The dihydrofuran template approach to furofuran synthesis†

David J. Aldous,[b] Andrei S. Batsanov,[a] Dmitrii S. Yufit,[a] Anne J. Dalençon,[a] William M. Dutton[a] and Patrick G. Steel*[a]

Received 6th April 2006, Accepted 30th May 2006
First published as an Advance Article on the web 30th June 2006
DOI: 10.1039/b604952d

Flash vacuum pyrrolysis of vinyl epoxides provides *cis*-dihydrofuran carboxylic esters in good yields and diastereoselectivities, which, on base-promoted epimerisation afford the complementary *trans* series. The compounds provide a viable template for a Lewis acid promoted cyclisation to provide the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane core found in the furofuran series of natural lignans. This strategy is stereodivergent and can be controlled to provide the *exo-exo*, *exo-endo* or *endo-endo* stereochemistries. The approach has been exemplified in syntheses of the sesamyl furofurans (±)-epiasarinin and (±)-asarinin.

Introduction

Detected in over seventy different plant species, lignans represent a major class of plant derived natural products with a common β–β linked phenyl propanoid skeleton. The furofurans, one of the main subsets of this family of natural products, are characterised by a 2,6-diaryl-3,7-dioxabicyclo[3,3,0]octane structure. Distinctions within this subclass can be made in the relative orientations and nature of the C-2 and C-6 aryl substituents. These may be the same or different representing the results of a homo- or hetero coupling of cinnamate units during the biosynthesis. Most commonly these aryl groups are located on the less hindered *exo* face although examples of both the *exo-endo* and *endo-endo* series are known, Fig. 1. Accompanying this structural and stereochemical diversity is a broad range of biological activities including anti-viral, anti-inflammatory and anti-oxidant properties.[1]

Given the wide range of biological activities displayed by the furofurans there have been considerable efforts to develop efficient synthetic strategies.[2] The vast majority of these have relied on ether bond formation to complete the ring system. The most common approach has been to formally disconnect the skeleton at both ether bonds and to prepare a tetradiol precursor. Although cyclisation to establish the furofuran skeleton can be achieved in a single operation under either basic or acidic conditions there are a number of disadvantages. The former requires all the stereochemistry to be established in the precursor and selective functionalisation of the different hydroxyl groups. Whilst acid promoted cyclisation does not have these requirements it only leads to the formation of the thermodynamically favoured *exo-exo* isomer. The other approaches construct the furan rings in a sequential manner using the conformation of an existing ring to help establish the key C-3 and C-7 stereocentres. These provide greater stereochemical diversity and have allowed examples of *endo-exo*-furofurans to be generated. However, as yet, none of these strategies have been reported to be applicable to the preparation of the *endo-endo* series.[3]

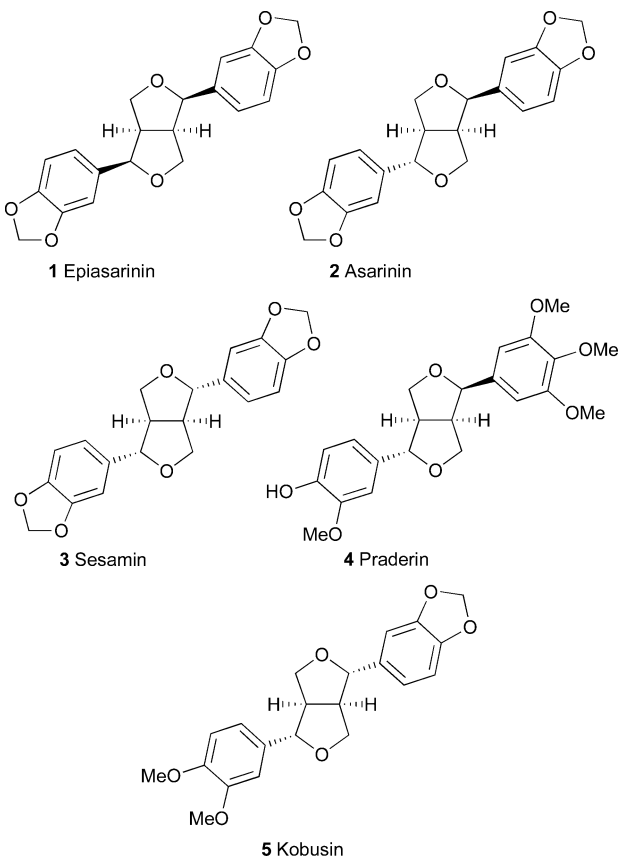
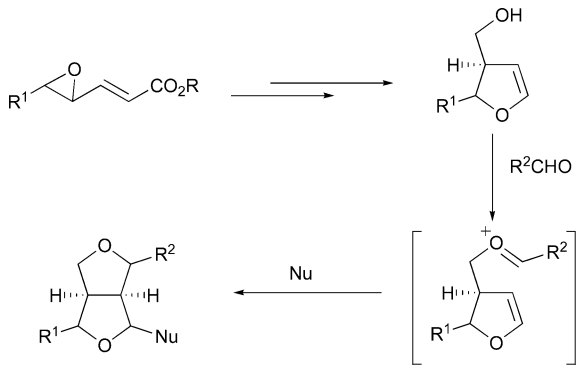


Fig. 1 Stereochemical and structural diversity in naturally occurring furofurans.

At the outset of this project, our aim was to develop a modular generic synthesis which could provide tuneable access to all the possible furofuran isomers. We envisaged a strategy employing a templated cationic cyclisation to establish the furofuran core *via* C–C bond formation and, in the process, setting the stereochemistry at C-2 and C-3, Scheme 1.[4] The key steps in this

[a]*Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE. E-mail: p.g.steel@durham.ac.uk; Fax: +44-(0)191-384-4737; Tel: +44-(0)191-334-2131*
[b]*Sanofi-Aventis Pharma Inc, Route 202-206, Bridgewater, P.O. Box 6800, New Jersey 08807, USA*

† Electronic supplementary information (ESI) available: Characterisation of compounds **7b**, **8b**, **10a**, **11a**, **19–24** and **27–32**. See DOI: 10.1039/b604952d

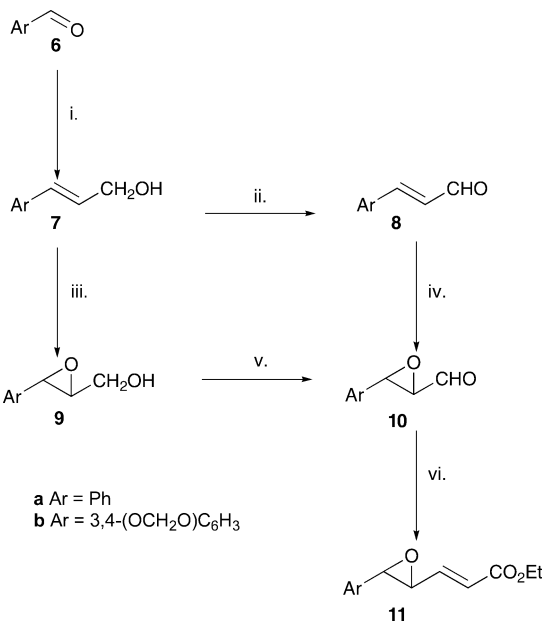


Scheme 1

included the exploitation of the thermal rearrangement of a vinyl epoxide to provide the dihydrofuran template and a subsequent Lewis acid promoted cyclisation to generate the furofuran skeleton with control of the stereochemistry. In previous preliminary communications we have described our initial results and in this paper we provide the full details of this work together with an analysis of the scope and limitations of such an approach.[5]

Results and discussion

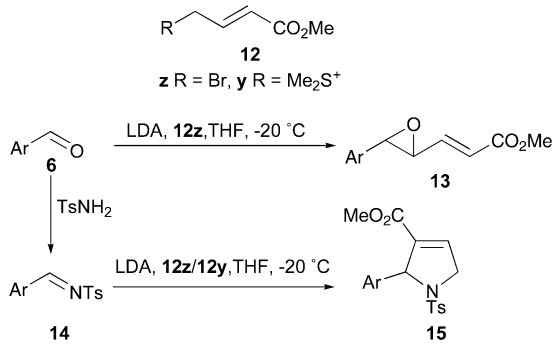
In our initial studies we explored the vinyl epoxide rearrangement of simple cinnamate derived substrates, Scheme 2. Whilst stereochemically pure *trans*-epoxy aldehyde could be prepared *via* successive epoxidation and oxidation of *trans*-cinnamyl alcohol, it proved more efficient, and amenable to 'scale up', to produce the aldehyde **10** through the aqueous base mediated epoxidation of cinnamaldehyde **8a** with hydrogen peroxide.[6] Whilst this produced a 7 : 3 mixture of isomers, this was of no concern as the vinyl epoxide–dihydrofuran rearrangement is stereoconvergent producing an isomer ratio independent of that of the starting epoxide. Conversion to the required rearrangement substrate was achieved using HWE olefination using triethylphosphonoacetate which afforded the enoate **11a** with complete *E* selectivity.



Scheme 2 *Reagents*: i. a) Ph_3PCHCO_2Et, 88%, b) DIBAL, THF, −78 °C, 80%; ii. MnO_2, **8b** 95%; iii. mCPBA, DCM, **9a** 92%; iv. ^tBuOOH, NaOH, **10a** 73%; v. SO_3·Py, DMSO, Et_3N, **10a** 55%; vi. $(EtO)_2P(O)CH_2CO_2Et$, NaH, PhMe, **11a** 68%.

Having established an efficient route capable of producing multigram quantities of rearrangement substrate we then attempted to extend this chemistry to the more electron rich substrates found in the natural furofurans. Whilst the required unsaturated aldehydes are not commercially available it was relatively straightforward to access them *via* a sequence of standard transformations, in good overall yields, Scheme 2. However, this approach subsequently foundered on the instability of the epoxide intermediates. For example, attempts to generate the epoxide from either alcohol **7b** or aldehyde **8b** using a range of epoxidation reagents (*m*CPBA, TBHP/OH^-, DMDO,[7] MMPP[8] *etc.*) failed with the only detectable material in the crude products corresponding to ring opened materials. Presumably the highly electron donating ring systems found in the natural systems activate the epoxide to hydrolysis.

This challenge forced us to consider alternative routes to the required vinyl epoxides and we were attracted to the vinylogous Darzens epoxidation of benzaldehyde using bromocrotonate and KO^{t}Bu in ^{t}butanol as described by Koppel.[9] Although initial attempts to reproduce this procedure were complicated by poor solubility, efficient conversion to the desired epoxides **11** could be achieved through the use of a combination of THF, strong base, excess crotonate anion and careful control of the reaction temperature. This modified protocol proved amenable to the preparation of a range of epoxides albeit as a mixture of *cis* and *trans* epoxide isomers. Since we were also interested in extending our approach to include the preparation of aza analogues of the furofurans, we wished to consider the analogous rearrangement of vinylaziridines. Such substrates could be prepared by the addition of a crotonate anion to the corresponding imine and there is precedent for such an approach. Dai *et al.* have described the reaction of tosylimines with 4-bromodimethylsulfonium crotonate **12y**, Scheme 3.[10] to afford a variety of aryl substituted vinyl aziridines in 35–50% yield. Encouraged by this precedent *N*-tosylbenzylimine **14** was combined with 4-bromocrotonate **12z** under our modified Darzens conditions. After purification by flash chromatography, a pure product was obtained in 17% yield. Whilst elemental analysis was consistent with the predicted molecular formula ($C_{19}H_{19}NO_4S$), ^{13}C NMR DEPT analysis showed the



Scheme 3

presence of a methylene group (δ_c 54.9 ppm) inconsistent with the expected aziridine structure. Ultimately, an X-ray crystal structure determination revealed that this 'aza Darzens' reaction had led to the 3-pyrroline **15**, Fig. 2. One possible pathway for the formation of this product would involve preferential reaction of the crotonate at the α-carbon followed by isomerisation and cyclisation. In an attempt to direct the reaction to the γ-position, the stronger anion stabilising sulfonium salt **12y** was prepared following protocols described by Nordlander[11] and the Dai process repeated. Surprisingly this too led to the formation of the 3-pyrrolidine, albeit in modest yield. At this stage we are unable to account for the divergence of our and Dai's observations. Potentially, the vinyl aziridine may be formed and undergoing a rapid rearrangement to give a pyrroline structure. There is precedent for such a pathway. For example, Somfai and Hirner have recently described the iodide promoted rearrangement of vinyl aziridines to pyrrolines in a microwave reactor.[12] Whilst not providing the desired vinyl aziridine this very direct preparation of pyrrolines is an area of ongoing study in our laboratories.

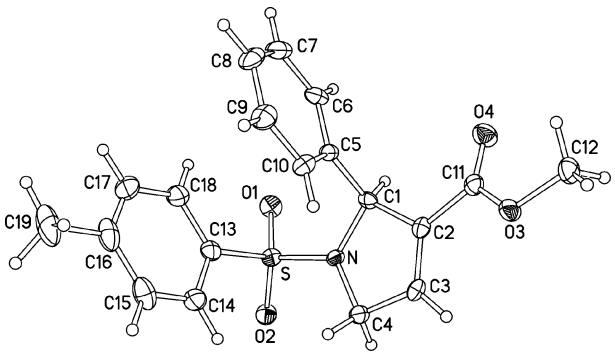
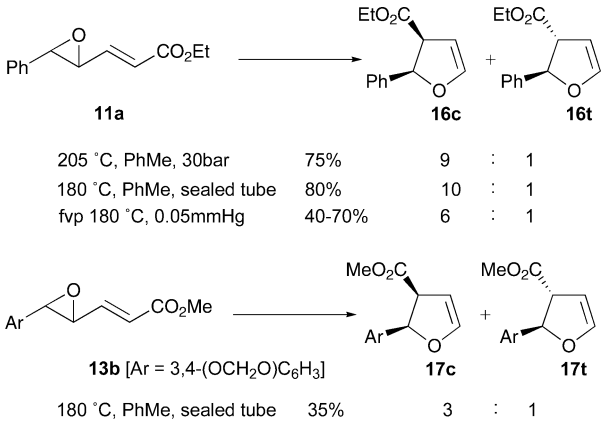


Fig. 2 X-Ray molecular structure of **15** (50% thermal ellipsoids).

With routes to the required vinyl epoxides now established we then turned to the key dihydrofuran rearrangement. In his pioneering work on this transformation Eberbach and Burchard had described the conversion of vinyl epoxide to dihydrofuran using flash vacuum pyrolysis (FVP) in which a solution of starting material in benzene was introduced under a nitrogen flow to a glass tube, packed with glass wool and heated to ~300 °C with the product being trapped in a flask cooled to −20 °C. However, relatively little additional experimental information is provided in these accounts.[13] Whilst, in preliminary studies, using phenyl substituted vinyl epoxide **11a** we were able to reproduce this transformation to generate a mixture of *cis*- and *trans*-dihydrofuran isomers, the yields and conversions were poor. After some experimentation it proved to be more efficient to operate at higher temperatures. Ultimately working at 450 °C and 0.02 mmHg with a 20 m glass tube packed with 5 g glass wool a 4.5 : 1 mixture of isomers could be obtained, albeit in variable yields (40–70%). The latter reflected the difficulties in achieving complete conversion of the starting material in a single cycle. Although simple recycling through the FVP system is possible this leads to lower yields. Consequently, alternative reproducible methods for undertaking this transformation were explored and it was discovered that the rearrangement could be induced by simply heating in sealed tubes or, on a larger scale, in an autoclave at 205 °C for 8 hours (at a measured pressure of 30 bar), Scheme 4. This latter process yielded multigram quantities of



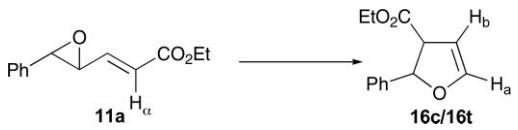
Scheme 4

a mixture of *cis*- and *trans*-dihydrofurans (**16*c***, **16*t***) in a 9 : 1 ratio in 70 to 85% yield. The isomers could be clearly characterised from the ^3J coupling between H-2 and H-3 (*trans* **16*t*** 2-H 5.84 ppm, doublet, $J = 7.5$ Hz; *cis* **16*c*** 2-H, 5.76 ppm, doublet, $J = 11.2$ Hz). Although simple arenes were compatible with this method, attempts to extend this approach to more electron rich substrates foundered, giving excessive levels of decomposition. Believing that neither starting materials nor products were compatible with the high temperatures for prolonged periods we returned to explore FVP protocols with a view to clearly defining suitable generic conditions.

At this stage we identified four major variables to consider in the optimisation of this pyrolysis. These were the method/temperature of volatilisation of the substrate, the temperature of the FVP tube, the nature and packing within the FVP tube and the pressure within the system. Using the vinyl epoxide **11a** as a model substrate a series of experiments were undertaken to define the optimum conditions using the simple apparatus available in the laboratory. This comprised a 20 cm long glass tube (10 mm od) passing through a horizontally mounted cylindrical oven and connected, *via* the drive motor of a Büchi Kügelrohr apparatus to ensure a homogeneous thermal cross section, to a cold trap to collect the product and to the high vacuum system.

In particular, more controlled sample input was achieved either by a flask heated within a Kügelrohr oven or by direct pyrolysis of a round bottom flask using a commercial heat gun. The balance between conversion, product formation and decomposition was ascertained by analysis of the ^{1}H NMR spectrum of the material collected in the cold trap, Table 1. Whilst it was easy to estimate the conversion and the *cis* : *trans* ratio from the integration of characteristic peaks (H_a and H_a) in the spectra, it was harder to deduce the amount of decomposition. Consequently, it was decided to use the integration of the area 9.6–9.4 ppm as a suitable marker for this pathway. On the basis that it was more easily reproducible, the initial study was conducted without column packing. Using 55 mg of starting phenyl vinyl epoxide **11a** (0.25 mmol), the effect of the temperatures $T1$ and $T2$ was explored. By increasing the FVP oven temperature ($T2$), the conversion improved up to 100%. However, the percentage of degradation also increased and the *cis* : *trans* selectivity was slightly reduced. As it proved harder to separate the desired dihydrofuran from the starting vinyl epoxide than from the degradation compounds, high temperatures

Table 1 FVP initiated rearrangements of vinyl epoxide **11**



Entry	*P*/mbar	*T*1/°C	*T*2/°C	**11a**/mmol	*cis* : *trans*[a] **16*c*** : **16*t***	Conversion[b] (%)	Degradation[c] (%)
1	0.02	87.5	400	0.25	1 : 8	54	5
2	0.04	100	400	0.25	1 : 10	50	1
3	0.02	100	450	0.25	1 : 7	88	6
4	0.02	100	475	0.25	1 : 6	88	8
5	0.01	100	475	1	1 : 6	97	12
6	0.04	100	500	0.25	1 : 4	100	30
7	0.04	>250[d]	500	1.5	1 : 9	50	5

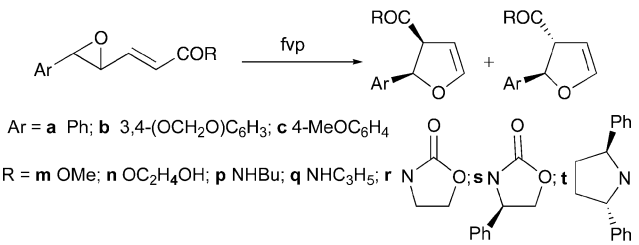
[a] Integrals $H_{a\,trans}/H_{a\,cis}$. [b] Integral ratio $(H_{a\,trans} + H_{a\,cis})/(H_{a\,trans} + H_{a\,cis} + H_?)$. [c] Integral ratio $H_{deg}/(H_b + H_{deg})$. [d] Heat gun used for volatilisation of substrate.

(475 °C) were preferred. When the reaction was scaled up, the conversion and the degradation both increased but the selectivity was maintained. For this substrate slow evaporation of the starting epoxide with a Kügelrohr oven at 100 °C led to a better conversion than a fast introduction with the heat gun. This is probably due to the concentration of the material in the FVP column and the reduction of the collisions with the column walls that induce the rearrangement. Having identified the optimum conditions for the rearrangement of phenyl vinyl epoxide **11a**, we then turned to explore various simple derivatives varying both the aryl component and the ester (amide) substituent, Table 2. The latter substrates were simply and efficiently prepared from ester **11a** by hydrolysis and coupling of the resultant acid with either an alcohol or an amine following standard protocols (see Experimental). In several cases, these vinyl epoxides required prolonged heating at significantly higher temperatures ($T1 \sim 150$ °C) to be volatilised which resulted in increased levels of decomposition. In these cases in order to minimise the contact time at high temperature, the direct heating method, using a heat gun, was used to introduce the starting vinyl epoxide rapidly into the FVP column.

In all cases the major product of vinyl epoxide–dihydrofuran rearrangement was the *cis*-isomer reflecting preferential involvement of an all *trans*-ylid intermediate and subsequent 6π-disrotary ring closure, Scheme 5.

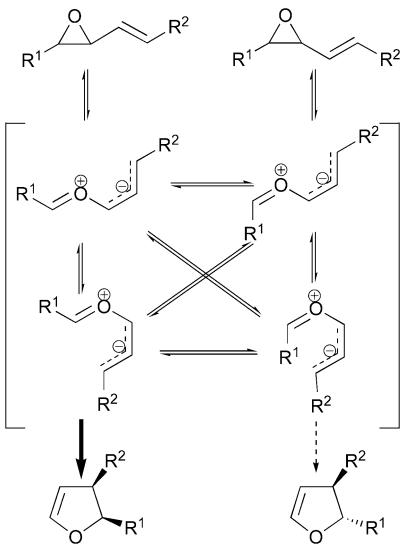
At this stage, during attempts to generate the corresponding amide by direct amidation of the *cis*-ester **16*c*** with an amine in refluxing toluene, it was observed that a slow epimerisation of the *cis*-dihydrofuryl ester occurs. Exploiting this observation, a range of different bases, including triethylamine, DIPEA, NaOEt and DBU, were examined with a view to enhancing this process, Table 3. However, initial experiments indicated that the reaction with these bases was very slow even in refluxing toluene and needed two to four weeks to convert all the *cis*-ester into the *trans* isomer. With these prolonged reaction times, decomposition products were observed. Fortunately, the use of catalytic quantities of base (10 mol% DBU) proved to be significantly more beneficial

Table 2 Rearrangement of vinyl epoxides by FVP



Entry	Vinyl epoxide (Ar,R)	*T*/°C	*P*/mbar	Product	Yield (%)	*cis* : *trans*
1	**18** (a,m)	475	0.04	**26**	80	10.2 : 1
2	**19** (a,n)	500	0.04	**27**	90	8.8 : 1
3	**20** (a,p)	480	0.03	**28**	60	8.6 : 1
4	**21** (a,q)	500	0.05	**29**	48[a]	9.0 : 1
5	**22** (a,r)	500	0.05	**30**	85	11.1 : 1
6	**23** (a,s)	500	0.05	**31**	67	6.1 : 1[b]
7	**24** (a,t)	500	0.04	**32**	43[c]	7.3 : 1[d]
8	**13** (b,m)	500	0.04	**17**	75	8.3 : 1
9	**25** (c,m)	500	0.04	**33**	67	8.3 : 1

[a] 75% conversion. [b] (50 : 36) : (8 : 6) mixture of diastereoisomers. [c] Crude yield. [d] (54 : 34) : (7 : 5) ratio of diastereoisomers.

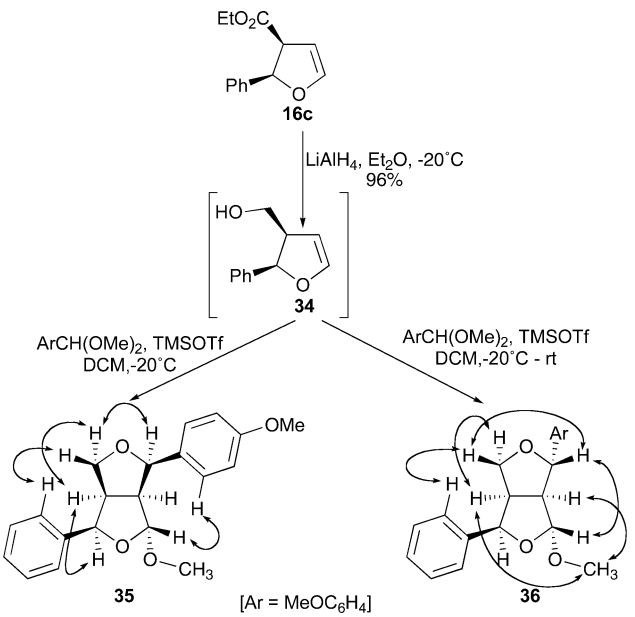


Scheme 5

affording a 19 : 1 *trans* : *cis* mixture (91% yield) after 12 hours at 110 °C with minimal decomposition (<5%). Since this process must proceed *via* the corresponding enolate attempts to trap this species to introduce further structural variation were undertaken. However all attempts using a variety of bases and electrophiles failed, affording complex intractable mixtures of products.

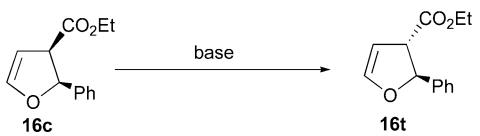
With this modification it was now possible to generate either the *cis* or *trans* isomer of the dihydrofuran from a single vinyl epoxide. In the final component of this study we then explored the possibilities for enantioselection in this process. In earlier studies using sealed tube methods we had explored various classical chiral auxiliaries including esters, amides and oxazolidinones.[14] However, these substrates had not survived our original attempts at FVP and we wished to apply our improved conditions to these substrates. Satisfyingly, both the phenyl oxazolidinone **23** (Table 2 entry 6) and the C-2 symmetrical diphenyl pyrrolidine **24** (Table 2 entry 7) containing vinyl epoxides now proved to be viable substrates, albeit in only moderate yields. However the selectivity was not significantly enhanced when compared with the earlier sealed tube experiments. Similarly, attempts to reduce the reaction temperature and restrict the conformational mobility of the substrates by Lewis acid activation were explored but proved not to be effective, even with substrates containing bidentate co-ordination sites *e.g.* **19** and **22**.

With the required dihydrofurans now readily accessible attention turned to their elaboration to the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane core found in the furofuran lignans. As indicated above, we hypothesised that this could be achieved by a Lewis acid mediated cyclisation of an oxacarbenium ion generated by the reaction of an acetal with the corresponding dihydrofuryl alcohol. Reduction of ester **16*c*** to the alcohol **34** with $LiAlH_4$ proceeded uneventfully. However, this compound proved to be unstable and was immediately used in the cyclisation reaction. Moreover, since attempts to pre-prepare the silyl enol ether were not viable, a solution of **34** was added to a premixed solution of the dimethyl 4-methoxybenzaldehyde dimethyl acetal and 1.1 equivalents of TMSOTf at −20 °C and stirred at this temperature for a further 16 h. Satisfyingly, following a basic methanol quench the *endo-endo*-furofuran acetal **35** could be isolated in 81% yield after purification by column chromatography, Scheme 6. Simply allowing the reaction to warm to room temperature for several hours prior to quenching afforded the corresponding *endo-exo*-furofuran acetal **36** as the major component (**36** : **35**



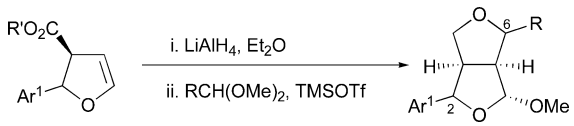
Scheme 6

Table 3 Isomerisation of *cis*-dihydrofuran ester **16*c***



Entry	Base	*T*/°C	Time/h	Yield (%)	*cis* : *trans* **16*c*** : **16*t***	Decomp. (%)
1	Et_3N	85	336	65	1 : 6.2	18
2	$^{i}Pr_2NEt$	110	672	48	1 : 4.5	36
3	DBU	80	240	55	1 : 4.2	28
4	DBU (10 mol%)	110	12	91	1 : 19	<5
5	EtONa	20	1	80	1 : 9	5
6	LDA	−78	1	0	—	100

Table 4 Synthesis of furofuran acetals by templated cyclisation



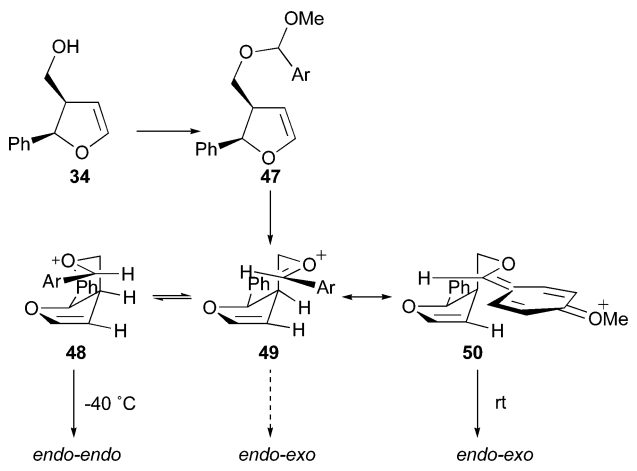
Entry	Ar^1	R	Method	T/°C	Yield (%)	Product ratio[a]
1	*endo*-Ph **16*c***	$MeOC_6H_4$	A	−20	81	**35** 1 : 0
2	*endo*-Ph**16*c***	$MeOC_6H_4$	B	−20	45	**36** 1 : 9
3	*endo*-Ph**16*c***	Ph	A	−20	64	**37** 1 : 0
4	*endo*-Ph**16*c***	Ph	B	−20	57	**37** 1 : 0
5	*endo*-Ph **16*c***	$(CH_2O_2)C_6H_3$	A	−20	36	**38** 3 : 1
6	*endo*-Ph **16*c***	$(CH_2O_2)C_6H_3$	A	−40	nd[b]	**38** 1 : 0
7	*endo*-Ph **16*c***	$(CH_2O_2)C_6H_3$	B	−20	38	**39** 0 : 1
8	*endo*-Ph **16*c***	4-BrC_6H_4	A	−20	31	**40** 1 : 0
9	*endo*-Ph **16*c***	4-BrC_6H_4	B	−20	27	**40** 1 : 0
10	*endo*-Ph **16*c***	CH_3	A	−20	30	**41** 1 : 0
11	*exo*-Ph **16*t***	$MeOC_6H_4$	A	−40	53	**42** 1 : 0
12	*exo*-Ph **16*t***	$MeOC_6H_4$	B	−40	45	**43** 1 : 4[c]
13	*endo*-$MeOC_6H_4$ **33*c***	Ph	A	−40	nd[b]	— 1 : 0[d]
14	*endo*-$MeOC_6H_4$ **33*c***	Ph	A	−78	23	**44** 1 : 0
15	*endo*-$(CH_2O_2)C_6H_3$ **17**	$MeOC_6H_4$	A	−40	53	**45** 1 : 0
16	*endo*-$(CH_2O_2)C_6H_3$ **17**	$(CH_2O_2)C_6H_3$	A	−40	55	**46** 1 : 0

[a] 6-*endo* : 6-*exo*. [b] Not determined, NMR scale experiment. [c] 4 : 1 *exo* : *endo* mixture of acetal epimers at C-4. [d] Mixture of epimers at C-2.

≥90 : ≤10) albeit in a reduced yield (45%). The stereochemistry was established by a combination of 2D NMR experiments and subsequent chemical modifications, *vide infra*.

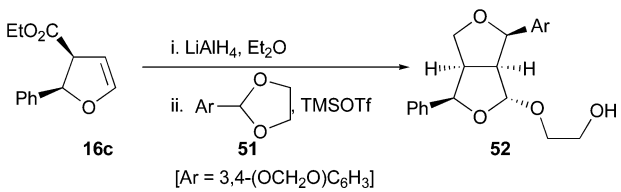
Subsequent experiments demonstrated that a variety of acetals were viable substrates although only those possessing electron donating substituents underwent the conversion to the *endo-exo* isomer at elevated temperatures, Table 4. With the more electron rich acetals this isomerisation occurs at −20 °C and lower reaction temperatures are required to isolate the *endo-endo* isomer as the exclusive product.

These observations can be rationalised by a stepwise process, Scheme 7, involving oxonium capture, transacetalisation and elimination to form a second, tethered, oxonium ion which is subsequently trapped by the proximal dihydrofuran. The oxonium ion intermediates can be expected to adopt a *trans* configuration and reaction with the enol ether occurs *via* a synclinal transition state **48** minimising strain in the tether and non-bonding interactions



Scheme 7

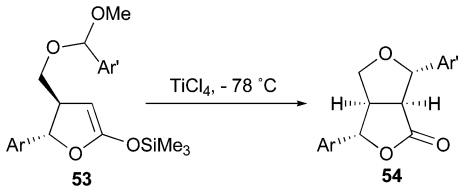
between the acetal substituent and the C-3 hydrogen. Capture of the resultant furofuryl oxonium ion with methanol then occurs from the less hindered *exo* face to give the observed product. Interestingly, an experiment using the dioxolane acetal **51** afforded the hydroxyethyl glycoside **52** as the major product (Scheme 8), even following a basic methanol quench, indicating that trapping of the intermediate furofuryl oxonium ion occurs *in situ* with the alcohol released from the initial acetal.



Scheme 8

With electron donating aryl substituents the increased stability of the oxonium ion renders the cyclisation and methanol capture reversible, ultimately leading to the more stable *exo* epimer, potentially *via* an *exo–trig* type ring closure onto the benzylic stabilised carbocation **50**. Whilst, for reasons outlined below, we favour such a pathway, it is not possible to exclude a process involving the rupture of the O^5–C^6 bond. In support with this latter hypothesis, reaction of the analogous *p*-methoxyphenyl substituted dihydrofuran with benzaldehyde dimethylacetal at −40 °C afforded a mixture of diastereomeric furofuran acetals epimeric at the *p*-methoxyphenyl bearing carbon (C^2), Table 4 entry 13. This requires fragmentation of the analogous O^1–C^2 bond to afford a stabilised benzylic carbocation and an aldehyde which recyclises to afford the more stabilised *exo*-aryl substituent. That this result reflected the thermodynamic equilibration of an initial *endo-endo* product was established by carrying out the reaction at −78 °C for only 1 h. This modification exclusively

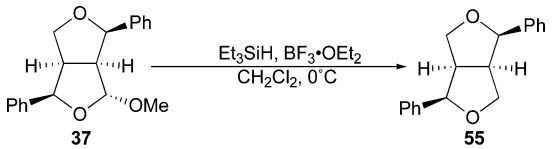
afforded the predicted *endo*-*endo* isomer in 23% yield accompanied by considerable amounts of recovered starting dihydrofuran, Table 4, entry 14. Whilst analogous processes have been described by Whiting *et al.*, using the related intramolecular Mukayaima aldol reaction, Scheme 9, the stereochemical outcomes differ.[4] For example, in this latter case, the $TiCl_4$ mediated reaction of a *p*-methoxyphenyl containing acetal **53** at −78 °C produced the 6-*exo* isomer **54** exclusively whilst the use of TMSOTf at 0 °C afforded variable mixtures of *endo* and *exo* products (65 : 35–9 : 91).



Scheme 9

In a similar fashion elaboration of the *trans*-dihydrofuran afforded the *endo* adduct as a kinetic product and the *exo* isomer following equilibration at room temperature. In the latter case, Table 4 entry 12, reflecting the increased crowding on the *exo* face of the bicyclo-octane skeleton, the isomerisation is considerably slower and affords a separable 81 : 19 mixture of *exo*-*exo* : *exo*-*endo* isomers after 3 h at room temperature. Consistent with this observation, trapping of the *exo*-*exo*-furofuryl oxonium ion with methanol produced a 4 : 1 mixture of epimers favouring the *exo*-methyl glycoside.

Having achieved a viable route to the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane core of the furofuran lignans attention then turned to the reduction of the glycosidic bond.[15] Initial treatment of the *endo*,*endo*-diphenyl furofuran acetal **37** with $BF_3{\cdot}OEt_2$ and Et_3SiH at 0 °C proceeded uneventfully, affording the corresponding furofuran **55** in 61%, Scheme 10. Importantly this compound showed just seven signals in the ^{13}C NMR spectrum consistent with a symmetrical product confirming the original assignment of the *endo*-*endo* stereochemistry following a kinetically controlled cyclisation.



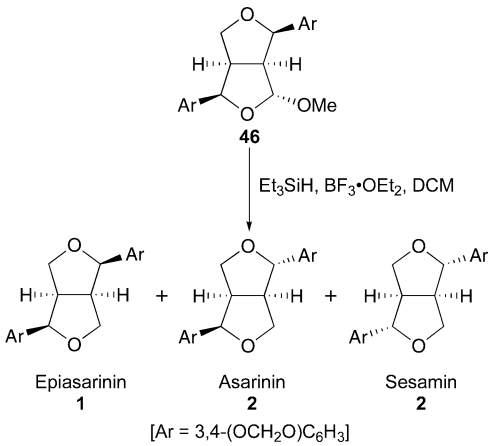
Scheme 10

With this positive result we then sought to exemplify the overall strategy with a synthesis of a naturally occurring *endo*,*endo*-furofuran lignan. In this, we opted to prepare the bis sesamyl substituted lignan, epiasarin **1**. This compound was first described by Beroza arising as a trace product from the acid treatment of the diastereomeric natural lignans asaranin **2** and sesamin **3**.[16] Subsequently, it has been shown to be a naturally occurring compound, being isolated from the plant species *Asiasarum heterotropoides* var. *mandshuricum*, which is used in traditional Chinese medicine as an anti-tussive, expectorant and anodyne. All three diastereoisomers are also reported to inhibit the enzyme Δ^5 desaturase, which catalyses the transformation of dihomo-γ-linolenic acid to arachidonic acid.[17] Whilst synthetic routes to both the *exo*-*exo*-sesamin and *exo*-*endo*-asarinin isomers have been reported,[18–20] there have not been any accounts of a selective approach to epiasarin or any other *endo*-*endo*-furofuran. Completion of this task simply required the reduction of methyl acetal **46**, Table 5. Disappointingly, applying the method used to reduce diphenyl analogue **37** led to complete decomposition. To reduce degradation the reduction was then attempted for a shorter time (4 hours) which led to the isolation of two furofuryl diastereoisomers. Analysis of the ^1H NMR spectrum of this mixture revealed four main signals between 2.5 and 5.5 ppm indicating that a symmetrical furofuran was produced and six signals in the same area for a product corresponding to an unsymmetrical furofuran. Comparison of the spectra of these two compounds with the reported data for asarinin **2**[19,21] and sesamin **3**[20,21] confirmed that these two diastereoisomers of epiasarinin has been obtained in a 1 : 3 ratio, Table 5 entry 3, and implied that epimerisation at C^2 and/or C^6 had occurred during the reduction. Subsequently, following considerable experimentation, Table 5, the optimum conditions were found to be the use of a larger excess of Et_3SiH (10 eq.) together with $BF_3{\cdot}OEt_2$ at either −40 °C for 15 h or −20 °C for 4 h. This avoided the formation of sesamin, which was difficult to separate from epiasarinin, and afforded, following careful flash chromatography using base (Et_3N) treated solvents, pure samples of (±)-epiasarinin **1** and (±)-asarinin **2** together with the starting acetal. The analytical data for (±)-asarinin **2** were identical to those reported in the literature. As expected, the ^{13}C NMR spectra of (±)-epiasarinin **1** contained ten signals consistent with a symmetrical structure. A subsequent single crystal X-ray analysis confirmed the *endo*-*endo* configuration of the disesamyl furofuran. The molecule (Fig. 3) has approximate C_2 symmetry. Both furan rings adopt envelope conformations with the O(3) and O(7) atoms displaced in the *endo* direction from the C(4)C(5)C(1)C(2) and C(6)C(5)C(1)–C(8) planes, respectively, which form an angle of 121°. Both methylenedioxyphenyl substituents are in equatorial orientations, their mean planes are nearly parallel to each other (angle 10°) and to the local twofold axis. Earlier, X-ray crystal structures of natural (*i.e.* chiral) asarinin[22] and sesamin[23] (but not epiasarinin) have been reported. The furan rings in asarinin adopt envelope conformations, one with an *exo*, the other with *endo* tilt of the O atom, whilst in sesamin both rings adopt twisted-envelope conformations. The dihedral angles at the C(1)–C(5) bond are the same as in **1**. The sesamin molecule also has approximate C_2 symmetry with nearly-parallel methylenedioxyphenyl groups (interplanar angle 8°), but the latter lie normally to the twofold axis, in contrast with **1**.

Attempts to further enhance this process through the use of alternative Lewis acids ($TiCl_4$, $Sc(OTf)_3$, DIBAL) proved ineffective. Similarly, whilst the use of a more powerful hydride source (Cl_3SiH) afforded faster reduction and exclusive formation of epiasarinin, this was accompanied by extensive decomposition which complicated purification and rendered the process less efficient.

Somewhat surprisingly, treatment of the C-6 *endo*-*p*-methoxyphenyl furofuran methyl acetal **35** under these optimised conditions (Et_3SiH (10 eq.), $BF_3{\cdot}OEt_2$, −40 °C, 4 h) led to complete inversion of the stereochemistry affording exclusive formation of the *endo*-*exo*-furofuran **56** as ascertained by NOESY experiments. Similar reduction of the isomeric acetal **36** led to the same product, Scheme 11.

Table 5 Reduction of acetal **46**



Entry	Reagents	Temp/°C	Time/h	Conversion (%)	Yield **1** (%)	Yield **2** (%)	Yield **3** (%)
1	Et_3SiH, $BF_3{\cdot}OEt_2$	0–rt	48	100	0	0	0
2	Et_3SiH, $BF_3{\cdot}OEt_2$	−78	4	0	—	—	—
3	Et_3SiH, $BF_3{\cdot}OEt_2$	−78–rt	4	100[a]	0	20	60
4	Et_3SiH, $BF_3{\cdot}OEt_2$	−40	4	10	10	0	0
5	Et_3SiH, $BF_3{\cdot}OEt_2$	−40	15	90	67	23	0
6	Et_3SiH, $BF_3{\cdot}OEt_2$	−20	4	89	68	21	0
7	Et_3SiH, $BF_3{\cdot}OEt_2$	−10	5	100[b]	3	25	47
8	Et_3SiH, $TiCl_4$	−78	5	100[c]	0	0	0
9	Et_3SiH, $Sc(OTf)_3$	−20	5	0	—	—	—
10	DIBAL-H	−20	5	0	—	—	—
11	Cl_3SiH, $BF_3{\cdot}OEt_2$	−40	1	100[d]	50	0	0

[a] 20% decomp. [b] 25% decomp. [c] 100% decomp. [d] 50% decomp.

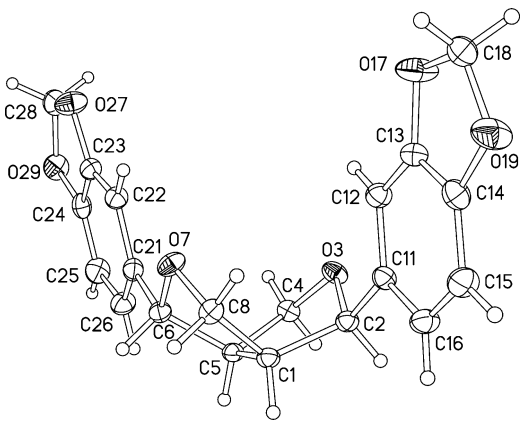
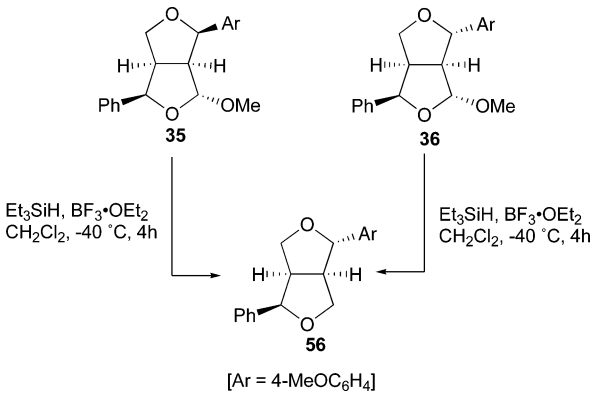


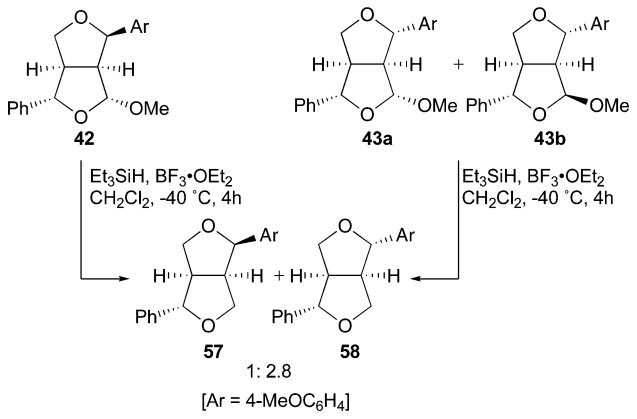
Fig. 3 X-Ray molecular structure of **1** (50% thermal ellipsoids).



Scheme 11

In a similar fashion, reduction of the *exo-endo*- and *exo-exo*-furofuryl acetals (**42** and **43a**,**b**) afforded a 1 : 2.8 mixture of two diastereoisomeric bicyclo-octanes regardless of the reaction time (1–16 h) and temperature (0–40 °C), Scheme 12. The two products were separated by flash chromatography and the pure samples were characterised. NOESY experiments clearly distinguished the *exo-endo*-furofuran **57** from the *exo-exo* diastereoisomer **58**, Fig. 4. The ratio of the two products was determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis of the crude reaction mixture using comparisons of the integrals for the 6-H and 2-H signals for the *exo-endo* isomer at 4.88 (d, $J = 5.4$ Hz) and 4.51 ppm (d, $J = 7.2$ Hz) and the *exo-exo* isomer for 6-H at 4.83 ppm (d, $J = 4.8$ Hz) and 4.77 ppm (d, $J = 4.5$ Hz) respectively.

The constant ratio suggested that these conditions were leading to a thermodynamic mixture. Consequently, whilst accepting that conversions may not be complete, lower temperatures and shorter reaction times were explored with a view to enhancing selectivity. Solutions of the acetal in DCM were cooled to −78 °C and treated with Et_3SiH and then $BF_3{\cdot}OEt_2$. After a reaction time of ~1 min, a rapid inverse quench, separation and concentration, the crude product mixtures were analysed using ^{1}H NMR spectroscopy and the isomer ratios were determined, Table 6.



Scheme 12

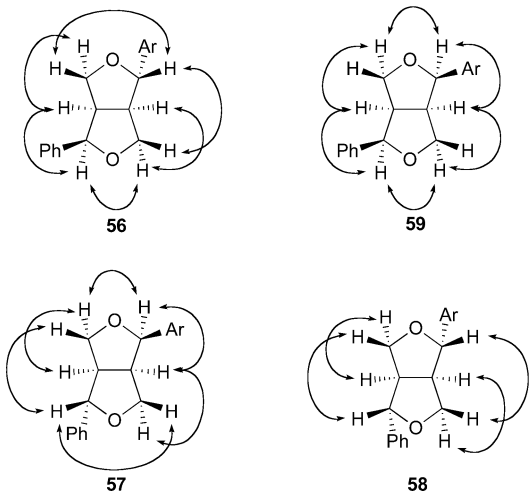
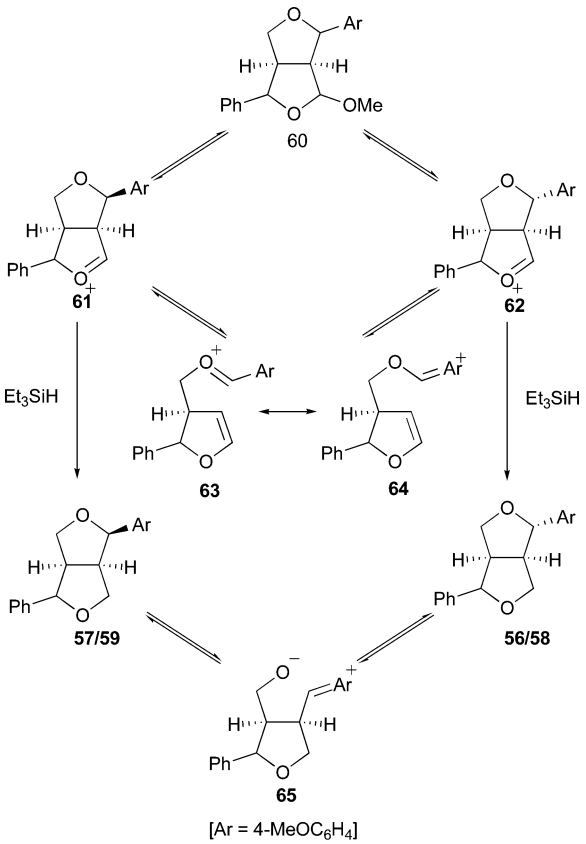


Fig. 4 Selected NOESY correlations of compounds **56–59**.

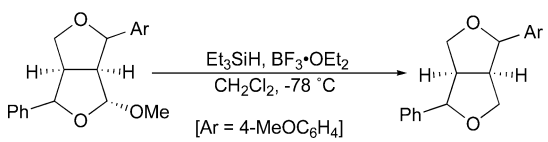
Under these conditions reduction occurred with greater retention of stereochemistry. Only in the case of the *endo-endo*-furofuran was significant isomerisation observed. In this case, Table 6 entry 4, a 40 : 60 mixture of two diastereoisomers was obtained, one of which could be identified as the *endo-exo*-furofuran **56** by comparison with an authentic sample isolated earlier. After separation by flash chromatography, the second compound was analysed and confirmed as the *endo-endo*-furofuran **59** using 2D NMR experiments, particularly NOESY spectra, Fig. 4. Interestingly, with both the *exo-exo*- and *endo-exo*-acetal isomers small amounts of the corresponding *exo-endo*- and *endo-endo*-furofurans respectively were detected.

As with the cyclisation process discussed above, these observations can be accounted for by a mechanism involving a sequence of oxonium ion intermediates, Scheme 13.[24] Different pathways can be proposed to explain the epimerisation which can occur before and/or after the reduction of the acetal bond. Initial elimination of the methoxide can be promoted by the oxygen of the furofuryl skeleton, forming a bicyclic intermediate **61/62** which can then undergo either reduction to give the bicyclooctane product or fragmentation to give the oxonium ion **63** assisted by the C-6 *p*-methoxyphenyl electron donating group. The presence of the latter group for fragmentation and isomerisation is imperative as the *endo-endo*-diphenyl furofuran **55** is stable to prolonged treatment under the reduction conditions. Alternatively



Scheme 13

Table 6 Lewis acid catalysed reduction of *p*-methoxyphenyl furofuran acetals



Entry	Acetal	Conversion	*exo-endo* **57**	*exo-exo* **58**	*endo-exo* **56**	*endo-endo* **59**
1	*exo-endo*	86%	100	0	—	—
2	*exo-exo*	100%	18	82	—	—
3	*endo-exo*	36%	—	—	92	8
4	*endo-endo*	73%	—	—	60	40

the *p*-methoxyphenyl group could directly promote the loss of methoxide to generate intermediate **64**. Whichever pathway is followed, on forming intermediates **63** or **64**, the stereochemistry at the C^6 position is lost. Alternatively, epimerisation can occur after reduction, as was demonstrated with epiasarinin. Again, this is promoted by electron donating aryl groups promoting fragmentation and forming a monocyclic ionic intermediate **65**. In this case, the loss of the stereochemistry at the C^6 position through formation of the benzylic carbocation and fragmentation of the C6–O5 bond.

Since the isomerisations during the reduction occur at lower temperatures and in shorter times (−78 °C, 1 min) than those used for the isomerisation of epiasarinin (−20 °C, 3 h) we favour the former pathway involving fragmentation of the C6–C7 bond regenerating a dihydrofuran intermediate. Similar intermediates are involved in the Lewis acid promoted cyclisation and a similar process would account for the contrathermodynamic isomerisations observed in the reduction of the *exo-exo*- and *endo-exo*-acetals. The contrast in stability between the sesamyl and *p*-methoxyphenyl substituted furofuran acetals is a little surprising. We suggest that the conformational restraints enforced by the methylene dioxy unit prevents the oxygen lone pair from fully contributing to the stability of a benzylic carbocation thus permitting reactions to be undertaken at higher temperatures and for longer periods of time without significant isomerisation occurring.

In conclusion this work has demonstrated that the templated Lewis acid promoted cyclisation of dihydrofuryl alcohols generated *via* the thermal rearrangement of vinyl epoxides provides an efficient entry to the furofuran skeleton. The ability to control the stereochemistry of both the template and the outcome of the cyclisation makes this a powerful strategy for the synthesis of this important class of natural products. In particular, the access to the more challenging *endo-endo* substituted furofuran skeleton renders the approach complementary to the other strategies reported to date. Whilst a current limitation to the approach lies in the need for an electron rich aryl substituent to promote the formation of the *exo* stereochemistry, a solution to this issue using a temporary directing group is under investigation and will be reported in due course. Future work in this area will seek to further enhance the stereochemical control of the reduction and extend the concept to unnatural analogues including aza- and ring expanded derivatives.

Experimental

All air and/or moisture sensitive reactions were carried out under an argon atmosphere. Solvents were purified following established protocols. Petrol refers to petroleum spirit boiling in the 40–60 °C range. Ether refers to diethyl ether. Commercially available reagents were used as received unless otherwise stated. Flash column chromatography was performed according to the method of Still *et al.*[25] using 200–400 mesh silica gel. Yields refer to isolated yields of products of greater than 95% purity as determined by ^1H + ^{13}C NMR spectroscopy or elemental analysis (Durham University Microanalytical Laboratory).

Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films between KBr plates (liquids) or as compression-formed discs made using KBr (solids) on a Perkin-Elmer FT-IR 1600 spectrometer. Unless otherwise stated ^1H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 200, Bruker AM-250, Varian Unity-300, Varian VXR-400 or Varian Inova-500 and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded at 63 MHz, 101 MHz or 126 MHz on a Bruker AM-250, Varian VXR-400 or Varian Inova-500 respectively, using the central resonance of $CDCl_3$ (δ_c = 77.0 ppm) as the internal reference. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm) and coupling constants are given in Hertz to the nearest 0.3 Hz. All ^{13}C spectra were proton decoupled. Assignment of spectra was carried out using DEPT, COSY, HSQC and NOESY experiments. Low-resolution mass spectra (EI or CI) were obtained on a Micromass Autospec Mass Spectrometer. Gas chromatography-mass spectra (GCMS, EI or CI) were taken using a Hewlett Packard 5890 Series II gas chromatograph, equipped with a 25 m 5% diphenyl–95 % dimethylpolysiloxane column and flame ionisation detection, connected to a VG Trio-1000 mass spectrometer. Electrospray mass spectra (ES) were obtained on a Micromass LCT Mass Spectrometer. High-resolution mass spectra were performed by the EPSRC service at the University of Swansea or on a Micromass Autospec Mass Spectrometer in Durham.

Detailed experimental procedures describing the formation and characterisation of compounds **7b**, **8b**, **10a**, **11a**, **19–24** and **27–32** can be found in the ESI.†

General procedure for the Darzens' reactions of 4-bromocrotonate 12z

LDA (2 eq.) {generated by the addition of a solution of *n*-BuLi in hexanes (2.2 eq.) to a solution of diisopropylamine (2 eq.) in THF (~1 M) at −20 °C under N_2} was added dropwise to a stirred solution of aldehyde (4 eq.) and methyl 4-bromocrotonate **12z** (1 eq.) in THF (~0.3 M of **12z**) under N_2 at −20 °C. Typically, the transfer lasted 1 hour for 20 mmol of crotonate. The reaction was stirred for 2 hours at −20 °C and then quenched with sat. NH_4Cl solution (40 ml). The layers were separated and the aqueous layer was extracted with ether (3 × 20 ml). The combined organic layers were then washed with sat. $NaHSO_3$ solution (prepared from 40 g of $NaHSO_3$ solid), sat. $NaHCO_3$ solution (20 ml) and brine (3 × 30 ml), dried ($MgSO_4$) and concentrated.

Methyl 5-(3′,4′-methylenedioxyphenyl)-4,5-epoxypent-2-enoate 13b. Reaction with piperonal (10.2 g, 68 mmol) following the general procedure and subsequent purification by flash chromatography (ether : petrol 1 : 3) afforded the title ester **13b** as a 3 : 4 mixture of *syn*- and *anti*-epoxides (2.95 g, 70%). The *syn*- and *anti*-epoxide isomers could be separated by preparative HPLC (hypersil semi-prep., 21.4 mm; 70% MeOH, 30% H_2O; 30 mg ml^{-1}). Data for *syn* isomer: υ_{max} 2992, 2781, 1719, 1179 cm^{-1}; δ_H (500 MHz): 6.80–6.73 (3 H, m, Ar-*H*), 6.47 (1 H, dd, J = 8, 15.8 Hz, 3-*H*), 6.19 (1 H, d, J = 15.8 Hz, 2-*H*), 5.97 (2 H, s, OCH_2O), 4.26 (1 H, d, J = 4 Hz, 5-*H*), 3.71 (1 H, dd, J = 4.0, 8.0 Hz, 4-*H*), 3.69 (3 H, s, 6-*H*); δ_C (125 MHz): 165.6 (*C*-1), 147.8, 147.5, 141.4 (*C*-3), 127.6, 126.3 (*C*-2), 119.9, 108.3, 106.7, 101.2 (OCH_2O), 59.4 (*C*-5), 58.0 (*C*-4), 51.7 (CH_3); *m/z* (EI): 248 (12%, M^+), 135 (100); *m/z* (CI, NH_3): 266 (20%, MNH_4^+), 252 (80), 233 (100); HRMS (ES) found MNa^+, 271.0593; $C_{13}H_{12}O_5$ requires M, 271.0582. Data for

anti isomer: υ_{max} 2992, 2781, 1719, 1179 cm^{-1}; δ_H (500 MHz): 6.82–6.71 (2 H, bs, Ar-*H*), 6.75 (1 H, dd, $J = 6.7$, 15.6 Hz, 3-*H*), 6.70 (1 H, s, Ar-*H*), 6.17 (1 H, d, $J = 15.6$ Hz, 2-*H*), 5.96 (2 H, s, OCH_2O), 3.76 (3 H, s, 6-*H*), 3.75 (1 H, d, $J = 1.8$ Hz, 5-*H*), 3.35 (1 H, dd, $J = 1.8$, 6.7 Hz, 4-*H*), δ_C (125 MHz): 166.0 (*C*-1), 148.1, 147.9, 143.8 (*C*-3), 129.8, 123.4 (*C*-2), 119.7, 108.4, 105.3, 101.2 (O*C*H$_2$O), 61.1 (*C*-5), 60.4 (*C*-4), 51.8 (O*C*H$_3$).

Methyl 5-(4′-methoxyphenyl)-4,5-epoxypent-2-enoate 13c. Reaction with 4-methoxybenzaldehyde (8.26 ml, 68 mmol) following the general Darzens' procedure and subsequent purification by flash chromatography (ether : petrol 1 : 3) afforded the title ester **13c** as a 1 : 2 mixture of *syn*- and *anti*-epoxides (2.21 g, 56%). The *syn*- and the *anti*-epoxides could be separated by preparative HPLC (hypersil semi-prep., 21.4 mm; 70% MeOH, 30% H_2O; 30 mg ml^{-1}). Data for the *syn* isomer: υ_{max} 2999, 2953, 2837, 1723 cm^{-1}; δ_H (500 MHz): 7.25 (2H, d, $J = 8.5$ Hz, Ar-*H*), 6.89 (2H, d, $J = 8.5$ Hz, Ar-*H*), 6.47 (1H, dd, $J = 8.0$, 15.8 Hz, 3-*H*), 6.19 (1H, d, $J = 15.8$ Hz, 2-*H*), 4.29 (1H, d, $J = 4.2$ Hz, 5-*H*), 3.81 (3H, s, 4′-OCH_3), 3.73 (1H, dd, $J = 4.2$, 8.0, 4-*H*), 3.67 (3H, s, CO_2CH_3); δ_C (125 MHz): 165.6 (*C*-1), 159.5, 141.6 (*C*-3), 127.6, 126.1 (*C*-2), 125.8, 113.8, 59.3 (*C*-5), 58.0 (*C*-4), 55.3 (4′-O*C*H$_3$), 51.7 (CO_2CH_3); *m*/*z* (ES$^+$): 257.1 (MNa$^+$), 491.2 (2MNa$^+$); HRMS (ES$^+$) found MNa$^+$, 257.0808; $C_{13}H_{13}O_4$ requires *M*, 257.0790.

***N*-Toluenesulfonyl-3-methoxycarbonyl-2-phenyl-3-pyrroline 15.** Reaction with *N*-tosylimine **14** (518 mg, 2.0 mmol, 2 eq.) following the general Darzens' procedure and subsequent purification by flash chromatography afforded the 3-pyrroline **15** (57 mg, 17%). Found: C, 63.71%; H, 5.54%; N, 3.92%; calc. for $C_{19}H_{19}NO_4S$: C, 63.85%; H, 5.36%; N, 3.92%; υ_{max} 1723, 1340, 1163 cm^{-1}; δ_H (200 MHz): 7.5–7.0 (9 H, m, Ar-*H*), 6.81 (1 H, ddd, $J = 1.8$, 2.1, 2.4 Hz, 4-*H*), 5.76 (1 H, ddd, $J = 1.8$, 2.4, 5.7 Hz, 2-*H*), 4.50 (1 H, dt, $J = 2.4$, 17.1 Hz, 5-H_a), 4.35 (1 H, ddd, $J = 2.1$, 5.7, 17.1 Hz, 5-H_b), 3.61 (3 H, s, OCH_3), 2.40 (3 H, s, ArCH_3); δ_C (63 MHz): 162.2 (*C*O), 143.3, 139.3, 135.7, 135.5 (*C*-4), 129.4, 128.3, 128.0, 127.7, 127.1, 68.9 (*C*-2), 54.9 (*C*-5), 51.8 (O*C*H$_3$), 21.4 (Ar*C*H$_3$); *m*/*z* (EI): 357 (7%, M$^{+\bullet}$), 280 (56, M − C_6H_5), 202 (100, M − $CH_3C_6H_4SO_2$), 170 (51), 155 (41), 91 (78).

General procedures for the thermal rearrangement of vinyl epoxides to dihydrofurans

Method A. A solution of the ethyl 3-(3′-phenyloxirin-2′-yl)propenoate **11a** in toluene (21.5 ml) (concentration 40 mg ml^{-1}, ~16.1 M) was placed in a 50 ml Carius tube. After degassing the solution, the tube was sealed under vacuum and heated at 180–200 °C. After 12 hours, the solvent was removed and the residue purified by flash chromatography to afford the desired dihydrofuran **16** (80% yield) in an isomeric ratio of 9 : 1 *cis* : *trans*.

Method B—autoclave route. A solution of ethyl 3-(3′-phenyloxirin-2′-yl)propenoate **11a**, (7 g, 32.1 mmol) in toluene (90 ml) was placed in a stainless steel bomb (100 ml). After degassing the solution the vessel was sealed and heated at 205 °C at a self-induced pressure of 30 bar for 8 hours. After cooling, the solution was concentrated and the residue purified by flash chromatography to afford the desired dihydrofuran **16** (5.1 g, 71% yield) in an isomeric ratio of 9 : 1 *cis* : *trans*.

Method C. A sample of the vinyl epoxide (~200 mg) was placed in a 10 ml flask and attached to the flash vacuum pyrolysis apparatus (FVP) as indicated in the schematic above. The apparatus was evacuated ($P \leq 0.04$ mbar) and the oven heated to the temperature (*T*2) shown in Table 2. When the apparatus had stabilised at these conditions the sample was heated in a Kügelrohr oven (KR) at 100 °C. The crude material was collected in the cold trap and purified by chromatography.

Method D. A sample of the vinyl epoxide was placed in a 10 ml rb flask and attached to the FVP apparatus as indicated in the schematic above. Silicone grease was used to seal each glass joint except the one used for substrate volatilisation for which high temperature grease (Rocol anti-seize compound J166®) was utilised. The apparatus was then evacuated ($P \leq 0.04$ mbar) and the oven heated to the temperature (*T*2) shown in Table 2. When the apparatus had stabilised at these conditions the sample was heated directly with a heat gun. The crude material collected in the cold trap was then purified by flash chromatography.

Ethyl 2-phenyl-2,3-dihydrofuryl-3-carboxylate 16[13]. Prepared by method A to afford the title dihydrofuran (80%) following flash chromatography as a separable mixture of *cis* and *trans* isomers. **16*c*** υ_{max} (LF): 2981, 1729, 1621, 1454, 1142 cm^{-1}; δ_H (300 MHz): 7.5–7.1 (5 H, m, Ar–*H*), 6.72 (1 H, d, $J = 4$ Hz, 5-*H*), 5.76 (1 H, d, $J = 11$ Hz, 2-*H*), 5.06 (1 H, dd, $J = 3$, 4 Hz, 4-*H*), 4.08 (1 H, dd, $J = 11$ Hz, 3 Hz 3-*H*), 3.6 (2 H, q, $J = 7$ Hz, CH_2), 0.80 (3 H, t, $J = 7$ Hz, CH_3); δ_C (75 MHz): 172 (C=O), 149 (*C*-5), 138, 128, 127, 126, 99 (*C*-4), 84 (*C*-2), 61 (O*C*H$_2$), 53 (*C*-3), 14 (*C*H$_3$); *m*/*z* (CI/NH$_3$) 236 (MNH$_4^+$), 219, 189, 145 (100%). **16*t*** δ_H (300 MHz): 7.41–7.34 (5 H, m, aromatics), 6.55 (1 H, t, $J = 2.4$ Hz, 5-*H*), 5.84 (1 H, d, $J = 7.5$ Hz, 2-*H*), 5.05 (1 H, t, $J = 2.7$ Hz, 4-*H*), 4.22 (2 H, q, $J = 7.2$ Hz, OCH_2), 3.73 (1 H, dt, $J = 2.4$, 7.5 Hz, 3-*H*), 1.29 (3 H, t, $J = 7.2$ Hz, CH_3).

2-(3′,4′-Methylenedioxyphenyl)-3-carbomethoxy-2,3-dihydrofuran 17. Following method D (500 °C, 0.04 mbar), vinyl epoxide **13b** (500 mg) was converted to the title dihydrofurans (75%, 8.3 : 1 *cis* : *trans*). Flash chromatography (ether : petrol 3 : 7) afforded the *cis*-dihydrofuran **17*c*** (66%) followed by small amounts of the corresponding *trans* isomer (8%). **17*c*** found: C, 62.80%; H, 4.85%; calc. for $C_{13}H_{12}O_5$: C, 62.90%; H, 4.87%; υ_{max} 1733, 1250 cm^{-1}; δ_H (300 MHz): 6.82–6.76 (3 H, m, Ar-*H*), 6.68 (1 H, t, 2.25 Hz, 5-*H*), 5.94 (2 H, s, OCH_2O), 5.67 (1 H, d, $J = 11.1$ Hz, 2-*H*), 5.04 (1 H, t, $J = 2.25$ Hz, 4-*H*), 4.06 (1 H, dt, $J = 2.25$, 11.1 Hz, 3-*H*), 3.30 (3 H, s, OCH_3); δ_C (125 MHz): 171.5 (C*O*), 148.8 (*C*-5), 147.4, 147.3, 131.0, 120.0, 107.8, 106.9, 101.0 (O*C*H$_2$O), 99.3 (*C*-4), 84.3 (*C*-2), 53.4 (*C*-3), 51.6 (O*C*H$_3$); *m*/*z* (EI) 248 (28.6%, M$^+$), 159 (100); (CI, NH$_3$) 266 (40%, MNH$_4^+$), 249 (100, MH$^+$). **18*t*** δ_H (300 MHz): 6.86–6.62 (3 H, m, Ar-*H*), 6.52 (1 H, t, $J = 2.2$ Hz, 5-*H*), 5.94 (2 H, s, OCH_2O), 5.72 (1 H, d, $J = 7.5$ Hz, 2-*H*), 5.03 (1 H, t, $J = 2.2$ Hz, 4-*H*), 3.80 (3 H, s, OCH_3), 3.42 (1 H, dt, $J = 2.2$, 7.5 Hz, 3-*H*); *m*/*z* (EI): 248 (43%, M$^{+\bullet}$), 159 (100%).

cis*-2-(4′-Methoxyphenyl)-3-carbomethoxy-2,3-dihydrofuran 33.** Following method C (500 °C, 0.04 mbar) the vinyl epoxide **25** was converted to the title dihydrofurans (75%, 8 : 1 *cis* : *trans*). Flash chromatography (ether : petrol 3 : 7) afforded the *cis*-dihydrofuran **33*c as single diastereoisomer (67%); υ_{max} 3001, 2951, 2838, 1731 cm^{-1}; δ_H (300 MHz): 7.24 (2 H, d, $J = 8.6$ Hz, Ar-*H*), 6.85 (2 H, d, $J = 8.6$ Hz, Ar-*H*), 6.75 (1 H, t, $J = 2.0$ Hz, 5-*H*),

5.72 (1 H, d, $J = 11.2$ Hz, 2-*H*), 5.03 (1 H, t, $J = 2.5$ Hz, 4-*H*), 4.06 (1 H, dt, $J = 2.2$, 11.2 Hz, 3-*H*), 3.79 (3 H, s, 4′-OCH_3), 3.21 (3 H, s, OCH_3); δ_C (75 MHz): 171.7 (*C*O), 159.3, 148.9 (*C*-5), 129.2, 127.6, 113.3, 99.1 (*C*-4), 84.2 (*C*-2), 55.2 (*C*-3), 53.4 (4′-O*C*H$_3$), 51.5 (O*C*H$_3$); *m*/*z* (ES$^+$): 257.1 (MNa$^+$); HRMS (ES$^+$) found MNa$^+$, 257.0774; $C_{13}H_{14}O_4Na$ requires *M*, 257.0790.

Ethyl *trans*-2-phenyl-2,3-dihydrofuran-3-carboxylate 16*t*. DBU (80 μL, 0.53 mmol) was added to a solution of *cis*-dihydrofuryl ester **16*c*** (560 mg, 2.57 mmol) in toluene (10 ml) under nitrogen at room temperature. The resulting mixture was heated under reflux for 15 hours. After cooling to room temperature, HCl_{aq} 1 M was added and the solution was filtered through a celite plug to decompose the resulting emulsion. The organic layer was then separated, washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (ether : petrol 1 : 3), afforded the *trans*-dihydrofuryl ester **16*t*** (510 mg, 91%).

General procedures for reduction and Lewis acid mediated cyclisation

Method A. A solution of dihydrofuran ester **16** (1.61 mmol) in ether (10 ml) was introduced slowly to a suspension of $LiAlH_4$ (150 mg, 3.95 mmol, 2.45 eq.) in ether (10 ml) at −40 °C under argon. The reaction mixture was stirred for 3 h at −40 °C under argon and quenched with distilled water (150 μl), NaOH 3 N (150 μl) and finally water (450 μl) before being filtered through a celite bed and concentrated to afford the corresponding 2-aryl-3-hydroxymethyl-2,3-dihydrofuran (>97%). This alcohol was unstable and was used directly without further purification.

A solution of the alcohol (1.58 mmol) in DCM (10 ml) was slowly added to a solution of acetal (4.08 mmol, 2.6 eq.) and TMSOTf (42.5 μl, 2.38 mmol, 1.5 eq.) in DCM (20 ml) at the temperature indicated in Table 4. The resulting solution (dark purple) was stirred for 17 hours at this temperature, under argon, before being quenched with methanol (2 ml) and then sat. aq. $NaHCO_3$ (15 ml). The aqueous layer was extracted with ether (3 × 15 ml). The combined organic layers were washed with aq. sat. $NaHSO_3$ (5 × 15 ml), to scavenge any unreacted aldehyde, and with brine (3 × 15 ml), dried over $MgSO_4$ and concentrated. The residue was then purified by flash chromatography to give the desired furofuran acetal.

Method B. Following reduction of the dihydrofuran ester **16** as described above, a solution of the resultant alcohol (1.58 mmol) in DCM (10 ml) was slowly added to a solution of acetal (4.08 mmol, 2.6 eq.) and TMSOTf (2.38 mmol, 1.5 eq.) in DCM (20 ml), under argon, at the temperature indicated in Table 4. The resulting solution (dark purple) was maintained at this temperature until all starting material was consumed. The reaction mixture was then allowed to warm to rt and stirred at this temperature for a further 3 h before being quenched with methanol (2 ml) and then sat. aq. $NaHCO_3$ (15 ml). The aqueous layer was extracted with ether (3 × 15 ml). The combined organic layers were washed with aq. sat. $NaHSO_3$ (5 × 15 ml), to scavenge any unreacted aldehyde, and with brine (3 × 15 ml), dried over $MgSO_4$ and concentrated. The residue was then purified by flash chromatography to give the desired furofuran acetal.

4-*exo*-Methoxy-6-*endo*-(4′-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 35. Reduction of ester **16*c*** and reaction, following method A, with 4-methoxybenzaldehyde dimethyl acetal, at −20 °C for 16 h, and purification by flash chromatography (petrol : EtOAc 94 : 6), produced the title furofuran acetal **35** as a white solid in 81% yield. Mp 65.1–65.8 °C; found: C, 73.68; H, 7.07; $C_{20}H_{22}O_4$ requires: C, 73.6; H, 6.79%; ν_{max} (ATR): 2880, 1580, 1320, 1065 cm^{-1}; δ_H (500 MHz): 7.45–7.39 (4 H, m, Ar-*H*), 7.35–7.30 (3 H, m, Ar-*H*), 6.93 (2 H, d, $J = 9$ Hz, Ar-*H*), 5.27 (1 H, d, $J = 6.5$ Hz, 2-*H*), 4.86 (1 H, d, $J = 6.5$ Hz, 6-*H*), 4.54 (1 H, s, 4-*H*), 3.82 (3 H, s, 4′-OCH_3), 3.64 (1 H, d, $J = 10$ Hz, 8-H_{endo}), 3.47 (1 H, dd, $J = 10$, 6 Hz, 8-H_{exo}), 3.17 (1 H, m, 1-*H*), 3.09 (3 H, s, 4-OCH_3), 3.05 (1 H, m, 5-*H*); δ_C (125 MHz): 159, 138, 131, 128, 126, 127, 127, 114, 105 (*C*-4), 83 (*C*-6), 82 (*C*-2), 69 (*C*-8), 56 (*C*-5), 55 (4′-O*C*H$_3$), 54 (*C*-1), 48 (4-O*C*H$_3$). *m*/*z* (EI): 326 (30%, M$^+$), 192 (100%), 159, 135, 117, 84.

4-*exo*-Methoxy-6-*exo*-(4′-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 36. Reduction of ester **16*c*** and reaction, following method B, with 4-methoxybenzaldehyde dimethyl acetal, at −20 °C for 14 h, and purification by flash chromatography (petrol : EtOAc 94 : 6), produced the title furofuran acetal **36** as a white solid in 68% yield. Mp 77–79 °C; found: C, 73.14; H, 6.68; calc. for $C_{20}H_{22}O_4$: C, 73.6; H, 6.74%; ν_{max} (ATR): 2880, 1512, 1234, 1205 cm^{-1}; δ_H (500 MHz): 7.3–7.2 (7 H, m, Ar-*H*), 6.84 (2 H, d, $J = 9$ Hz, Ar-*H*), 5.31 (1 H, d, $J = 6$ Hz, 2-*H*), 5.04 (1 H, s, 4-*H*), 4.51 (1 H, s, 6-*H*), 3.73 (3 H, s, 4′-OCH_3), 3.67 (1 H, d, $J = 9$ Hz, 8-H_{endo}), 3.33 (3 H, s, 4-OCH_3), 3.32 (1 H, m, 1-*H*), 3.22 (1 H, dd, $J = 9$, 6 Hz, 8-H_{exo}), 2.91 (1 H, m, 5-*H*); δ_C (125 MHz): 159, 138, 132, 128, 127, 127, 125, 114, 107 (*C*-4), 85 (*C*-6), 79 (*C*-2), 69 (*C*-8), 60 (*C*-5), 55.3 (4′-O*C*H$_3$), 54.7 (*C*-1), 49 (4-O*C*H$_3$); *m*/*z* (EI): 326 (34%, M$^+$), 192, 159, 135, 91, 84 (100).

4-Methoxy-6-*endo*-phenyl-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]-octane 37. Reduction of ester **16*c*** and reaction, following method A, with benzaldehyde dimethylacetal, at −20 °C for 16 h, and purification by flash chromatography (petrol : EtOAc 94 : 6), produced the title furofuran acetal **37** as a white solid in 64% yield. Mp 65.1–65.8 °C; found: C, 76.63; H, 6.63; $C_{19}H_{20}O_3$ requires: C, 77.00; H, 6.80%; ν_{max} (ATR): 2897, 1568, 1274, 1049 cm^{-1}; δ_H (500 MHz) 7.40–7.3 (10 H, m, Ar-*H*), 5.36 (1 H, d, $J = 6$ Hz, 2-*H*), 4.94 (1 H, d, $J = 6.5$ Hz, 6-*H*), 4.51 (1 H, s, 4-*H*), 3.70 (1 H, d, $J = 11$ Hz, 8-H_{endo}), 3.49 (1 H, dd, $J = 11$, 6 Hz, 8-H_{exo}), 3.19 (1 H, m, 1-*H*), 3.16 (1 H, m, 5-*H*), 3.14 (3 H, s, 4-OCH_3); δ_C (125 MHz): 139, 138, 129, 128, 127, 127, 127, 126, 105 (*C*-4), 83 (*C*-6), 82 (*C*-2), 69 (*C*-8), 56 *C*-5), 54 (*C*-1), 48 (O*C*H$_3$); *m*/*z* (EI): 296 (8%, M$^+$), 265, 159, 134, 117, 84 (100).

4-*exo*-Methoxy-6-*endo*-(3′,4′-methylenedioxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 38. Reduction of ester **16*c*** and reaction, following method A, with 3,4-methylenedioxybenzaldehyde dimethyl acetal, at −20 °C for 16 h, and purification by flash chromatography (petrol : ethyl acetate 94 : 6), produced the title furofuran acetal **38** as a yellow waxy solid in 27% yield accompanied by a small amount of the *endo-exo* isomer (9%). Found: C, 70.21; H, 6.14; calc. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92%; ν_{max} (ATR): 2902, 1493, 1251, 949 cm^{-1}; δ_H (500 MHz): 7.40–7.25 (6 H, m, Ar-*H*), 6.8–6.65, (2 H, m, Ar–*H*), 5.95 (2 H, s, OCH_2O), 5.42 (1 H, d, $J = 6$ Hz, 2-*H*), 5.10 (1 H, s, 4-*H*), 4.48 (1 H, d, $J = 7$ Hz, 6-*H*), 3.70 (1 H, m, 8-H_{endo}), 3.40 (3 H, s, OCH_3), 3.38 (1 H, m, 1-*H*), 3.30 (1 H, m, 8-H_{exo}), 2.90 (1 H, dd, $J = 7$, 5 Hz, 5-*H*); δ_C (125 MHz): 148, 147, 138, 135, 128, 127, 126, 120, 108, 106,

107 (*C*-4), 101 (O*C*H$_2$O), 85 (*C*-6), 79 (*C*-2), 69 (*C*-8), 61 (*C*-5), 55 (O*C*H$_3$), 49 (*C*-1); *m*/*z* (EI): 340 (4%, M$^+$), 308, 295 (100), 280, 202, 173, 121, 77.

4-*exo*-Methoxy-6-*exo*-(3′,4′-methylenedioxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 39. Reduction of ester **16*c*** and reaction, following method B, with 3,4-methylenedioxybenzaldehyde dimethyl acetal, at −20 °C for 16 h, and purification by flash chromatography (petrol : ethyl acetate 94 : 6), produced the title furofuran acetal **39** as a yellow waxy solid in 38% yield. Found: C, 69.97; H, 6.12; calc. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92%; ν_{max} (ATR): 2893, 1489, 1249, 1039 cm^{-1}. δ_H (500 MHz): 7.20–7.15 (6 H, m, Ar-*H*), 6.81 (1 H, s, Ar-*H*), 6.63 (1 H, d, $J = 5$ Hz, Ar-*H*), 6.39 (1 H, s, 4-*H*), 5.85 (2 H, s, OCH_2O), 5.42 (1 H, s, 6-*H*), 3.92 (1 H, d, $J = 5$ Hz, 2-*H*), 3.42 (2 H, m, 8-H_2), 3.12 (3 H, s, OCH_3), 2.96 (1 H, m, 5-*H*), 2.4 (1 H, m, 1-*H*). δ_C (125 MHz): 147, 146, 140, 139, 128, 127.5, 127, 120, 108, 105, 106 (*C*-4), 101 (OCH_2O), 87 (*C*-6), 86 (*C*-2), 70 (*C*-8), 57 (*C*-5), 56 (O*C*H$_3$), 54 (*C*-1); *m*/*z* (EI): 340 (7%, M$^+$), 190, 121 (100), 91, 77.

4-*exo*-Methoxy-6-*endo*-(4′-bromophenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 40. Reduction of ester **16*c*** and reaction, following method A, with 4-bromobenzaldehyde dimethyl acetal, at −20 °C for 16 h, and purification by flash chromatography (petrol : ethyl acetate 94 : 6), produced the title furofuran acetal **40** as a pale yellow amorphous solid in 31% yield. Found: C, 60.39; H, 5.06; calc. for $C_{19}H_{19}BrO_3$: C, 60.81; H, 5.10%; ν_{max} (ATR) 2931, 1487, 1452, 1266, 1069 cm^{-1}; δ_H (500 MHz): 7.5–7.1 (9 H, m, Ar–*H*), 5.28 (1 H, d, $J = 6$ Hz, 2-*H*), 4.82 (1 H, d, $J = 6$ Hz, 6-*H*), 4.40 (1 H, s, 4-*H*), 3.60 (1 H, d, $J = 9$ Hz, 8-H_{endo}), 3.40 (1 H, dd, $J = 5$, 9 Hz, 8-H_{exo}), 3.12 (1 H, m, 1-*H*), 3.10 (3 H, s, OCH_3), 3.05 (1 H, m, 5-*H*); δ_C (125 MHz): 138, 137, 132, 129, 128, 128, 127, 126, 105 (*C*-4), 82 (*C*-6), 81 (*C*-2), 69 (*C*-8), 56 (*C*-5), 54 (*C*-1), 48 (O*C*H$_3$). *m*/*z* (EI): 376 (23%, M$^+$), 374 (24, M$^+$), 345, 343, 269, 267, 134, 121, 84.

4-*exo*-Methoxy-6-*endo*-methyl-2-*endo*-phenyl-3,7-dioxabicyclo-[3.3.0]octane 41. Reduction of ester **16*c*** and reaction, following method A, with acetaldehyde dimethyl acetal, at −20 °C for 16 h, and purification by flash chromatography produced the title furofuran acetal **41** as a white waxy solid in 30% yield. Found: C, 71.69; H, 7.67; calc. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%; ν_{max} (ATR): 2933, 1453, 1100, 1025 cm^{-1}; δ_H (500 MHz): 7.4–7.1 (5 H, m, Ar-*H*), 5.23 (1 H, d, $J = 5$ Hz, 2-*H*), 5.08 (1 H, s, 4-*H*), 3.82 (1 H, m, 6-*H*), 3.38 (1 H, d, $J = 7$ Hz, 8-H_{endo}), 3.32 (3 H, s, OCH_3), 3.23 (1 H, m, 8-H_{exo}), 3.08 (1 H, m, 5-*H*), 2.88 (1 H, m, 1-*H*), 1.35 (3 H, d, 7 Hz, 6-CH_3); δ_C (125 MHz): 137, 127, 126, 125, 103 (*C*-4), 80 (*C*-2), 75 (*C*-6), 67 (*C*-8), 56 (*C*-1), 53 (O*C*H$_3$), 48 (*C*-5), 15 (6-*C*H$_3$); *m*/*z* (EI): 234 (11%, M$^+$), 203, 129, 121 (100), 105, 91, 84, 77.

4-*exo*-Methoxy-6-*endo*-(4′-methoxyphenyl)-2-*exo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 42. Reduction of *trans* ester **16*t*** and reaction, following method A, with 4-methoxybenzaldehyde dimethyl acetal, at −40 °C for 4 h, and purification by flash chromatography (ether : petrol : triethylamine 25 : 75 : 1), afforded the title *exo*-*endo*-furofuryl acetal **42** (53%). υ_{max} 2955, 2927, 2854 cm^{-1}; δ_H (500 MHz): 7.43–7.32 (7 H, m, Ar-*H*), 6.93 (2 H, d, $J = 9$ Hz, Ar-*H*), 4.95 (1 H, d, $J = 7.3$ Hz, 6-*H*), 4.90 (1 H, d, $J = 5.6$ Hz, 2-*H*), 4.37 (1 H, d, $J = 1.8$, 4-*H*), 4.16 (1 H, d, $J = 9.2$ Hz, 8-H_{endo}), 3.86–3.82 (4 H, m, 4′-OCH_3, 8-H_{exo}), 3.17–3.08 (5 H, m, 4-OCH_3, 5-*H*, 1-*H*); δ_C (500 MHz) 158.9, 142.5, 130.2, 128.5, 127.6, 127.5, 126.4, 113.7, 108.0 (*C*-4), 88.1 (C-2), 82.0 (*C*-6), 71.6 (*C*-8), 56.3 (*C*-5), 55.4 (4-O*C*H$_3$), 55.2 (4′-O*C*H$_3$), 52.6 (*C*-1); *m*/*z* (EI): 326 (8%, M$^{+\bullet}$), 192 (100); *m*/*z* (ES$^+$): 348.9 (MNa$^+$), 674.9 (2MNa$^+$); HRMS (ES) found MNa$^+$, 349.1397; $C_{20}H_{22}NaO_4$ requires *M*, 349.1416.

4-Methoxy-2-*exo*-phenyl-6-*exo*-*p*-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane 43a,b. Reduction of *trans* ester **16*t*** and reaction, following method B, with 4-methoxybenzaldehyde dimethyl acetal, at −20 °C for 16 h, and purification by flash chromatography (ether : petrol : triethylamine 25 : 75 : 1), afforded the title furofuran acetals (45%) as a mixture of methyl acetals in a 4 : 1 *exo* : *endo* ratio accompanied by a small amount (11%) of the corresponding *exo*-*endo*-furofuran **42**. 4-*exo*-Methoxy-2-*exo*-phenyl-6-*exo*-*p*-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane **43a** υ_{max}: 2955, 2835 cm^{-1}; δ_H (500 MHz): 7.42–7.29 (7 H, m, Ar-*H*), 6.91 (2 H, d, $J = 8.5$ Hz, Ar-*H*), 5.09 (1 H, s, 4-*H*), 5.07 (1 H, d, $J = 6.4$ Hz, 2-*H*), 4.86 (1 H, d, $J = 7.5$ Hz, 6-*H*), 4.27 (1 H, dd, $J = 6.0$, 9.0 Hz, 8-H_{exo}), 4.05 (1 H, dd, $J = 2.6$, 9.1 Hz, 8-H_{endo}), 3.81 (3 H, s, 4′-OCH_3), 3.40 (3 H, s, 4-OCH_3), 3.26–3.20 (1 H, m, 1-*H*), 2.99 (1 H, t, $J = 6.0$ Hz, 5-*H*); δ_C (500 MHz): 159.3, 142.4, 133.4, 128.56, 127.7, 127.2, 126.5, 114.0, 108.3 (*C*-4), 88.4 (*C*-2), 83.2 (*C*-6), 72.6 (*C*-8), 61.2 (*C*-1), 55.3 (OCH$_3$ Ar), 55.2 (C^9), 53.0 (C-1); *m*/*z* (ES$^+$): 348.9 (MNa$^+$), 674.9 (2MNa$^+$); HRMS (ES) found MNa$^+$, 349.1407; $C_{20}H_{22}NaO_4$ requires *M*, 349.1416. 4-*endo*-Methoxy-2-*exo*-phenyl-6-*exo*-*p*-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane **43b** υ_{max} 2955, 2835 cm^{-1}; δ_H (500 MHz) 7.38–7.26 (7 H, m, Ar-*H*), 6.89 (2 H, d, $J = 8.5$ Hz, Ar-*H*), 5.44 (1 H, d, $J = 4$ Hz, 6-*H*), 5.30 (1 H, d, $J = 5.8$ Hz, 4-*H*), 4.90 (1 H, d, $J = 7.3$, 2-*H*), 4.06 (1 H, dd, $J = 6.7$, 8.9 Hz, 8-H_{exo}), 3.95 (1 H, dd, $J = 4.3$, 8.9 Hz, 8-H_{exo}), 3.80 (3 H, s, 4′-OCH_3), 3.51 (3 H, s, 4-OCH_3), 3.41–3.39 (1 H, m, 5-*H*), 3.15–3.00 (1 H, m, 1-*H*); δ_C (500 MHz): 158.8, 137.7, 134.4, 129.3, 128.6, 128.0, 127.2, 126.1, 104.7 (*C*-1), 83.1 (*C*-2), 79.0 (*C*-6), 70.2 (*C*-8), 58.1 (*C*-5), 55.7 (4-O*C*H$_3$), 55.3 (4′-O*C*H$_3$), 55.1 (C-1); *m*/*z* (ES$^+$): 348.9 (MNa$^+$), 674.9 (2MNa$^+$); HRMS (ES) found MNa$^+$, 349.1449; $C_{20}H_{22}NaO_4$ requires *M*, 349.1416.

4-*exo*-Methoxy-2-*endo*-4′-methoxyphenyl-6-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane 44. Reduction of *cis* ester **33*c*** and reaction, following method A, with benzaldehyde dimethyl acetal, at −78 °C for 1 h, and purification by flash chromatography (ether : petrol : triethylamine 25 : 75 : 1), afforded the *endo*-*endo*-furofuran acetal **44** (23%). υ_{max} 2927 cm^{-1}; δ_H (500 MHz): 7.41–7.23 (7 H, m, Ar-*H*), 6.94 (2 H, d, $J = 8.7$, Ar-*H*), 5.31 (1 H, d, $J = 5.4$ Hz, 2-*H*), 4.93 (1 H, d, $J = 5.8$ Hz, 6-*H*), 4.48 (1 H, s, 4-*H*), 3.83 (3 H, s, 4′-OCH_3), 3.72 (1 H, d, $J = 10.0$ Hz, 8-H_{endo}), 3.51–3.46 (1 H, m, 8-H_{exo}), 3.19–3.06 (5 H, m, 1-*H*, 5-*H*, 4-OCH_3); δ_C (125 MHz): 158.9, 138.6, 130.3, 128.3, 127.8, 127.3, 126.0, 113.8, 105.3 (*C*-4), 82.9 (*C*-6), 81.4 (*C*-2), 68.8 (*C*-8), 56.1 (4-O*C*H$_3$), 55.3 (4′-O*C*H$_3$), 54.3(*C*-1), 48.1 (*C*-5); *m*/*z* (ES): 349.1 (MNa$^+$); HRMS (ES) found MNa$^+$, 349.1407. $C_{20}H_{22}NaO_4$ requires *M*, 349.1416.

4-*exo*-Methoxy-2-*endo*-(3′,4′-methylenedioxyphenyl)-6-*endo*-*p*-methoxyphenyl-3,7-dioxabicyclo[3.3.0]octane 45. Reduction of ester **17*c*** and reaction, following method A, with piperonal dimethyl acetal, at −40 °C for 17 h, and purification by flash chromatography (petrol : ether 7 : 3), gave the title furofuran acetal **45** in 53% yield. υ_{max} 2928, 1513, 1489, 1248 cm^{-1}; δ_H (500 MHz)

7.31 (2 H, d, $J = 8.5$ Hz, Ar-*H*), 6.94–6.92 (3 H, m, Ar-*H*), 6.64 (2 H, broad s, Ar-*H*), 5.97 (2 H, s, OCH_2O), 5.25 (1 H, d, $J = 6$ Hz, 2-*H*), 4.87 (1 H, d, $J = 6.5$ Hz, 6-*H*), 4.49 (1 H, s, 4-*H*), 3.83 (3 H, s, 4′-OCH_3), 3.73 (1 H, dd, $J = 1.5$, 6.5 Hz, 8-H_{endo}), 3.51–3.48 (1 H, m, 8-H_{exo}), 3.15 (3 H, s, 4-CH_3), 3.14–2.95 (2 H, m, 1-*H*, 5-*H*); δ_C (125 MHz) 158.8, 147.7, 146.8, 132.2, 130.6, 127.3, 119.8, 113.7, 108.2, 107.3, 105.3 (*C*-4), 101.0 (OCH_2O), 82.7 (*C*-6), 81.5 (*C*-2), 68.7 (*C*-8), 56.0 (*C*-5), 55.2 (4′-OCH_3), 54.3 (4-OCH_3), 48.1 (*C*-1); *m/z* (EI): 370 (27%, M^+).

3,7-Dioxa-4-methoxy-2,6-bis-*endo*-[3′,4′-methylenedioxyphenyl]-bicyclo[3.3.0]octane 46. Reduction of ester **18*c*** and reaction, following method A, with piperonal dimethyl acetal, at −40 °C for 17 h, and purification by flash chromatography (petrol : ether 7 : 3), the title furofuran acetal **46** was obtained in 55% yield. Found MNa^+, 407.1139. $C_{21}H_{20}O_7Na$ requires *M*, 407.1107. υ_{max} 2894, 1503, 1489, 1444, 1239, 1098, 1063, 1037 cm^{-1}; δ_H (300 MHz): 6.91–6.82 (6 H, m, aromatics), 5.98 (2 H, s, OCH_2O), 5.97 (2 H, s, OCH_2O), 5.25 (1 H, d, $J = 6$, 2-*H*), 4.82 (1 H, d, $J = 5.7$, 6-*H*), 4.53 (1 H, s, 4-*H*), 3.71 (1 H, d $J = 8.4$, 8-H_{endo}), 3.50–3.44 (1 H, m, 8-H_{exo}), 3.17 (3 H, s, OCH_3), 3.15–3.09 (2 H, m, 1-*H*, 5-*H*). δ_C (125 MHz): 147.7, 147.6, 146.8, 146.7, 132.7, 132.4, 120.0, 119.5, 108.5, 108.4, 107.6, 107.1 (aromatics), 105.5 (*C*-4), 101.2 (OCH_2O), 82.9 (*C*-6), 81.7 (*C*-2), 68.9 (*C*-8), 56.3 (*C*-3), 54.6 (OCH_3), 48.3 (*C*-1). *m/z* (EI): 384 (32%) (M^+), 203 (42%), 178 (99%), 84 (100%); *m/z* (CI, CH_4): 385 (MH^+), 353, 307, 135, 57 (100%).

2,6-*endo*-Diphenyl-3,7-dioxabicyclo[3.3.0]octane 55. Boron trifluoride diethyl ether complex ($BF_3{\cdot}Et_2O$) (200 μl, 1.25 mmol) was added to a stirred solution of triethylsilane (Et_3SiH) (1.5 ml, 18 mmol) and methyl acetal **37** (110 mg, 0.37 mmol) in DCM (20 ml) at 0 °C. On addition of $BF_3{\cdot}OEt_2$ the reaction mixture immediately turned dark green and after 30 minutes the reaction was warmed to room temperature and stirred for 30 hours before $NaHCO_3$ (aq) (20 ml) was added. The organic layer was washed with $NaHCO_3$ (aq) (20 ml) and the combined aqueous phases were back extracted with DCM (20 ml). The combined organic phases were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resulting residue was purified by flash chromatography eluting with 3% ethyl acetate in petrol to yield the desired symmetrical lignan **55** (60 mg, 61%), which solidified on standing to a white solid and was recrystallized with ether–petrol. Mp 73–74 °C. Found: C, 80.92; H, 6.76; calc. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81 %; υ_{max} (ATR) 3002, 1524, 1241, 911 cm^{-1}; δ_H (300 MHz): 7.45–7.32 (10 H, m, Ar-*H*), 4.91 (2 H, d, $J = 6$ Hz, 6-*H*, 2-*H*), 3.74 (2 H, m, 4-H_{endo}, 8-H_{endo}), 3.59 (2 H, m, 4-H_{exo}, 8-H_{exo}), 3.15 (1 H, m, 1-*H*), 3.12 (1 H, m, 5-*H*). δ_C (50 MHz): 138, 128, 127, 126, 84 (*C*-2,*C*-6), 69 (*C*-4, *C*-8), 54 (*C*-1, *C*-5). *m/z* (EI): 266 (45%, M^+), 189, 165, 117 (100), 84.

2-*endo*,6-*endo*-Bis(3′,4′-methylenedioxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane 1. Triethylsilane (220 μL, 2.6 mmol) was slowly added to a solution of acetal **46** (100 mg, 0.26 mmol), in DCM (6 ml) at −40 °C under argon. $BF_3{\cdot}OEt_2$ (50 μL, 0.275 mmol), was then added under the same conditions and the colour of the solution turned to dark red. The resulting solution was stirred for 15 hours at −40 °C under argon before being poured into a saturated solution of sodium bicarbonate. The aqueous layer was extracted with ether (3 × 5 ml) and the combined organic layers were washed with brine (3 × 5 ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (ether : petrol : triethylamine 25 : 75 : 1) to afford epiasarinin **1** (25 mg, 27%) and asarinin **2** (3 mg, 3.3%) and a mixture of these two diastereoisomers and the starting material (37 mg, 40%) which could be recycled. Epiasarinin **1** mp 140–142 °C; found: C, 67.60%; H, 5.13%; calc. for $C_{20}H_{18}O_6$: C, 67.79%; H, 5.12%; υ_{max} 2922, 1460, 1376, 1253 cm^{-1}; δ_H (500 MHz): 6.89 (2 H, s, Ar-*H*), 6.82 (4 H, s, Ar-*H*), 5.97 (4 H, s, OCH_2O), 4.87 (2 H, d, $J = 5.04$ Hz, 2-*H*, 6-*H*), 3.72 (2 H, d, $J = 9.7$ Hz, 4-H_{endo}, 8-H_{endo}), 3.52 (2 H, dd, $J = 9.45$, 6.85 Hz, 4-H_{exo}, 8-H_{exo}), 3.13 (2 H, m, 1-*H*, 5-*H*); δ_C (125 MHz): 147.6, 146.7, 132.1, 119.5, 108.1, 107.1, 100.9 (OCH_2O), 84.1 (*C*-2, *C*-6), 68.7 (*C*-4, *C*-8), 49.5 (*C*-1, *C*-5); *m/z* (ES^+): 377.1 (MNa^+), 731 (M_2Na^+). Asarinin **2** υ_{max} 2922, 1460, 1376, 1253; δ_H (500 MHz): 6.86–6.78 (6 H, m, Ar-*H*), 5.96 (2 H, s, OCH_2O), 5.95 (2 H, s, OCH_2O), 4.83 (1 H, d, $J = 5.15$, 2-*H*), 4.39 (1 H, d, $J = 6.86$, 6-*H*), 4.09 (1 H, d, $J = 9.3$ Hz, 4-H_{endo}), 3.83–3.80 (2 H, m, 4-H_{exo}, 8-H_{endo}), 3.31–3.29 (2 H, m, 1-*H*, 8-H_{exo}), 2.88–2.83 (1 H, m, 5-*H*); δ_C (125 MHz): 147.9, 147.6, 147.2, 146.5, 135.0, 132.2, 119.6, 118.7, 108.5, 106.5, 106.4, 101.0, 100.9 (OCH_2O), 87.6 (*C*-6), 82.0 (*C*-2), 70.9 (*C*-4), 69.7 (*C*-8), 54.6 (*C*-5), 50.1 (*C*-1).

General procedures for reduction of 4-methoxyphenyl substituted furofuryl acetals

Method A. Triethylsilane (10 eq.) was slowly added to a solution of acetal (1 eq.), in DCM at −78 °C under argon. $BF_3{\cdot}OEt_2$ (1.7 eq.) was then added at −78 °C and the colour of the solution turned to dark red. The resulting solution was stirred for 1 min at −78 °C under argon before being poured into a saturated solution of sodium bicarbonate. The resulting mixture was filtered through a Whatman PTFE filter tube and concentrated. The residue was then purified by flash chromatography (ether : petrol : triethylamine 25 : 75 : 1) to afford the desired furofuran.

Method B. Triethylsilane (10 eq.) was slowly added to a solution of acetal (1 eq.), in DCM at 0 °C under argon. $BF_3{\cdot}OEt_2$ (1.7 eq.) was then added at 0 °C and the resulting solution was stirred for 1 hour at 0 °C under argon before being poured into a saturated solution of sodium bicarbonate. The resulting mixture was filtered through a Whatman PTFE filter tube and concentrated. The residue was then purified by flash chromatography (ether : petrol : triethylamine 25 : 75 : 1) to afford the desired furofuran.

Method C. Triethylsilane (10 eq.) was slowly added to a solution of acetal (1 eq.), in DCM at −20 °C under argon. $BF_3{\cdot}OEt_2$ (1.7 eq.) was then added at −20 °C and the resulting solution was stirred for 4 hours at −20 °C under argon before being poured into a saturated solution of sodium bicarbonate. The resulting mixture was filtered through a hydrophobic frit and concentrated.

2-*exo*-Phenyl-6-*endo*-4′-methoxyphenyl-3,7-dioxabicyclo[3.3.0]-octane 57. υ_{max} 2961, 2928, 2872, 1455, 1190 cm^{-1}; δ_H (500 MHz, $CDCl_3$–C_6D_6): 7.32–7.19 (7 H, m, Ar-*H*), 6.83 (2 H, d, $J = 8.7$ Hz, Ar-*H*), 4.67 (1 H, d, $J = 5.9$ Hz, 6-*H*), 4.44 (1 H, d, $J = 6.8$ Hz, 2-*H*), 4.03 (1 H, d, $J = 9.4$ Hz, 8-H_{endo}), 3.78 (1 H, t, $J = 8.8$ Hz, 4-H_{exo}), 3.64 (1 H, dd, $J = 6.2$, 9.4 Hz, 8-H_{exo}), 3.57 (3 H, s, 4′-OCH_3), 3.38–3.30 (1 H, m, 4-H_{endo}), 3.10–3.03 (1 H, m, 5-*H*), 2.73–2.68

(1 H, m, 1-*H*); δ_C (125 MHz): 158.6, 141.3, 130.4, 128.6, 127.8, 126.7, 126.0, 113.7, 87.7 (*C*-6), 82.0 (*C*-2), 71.1, 69.8 (*C*-4, *C*-8), 55.2 (4′-O*C*H$_3$), 54.7 (*C*-1), 50.2 (*C*-5); *m*/*z* (ES$^+$): 319.1 (MNa$^+$), 731 (2MNa$^+$); HRMS (ES) found MNa$^+$, 319.1322; $C_{19}H_{20}NaO_3$ requires *M*, 319.1310.

2-*exo*-Phenyl-6-*exo*-4′-methoxyphenyl-3,7-dioxabicyclo[3.3.0]-octane 58. υ_{max} 2957, 2929, 2855, 1512, 1247, 1033 cm^{-1}; δ_H (500 MHz): 7.37–7.27 (7 H, m, Ar-*H*), 6.89 (2 H, d, 8.8 Hz, Ar-*H*), 4.83 (1 H, d, *J* = 4.9 Hz, 2-*H*), 4.77 (1 H, d, *J* = 4.9 Hz, 6-*H*), 3.80 (3 H, s, 4′-OC*H*$_3$), 4.29–4.24 (2 H, m, 4-H_{endo}, 8-H_{endo}), 3.93–3.89 (2 H, m, 4-H_{exo}, 8-H_{exo}), 3.16–3.07 (2 H, m, 1-*H*, 5-*H*); δ_C (125 MHz): 159.2, 141.2, 133.0, 128.6, 127.6, 127.4, 125.9, 113.9, 85.9 (*C*-2), 85.6 (*C*-6), 71.85, 71.80 (*C*-4, *C*-8), 55.3 (4′-O*C*H$_3$), 54.4, 54.2 (*C*-5, *C*-1); *m*/*z* (ES$^+$): 319.1 (MNa$^+$), 731 (2MNa$^+$); HRMS (ES) found MNa$^+$, 319.1306; $C_{19}H_{20}NaO_3$ requires *M*, 319.1310.

2-*endo*-Phenyl-6-*endo*-4′-methoxyphenyl-3,7-dioxabicyclo[3.3.0]-octane 59. υ_{max} 2958, 2931, 2855, 1513, 1248 cm^{-1}; δ_H (500 MHz): 7.40–7.29 (7 H, m, Ar-*H*), 6.92 (2 H, d, *J* = 9 Hz, Ar-*H*), 4.97 (1 H, d, *J* = 5.7 Hz, 2-*H*), 4.93 (1 H, d, *J* = 5.9 Hz, 6-*H*), 3.83 (3 H, s, 4′-OC*H*$_3$), 3.13 (1 H, dd, *J* = 2.3, 9.6 Hz, 4-H_{endo}), 3.67 (1 H, dd, *J* = 2.2, 9.4 Hz, 8-H_{endo}), 3.55 (1 H, dd, *J* = 7.3, 9.6 Hz, 4-H_{exo}), 3.53 (1 H, dd, *J* = 7.3, 9.4 Hz, 8-H_{exo}), 3.29–3.08 (2 H, m, 1-*H*, 5-*H*); δ_C (125 MHz): 138.9, 130.6, 128.6, 128.3, 127.6, 126.3, 113.7, 84.3 (*C*-2), 84.0 (*C*-6), 68.85 (*C*-4), 68.75 (*C*-8), 55.3 (4′-O*C*H$_3$), 49.6 (*C*-5), 49.5 (*C*-1); *m*/*z* (ES$^+$): 319.1 (MNa$^+$), 731 (2MNa$^+$); HRMS (ES) found MNa$^+$, 319.1317; $C_{19}H_{20}NaO_3$ requires *M*, 319.1310.

Found: C, 76.12; H, 6.85; calc. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80%; υ_{max} 2957, 2871, 2835, 1513, 1248, 1055 cm^{-1}; δ_H (500 MHz): 7.38–7.29 (7 H, m, Ar-*H*), 6.90 (2 H, d, *J* = 9 Hz, Ar-*H*), 4.93 (1 H, d, *J* = 5.9 Hz, 2-*H*), 4.44 (1 H, d, *J* = 7.25 Hz, 6-*H*), 4.13 (1 H, d, *J* = 9.5 Hz, 4-H_{endo}), 3.88–3.80 (2 H, m, 8-H_{exo}, 4-H_{exo}), 3.81 (3 H, s, 4′-OC*H*$_3$), 3.42–3.38 (1 H, m, 1-*H*), 3.26 (1 H, d, *J* = 9 Hz, 8-H_{endo}), 2.95–2.90 (1 H, m, 5-*H*); δ_C (125 MHz): 158.3, 138.4, 133.1, 128.6, 127.5, 127.1, 125.6, 113.9, 87.5 (*C*-6), 82.2 (*C*-2), 70.9 (*C*-4), 69.7 (*C*-8), 55.3 (4′-O*C*H$_3$), 54.5 (*C*-5), 50.1 (*C*-1); *m*/*z* (ES$^+$): 319.1 (MNa$^+$), 731 (2MNa$^+$); HRMS (ES) found MNa$^+$, 319.1296; $C_{19}H_{20}NaO_3$ requires *M*, 319.1310.

Table 7 Crystal data and experimental details

Compound	**1**	**15**
Formula	$C_{20}H_{18}O_6$	$C_{19}H_{19}NO_4S$
*F*w	354.34	357.41
Temperature, K	120	110
Symmetry	Monoclinic	Triclinic
Space group	$P2_1/n$ (#14)	*P*-1 (#2)
a, Å	8.193(1)	5.8932(4)
b, Å	7.444(1)	9.2189(7)
c, Å	26.234(3)	16.199(1)
α, °	90	87.502(3)
β, °	96.98(1)	89.201(3)
γ, °	90	77.553(3)
V, Å^3	1588.0(3)	858.6(1)
Z	4	2
D_x, g cm^{-3}	1.482	1.383
μ, mm^{-1}	0.11	0.21
Refls. meas.	18649	8583
Unique refls.	4226	3371
R_1, wR_2, %[a]	4.5, 11.8	5.7, 13.5

[a] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$ for all data, $R_1 = \Sigma ||F_c| - |F_o||/\Sigma |F_o|$ for reflections with $I > 2\sigma(I)$.

X-Ray crystallography

Diffraction experiments were carried out on a Siemens SMART 3-circle diffractometer (1 K CCD area detector), using graphite-monochromated MoK_α radiation (λ = 0.71073 Å) and a Cryostream open-flow N_2 gas cryostat. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL 5.10 programs (Bruker AXS, Madison, Wisconsin, USA, 1997). Crystal data are listed in Table 7. CCDC deposition numbers 603915 (**1**) and 603916 (**15**).‡

Acknowledgements

We thank the EPSRC and Sanofi-Aventis for financial support of this work (CASE awards to WMD and AJD), The EPSRC Mass Spectrometry Service for accurate mass determinations, Dr A. M. Kenwright for assistance with NMR experiments and Dr M. Jones for mass spectra.

References

1 R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75.
2 R. C. D. Brown and N. A. Swain, *Synthesis*, 2004, 811.
3 There have been a number of stereoselective syntheses of *endo-endo* furofuranones. However, the conversion of these to the parent furofuran has either not been attempted or proceeds with epimerisation, see ref. 2 for examples.
4 D. R. Stevens, C. P. Till and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1992, 185.
5 D. J. Aldous, W. M. Dutton and P. G. Steel, *Synlett*, 1999, 474; D. J. Aldous, A. J. Dalencon and P. G. Steel, *Org. Lett.*, 2002, **4**, 1159; D. J. Aldous, A. J. Dalencon and P. G. Steel, *J. Org. Chem.*, 2003, **68**, 9159.
6 G. B. Payne, *J. Org. Chem.*, 1960, **25**, 275.
7 D. Yang, M. K. Wong and Y. C. Yip, *J. Org. Chem.*, 1995, **60**, 3887.
8 P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney and N. Thompson, *Synthesis*, 1987, 1015.
9 G. A. Koppel, *Tetrahedron Lett.*, 1972, 1507.
10 A. H. Li, L. X. Dai and X. L. Hou, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2725; A. H. Li, L. X. Dai, X. L. Hou and M. B. Chen, *J. Org. Chem.*, 1996, **61**, 4641.
11 J. R. Neff, R. R. Gruetzmacher and J. E. Nordlander, *J. Org. Chem.*, 1974, **39**, 3814.
12 S. Hirner and P. Somfai, *Synlett*, 2005, 3099.
13 W. Eberbach and B. Burchard, *Chem. Ber.*, 1978, **111**, 3665.
14 A. S. Batsanov, A. Byerley, J. Howard and P. G. Steel, *Synlett*, 1996, 401.
15 A. Pelter, R. S. Ward, P. Collins, R. Venkateswarlu and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1*, 1985, 587; A. Pelter, R. S. Ward, R. Venkateswarlu and C. Kamakshi, *Tetrahedron*, 1992, **48**, 7209.
16 M. Beroza, *J. Am. Chem. Soc.*, 1956, **78**, 5082.
17 S. Shimizu, H. Kawashima, K. Akimoto, Y. Shinmen, H. Sugano and H. Yamada, *Phytochemistry*, 1992, **31**, 757.
18 J. C. Kim, K. H. Kim, J. C. Jung and O. S. Park, *Tetrahedron: Asymmetry*, 2006, **17**, 3; B. Banerjee and S. C. Roy, *Synthesis*, 2005, 2913; D. Enders, V. Lausberg, G. Del Signore and O. M. Berner, *Synthesis*, 2002, 515; K. K. Rana, C. Guin and S. C. Roy, *Tetrahedron Lett.*, 2000, **41**, 9337; H. M. Hull, R. G. Jones and D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1779; G. Maiti, S. Adhikari and S. C. Roy, *J. Chem. Soc., Perkin Trans. 1*, 1995, 927; K. Samizu and

‡ CCDC reference numbers 603915 and 603916. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604952d

K. Ogasawara, *Chem. Lett.*, 1995, 543; S. Takano, K. Samizu and K. Ogasawara, *Synlett*, 1993, 785; S. Takano, T. Ohkawa, S. Tamori, S. Satoh and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 189; M. Beroza and M. S. Schechter, *J. Am. Chem. Soc.*, 1956, **78**, 1242.
19 R. C. D. Brown, C. J. Bataille, G. Bruton, J. D. Hinks and N. A. Swain, *J. Org. Chem.*, 2001, **66**, 6719.
20 H. Suginome, K. Orito, K. Yorita, M. Ishikawa, N. Shimoyama and T. Sasaki, *J. Org. Chem.*, 1995, **60**, 3052.
21 A. Pelter, R. S. Ward, E. Venkatarao and K. V. Sastry, *Tetrahedron*, 1976, **32**, 2783.
22 F. A. Macias, E. Zubia, L. Quijano, F. R. Franczek and N. H. Fischer, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1992, **C48**, 2240; S. G. Il'in, A. A. Artyukov, T. Y. Kochergina, S. V. Lindeman and Y. T. Struchkov, *Khim. Prir. Soedin.*, 1994, 567 (in Russian);; R. Mata, M. L. Macias, I. S. Rojas, B. Lotina-Hennsen and R. A. Toscano, *Phytochemistry*, 1998, **49**, 441; V. S. Parmar, S. C. Jain, S. Gupta, S. Talwar, V. K. Rajwanshi, R. Kumar, A. Azim, S. Malhotra, N. Kumar, R. Jain, N. K. Sharma, O. D. Tyagi, S. J. Lawrie, W. Errington, O. W. Howarth, C. E. Olsen, S. K. Singh and J. Wengel, *Phytochemistry*, 1998, **49**, 1069.
23 P. W. Baures, M. Miski and D. S. Eggleston, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1992, **C48**, 574.
24 A. Pelter and R. S. Ward, *Heterocycles*, 1994, **37**, 137.
25 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.