Sequential kinetic resolution of C_2-symmetric compounds as a key step in two-directional synthesis: structural requirements for efficient resolution of difuryl diols

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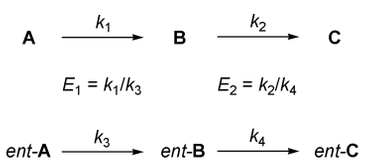
The C_2-symmetrical diols (*R**,*R**)-1,4-difuran-2-yl-butane-1,4-diol **13** and (1*R**,3*S**,4*S**,6*R**)-3,4-bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-yl-hexane-1,6-diol **26** were synthesised in a two-directional manner: the reductions of (3*R**,4*R**)-3,4-bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-dione with DIBAL-H and Red-Al were remarkably [1,3]*syn* selective, presumably as a result of reduction of chelates formed from the 3-silyloxy-1-(2-furyl)ketones. Sequential Sharpless kinetic resolutions of **13** and **26** were studied. The first step of the kinetic resolution of **26** was shown to proceed with an enantioselectivity factor of $E = 1.9$, and sequential resolution yielded the doubly oxidised product in 43% yield and 43% ee; this compares favourably with the enantiomeric excess (24% ee at 43% completion) of a product derived from a similarly enantioselective conventional kinetic resolution. The structural features of C_2-symmetric substrates which are required for efficient sequential kinetic resolution, and the relevance of these reactions in two-directional syntheses, are discussed.

Introduction

Kinetic resolution reactions[1] involve an inevitable trade-off between yield and enantiomeric excess. These reactions are best characterised by an enantioselectivity factor (E) which describes the relative rate of reaction of the enantiomeric starting materials since this parameter remains constant throughout the course of the reaction. In kinetic resolutions, the enantiomeric excess (ee) of the reactant tends asymptotically to 100% as the reaction proceeds, though the conversion at which a particular enantiomeric excess (*e.g.* 95% ee) is reached depends on E. In contrast, the maximum possible enantiomeric excess of the product is observed at low conversion: this enantiomeric excess is determined by E and is inevitably eroded as the reaction proceeds.

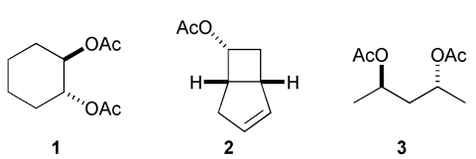
Sequential kinetic resolutions are kinetic resolutions in which the starting material, A, participates in two (or more) enantioselective steps in its conversion into the product, C (Scheme 1).



Scheme 1

Sequential kinetic resolutions can be significantly more efficient than conventional kinetic resolutions, and can yield products with enantiomeric excesses higher than would be obtained from similarly enantioselective conventional kinetic resolutions. This phenomenon which can be qualitatively understood in terms of the "proof-reading" introduced: under optimised conditions, the "wrong" (slower reacting) enantiomer is unlikely to react twice with the chiral reagent, a fate which would compromise the enantiomeric excess of the product, C.

Quantitative analyses of the kinetics of sequential kinetic resolutions have shown that the strategy is most effective when the rates of the two enantioselective steps are similar (relative rate < *ca.* 5) and when both of the steps are at least moderately enantioselective.[2–4] The rates of lipase-catalysed hydrolysis of the acetates of **1** were rendered comparable by differential partitioning of the reacting compounds (A and B; Scheme 1) between reacting (aqueous) and inert (organic) phases; this approach resulted in remarkable levels of enantioselectivity for the sequential kinetic resolution process.[5] The transesterification[4] of the acetate **2** and the acylation[2] of the diol **3** are biocatalytic sequential kinetic resolutions which have also been optimised. Other sequential kinetic resolutions, though often highly enantioselective, do not exhibit efficiencies over and above those expected for conventional kinetic resolution processes.[6,7]



1 **2** **3**

We reasoned that C_2-symmetrical difuryl diols **4** with an achiral or C_2-symmetrical linking chain, L, would be excellent candidates for sequential Sharpless[8] kinetic resolution (Scheme 2). It was thought that, unlike many enzymes, the Sharpless catalyst would be largely sensitive to *local* structural features of the substrate; therefore, provided that the linking chain, L, was sufficiently long, the rate of oxidation of both furyl alcohols in the more reactive enantiomer of **4** (which have the same absolute stereochemistry) would be comparable. Similarly, the rate of oxidation of both alcohols in the less reactive enantiomer of **4** would also be expected to be comparable. In other words, it was expected that the rate of oxidation of **4** would be roughly twice that of the intermediate **5**, and the enantioselectivity (E_1 and E_2) of each of the steps would be similar. These kinetic parameters would be suitable for highly efficient sequential kinetic resolution.[2–4] Previously, we have shown that the dipyranone **7** is a precursor of highly functionised bis-tetrahydropyrans; for example, **7** is a key intermediate in the synthesis of both symmetrical (*e.g.* **8**) and unsymmetrical (*e.g.* **9**) *C*-linked disaccharide mimetics.[9]

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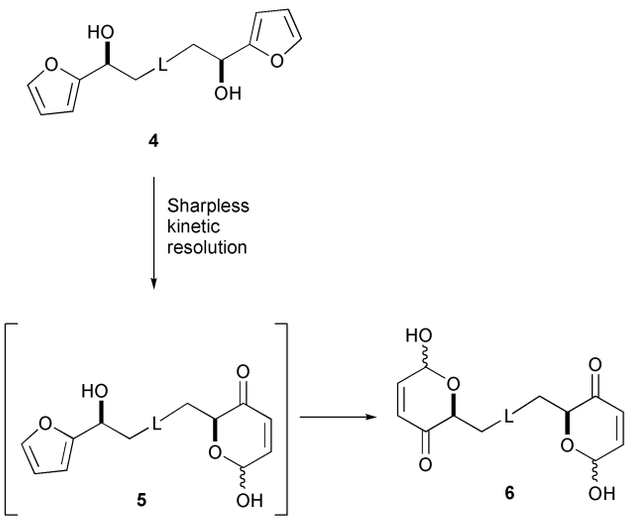
Synthesis of C_2-symmetrical difuryl diols

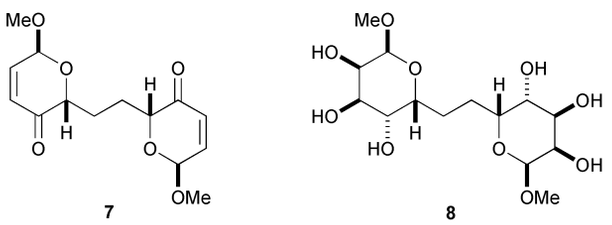
Addition of 2-lithiofuran to the Weinreb diamide **11**, prepared from succinyl chloride, gave the diketone **12** in 83% yield (Scheme 3). The diketone **12** was reduced with sodium borohydride to give the corresponding diols as a 62:38 mixture of diastereoisomers in >98% yield; the ^{1}H NMR spectra of these diastereoisomers were extremely similar, but the compounds could be distinguished by careful inspection of their ^{13}C NMR spectra. In order to determine their relative configuration, the diols **13** and **14** were converted into the corresponding di-*tert*-butylsilylene derivatives **15** and **16** by treatment with pyridine and di-*tert*-butylsilyl ditrifluoromethanesulfonate **17**.[10] The diastereomeric cyclic compounds **15** and **16** were distinguished by analysis of their ^{1}H and ^{13}C NMR spectra: the *tert*-butyl groups of C_2-symmetric (racemic) **15** were homotopic whereas those of the *meso* compound **16** were diastereotopic. † The *meso* diol **14** was readily purified (to give a >98:2 mixture of diastereoisomers) by selective crystallisation from chloroform; after two crystallisations, the mother liquors were highly enriched (**13**:**14** >90:10) in the C_2-symmetrical diol **13**.

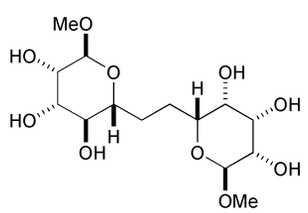
Similarly, the difuryl dione **25** was synthesised by addition of 2-lithiofuran to either the Weinreb diamide **22** or the morpholine diamide **24**, prepared by dihydroxylation and silylation of the corresponding β,γ-unsaturated diamides (Scheme 4). Attempted addition of 2-lithiofuran directly to the β,γ-unsaturated diamide **23** resulted in enolisation and, hence, formation of the conjugated enamide.

The reduction of the dione **25** was studied using a range of reducing agents; in each case, the mixture of diastereoisomeric products **26a**–**c** was determined by analytical HPLC (Scheme 5 and Table 1). Reduction of the dione **25** with sodium borohydride was almost stereorandom, resulting in an essentially statistical mixture of the three possible diastereoisomeric products (entry 1, Table 1). The diols **26a**–**c** were, however, readily separable by flash chromatography, and their relative stereochemistry could be assigned. The diol **26b** was easily identified since it was the only possible unsymmetrical diastereoisomeric product. The C_2-symmetrical diols **26a** and **26c** were



Scheme 2





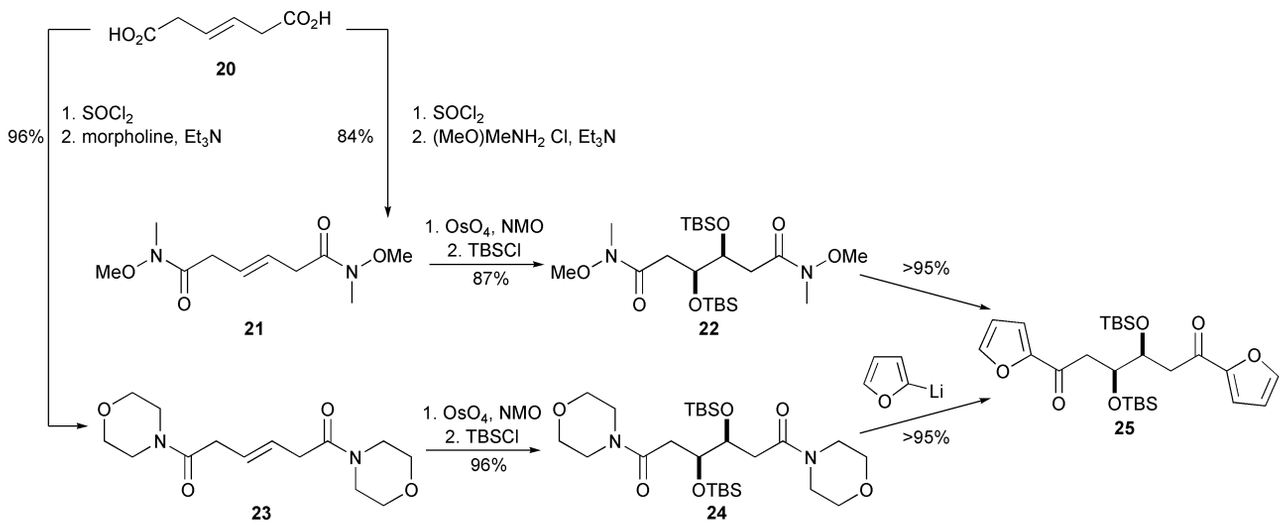
† An approach which was designed to *control* the 1,4-stereochemistry of **13** using a remote participating group[11] was briefly investigated. However, treatment of the diacetal **18** with furan and boron trifluoride etherate gave only the difuran **19**.

Scheme 3

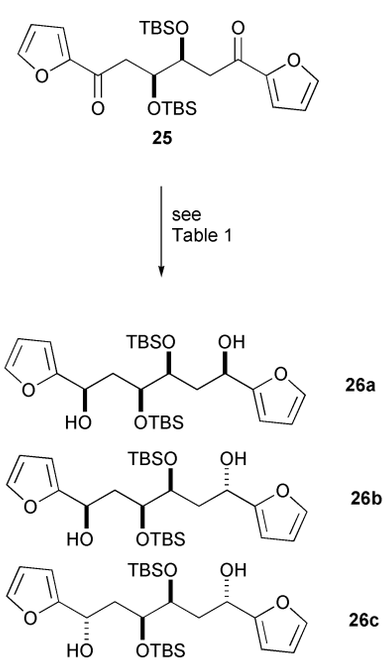
Table 1 Reduction of the dione **25**

Entry	Conditions	Dias. ratio[a] **26a**:**26b**:**26c**	Yield[b] (%)
1	$NaBH_4$, EtOH, 20 °C	29:52:18	92
2	DIBAL-H, toluene, −78 °C	60:30:10	>98
3	$NaBH_4$, $CeCl_3$, MeOH, −40 °C	46:32:22	95
4	K-selectride, THF, −78 °C	49:31:20	[c]
5	Red-Al, toluene, −78 °C	73:25:<2	75

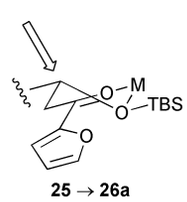
[a] Determined by analytical HPLC. [b] Yield of mixture of diastereomeric products **26**. [c] Not determined.



Scheme 4



Scheme 5



25 → **26a**

Fig. 1

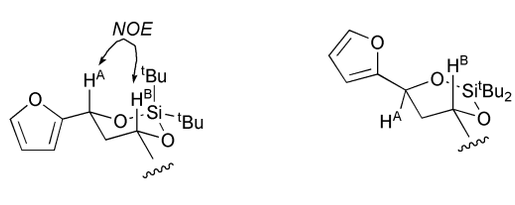


Fig. 2

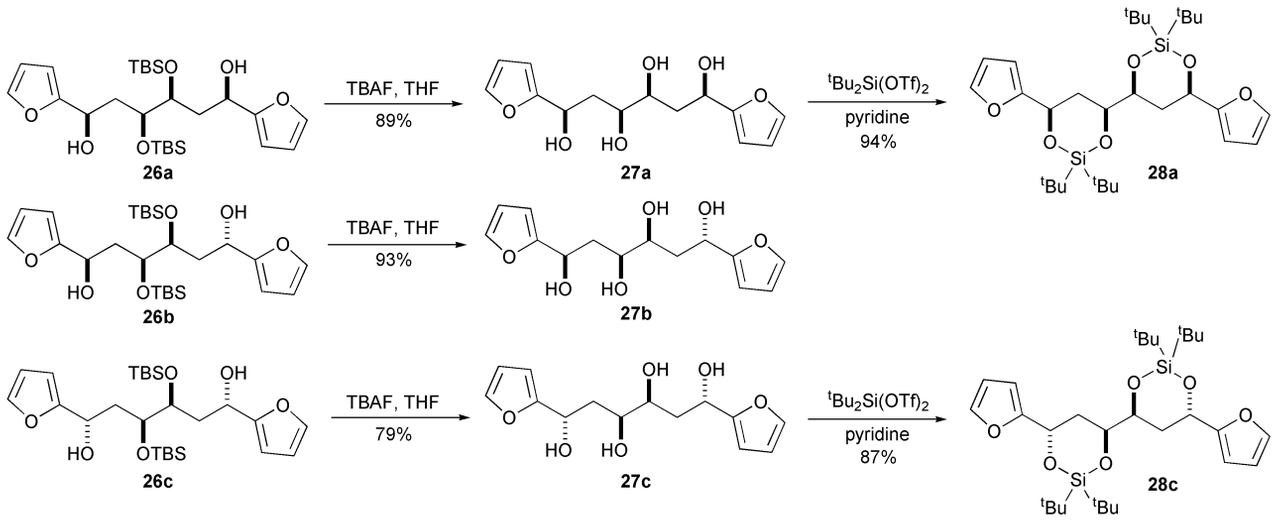
distinguished by conversion into the cyclic derivatives **28a** and **28c** (Scheme 6). Hence, deprotection (⟶ **27**) and treatment with pyridine and di-*tert*-butylsilyl ditrifluoromethanesulfonate **17**, gave the bis(di-*tert*-butylsilylene) derivatives **28**, whose relative configuration could be deduced by careful analysis of their 500 MHz ^{1}H NMR spectra (Fig. 2).

The remaining reductions were, however, significantly more ^{1,3}*syn* selective than those of other β-silyloxy ketones (entries 2–5, Table 1).[12] In particular, the reduction of the dione **25** with Red-Al at −78 °C was remarkably stereoselective. The 73:25:<2 mixture of products obtained reflects approximately 85:15 ^{1,3}*syn*:^{1,3}*anti* facial stereoselectivity for each reduction step, and highlights the importance of good levels of substrate control in two-directional synthetic steps (compare entries 1–3 with entres 4–5, Table 1). We ascribe the ^{1,3}*syn* selectivity observed to the particular Lewis basicity of furan-2-yl ketones: axial attack of the reducing agent on the chelate shown in Fig. 1 would give the observed ^{1,3}*syn* diol derivatives. ‡

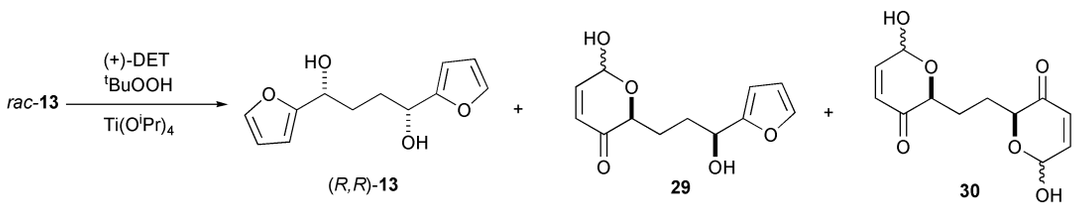
Sequential kinetic resolution of the difuryl diol 13

The Sharpless kinetic resolution of the C_2-symmetrical difuryl diol **13** was investigated (Scheme 7). Hence, the diol **13** was treated with (+)-L-diethyl tartrate, titanium tetraisopropoxide

‡ For reductions of six-membered chelates formed from β-hydroxy ketones, see ref. 13.



Scheme 6

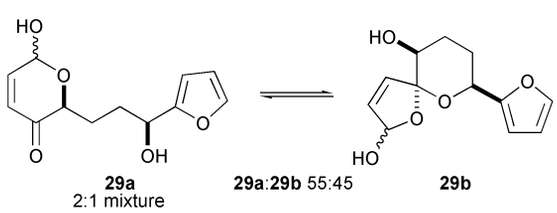


Scheme 7

and two equivalents of *tert*-butyl hydroperoxide, and the enantiomeric excess of the diol was monitored as a function of its conversion by chiral analytical HPLC. The enantioselectivity of the first oxidation step, E_1, was found to be 4.8.§

The relative rate of the oxidation steps (**13** ⟶ **29** and **29** ⟶ **30**) was assessed by kinetic resolution of the racemic diol **13**. When 0.80 equivalents of *tert*-butyl hydroperoxide were used as the limiting reagent, (*R,R*)-**13** was recovered with 84% ee. In order to obtain starting material with this enantiomeric excess from a kinetic resolution with an enantioselectivity factor of 4.8, 0.73 equivalents of the diol must have been consumed. This preliminary result suggested that the first step of the kinetic resolution was much faster than the second since virtually all of the *tert*-butyl hydroperoxide must have been consumed in the oxidation of the diol **13**.

Analysis of the 500 MHz ^{1}H NMR spectrum of the intermediate **29** in $CDCl_3$ revealed it to exist as a 55:45 mixture of the open (**29a**) and closed (**29b**) forms (Scheme 8).¶ The formation of the closed form **29b** may provide a means for the communication of information between the remote ring systems: in the closed form **29b**, the furyl alcohol is unavailable for coordination to the Sharpless catalyst which would impede the second oxidation step. The diol **13** does not, therefore, have the required structural features for efficient sequential kinetic resolution by Sharpless asymmetric oxidation, since the rates of the enantioselective steps are not comparable.



Scheme 8

Sequential kinetic resolution of the difuryl diol 26a

The Sharpless kinetic resolution of the C_2-symmetrical diol **26a** was also investigated. The mole fractions of the starting material **26a**, the intermediate **31** and the product **32** were monitored by analytical HPLC (see Scheme 9 and Fig. 3). The reaction was a clean process, with no significant by-products appearing until about 1.6 equivalents of *tert*-butyl hydroperoxide had been consumed. The oxidation was, however, much more sluggish than that of **13**, and took more than 10 hours to reach *ca.* 80% completion. The enantiomeric excess of the remaining starting material was determined at six distinct conversions, and the enantioselectivity of the first step, E_1, was

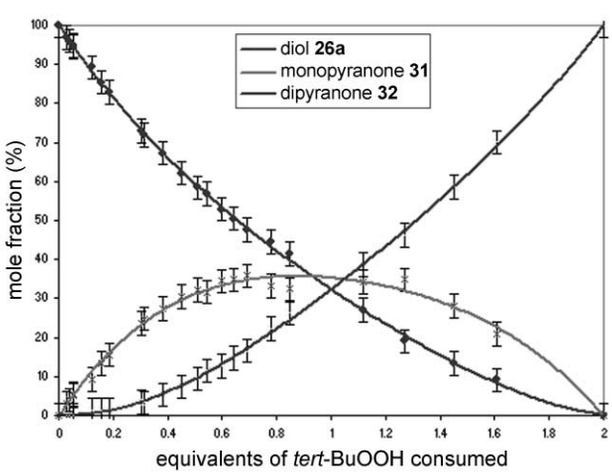
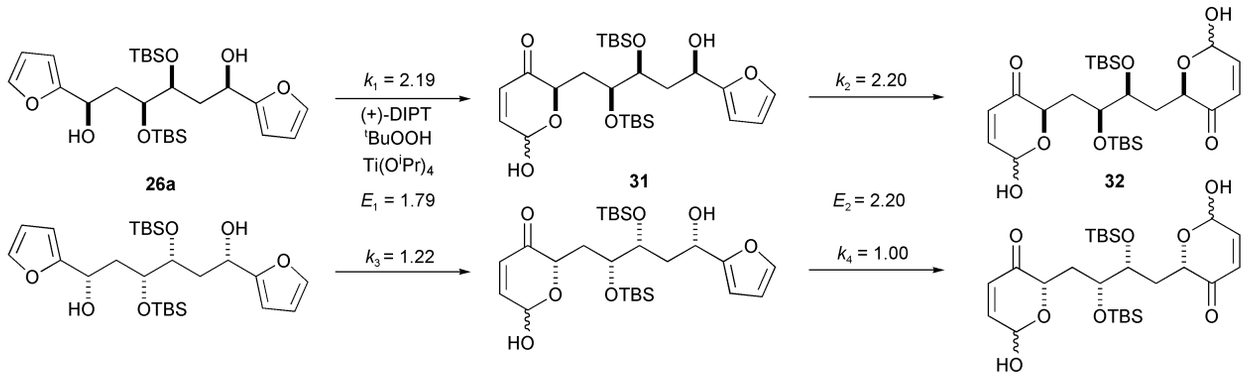


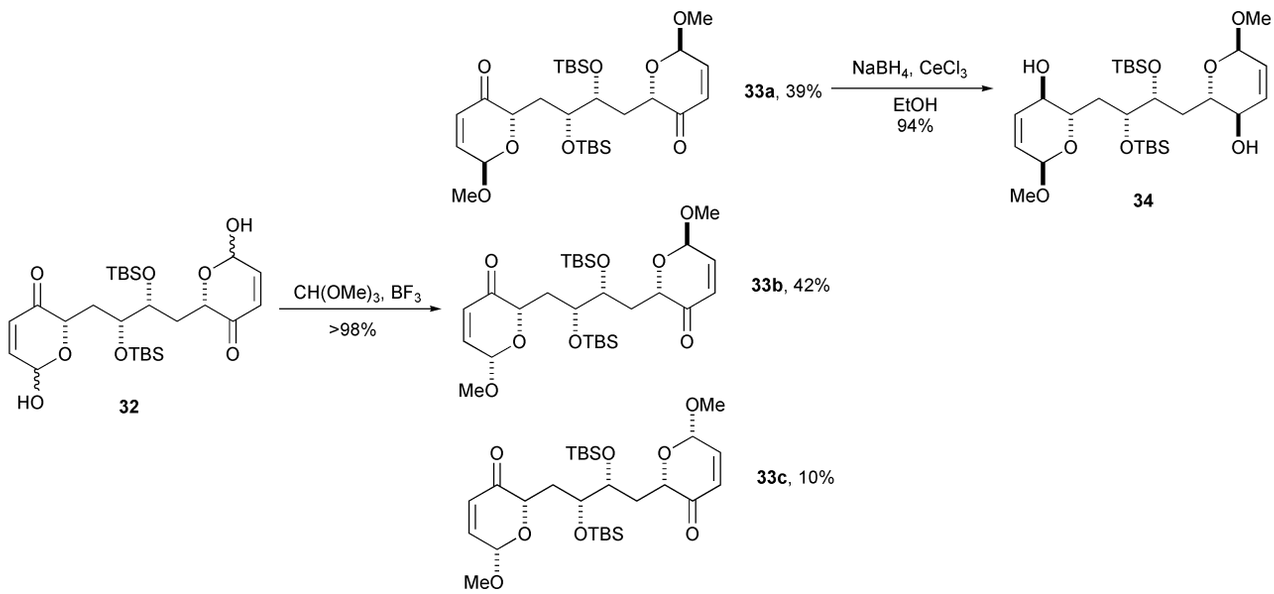
Fig. 3 Mole fractions of components in the sequential kinetic resolution of the diol **26a**.

§ For a kinetic resolution, the relative reaction rate of the enantiomeric starting materials, *E*, can be determined from the enantiomeric excess of the remaining starting material (e_{SM} = enantiomeric excess/100) at any conversion (c = percentage conversion/100): $E = [\ln(1 - c)(1 - e_{SM})]/[\ln(1 - c)(1 + e_{SM})]$.[1] E_1 was determined from the straight line graph obtained by plotting $[\ln(1 - c)(1 - e_{SM})]$ against $[\ln(1 - c)(1 + e_{SM})]$ using six independent measurements of c and e_{SM}.

¶ **29a** existed as a 2:1 mixture of anomers; **29b** was present as a >90:10 mixture of anomers (see Scheme 8).



Scheme 9



Scheme 10

found to be 1.9. The rate and enantioselectivity of the oxidation of **26a** were much lower than those observed in asymmetric oxidations of simple furan-2-yl alcohols,[8b] and may stem from chelation of the 3-silyloxy alcohol functionality to the titanium catalyst.

Although the enantioselectivity of the process **26a** ⟶ **31** is disappointing, it did at least provide an opportunity to assess the increased efficiency of a sequential kinetic resolution over a conventional kinetic resolution.‖ Crucially, the evolution of the components as a function of conversion (Fig. 3) suggested that the oxidation of **26a** satisfied one of the conditions required for efficient sequential kinetic resolution: at intermediate stages in the reaction, there was a significant concentration of both the starting material and the intermediate,** indicating that the rates of the enantioselective steps were similar. The presence of the intermediate **31** in the reaction mixture provides a mechanism for "proof-reading" the first enantioselective step; when a molecule of the slower reacting enantiomer of **26a** is oxidised, a molecule of the intermediate **31** is produced which also contains the "slower reacting" furyl alcohol. This molecule is, therefore, forced to compete on unfavourable terms for the catalyst. The product **32** is, therefore, further enriched in the faster reacting enantiomer.

We have determined the relative oxidation rates (k_1, k_2, k_3, k_4, Scheme 9) which best account for the observed evolution of the mole fractions of **26a**, **31** and **32** as a function of consumption of *tert*-butyl hydroperoxide;†† the relative rates shown in Scheme 9 best fit the data (correlation coefficient, 0.9998). These data (in which $E_1 = k_1/k_3 = 1.79$) concur with the independent measurement of the enantioselectivity of the first step (E_1 = 1.9) which had been made by monitoring the enantiomeric excess of the starting material, **26a**. To a first approximation, the conditions for an optimised sequential kinetic resolution are satisfied:[2–4] the asymmetric steps are comparably enantioselective and proceed at similar rates.

In a separate experiment, the racemic diol **26a** was kinetically resolved under the same reaction conditions (Scheme 9). The reaction was followed by HPLC, and the reaction was quenched when the yield of the dipyranone **32** was 42%. The determination of the enantiomeric excess of **32** was complicated by its existence as a mixture of three diastereomeric hemiacetals. Hence, **32** was protected as the acetals **33** and the three anomeric products were separated by preparative HPLC (Scheme 10). Luche[15] reduction of the C_2-symmetric dipyranone **33a** gave the C_2-symmetric diol **34**. The diol **34** was converted into the corresponding (*R*)-Mosher's diester,[16] and the ratio of diastereomeric products was determined by 500

‖ The enantiomeric excesses possible for a given yield of product can be calculated for conventional[1] and optimised sequential[2–4] kinetic resolutions. The *difference* between the enantiomeric excesses possible for a *ca.* 50% yield of product is greater when the enantioselectivity factor, *E*, is low. We estimate that the error associated with measuring enantiomeric excesses by chiral HPLC is *ca.* ±3%.

** After consumption of just 0.2 eq. of *tert*-butyl hydroperoxide, there is about 0.17 eq. of the intermediate **31** present. There is still 0.32 eq. of starting material remaining at the half-way stage, and 0.10 equivalents remaining after consumption of 1.6 equivalents of *tert*-butyl hydroperoxide.

†† The rate equations for consecutive reactions may be solved analytically, see ref. 14. Values of k_1, k_2, k_3, k_4, were determined which best fitted the experimental data.

MHz ^{1}H NMR spectroscopy. The diol **34**, and hence the dipyranone **32**, was shown to have 43 ± 3% ee.

The efficiency of the sequential kinetic resolution of **26a** may be assessed by comparing the enantiomeric excess of **32** with that possible in a similarly enantioselective conventional kinetic resolution. In a conventional kinetic resolution with enantioselectivity factor, $E = 1.9$, it is possible to obtain a 42% yield of product with 24% ee.‡‡ The product of the sequential kinetic resolution of **26a** was the dipyranone **32** which was shown to have 43% ee. The sequential kinetic resolution of **32** did, therefore, provide a product with significantly higher enantiomeric excess than would be possible in a conventional kinetic resolution with enantioselectivity, $E = 1.9$. Furthermore, our kinetic data (Scheme 9) indicate that it would be possible to obtain, at low conversion, the product **32** with 58% ee; this compares favourably with the maximum enantiomeric excess (31% ee) possible for a conventional kinetic resolution with $E = 1.9$.

Summary

The sequential Sharpless kinetic resolutions of the C_2-symmetric diols **13** and **26** were investigated. The product of the sequential kinetic resolution of **26** was shown to have an enantiomeric excess which was significantly higher than that which could have been obtained in a similarly enantioselective conventional kinetic resolution. This improved efficiency stems from the combined effect of the two enantioselective steps involved. In contrast, the sequential kinetic resolution of the diol **13** did not have the structural features required for efficient sequential kinetic resolution by Sharpless asymmetric oxidation, since the rates of the enantioselective steps are not comparable.

C_2-Symmetric substrates can be good candidates for efficient sequential kinetic resolution provided that the product of the first enantioselective step undergoes enantioselective functionalisation at a similar rate. This condition is likely to be satisfied if the homotopic functional groups are at either end of a long C_2-symmetric chain. Oxidation of one of the furyl alcohols of **13** resulted in the formation of the pyranone **29** which existed as a mixture of open (**29a**) and closed (**29b**) forms (Scheme 8); the formation of **29b** provided a mechanism for communication between the reacting groups of **13**, which may have retarded the second enantioselective step. In contrast, the homotopic furyl alcohols of **26** were rather more remote; their rate of oxidation was, to a first approximation, independent of the oxidation level of the other, remote ring. The strategy is likely to be of value in two-directional syntheses[17] which involve the elaboration of C_2-symmetric chains.

Experimental

General methods have been described previously.[18] All non-aqueous reactions were performed under an atmosphere of nitrogen. Preparative and analytical HPLC were conducted on a Gynkotek HPLC system with diode array detection; unless otherwise stated, the column oven was set at 24 °C. Econosil columns (silica particle size: 10 μm) were used for preparative (22 × 250 mm) and analytical (4.6 × 250 mm) work, and a Chiracel OD column (4.6 × 250 mm) was used for chiral analytical HPLC; unless otherwise stated samples were calibrated against external standard samples dissolved in methanol. Microanalyses were carried out by staff of the Department of Chemistry using a Carlo Erba 1106 automatic analyser.

‡‡ The relation between the relative rate of reaction of the enantiomeric starting materials, E, and the enantiomeric excess of the product of a conventional kinetic resolution (e_p = enantiomeric excess/100) at any conversion (c = percentage conversion/100) is given by relation: $E = \ln[1 - c(1 + e_p)]/\ln[1 - c(1 - e_p)]$.[1]

N,*N*′-Dimethoxy-*N*,*N*′-dimethylsuccinamide 11

Triethylamine (100.1 ml, 720 mmol) was added slowly by cannulation to a stirred suspension of *N*,*O*-dimethylhydroxylamine (36.0 g, 369 mmol) and succinyl chloride (19.35 ml, 175.6 mmol) in dichloromethane (400 ml) at 0 °C under N_2. After stirring for 2 h the solution was allowed to warm to room temperature and quenched with saturated aqueous sodium bicarbonate solution (200 ml). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 100 ml). The combined organic extracts were washed with brine (75 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the diamide **11** (29.46 g, 83%) as light brown needles, mp 65.1–67.2 °C; R_f 0.23 (9:1 EtOAc–petrol); (Found: C, 47.0; H, 7.90; N, 13.7; $C_8H_{16}N_2O_6$ requires C, 47.1; H, 7.85; N, 13.7%); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2947, 1661, 1651, 1443, 1390 and 1193; δ_H (300 MHz; $CDCl_3$) 3.75 (6H, s, OCH_3), 3.19 (6H, s, NCH_3) and 2.78 (4H, s, CH_2); δ_C(75 MHz; $CDCl_3$) 173.8 (C=O), 61.6 (OCH_3), 32.6 and 26.8; *m*/*z* (EI) 144 (100%, $M^+ - N(CH_3)OCH_3$), 113 (25) and 55 (43).

1,4-Difuran-2-ylbutane-1,4-dione 12

n-Butyllithium (214 ml of a 1.6 mol solution in hexanes, 341 mmol) was slowly added over 10 min to a stirred solution of furan (24.8 ml, 341 mmol) in THF (200 ml) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, a solution of the diamide **11** (29.0 g, 142 mmol) in THF (150 ml) added slowly at 0 °C, stirred for a 2 h at 0 °C and allowed to warm to room temperature. After 16 h, the gelatinous reaction mixture was quenched with saturated aqueous ammonium chloride solution (100 ml), stirred and the layers separated. The aqueous layer was extracted with chloroform (3 × 75 ml) and the combined organic extracts washed with brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the *diketone* **14** which was purified by recrystallisation from EtOAc–hexane to give the diketone **12** (23.07 g, 74%) as brown prisms, mp 112–114 °C (from EtOAc–hexane); R_f 0.31 (3:7 from EtOAc–petrol); (Found: MH^+ 219.0655; $C_{12}H_{10}O_4$ requires *MH*, 219.0657); ν_{max}/cm^{-1} ($CHCl_3$ solution) 1661 (C=O), 1651, 1574, 1469, 1324 and 1036; δ_H (300 MHz; $CDCl_3$) 7.61 (2H, dd, *J* 1.7 and $^4J_{HH}$0.6, furyl 5-H), 7.25 (2H, dd, *J* 3.6 and $^4J_{HH}$0.6, furyl 3-H), 6.55 (2H, dd, *J* 3.6 and *J* 1.7, furyl 4-H) and 3.30 (4H, s, CH_2); δ_C(75 MHz; $CDCl_3$) 188.0 (C=O), 152.8 (furyl 2-C), 146.8 (furyl 5-C), 117.6 (furyl), 112.6 (furyl) and 32.3 (2-C and 3-H); *m*/*z* (EI) 218 (21%, M^+), 123 (28), 95 (100) and 39 (27).

(*R*,*S*)-1,4-Difuran-2-ylbutane-1,4-diol 14 and (*R**,*R**)-1,4-difuran-2-ylbutane-1,4-diol 13

Sodium borohydride (7.78 g, 206 mmol) was added slowly in small portions to a stirred solution of the dione **12** (22.00 g, 102.8 mmol) in THF (300 ml) at room temperature. The reaction mixture was stirred for 7 h and quenched with aqueous ammonium chloride (50 ml). The layers were separated and the aqueous layer extracted with chloroform (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 4:6 EtOAc–petrol to give a crude product (17.20 g, 75%; **13**:**14** 38:62) which was recrystallised from chloroform to give the *diol* **14** as colourless prisms (8.81 g, **14**:**13** >98:2). A further recrystallisation from chloroform afforded a second crop (0.64 g, 41% overall) of the *diol* **14**, mp 104.2–105.3 °C (from chloroform); R_f 0.37 (1:1 EtOAc–petrol); (Found: C, 64.9; H, 6.50; $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.35%); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3343 (O–H), 2963, 2930, 1144, 1057,1008 and 970; δ_H(300 MHz; DMSO-d_6) 7.55 (2H, dd, *J* 1.8 and $^4J_{HH}$0.9, furyl 5-H), 6.36 (2H, dd, *J* 3.2 and *J* 1.8, furyl 4-H), 6.20 (2H, dd, *J* 3.2 and $^4J_{HH}$0.9, furyl 3-H), 5.26 (2H, m, C*H*OH), 4.48 (2H, d, *J* 4.1, OH), 1.77 (2H, ddd, $^2J_{HH}$ 9.9, *J* 5.8 and 3.8, 2-H_a and 3-H_a) and

1.61 (2H, ddd, $^2J_{HH}$ 9.9, *J* 5.8 and 3.8, 2-H_b and 3-H_b); δ_C(75 MHz; DMSO-d_6) 158.4 (furyl 2-C), 141.9 (furyl 5-H), 110.4 (furyl), 105.5 (furyl), 66.2 (CHO) and 32.3 (CH_2); *m*/*z* (EI) 222 (14%, M^+), 205 (80, $M^+ - OH$), 187 (18), 137 (100) and 110 (29).

Evaporation of the filtrate gave the diol **13** (7.8 g, 34%; **13**:**14** >90:10) as a colourless oil, R_f 0.37 (1:1 EtOAc–petrol); (Found: C, 64.6; H, 6.65; $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.35%); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3343 (O–H), 2963, 2930, 1144, 1057,1008 and 970; δ_H(300 MHz; DMSO-d_6) 7.55 (2H, dd, *J* 1.8 and $^4J_{HH}$0.9, furyl 5-H), 6.36 (2H, dd, *J* 3.2 and *J* 1.8, furyl 4-H), 6.20 (2H, dd, *J* 3.2 and $^4J_{HH}$0.9, furyl 3-H), 5.26 (2H, m, C*H*OH), 4.48 (2H, d, *J* 4.1, OH), 1.77 (2H, ddd, $^2J_{HH}$ 9.9, *J* 5.8 and 3.8, 2-H_A and 3-H_A) and 1.61 (2H, ddd, $^2J_{HH}$ 9.9, *J* 5.8 and 3.8, 2-H_B and 3-H_B); δ_C(75 MHz; DMSO-d_6) 158.4 (furyl 2-C), 141.9 (furyl 5-H), 110.4 (furyl), 105.5 (furyl), 66.1 (CHO) and 32.1 (CH_2); *m*/*z* (EI) 222 (14%, M^+), 205 (80, $M^+ - OH$), 187 (18), 137 (100) and 110 (29).

The diols **13** and **14** could be distinguished by careful examination of the peaks in their ^{13}C NMR spectra corresponding to C-1 and C-4.

(*E*)-Hex-3-enedioic acid bis(methoxymethylamide) 21

A slurry of *trans*-hydromuconic acid (1.00 g, 6.94 mmol) in chloroform (30 ml) was stirred at 0 °C under N_2. The solution was treated with *N,O*-dimethylhydroxylamine hydrochloride (1.62 g, 16.66 mmol), 1-hydroxybenzotriazole (2.25 g, 16.66 mmol), 4-methylmorpholine (4.57 ml, 41.64 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.73 g, 19.43 mmol). The reaction was allowed to warm to room temperature and stirred for a further 24 h before quenching with water (50 ml). The organic layer was washed with aqueous 10% hydrochloric acid (2 × 50 ml), saturated aqueous sodium bicarbonate (30 ml) and water (30 ml), dried ($MgSO_4$) and the organic layer of the solvent was removed under reduced pressure to give the *diamide* **21** (1.426 g, 89%) as colourless prisms, mp 62.9–63.5 °C; R_f 0.23 (EtOAc); (Found MNa^+ 253.1166; $C_{10}H_{18}N_2O_4$ requires *MNa*, 253.1164); ν_{max} ($CHCl_3$ solution) 3496, 2941, 1658 (C=O), 1424 (C=C), 1387, 1179 and 1106; δ_H (300 MHz; $CDCl_3$) 5.74 (2H, td, *J* 6.9 and 1.5, C=C*H*), 3.71 (6H, s, CH_3), 3.23 (4H, broad s, CH_2) and 3.18 (6H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 171.5 (C=O), 125.4 (C=C), 60.4 (CH_3), 34.9 (CH_3) and 31.1 (CH_2); *m*/*z* (ES) 253.1 (MNa, 100%).

(*E*)-Hex-3-enedioic acid bis(methoxymethylamide) 21

trans-Hydromuconic acid (10.00 g, 28.29 mmol) and thionyl chloride (25 ml) were refluxed under N_2 for 2 h. Excess thionyl chloride was removed under reduced pressure to give the corresponding acid chloride which was dissolved in dichloromethane (30 ml). The solution was added slowly to a stirred slurry of *N,O*-dimethylhydroxylamine hydrochloride (6.07 g, 62.24 mmol) and triethylamine (19.6 ml, 0.141 mol) in dichloromethane (200 ml) at 0 °C under N_2. The reaction mixture was stirred at room temperature for a further 6 h, quenched with water (100 ml), the organic layer washed with saturated aqueous sodium bicarbonate (2 × 50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the *diamide* **21** (5.47 g, 84%), spectroscopically identical to that obtained previously.

(*E*)-1,6-Dimorpholin-4-ylhex-3-en-1,6-dione 23

By the same general method, morpholine (6.07 g, 0.133 mol) gave the *morpholine amide* **23** (15.06 g, 96%) as colourless prisms, mp 112.4–113.1 °C; R_f 0.19 (95:5 EtOAc–MeOH); (Found MNa^+ 305.1493; $C_{14}H_{22}N_2O_4$ requires *MNa*, 305.1477); ν_{max} ($CHCl_3$ solution) 3456, 2865, 1663 (C=O), 1434 (C=C), 1273, 1225, 1111 and 1030; δ_H (300 MHz; $CDCl_3$) 5.70 (2H, tt, *J* 3.7 and 1.5, C=C*H*), 3.74–3.57 (14H, m, CH_2morp), 3.47 (4H, t, *J* 4.9) and 3.15 (4H, dd, *J* 3.7 and 1.5, CH_2); δ_C (75 MHz; $CDCl_3$) 170.0 (C=O), 126.8 (C=C), 67.2, 46.5 and 42.3; *m*/*z* (ES) 305.1 (MNa, 100%).

(3*R**,4*R**)-3,4-Bis(*tert*-butyldimethylsilyloxy)hexanoic acid bis(methoxymethylamide) 22

Osmium tetroxide (10 mg) was added to a stirred solution of amide **21** (4.50 g, 19.57 mmol) and NMO (4.58 g, 39.14 mmol) in dichloromethane (15 ml) at room temperature under N_2. The solution was stirred for 17 h before the solvent was removed under reduced pressure. The residue was dissolved in dry DMF (10 ml), imidazole (3.99 g, 58.71 mmol) and *tert*-butyldimethylsilyl chloride (7.43 g, 48.9 mmol) added, stirred for 24 h and the solvent removed at 80 °C under reduced pressure. The residue was partitioned between EtOAc (200 ml) and saturated aqueous sodium bicarbonate (100 ml), the organic layer washed with water (2 × 50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was filtered through a plug of silica to give the *silyl diether* **22** (8.38 g, 87%) as a colourless oil, R_f 0.15 (EtOAc); (Found: MH^+ 493.3133; $C_{22}H_{48}N_2O_6Si_2$ requires *MH*, 493.3129); ν_{max} ($CHCl_3$ solution) 3447, 2939 (C–H), 2857, 1785, 1664 (C=O), 1472, 1413, 1388, 1256 and 1096; δ_H (300 MHz; $CDCl_3$) 4.20 (2H, d, *J* 7.1, C*H*OSi), 3.59 (6H, s, OMe), 3.08 (6H, s, NMe), 2.46 (4H, m, CH_2), 0.73 (18H, s, ^{t}Bu), 0.00 (6H, s, SiMe) and −0.09 (6H, s, SiMe); *m*/*z* (ES) 493.3 (MH, 100%).

(3*R**,4*R**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-dimorpholin-4-ylhexane-1,6-dione 24

By the same general method, osmium tetroxide (10 mg), the amide **23** (612 mg, 2.154 mmol), NMO (504 mg, 4.308 mmol), imidazole (439 mg, 6.462 mmol) and *tert*-butyldimethylsilyl chloride (813 mg, 5.385 mmol) gave the silyl diether **24** (1.124 g, 96%) as colourless prisms, mp 97.4–98.6 °C; R_f 0.19 (85:15 EtOAc–MeOH); (Found: MNa^+ 567.3253; $C_{26}H_{52}N_2O_6Si_2$ requires *MNa*, 567.3262); ν_{max} ($CHCl_3$ solution) 3447, 2956 (C–H), 2929, 2857, 1646 (C=O), 1438, 1253, 1117 and 1067; δ_H (300 MHz; $CDCl_3$) 4.27 (2H, d, *J* 8.5 O–C*H*), 3.65–3.49 (16H, m, CH_2morp), 2.53 (2H, d, *J* 14.2, CH_AH_B), 2.35 (2H, dd, *J* 14.2 and 8.5, CH_AH_B), 0.83 (18H, s, ^{t}Bu), 0.09 (6H, s, $SiCH_3$) and 0.00 (6H, s, $SiCH_3$), δ_C (75 MHz; $CDCl_3$) 170.7 (C=O), 72.5, 67.3, 67.1, 46.8, 42.5, 34.2, 26.2 (^{t}Bu), 18.3, −4.3 and −4.4; *m*/*z* (ES) 567.3 (MNa, 100%).

(3*R**,4*R**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-dione 25

Butyllithium (4.72 ml, 7.17 mmol, as a 1.52 M solution in hexanes) was added slowly to a stirred solution of furan (568 µl, 7.82 mmol) in dry THF (15 ml) at −78 °C under N_2. The solution was allowed to warm to 0 °C, stirred for 30 min, added slowly by cannulation into a stirred solution of **22** (1.603 g, 3.26 mmol) in THF (10 ml) at −40 °C. The solution was stirred for a further 6 h before quenching with saturated aqueous ammonium chloride (20 ml). The solution was allowed to warm to room temperature and the aqueous layer extracted with EtOAc (3 × 20 ml), the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was pre-absorbed onto silica gel and purified by flash chromatography, eluting with 7:93 EtOAc–petrol to give the *diketone* **25** (1.627 g, 98%) as a colourless oil, R_f 0.42 (9:1 EtOAc–petrol); ν_{max} ($CHCl_3$ solution) 2955 (C–H), 2930, 2858, 1677 (C=O), 1569, 1470, 1392, 1314, 1257 and 1099; δ_H (300 MHz; $CDCl_3$) 7.52 (2H, dd, *J* 1.7 and 0.7, furyl 5-H), 7.15 (2H, dd, *J* 3.2 and 0.7, furyl 3-H), 6.47 (2H, dd, *J* 3.2 and 1.7, furyl 4-H), 4.34 (2H, dt, *J* 9.0 and 4.7, O–C*H*), 2.97 (4H, d, *J* 4.7, CH_2), 0.70 (18H, s, ^{t}Bu), 0.00 (6H, s, $SiCH_3$) and −0.17 (6H, s, $SiCH_3$), δ_C (75 MHz; $CDCl_3$) 188.6 (C=O), 153.8 (furyl 2-C),

146.7 (furyl 5-C), 117.7 (furyl), 112.7 (furyl), 71.8 (C–O), 40.5 (CH_2), 26.1 (^{t}Bu), 18.2, −4.3 ($SiCH_3$) and −4.5 ($SiCH_3$).

(3*R**,4*R**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-dione 25

By the same general method, butyllithium (7.39 ml, 11.47 mmol, as a 1.52 M solution in hexanes), furan (909 µl, 12.51 mmol) and **24** (2.85 g, 5.22 mmol) gave the *diketone* **25** (2.642 g, >98%) as a colourless oil, spectroscopically identical to that obtained previously.

(1*R**,3*S**,4*S**,6*R**)-, (1*R**,3*S**,4*S**,6*S**)- and (1*R**,3*R**,4*R**,6*R**)- 3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-diol 26a, 26b and 26c

Sodium borohydride (13 mg, 0.34 mmol) was added to a stirred solution of the *diketone* **25** (53.4 mg, 0.11 mmol) in methanol (1.5 ml) at 0 °C under N_2. The solution was stirred for 4 h before quenching with saturated aqueous ammonium chloride (0.5 ml). The solution was partitioned between chloroform (10 ml) and water (10 ml) and the organic layers dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. Analysis by 300 MHz ^{1}H NMR spectroscopy and analytical HPLC (gradient elution: 99:1 ⟶ 98:2 hexane–IPA over 30 min, with detection at 220 nm) revealed a 29:53:18 mixture of the diols **26a**, **26b** and **26c** (51.7 mg, 92%). Preabsorbtion onto silica gel and purification by flash chromatography (gradient elution: 5:95 ⟶ 25:75 EtOAc–petrol) gave the *diol* **26a** as colourless prisms, mp 93.2–95.0 °C; R_f 0.24 (2:8 EtOAc–petrol); retention time 19.5 min; (Found MNa^+ 533.2740; $C_{26}H_{46}O_6Si_2$ requires *MNa*, 533.2731); ν_{max} ($CHCl_3$ solution) 3411, 2930 (C–H), 2858, 1463, 1257, 1099 and 836; δ_H (300 MHz; $CDCl_3$) 7.32 (2H, dd, *J* 1.8 and 0.8, furyl 5-H), 6.29 (2H, dd, *J* 3.2 and 1.8, furyl 4-H), 6.22 (2H, dd, *J* 3.2 and 0.8, furyl 3-H), 4.80 (2H, t, *J* 6.9, 1-H and 6-H), 3.68 (2H, app t, *J* 3.8, 3-H and 4-H), 2.75 (2H, broad s, OH), 2.30 (2H, ddd, *J* 13.8, 6.9 and 2.8, CH_aH$_b$), 1.95 (2H, ddd, *J* 13.8, 6.9 and 2.0, CH$_a$$H_b$), 0.85 (18H, s, ^{t}Bu), 0.11 (6H, s, $SiCH_3$) and 0.00 (6H, s, $SiCH_3$); δ_C (75 MHz; $CDCl_3$) 156.5 (furyl 2-C), 142.3 (furyl 5-C), 110.6 (furyl), 106.8 (furyl), 73.5 (C–O), 66.9 (C–O), 36.9 (CH_2), 26.2 (^{t}Bu), 18.3, −3.6 ($SiCH_3$) and −4.6 ($SiCH_3$); *m*/*z* (ES) 533.3 (MNa, 100%).

Also obtained was the diol **26b** (26 mg, 45%) as colourless prisms, R_f 0.31 (15:85 EtOAc–petrol); retention time 11.5 min; (Found: MNa^+ 533.2729; $C_{26}H_{46}O_6Si_2$ requires *MNa*, 533.2731); ν_{max} ($CHCl_3$ solution) 3427, 2956 (C–H), 2930, 2858, 1472, 1389, 1257, 1141, 1070 and 1008; δ_H (300 MHz; $CDCl_3$) 7.27 (1H, dd, *J* 2.0 and 0.8, furyl 5-H), 7.26 (1H, dd, *J* 1.9 and 0.8, furyl 5-H), 6.24 (2H, dd, *J* 3.1 and 2.0, furyl 3-H), 6.16 (1H, dd, *J* 3.1 and 0.8, furyl 4-H), 6.14 (1H, dd, *J* 3.1 and 0.8, furyl 4-H), 4.78 (1H, app t, *J* 6.7), 4.69 (1H, d, *J* 10.0), 3.93 (1H, dt, *J* 8.2 and 3.5), 3.70 (1H, dt, *J* 8.2 and 3.5), 2.40 (2H, broad s, OH), 2.25 (1H, ddd, *J* 13.8, 7.9 and 3.5, CH_aH$_b$), 2.09 (1H, ddd, *J* 13.8, 7.9 and 3.3, CH_aH$_b$), 1.89 (1H, ddd, *J* 13.8, 7.2 and 2.6, CH$_a$$H_b$), 1.76 (1H, ddd, *J* 13.8, 7.7 and 2.3, CH$_a$$H_b$), 0.83 (9H, s, ^{t}Bu), 0.79 (9H, s, ^{t}Bu), 0.02 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$), and −0.09 (3H, s, $SiCH_3$), δ_C (75 MHz; $CDCl_3$) 156.5 (furyl 2-C), 158.3 (furyl 2-C), 142.3 (furyl 5-C), 142.2 (furyl 5-C), 110.6 (furyl), 110.6 (furyl), 106.8(furyl), 105.7 (furyl), 73.8 (C–O), 71.8 (C–O), 67.0 (C–O), 64.9 (C–O), 37.0 (CH_2), 36.9 (CH_2), 26.3 (^{t}Bu), 26.2 (^{t}Bu), 18.4, −3.5 (SiMe), −3.8 (SiMe), −4.6 (SiMe) and −4.7 (SiMe); *m*/*z* (ES) 533.3 (MNa, 100%).

Also obtained was the diol **26c** (8 mg, 15%) as a colourless flocculent solid; R_f 0.35 (1:9 EtOAc–petrol); retention time 6.9 min; (Found: MNa^+ 533.2734; $C_{26}H_{46}O_6Si_2$ requires *MNa*, 533.2731); ν_{max} ($CHCl_3$ solution) 3425, 2930 (C–H), 2858, 1659, 1470, 1259 and 1072; δ_H (300 MHz; $CDCl_3$) 7.22 (2H, dd, *J* 1.8 and 0.9, furyl 5-H), 6.19 (2H, dd, *J* 3.2 and 1.8, furyl 4-H), 6.47 (2H, dd, *J* 3.2 and 0.9, furyl 3-H), 4.67 (2H, app t, *J* 4.9, 1-H and 6-H), 3.94 (2H, unresolved, 3-H and 4-H), 2.55 (2H, d, *J* 4.1, OH), 2.08 (2H, ddd, *J* 14.1, 7.1 and 3.6, CH_aH$_b$), 1.74 (2H, ddd, *J* 14.1, 8.5 and 2.1, CH$_a$$H_b$), 0.78 (18H, s, ^{t}Bu), 0.01 (6H, s, $SiCH_3$) and 0.00 (6H, s, $SiCH_3$), δ_C (75 MHz; $CDCl_3$) 157.6 (furyl 2-C), 142.2 (furyl 5-C), 110.6 (furyl), 105.7 (furyl), 72.1 (C–O), 65.1 (C–O), 37.3 (CH_2), 26.3 (^{t}Bu), 18.4, −3.8 ($SiCH_3$) and −4.5 ($SiCH_3$); *m*/*z* (ES) 533.3 (MNa, 100%).

Reduction of the diketone 25 with DIBAL-H

DIBAL-H (390 µl of a 1 M solution in toluene, 0.39 mmol) was added to a stirred solution of the diketone **25** (90.0 mg, 0.177 mmol) in toluene (1.0 ml) at −78 °C under N_2. The solution was stirred for 2 h, quenched with methanol (0.5 ml), warmed to room temperature, a saturated aqueous solution of sodium potassium tartrate (4 ml) added, stirred vigorously until the two layers separated and the aqueous layer extracted with EtOAc (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. Analysis by 300 MHz ^{1}H NMR spectroscopy and analytical HPLC revealed a 60:30:10 mixture of diols **26a**, **26b** and **26c** (90.2 mg, >98%). Preabsorbtion onto silica gel and purification by flash chromatography (gradient elution: 5:95 ⟶ 25:75 EtOAc–petrol) gave the *diol* **26a** (54 mg, 60%), the *diol* **26b** (26 mg, 29%) and *diol* **26c** (7 mg, 8%).

(1*R**,3*S**,4*S**,6*S**)-1,6-Difuran-2-ylhexane-1,3,4,6-tetraol 27b

Tetra-*n*-butylammonium fluoride (400 µl, 0.4 mmol, 1 M solution in THF) was added to a stirred solution of *diol* **26b** (90 mg, 0.18 mmol) in THF (1.7 ml) at room temperature under N_2. The solution was stirred 24 h, the solvent evaporated under reduced pressure and the residue pre-absorbed on to silica gel and purified by flash chromatography, eluting with 1:1 EtOAc–petrol and then EtOAc, to give the *tetrol* **27b** (184 mg, 93%) as colourless prisms, R_f 0.52 (EtOAc); (Found MNa^+ 305.1007; $C_{14}H_{18}O_6$ requires *MNa*, 305.1001); ν_{max} ($CHCl_3$ solution) 3373, 2960 (C–H), 1634, 1424, 1148, 1065 and 1011; δ_H (300 MHz; $CDCl_3$) 7.30 (1H, dd, *J* 1.8 and 0.8, furyl 5-H), 7.28 (1H, dd, *J* 1.8 and 0.8, furyl 5-H), 6.27 (2H, dd, *J* 3.1 and 0.8, furyl 4-H), 6.21 (1H, dd, *J* 3.1 and 1.8, furyl 3-H), 6.19 (1H, dd, *J* 3.1 and 1.8, furyl 3-H), 4.92 (2H, dd, *J* 7.1 and 4.9, 1-H and 6-H), 4.45 (1H, broad s, OH), 4.31 (1H, broad s, OH), 4.21 (2H, broad s, OH), 3.65 (2H, m, 3-H and 4-H) and 1.95 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 156.9 (furyl 2-C), 156.2 (furyl 2-C), 142.5 (furyl 5-C), 142.3 (furyl 5-C), 110.6 (furyl), 106.6 (furyl), 106.3 (furyl), 74.3 (C–O), 71.5 (C–O), 67.2 (C–O), 64.9 (C–O), 38.4 (CH_2) and 38.3 (CH_2); *m*/*z* (ES) 305.2 (MNa, 100%).

(1*R**,3*S**,4*S**,6*R**)-1,6-Difuran-2-ylhexane-1,3,4,6-tetraol 27a

By the same method, the *diol* **26a** (160 mg, 0.31 mmol) gave the *tetrol* **27a** (45 mg, 89%) as colourless prisms, R_f 0.17 (95:5 EtOAc–MeOH); (Found MNa 305.1004; $C_{14}H_{18}O_6$ requires *MNa*, 305.1001); ν_{max} ($CHCl_3$ solution) 3330, 2924 (C–H), 1644, 1445, 1066 and 1045; δ_H (300 MHz; $CDCl_3$) 7.32 (2H, dd, *J* 1.7 and 0.7, furyl 5-H), 6.28 (2H, dd, *J* 3.2 and 1.7, furyl 3-H), 6.21 (2H, dd, *J* 3.2 and 0.7, furyl 4-H), 4.92 (2H, dd, *J* 8.9 and 4.2, 1-H and 6-H), 4.37 (4H, broad s, OH), 3.67 (2H, d, *J* 9.4, 3-H and 4-H) and 1.89–2.12 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 156.3 (furyl 2-C), 142.2 (furyl 5-C), 110.6 (furyl), 106.5 (furyl), 74.2 (C–O), 67.3 (C–O) and 38.2 (CH_2); *m*/*z* (ES) 305.2 (MNa, 100%).

(1*R**,3*R**,4*R**,6*R**)-1,6-Difuran-2-ylhexane-1,3,4,6-tetraol 27c

By the same method, the *diol* **26c** (64 mg, 0.125 mmol) gave the *tetrol* **27c** (28 mg, 79%) as colourless prisms, R_f 0.39 (9:1 EtOAc–petrol); (Found MNa^+ 305.0996; $C_{14}H_{18}O_6$ requires *MNa*, 305.1001); ν_{max} ($CHCl_3$ solution) 3330, 2966 (C–H), 2929, 1639, 1434, 1312, 1230, 1148, 1071 and 1020; δ_H (300 MHz; CD_3OD) 7.14 (2H, dd, *J* 1.8 and 0.8, furyl 5-H), 6.09 (2H, dd, *J* 3.2 and 1.8, furyl 3-H), 5.97 (2H, dd, *J* 3.2 and 0.8,

furyl 4-H), 4.61 (2H, unresolved, 1-H and 6-H), 3.50 (2H, m, 3-H and 4-H) and 1.67 (4H, m, CH_2); δ_C (75 MHz; CD_3OD) 159.2 (furyl 2-C), 143.0 (furyl 5-C), 111.2 (furyl), 106.4 (furyl), 72.0 (C–O), 65.1 (C–O) and 40.2 (CH_2); *m*/*z* (ES) 305.2 (MNa, 100%).

(4*R**, 7*R**)-2,2-Di-*tert*-butyl-4,7-difuran-2′-yl-1,3-dioxa-2-silacycloheptane 15

To a solution of the diol **13** (53 mg, 0.24 mmol) and pyridine (80 μl, 0.98 mmol) in THF (1 cm^3) at 0 °C was added di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (95 μl, 0.26 mmol). After 10 minutes the solution was quenched by addition of an aqueous solution of sodium bicarbonate (5 cm^3) and the aqueous layer was extracted with dichloromethane (3 × 15 cm^3). The combined organics were dried ($MgSO_4$) and reduced under reduced pressure to afford a crude product which was purified by flash column chromatography, eluting with 95:5 light petroleum–ethyl acetate to give the *di-tert-butylsilylene derivative* **15** (78 mg, 90%) as colourless needles, R_f 0.72 (4:1 petrol–EtOAc); (Found: M^+ 362.1914; $C_{20}H_{30}O_4Si$ requires *M*, 362.1913); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2963, 2930, 1141, 1057, 1008 and 970; δ_H (300 MHz; $CDCl_3$) 7.35 (2H, d, *J* = 1.8, 5′-H), 6.34 (2H, dd, *J* = 3.3 and 1.8, 4′-H), 6.25 (2H, d, *J* = 3.3, 3′-H), 5.13 (2H, m, 4-H and 7-H), 2.33 (2H, m, 5-H and 6-H), 1.88 (2H, ddd, *J* 13.0, 6.8 and 2.9, 5-H and 6-H), 1.10 (18H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 158.2, 141.6, 110.5, 104.8, 72.7, 36.8, 28.5, 21.9; *m*/*z* (EI) 362 (100%, M^+).

(4*R*,7*S*)-2,2-Di-*tert*-butyl-4,7-di-furan-2′-yl-1,3-dioxa-2-silacycloheptane 16

By the same general method, the diol **14** (58 mg, 0.26 mmol), pyridine (87 μl, 1.07 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (114 μl, 0.31 mmol) gave a crude product which was purified by flash column chromatography, eluting with 95:5 light petroleum–ethyl acetate, to give the *di-tert-butylsilylene derivative* **16** (87 mg, 92%) as colourless needles, R_f 0.70 (4:1 petrol–EtOAc); (Found: 362.1918; $C_{20}H_{30}O_4Si$ requires *M*, 362.1913); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2963, 2930, 1141, 1057, 1008 and 970; δ_H (300 MHz; $CDCl_3$) 7.33 (2H, dd, *J* = 1.9 and 0.8, 5′-H), 6.31 (2H, dd, *J* = 3.3 and 1.9, 4′-H), 6.25 (2H, dt, *J* = 3.3 and 0.8, 3′-H), 5.01 (2H, m, 4-H and 7-H), 1.88–1.93 (4H, m, 5-H_2 and 6-H_2), 1.05 (9H, s, ^{t}Bu) and 0.90 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 157.3, 141.7, 110.5, 106.4, 68.6, 32.4, 27.9, 27.6, 21.0, 20.9; *m*/*z* (EI) 362 (100%, M^+).

(4*R**,6*S**,4′*R**,6′*S**)-2,2,2′,2′-Tetra-*tert*-butyl-6,6′-difuran-2-yl[4,4′]bi{[1,3,2]dioxasilinane} 28a

By the same general method, the *tetrol* **27a** (42.2 mg, 0.150 mmol) gave **28a** (79 mg, 94%) as a colourless oil, R_f 0.74 (5:95 EtOAc–petrol); ν_{max} ($CHCl_3$ solution) 2934 (C–H), 2859, 1473, 1365, 1150, 1111 and 1002; δ_H (500 MHz; $CDCl_3$) 7.29 (2H, dd, *J* 1.8 and 0.9, furyl 5-H), 6.26 (2H, dd, *J* 3.2 and 1.8, furyl 3-H), 6.17 (2H, dd, *J* 3.2 and 0.9, furyl 4-H), 5.12 (2H, dd, *J* 11.7 and 2.5), 4.15 (2H, dd, *J* 10.7 and 1.4), 2.06 (2H, app dt, *J* 13.9 and 10.7, CH_AH$_B$), 1.93 (2H, ddd, *J* 13.9, 2.5 and 1.4, CH$_A$$H_B$), 0.99 (18H, s, ^{t}Bu), 0.94 (18H, s, ^{t}Bu); δ_C (125 MHz; $CDCl_3$) 156.2 (furyl 2-C), 140.5 (furyl 5-C), 109.0 (furyl), 103.8 (furyl), 75.1, 69.3, 34.0, 26.6, 24.8, 21.9 and 18.9.

NOE enhancements were observed between from 2-H to 6-H, and from 6-H to 2-H.

(4*R**,6*R**,4′*R**,6′*R**)-2,2,2′,2′-Tetra-*tert*-butyl-6,6′-difuran-2-yl[4,4′]bi{[1,3,2]dioxasilinane} 28c

By the same general method, the *tetrol* **27c**(8.1 mg, 15.8 μmol) gave **28c** (7.8 mg, 87%) as a colourless oil, R_f 0.79 (5:95 EtOAc–petrol); ν_{max} ($CHCl_3$ solution) 2934 (C–H), 2896, 2860, 1722, 1473, 1389, 1365, 1261 and 1107; δ_H (500 MHz; $CDCl_3$) 7.38 (2H, dd, *J* 1.8 and 0.9, furyl 5-H), 6.33 (2H, dd, *J* 3.2 and 1.8, furyl 3-H), 6.25 (2H, dd, *J* 3.2 and 0.9, furyl 4-H), 5.35 (2H, br d, *J* 6.3), 4.19 (2H, br d, *J* 10.6), 2.34 (2H, ddd, *J* 15.2, 10.6 and 6.3, CH_AH$_B$), 1.93 (2H, dt, *J* 15.2 and 1.8, CH$_A$$H_B$), 1.08 (18H, s, ^{t}Bu), 0.95 (18H, s, ^{t}Bu); δ_C (125 MHz; $CDCl_3$) 156.7 (furyl 2-C), 141.7 (furyl 5-C), 110.1 (furyl), 106.0 (furyl), 72.2, 67.8, 33.3, 27.2, 27.0, 21.9 and 20.9.

(*R**)-2-[(2*S**′, 3*S**′,5*R**′)-2′,3′-Bis(*tert*-butyldimethylsilyloxy)-5′-furan-2-yl-5′-hydroxypentyl]-6-hydroxy-6*H*-pyran-3-one 31

tert-Butyl hydroperoxide (150 μl, 0.75 mmol, 5 M solution in decanes) was added to a stirred solution of the diol **26a** (295.5 mg, 0.577 mmol) and vanadyl acetylacetonate (2 mg, catalytic) in dichloromethane (10 ml) at room temperature under N_2. The solution was stirred for 1.5 h before quenching with a saturated aqueous solution of ferrous sulfate–tartaric acid. The aqueous layer was extracted with dichloromethane (3 × 20 ml) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure to give a residue which was pre-absorbed on to silica gel and purified by flash chromatography (gradient elution: 2:8 ⟶ 6:4 EtOAc–petrol gradient to give the *monopyranone* **31** (112 mg, 37%; 7:3 mixture of anomers), as a semi-crystalline solid, R_f 0.24 (4:6 EtOAc–petrol); (Found: MNa, 549.2676; $C_{26}H_{46}O_7Si_2$ requires *MNa*, 549.2680); ν_{max} ($CHCl_3$ solution) 3387 (O–H), 2930 (C–H), 2895, 2858, 1696, 1472, 1258 and 1104; δ_H (300 MHz; $CDCl_3$) 7.29 (1H, dd, *J* 1.8 and 0.9, furyl 5-H$^{maj+min}$), 6.83 (1H, dd, *J* 10.2 and 1.5, 5-H^{min}), 6.78 (1H, dd, *J* 10.2 and 3.3, 5-H^{maj}), 6.25 (1H, dd, *J* 3.1 and 1.8, furyl 3-H$^{maj+min}$), 6.18 (1H, d, *J* 3.1 and 0.9, furyl 4-H$^{maj+min}$), 6.03 (1H, dd, *J* 10.2 and 1.3, 4-H^{min}), 5.98 (1H, d, *J* 10.2, 4-H^{maj}), 5.54 (1H, broad s, 6-H$^{maj+min}$), 4.76 (1H, t, *J* 6.7, 5′-H$^{maj+min}$), 4.63 (1H, dd, *J* 7.7 and 4.6, 2-H^{maj}), 4.18 (1H, dd, *J* 6.9 and 5.9, 2-H^{min}), 3.96 (1H, m, 2′-H$^{maj+min}$), 3.84 (1H, broad, OH^{maj}), 3.61 (1H, m, H$^{maj+min}$), 3.04 (1H, broad, CHO*H* $^{maj+min}$), 2.40 − 2.18 (2H, m, $CH_2$$^{maj+min}$), 1.98–1.62 (2H, m, $CH_2$$^{maj+min}$), 0.82 (9H, s, ^{t}Bu^{maj}), 0.82 (9H, s, ^{t}Bu^{min}), 0.79 (9H, s, ^{t}Bu^{min}), 0.79 (9H, s, ^{t}Bu^{maj}), 0.04 (3H, s, SiCH$_3$^{maj}), 0.02 (3H, s, SiCH$_3$^{min}), 0.00 (3H, s, SiCH$_3$^{maj}), −0.01 (3H, s, SiCH$_3$^{min}), −0.06 (3H, s, SiCH$_3$^{min}), −0.08 (3H, s, SiCH$_3$^{maj}), −0.11 (3H, s, SiCH$_3$^{min}), −0.13 (3H, s, SiCH$_3$^{maj}); δ_C (75 MHz; $CDCl_3$) 197.3 (C=O), 156.4 (furyl 2-C), 144.6, 142.4 (furyl 5-C), 127.9, 110.6 (furyl), 106.8 (furyl), 88.2, 73.2, 71.3, 67.0, 60.9, 36.5, 31.9, 26.2, 26.2, −3.6, −3.8, −3.9 and −4.4; *m*/*z* (ES) 549.5 (MNa, 100%).

Also obtained was the *dipyranone* **32** (75 mg, 24%), spectroscopically to that obtained below.

Dipyranone 32

By the same general method, *tert*-butyl hydroperoxide (200 μl, 1.00 mmol, 5 M solution in decanes), the diol **26a** (153.6 mg, 0.300 mmol) and vanadyl acetylacetonate (2 mg, catalytic) gave a crude product, which was purified by flash chromatography, eluting with 1:1 EtOAc–petrol, to give the *dipyranone* **32** (159 mg, 98%; mixture of anomers) as a colourless oil, R_f 0.16 (4:6 EtOAc–petrol); (Found: MNa 565.2610; $C_{26}H_{46}O_8Si_2$ requires *MNa*, 565.2629); ν_{max} ($CHCl_3$ solution) 3401 (O–H), 2955 (C–H), 2930, 2858, 1698, 1472, 1259, 1096 and 1032; δ_H (300 MHz; $CDCl_3$) 6.84 (2H, dd, *J* 10.2 and 1.5, 5-H^{min}), 6.79 (2H, dd, *J* 10.2 and 3.3, 5-H^{maj}), 6.01 (2H, dd, *J* 10.2 and 0.8, 4-H^{maj}), 6.00 (2H, dd, *J* 10.2 and 0.5, 4-H^{min}), 5.56 (2H, d, *J* 2.8, 6-H$^{maj+min}$), 4.61 (2H, td, *J* 7.7 and 5.9, 2-H^{maj}), 4.18 (2H, td, *J* 6.7 and 6.4, 2-H^{min}), 3.97 (2H, t, *J* 5.4, H$^{maj+min}$), 3.70 (2H, broad, OH$^{maj+min}$), 2.34 (2H, m, $CH_2$$^{maj+min}$), 1.64 (2H, m, $CH_2$$^{maj+min}$), 0.80 (9H, s, ^{t}Bu^{min}), 0.79 (9H, s, ^{t}Bu^{maj}), 0.02 (3H, s, SiCH$_3$^{min}), 0.00 (3H, s, SiCH$_3$^{maj}), −0.02 (3H, s, SiCH$_3$^{min}), −0.04 (3H, s, SiCH$_3$^{maj}); δ_C (75 MHz; $CDCl_3$) 197.3 (C=O), 144.4, 128.1, 88.2, 71.7, 32.3, 26.2, 18.4, −3.9 and −4.1; *m*/*z* 565.9 (MNa, 100%).

1,2-Bis[(2*R*)-6-hydroxy-6*H*-pyran-3-on-2-yl]ethane

By the same general method, the diol *rac*-**13** (775 mg, 3.49 mmol) gave a crude product after 6 h. Filtration gave the *dipyranone* (842 mg, 95%, 75:25 anomeric mixture) as colourless prisms, mp 164.1–165.8 °C (from MeOH); R_f 0.58 (4:1 EtOAc–petrol); (Found: C, 56.5; H, 5.60; $C_{12}H_{14}O_6$ requires C, 56.7; H, 5.55%); ν_{max}/cm^{-1} (thin film) 3383 (OH), 1655, 1596, 1261 and 799; δ_H (300 MHz; DMSO-d_6) 7.28 (0.5H, d, *J* 7.3, OH), 7.02 (1.5H, dd, *J* = 10.2 and 3.5, 5-H), 7.01 (0.5H, m, 5-H), 6.98 (1.5H, d, *J* 6.6, OH), 6.06 (0.5H, br d, *J* 10.2, 4-H), 5.98 (1.5H, d, *J* 10.2, 4-H), 5.57 (0.5H, m, 6-H), 5.48 (1.5H, d, *J* 9.4 and 3.5, 6-H), 4.50 (1.5H, br d, *J* 8.4, 2-H), 4.40 (0.5H, br d, *J* 6.6, 2-H), 2.00–1.81 (2H, m, CH_2) and 1.61–1.52 (2H, m, CH_2); δ_C (75 MHz; d_4-MeOH) 198.9^{maj}, 198.4^{min}, 151.6^{min}, 148.1^{maj}, 129.2^{min}, 127.6^{maj}, 92.3^{min}, 88.7^{maj}, 79.1^{maj}, 75.0^{min}, 26.7^{min}, 26.3^{maj}; *m*/*z* (EI) 236 (7%, $M^+ - CO$), 151 (30), 123 (30), 110 (26), 95 (80), 85 (86), 84 (63), 55 (100) and 44 (63).

Kinetic resolution of the difuryl diol *rac*-13

(+)-L-Diethyl tartrate (0.46 ml, 2.70 mmol) and titanium tetraisopropoxide (0.6 ml, 2.25 mmol) were added to a stirred solution of the diol *rac*-**13** (250 mg, 1.13 mmol) in dry dichloromethane (10 ml) at −40 °C. The reaction was stirred for 30 min, *tert*-butyl hydroperoxide (0.49 ml of a 5.0 M solution in decane, 2.48 mmol) added, stirred at −40 °C for 4 h and warmed to room temperature overnight. The reaction mixture was quenched with water (10 ml), allowed to warm to room temperature and filtered through Celite with dichloromethane (25 ml). The organic layers were combined and evaporated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 3:2 EtOAc–petrol to give (*2S*)-2-[(*S*)-3′-furan-2-yl-3′-hydroxypropyl]-6-hydroxy-6*H*-pyran-3-one **29** (52 mg, 21%). Analysis of the product by 500 MHz ^{1}H NMR spectroscopy revealed a 55:45 mixture of the pyranone **29a** (2:1 mixture of anomers) and the spirocycle **29b** (>90:10 mixture of anomers), R_f 0.25 (3:2 EtOAc–petrol); $[a]_D$ +30.2 (*c* 0.1 in $CHCl_3$); (Found: MNa, 261.0740; $C_{12}H_{14}O_5$ requires *MNa*, 261.0739); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3300 (OH), 3000–2850 (CH) and 1680 (C=O); δ_H (300 MHz; $CDCl_3$) 7.36 (1.0H, m, furan H-5), 6.92 (0.2H, dd, *J* 10.3 and 1.5, H-5 pyranone^{min}), 6.88 (0.35H, dd, *J* 10.3 and 3.4, H-5 pyranone^{maj}), 6.35–6.20 (2.0H, m, furan H-4 and H-3), 6.14 (0.20H, dd, *J* 10.3 and 1.5, H-4 pyranone^{min}), 6.10 (0.35H, d, *J* 10.3, H-4 pyranone^{maj}), 5.85 (0.90H, m, 4-H and 5-H spirocycle), 5.64 (0.55H, m, H-6 pyranone), 5.05 (0.45 H, m, 6-H spirocycle), 4.70 (0.55H, m, H-3′ pyranone), 4.60 (0.45H, dd, *J* 8.0 and 3.5, H-3′ spirocycle), 4.0–3.7 (1.0H, m, 2-H), 3.1–2.8 (2.0H, m, OH) and 2.3–1.8 (4.0H, CH_2); *m*/*z* (ES) 261 (100, MNa^+).

In a separate experiment, the reaction was followed by analytical chiral HPLC using an internal anthracene standard (Chiracel OD column, eluting with 80:20 hexane–isopropanol; flow: 1 ml min^{-1}; monitoring at λ_{max} 216 nm), retention times: 4.0 min (anthracene), 9.0 min (first enantiomer, **13**) and 9.8 min (second enantiomer, **13**).

Kinetic resolution of the diol 26a

(+)-L-DIPT (160 μl, 0.937 mmol) and titanium(IV) isopropoxide (186 μl, 0.625 mmol) were stirred in dry dichloromethane (5 ml) at −40 °C over 3 Å molecular sieves (0.2 g) for 30 min, and a solution of the diol **26a** (400 mg, 0.781 mmol) in dry dichloromethane (10 ml) was added. After stirring for a further 15 min, *tert*-butyl hydroperoxide (1.95 mmol, 379 μl, 5.15 M solution in decane) was added and the reaction was maintained at −40 °C while the experiment was conducted. At given time intervals, aliquots of approximately 0.1 ml were transferred to a 4 ml vial containing dichloromethane (0.5 ml) and an aqueous solution (2.0 ml; 0.5 M in ferrous sulfate and 0.5 M in tartaric acid), shaken, the organic layer dried ($MgSO_4$) and filtered through a pipette containing a plug of cotton wool, diluted with methanol to a total volume of 2.0 ml, filtered through a HPLC filter and analysed by analytical HPLC (gradient elution: 50:50 ⟶ 90:10 acetonitrile–water over 15 min then 90:10 acetonitrile–water over 10 min; flow: 1.0 ml min^{-1}; monitoring at 200, 214 and 225 nm), retention times: **26a**, 18.7 min; **31**, 16.9 min; **32**, 15.4 min. The enantiomeric excesses of aliquots of **26a** were determined by chiral analytical HPLC (gradient elution: 99.6:0.4 ⟶ 97.5:2.5 hexane–isopropanol over 30 min; flow: 1 ml min^{-1}; observation at λ_{max}, 219 nm), retention times, 24.4 and 26.2 min.

In a separate experiment, the reaction of the diol **26a** (400 mg, 0.781 mmol) was monitored by analytical HPLC. When the mole fraction of the dipyranone was 42%, the reaction was quenched at −40 °C by the addition of an aqueous solution (40 ml; 0.5 M in ferrous sulfate and 0.5 M in tartaric acid), the layers separated and the aqueous layer extracted with dichloromethane (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was pre-absorbed onto silica gel and purified by flash chromatography (gradient elution: 2:8 ⟶ 6:4 EtOAc–petrol) to give the *dipyranone* **32** (175 mg, 42%), $[a]_D$ −5.4 (*c* 0.14, $CHCl_3$), spectroscopically identical to that obtained previously. The absolute configuration of the product was not determined.

Also obtained was the diol **26a** (120 mg, 30%), spectroscopically identical to that obtained previously.

(2*S*)-2-{(2*R*,3*R*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-[(*S*)-3-oxo-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]butyl}-6-methoxy-6*H*-pyran-3-one 33

Boron trifluoride diethyl etherate complex (5 μl, 39 μmmol) was added to a stirred solution of the dipyranone **32** (43 mg, 79 μmol) and trimethyl orthoformate (100 μl, 0.92 mmol) in dichloromethane (2 ml) at room temperature. Stirring was continued for 10 min before the reaction was quenched with saturated aqueous sodium bicarbonate (2 ml), the layers separated and the organic layer dried ($MgSO_4$) and evaporated under reduced pressure to give the acetals **33** (45 mg, >98%), $[a]_D$ −3.4 (*c* 0.53, $CHCl_3$). A sample of the acetals **33** (12.2 mg) was purified by preparative HPLC (gradient elution: 90:10 ⟶ 96:4 acetonitrile–water over 35 min, monitoring at 200 nm) gave the acetal **33a** (4.8 mg, 39%) as a colourless oil, R_f 0.32 (2:8 EtOAc–petrol); retention time, 17.4 min; (Found MNH_4^+ 588.3378. $C_{28}H_{50}Si_2O_8$ requires MNH_4, 588.3388); ν_{max} ($CHCl_3$ solution) 2929 (C–H), 2857, 1698 (C=O), 1476, 1391, 1259, 1101 and 1054 δ_H (300 MHz; $CDCl_3$) 6.80 (2H, dd, *J* 10.2 and 3.3, 5-H), 6.05 (2H, d, *J* 10.2, 4-H), 5.08 (2H, d, *J* 3.3, 6-H), 4.57 (2H, dd, *J* 8.3 and 3.9, 2-H), 4.15 (2H, d, *J* 9.0, 2-H′ and 3-H′), 3.50 (6H, s, OMe), 2.32 (2H, ddd, *J* 13.8, 8.7 and 2.1, CH_aH_b), 1.74 (2H, ddd, *J* 13.8, 8.3 and 3.9, CH_aH_b), 0.87 (18H, s, ^{t}Bu), 0.13 (6H, s, $SiCH_3$), 0.00 (6H, s, $SiCH_3$); *m*/*z* (ES) 593.7 (100%, MNa).

Also obtained was the acetal **33b** (5.1 mg, 42%) as a colourless oil, R_f 0.32 (2:8 EtOAc–petrol); retention time, 16.4 min; (Found MNH_4^+ 588.3378. $C_{28}H_{50}Si_2O_8$ requires MNH_4, 588.3388); ν_{max} ($CHCl_3$ solution) 2930 (C–H), 2857, 1699 (C=O), 1472, 1391, 1259, 1103 and 1051; δ_H (300 MHz; $CDCl_3$) 6.76 (1H, dd, *J* 10.2 and 1.8, 5-H), 6.73 (1H, dd, *J* 10.2 and 3.3, 5-H), 6.02 (1H, d, *J* 10.2, 4-H), 5.97 (1H, d, *J* 10.2, 4-H), 5.14 (1H, s, 6-H), 5.01 (1H, d, *J* 3.3, 6-H), 4.47 (1H, dd, *J* 8.5 and 3.8, 2-H), 4.20 (1H, dd, *J* 8.2 and 4.9, 2-H), 4.05 (1H, dd, *J* 9.5 and 3.3, 2-H′ or 3-H′), 3.97 (1H, dt, *J* 8.2 and 3.9, 2-H′ or 3-H′) 3.49 (3H, s, OMe), 3.43 (3H, s, OMe), 2.34 (1H, ddd, *J* 14.0, 8.5 and 3.6, CH_aH_b), 2.25 (1H, ddd, *J* 13.6, 8.5 and 2.8, CH_aH_b), 1.77 (1H, ddd, *J* 14.0, 8.7 and 4.9, CH_aH_b), 1.65 (1H, ddd, *J* 13.6, 8.7 and 4.1, CH_aH_b), 0.81 (9H, s, ^{t}Bu), 0.78 (9H, s, ^{t}Bu), 0.08 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$) and -0.09 (3H, s, $SiCH_3$, H^{maj}); *m*/*z* (ES) 593.7 (100%, MNa).

Also obtained was the acetal **33c** (1.2 mg, 10%) as a colourless oil, R_f 0.32 (2:8 EtOAc–petrol); retention time, 15.5 min;

(Found MNH_4^+ 588.3378. $C_{28}H_{50}Si_2O_8$ requires *MNH*$_4$, 588.3388); ν_{max} ($CHCl_3$ solution) 2928 (C–H), 2857, 1699 (C=O), 1475, 1392, 1261, 1103 and 1050; δ_H (300 MHz; $CDCl_3$) 6.77 (2H, dd, *J* 10.2 and 1.8, 5-H), 6.02 (2H, dd, *J* 10.2 and 1.0, 4-H), 5.14 (2H, s, 6-H), 4.20 (2H, dd, *J* 8.4 and 4.8, 2-H), 3.94 (2H, ddd, *J* 7.9, 5.6 and 2.8, 2-H′ and 3-H′), 3.50 (6H, s, OMe), 2.36 (2H, ddd, *J* 14.1, 8.4 and 2.8, CH_aH_b), 1.76 (2H, ddd, *J* 14.1, 7.9 and 4.8, CH_aH_b), 0.80 (18H, s, ^{t}Bu), 0.04 (6H, s, $SiCH_3$), 0.00 (6H, s, $SiCH_3$); *m*/*z* (ES) 593.7 (100%, MNa).

(2*S*,3*R*,6*R*)-2-{(2*R*,3*R*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-[(2*S*,3*R*,6*R*)-3-hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]butyl}-3-hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-3-ol 34

The diacetal **33a** (10 mg, 17.5 μmol) and cerium chloride heptahydrate (49 mg, 0.131 mmol) were stirred under nitrogen at −40 °C in ethanol (1.5 ml) and sodium borohydride (4.4 mg, 0.115 mmol) was added in one portion. The solution was stirred for 8 h, quenched with water (0.2 ml) and evaporated to dryness under reduced pressure. The residue was pre-absorbed onto silica and purified by flash chromatography, eluting with 2:8 EtOAc–petrol, to give the diol **34** (9.4 mg, 94%) as a colourless oil, R_f 0.21 (2:8 EtOAc–petrol); $[\alpha]_D$ −8.3 (*c* 0.09, $CHCl_3$); (Found MNH_4^+ 592.3698. $C_{28}H_{54}Si_2O_8$ requires *MNH*$_4$, 592.3701); ν_{max} ($CHCl_3$ solution) 3434 (O–H), 2955 (C–H), 2929, 2857, 1472, 1255, 1054 836; δ_H (500 MHz; $CDCl_3$) 5.82 (2H, d, *J* 10.2, 5-H), 5.61 (2H, dt, *J* 10.2 and 1.6, 4-H), 4.69 (2H, s, 6-H), 4.07 (2H, ddd, *J* 8.7, 2.1 and 1.6, 3-H), 3.87 (2H, d, *J* 8.7, 2-H′ and 3-H′), 3.68 (2H, td, *J* 8.7 and 2.1, 2-H), 3.27 (6H, s, OMe), 1.75–1.97 (4H, m, CH_2), 0.80 (18H, s, ^{t}Bu), 0.03 (6H, s, $SiCH_3$), 0.00 (6H, s, $SiCH_3$). *m*/*z* (ES) 592.4 (MH_4, 100%).

(*R*)-Mosher's diester of the diol 34

(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (6.7 μl, 0.036 mmol) was added to a stirred solution of the diol **34** (5 mg, 8.68 μmol) in pyridine (4 drops) and carbon tetrachloride (12 drops). The reaction mixture was stirred for 48 hours at room temperature, diluted with chloroform (3 ml) and washed with saturated aqueous sodium bicarbonate solution (2 × 0.5 ml) and brine (1 ml). The layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was pre-absorbed on silica gel and purified by flash chromatography, eluting with 3:7 EtOAc–petrol, to give the *diester* (8.7 mg, 94%; 71:29 mixture of diastereoisomers) as a viscous oil, R_f 0.35 (3:7 EtOAc–petrol); (Found MNH_4^+ 1024.4497. $C_{48}H_{68}Si_2F_6O_{12}$ requires *MNH*$_4$, 1024.4505); ν_{max} ($CHCl_3$ solution) 2957, 2930, 2857, 1750, 1472, 1400, 1260, 1188, 1170, 1104, 1056, 967; δ_H (500 MHz; $CDCl_3$) 7.43 (4H, d, *J* 8.1, Ar), 7.29 (6H, m, Ar), 5.92 (2H, d, *J* 10.2, 4-H^{maj}), 5.86 (2H, d, *J* 10.3, 4-H^{min}), 5.80 (2H, d, *J* 10.2, 5-H^{maj}), 5.65 (2H, d, *J* 10.3, 5-H^{min}), 5.30 (2H, t, *J* 9.8, 3-H$^{maj+min}$), 4.80 (2H, s, 6-H^{maj}), 4.73 (2H, s, 6-H^{min}), 4.10 (2H, m, 2-H^{min} or C*H*OTBS^{min}), 4.06–3.92 (4H, m, 2-H^{min} or C*H*OTBS^{maj}), 3.65 (2H, m, 2-H^{min} or C*H*OTBS^{min}), 3.49 (3H, s, OMe^{min}), 3.46 (3H, s, OMe^{min}), 3.38 (3H, s, OMe^{maj}), 3.34 (3H, s, OMe^{maj}), 2.11–1.74 (4H, m, CH_2), 0.82 (18H, s, ^{t}Bu), 0.80 (18H, s, ^{t}Bu), 0.02 (3H, s, SiMe), −0.01 (3H, s, SiMe), −0.05 (3H, s, SiMe) and −0.07 (3H, s, SiMe); *m*/*z* (ES) 1024.5 (MNH_4^+, 100%).

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