane (1.00 mL, 16.1 mmol) to give a yellow solution. After a further 30 minutes, the reaction was quenched by addition of saturated ammonium chloride (2 mL). The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography (40 : 60 diethyl ether–petrol) to afford the title compound as a 1 : 1 mixture of diastereoisomers and as a pale yellow oil (44 mg, 0.15 mmol, 42%). The spectroscopic data are quoted for the mixture of diastereoisomers (Found M + $H^+$ 298.1836, $C_{15}H_{28}NO_3Si$ requires 298.1838, deviation 0.67 ppm); $\nu_{max}$(film)/cm$^{-1}$ 2954, 1629; $\delta_H$ (300 MHz; $CDCl_3$) −0.01 and 0.05 (9H, s), 1.37 and 1.38 (3H, s), 1.55–1.94 (4H, m), 3.00–3.28 (2H, m), 3.23 and 3.26 (3H, s), 3.44–3.60 (2H, m), 4.14–4.24 (1H, m), 4.49 and 4.50 (1H, dd, *J* 14.0 and 1.5), 4.61 and 4.62 (1H, dd, *J* 14.0 and 1.5), 6.01 (1H, s); $\delta_C$ (75 MHz; $CDCl_3$) −1.27, −1.06, −0.77, 19.89, 24.80, 25.68, 26.00, 26.29, 26.51, 28.73, 46.22, 46.35, 47.24, 56.63, 58.20, 58.33, 58.56, 58.87, 58.92, 71.79, 72.09, 73.87, 74.49, 74.85, 75.08, 96.25, 96.55, 96.89, 136.74, 136.79, 137.01, 144.67, 145.29, 145.59, 170.86, 171.04; *m*/*z* (CI) 298 (M + 1, 100%), 90 (22).

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