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Asymmetric Synthesis of Butenolide and Butyrolactone Derivatives

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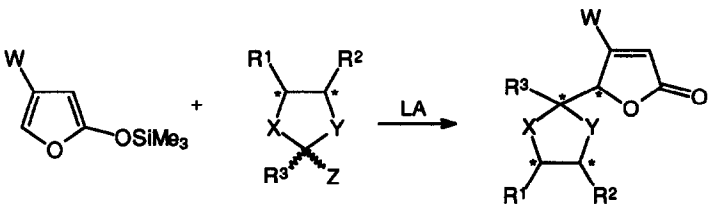
Abstract. 2-Trimethylsiloxyfuran and 4-methoxy-2-trimethylsiloxyfuran, which are readily prepared from butenolide and methyl tetronate respectively, have been reacted with a series of homochiral ortho-esters and oxazolidine derivatives in the presence of Lewis acids to afford homochiral 2(5*H*)-furanone derivatives. The structures of these products have been determined using nmr spectroscopy and, where possible, by X-ray analysis. Preliminary experiments have been carried out involving conjugate addition to these unsaturated lactones, demonstrating their potential as substrates for natural product synthesis.

Homochiral butenolide derivatives constitute an important class of natural products[1-4] and are also excellent substrates for carrying out asymmetric tandem conjugate addition and Diels Alder reactions[5-8] leading to other five-membered lactone-containing compounds. As a possible route to the asymmetric synthesis of such compounds we have investigated the Lewis acid catalysed reaction of 2-trimethylsiloxyfuran (**1**) and 4-methoxy-2-trimethylsiloxyfuran (**2**) with a series of acyl cation equivalents (**3**) derived from readily available homochiral diols and amino-alcohols (Scheme 1).

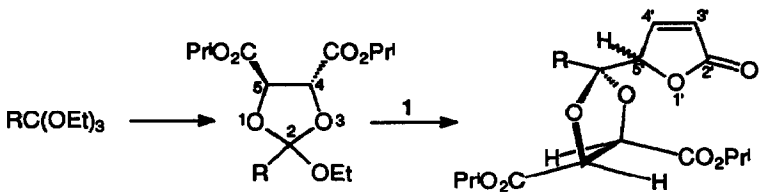


1 W = H
2 W = OMe

3

Scheme 1

We first of all investigated the reaction of (**1**) with the cyclic ortho-esters (**4**) derived from L-diisopropyl tartrate (L-DIPT) (Scheme 2). The ortho-esters (**4a-c**) were readily prepared by reacting L-DIPT with an excess of triethyl orthobenzoate, orthoacetate and orthoformate respectively.[9,10] Reaction of (**4a**) and (**4b**) with (**1**) in the presence of a Lewis acid gave the diastereomerically enriched butenolides (**5a**) and (**5b**) respectively, in low to moderate yield and with relatively poor diastereofacial selectivity (Table 1). This is in contrast with the work of Umani-Ronchi *et al.*[9,10] who reacted (**4a**) and (**4b**) with enol ethers derived from ketones and, at least in some cases (*E*-enol ethers), obtained relatively high diastereofacial selectivities. The ^{1}H and ^{13}C nmr spectra of (**4a-c**), (**5a**) and (**5b**) are listed in Tables 3 and 4. The two diastereoisomers of (**5a**) were separated by fractional crystallisation from ether and ether-petroleum ether. Tentative structures were assigned to the two isomers based on NOe measurements (Figure 1).



4a R = Ph
4b R = Me
4c R = H

5a R = Ph
5b R = Me

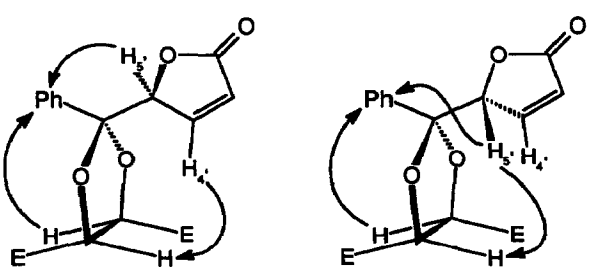
Scheme 2

Table 1. Lewis acid catalysed reactions of chiral ortho-esters (4a,b) with trimethylsiloxyfuran (1)

R	Lewis Acid	Conditions	Yield (%)[a]	Isomer Ratio[b]
Ph	$ZnCl_2$	-78°C, 4h., r.t., 2 days	25	33 : 67
	$BF_3.Et_2O$	-78°C, 4h., r.t., 2 h.	27	37 : 63
	$ZnCl_2$	-16°C, 2h.	21	35 : 65
	$TiCl_4$	-78°C, 4h., r.t., 2 days	3	-
	$SnCl_4$	-20°C, 2h.	4	-
	$BF_3.Et_2O$	-78°C, 7h.	33	38 : 62
	$ZnCl_2$	-78°C, 7h.	55	35 : 65
	$SnCl_4$	-78°C, 7h.	26	40 : 60
Me	$ZnCl_2$	-78°C, 7h.	39	43 : 57

[a] isolated product, after flash chromatography

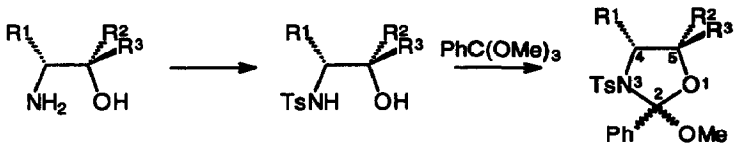
[b] determined by ^1H n.m.r. on crude product.



(isomer 1) **5a** (isomer 2) (E = CO_2Pr^i)

Figure 1

We therefore turned our attention to the use of the oxazolidine based acyl cation equivalents (**8a-c**). These were prepared using known methodology starting from (*R*)-phenylglycinol (**6a**), (*1R*, 2*R*)-norpseudoephedrine (**6b**), and (1*R*, 2*S*)-norephedrine (**6c**), respectively.[11-15] In each case the products were obtained as a mixture of two possible diastereoisomers (Scheme 3), the mixture being used as such since the reactions involved carbocation formation at C-2. In practice (**8c**) was only obtained in low yield and was not used further.



6 **7** **8**

a R^1 = Ph, R^2 = R^3 = H
b R^1 = Me, R^2 = H, R^3 = Ph
c R^1 = Me, R^2 = Ph, R^3 = H

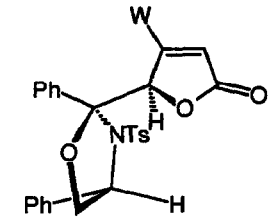
Scheme 3

We next investigated the reaction of (**8a**) and (**8b**) with (**1**) and (**2**). In each case four diastereoisomeric products can be formed. For example, reaction of (**8a**) with (**1**) can in principle give rise to four adducts (**9a-d**). Analogous products can also be formed from the reaction of (**8b**) with (**1**), and from the reactions of (**8a**) and (**8b**) with (**2**) (Scheme 4). Boron-trifluoride etherate was found to be the best Lewis acid for these reactions and, in all cases, stereoselectivity was observed. Thus, the reaction of (**8a**) with (**1**) gave a mixture of two adducts (**9a**) and (**9b**) (ratio 1 : 2) (Table 2). These were separated and purified by column chromatography. The structures were assigned on the basis of their ^{1}H and ^{13}C nmr spectra (Tables 5 and 6), and in particular on the basis of NOe data (Figure 2). The structure of (**9a**) was confirmed by X-ray analysis (Figure 3a). The reaction of (**8a**) with (**2**) gave a single adduct (**10a**), although in lower yield, while the reaction of (**8b**) with (**1**) and (**2**) gave (**11d**) and (**12c**) respectively (Table 2). Structures were assigned to these products on the basis of nmr and NOe data (Figure 2) and are supported in the case of (**11d**) by X-ray analysis (Figure 3b).

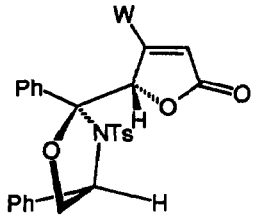
Table 2. Lewis acid catalysed reactions of chiral oxazolidines with trimethylsiloxyfurans

Oxazolidine	Furan	Lewis Acid	Conditions	Product	Yield[a]	Isomer Ratio[b]
8a	**1**	$BF_3.Et_2O$	-78°C,3h	**9a,b**	62	33 : 67
"	"	"	-100°C,3h	**9a,b**	57	40 : 60
"	**2**	"	-78°C,3½h	**10a**	38	100 : 0
8b	**1**	"	-78°C,3h	**11d**	49	100 : 0
"	"	"	-100°C,3h	**11d,c**	62	77 : 23
"	**2**	"	-78°C,4h	**12c**	49	100 : 0

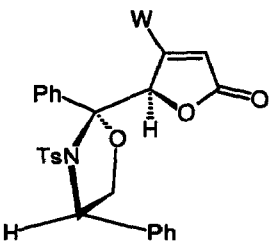
[a] isolated product, after flash chromatography.
[b] determined by ^{1}H nmr on crude product.



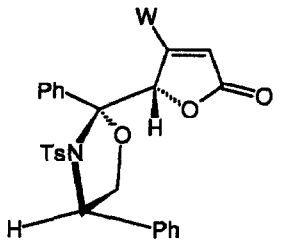
9a W = H
10a W = OMe



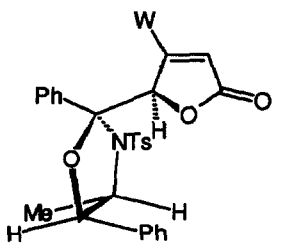
9b W = H
10b W = OMe



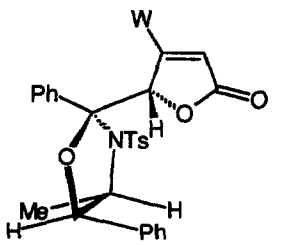
9c W = H
10c W = OMe



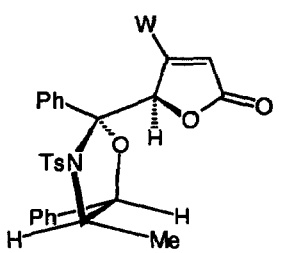
9d W = H
10d W = OMe



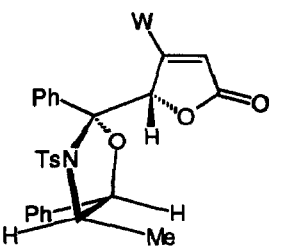
11a W = H
12a W = OMe



11b W = H
12b W = OMe

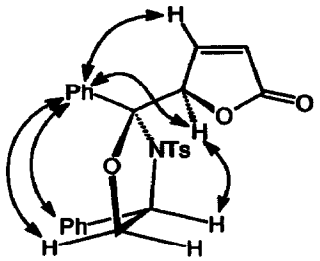


11c W = H
12c W = OMe

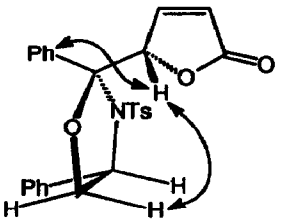


11d W = H
12d W = OMe

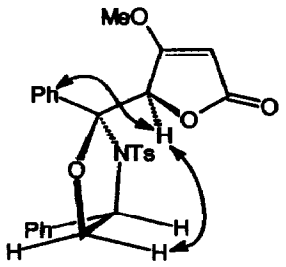
Scheme 4



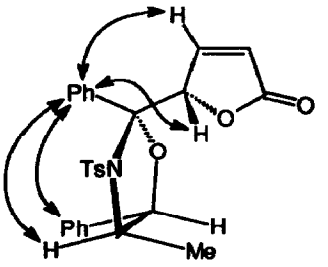
9a



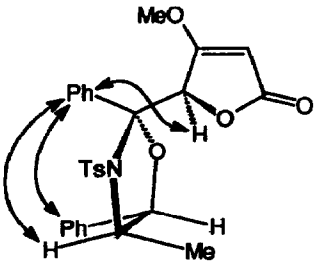
9b



10a



11d



12c

Figure 2

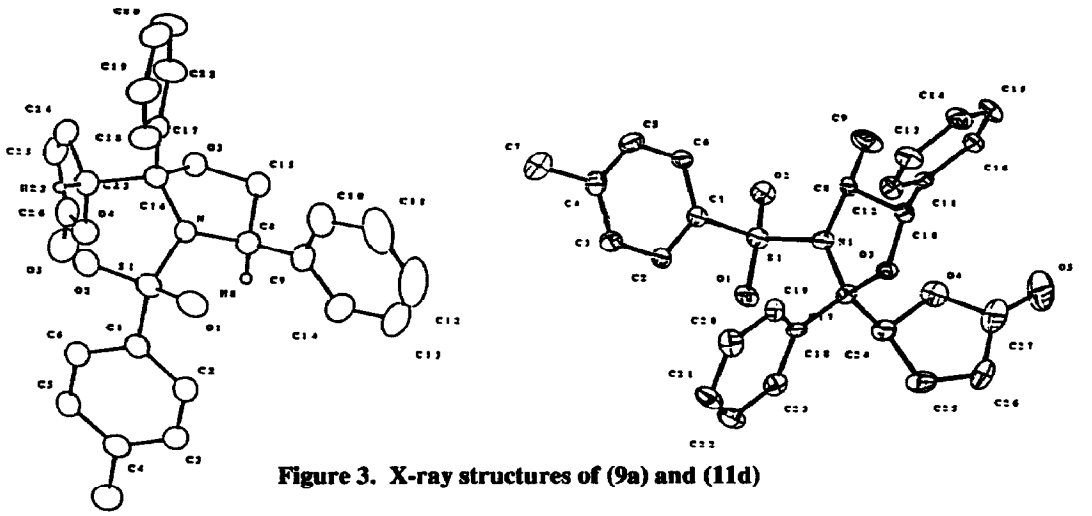
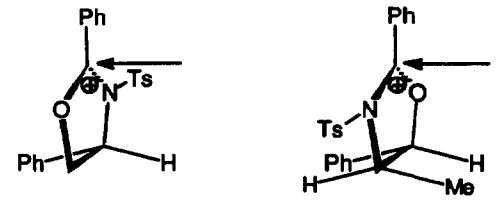


Figure 3. X-ray structures of (9a) and (11d)

These results indicate that the configuration at C-2 in the products (**9-12**) is determined by the choice of the chiral auxiliary used. Thus, the reactions of (**8a**), derived from (*R*)-phenyl-glycinol (**6a**), afford the *S*-configuration at this centre, while those of (**8b**), derived from (1*R*, 2*R*)-norpseudo-ephedrine (**6b**), give the *R*-configuration at this position. In both cases this corresponds to

attack from the side opposite to the phenyl substituent (Figure 4), despite the fact that in (**8b**) there is a methyl substituent present on this side of the oxazoline ring. It appears therefore that the influence of the bulky phenyl substituent at C-4 in (**8a**) and at C-5 in (**8b**) is the controlling factor which determines the facial selectivity of the acyl cation equivalent.



(derived from **8a**) (derived from **8b**)

Figure 4

On the other hand, it would seem that the choice of the siloxyfuran controls the preferred configuration at C-5'. Thus, the reactions of both (**8a**) and (**8b**) with (**1**) give the *S*-configuration at this position in the major products (**9b**) and (**11d**), while those of (**8a**) and (**8b**) with (**2**) afford the *R*-configuration at this centre in the products (**10a**) and (**12c**).

Two possible arrangements leading to (**9b**) and (**11d**) are shown in Figure 5a and two arrangements leading to (**10a**) and (**12c**) are shown in Figure 5b. The above results suggest that the facial selectivity of the furan relative to the cation is reversed by the presence of the 4-methoxy substituent. It seems likely on steric grounds that arrangements (i) and (iv) will be favoured. Indeed, by varying the groups on Si it may be possible to enhance the stereoselectivity observed. The position of the NTs group (X or Y) apparently has no effect on the relative orientation of the reactants.

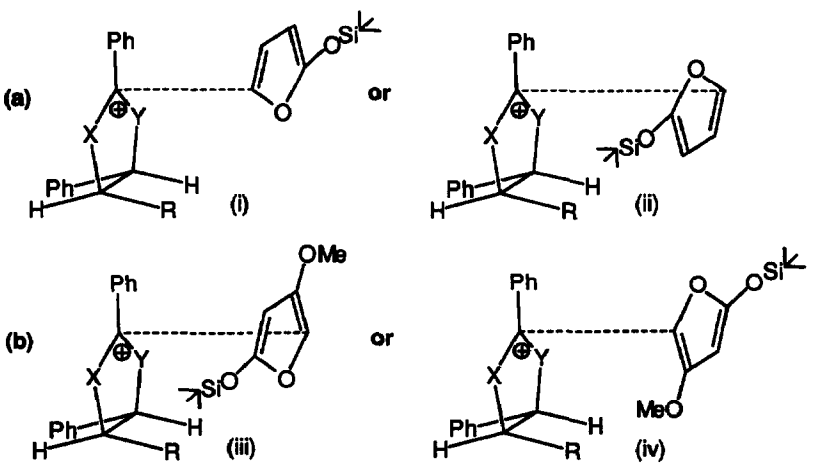
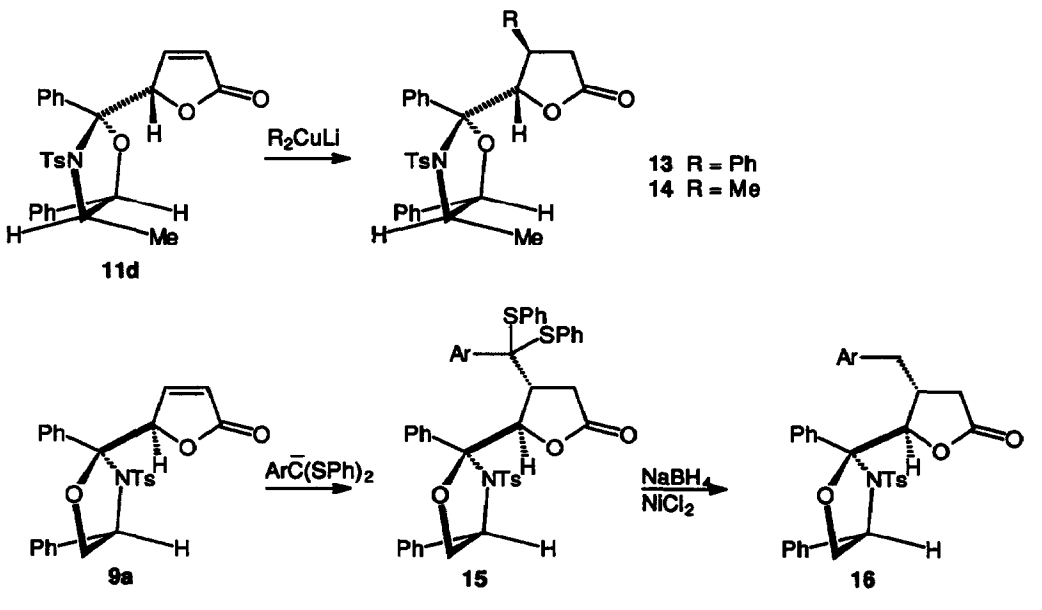


Figure 5 (R = H or Me)

Finally, we have made a preliminary study of the feasibility of conducting conjugate addition reactions of carbon nucleophiles on compounds (**11d**) and (**9a**). We initially studied the addition of $LiCuPh_2$ and $LiCuMe_2$ to compound (**11d**). As expected, and in line with our earlier work on related systems,[5,6] in both cases conjugate addition occurred *trans* to the original substituent on the five membered ring leading to the products (**13**) and (**14**) respectively (Scheme 5). However, the yield of these products was low. Attempts to use other simple organomagnesium and organocuprate reagents were unsuccessful giving in most cases complex mixtures of products. The reaction of the lithium derivative of 3,4-dimethoxybenzaldehyde bis(phenylthio)acetal with butenolide (**9a**) proceeded in 78% yield to give the *trans*-disubstituted butyrolactone (**15**). Furthermore, treatment of (**15**) with nickel boride[16] proceeded in 72% yield to give the related sulphur-free compound (**16**). The butenolides prepared in this paper therefore represent alternative, readily available starting materials for the asymmetric synthesis of natural products such as lignans.[17]



Ar = 3,4-dimethoxyphenyl

Scheme 5

Table 3. ^{1}H nmr spectra of (4a-c), (5a) and (5b).[a]

	(4a) (JHz)	(4b) (JHz)	(4c) (JHz)	(5a) (1st isomer) (JHz)	(5a) (2nd isomer) (JHz)	(5b)[b]
H-2	-	-	6.07s	-	-	-
H-4	5.04d(5.64)	4.64d(5.80)	4.63d(4.43)	4.87d(6.05)	4.92d(5.10)	4.82d(5.18)
H-5	4.78d(5.64)	4.86d(5.80)	4.95d(4.43)	4.77d(6.05)	4.85d(5.10)	4.77d(5.180
Pr^i	5.17sept(6.28) 5.04sept(6.24) 1.18d(6.24) 1.24d(6.28) 1.32d(6.28) 1.33d(6.24)	5.12sept(6.26) 1.30d(6.26) 1.31d(6.26)	5.12sept(6.24) 5.11sept(6.26) 1.30d(6.24) 1.29d(6.26)	5.16sept(6.26) 4.89sept(6.24) 1.08d(6.24) 1.14d(6.24) 1.28d(6.26) 1.29d(6.26)	5.18sept(6.26) 4.86sept(6.24) 1.04d(6.25) 1.14d(6.25) 1.32d(6.24) 1.33d(6.27)	5.12sept(6.24) 1.30d(6.24) 1.31d(6.24)
OEt	1.18t(7.11) 3.63q(7.11)	1.16t(7.07) 3.65q(7.07)	1.21t(7.05) 3.69q(7.05)	- -	- -	- -
Ph	7.33-7.70m	-	-	7.36-7.53m	7.34-7.50m	-
CH_3	-	1.66s	-	-	-	1.42s/1.51s
H-3'	-	-	-	6.13dd(2.03,5.77)	6.02dd(2.06,5.74)	6.22t/6.25t
H-4'	-	-	-	7.36dd(1.62,5.77)	7.27dd(1.60,5.74)	7.51t/7.54t
H-5'	-	-	-	5.32dd(1.62,2.03)	5.36dd(1.60,2.06)	5.11m

a) Spectra recorded in $CDCl_3$ solution.

b) Mixture of 2 diastereoisomers.

Table 4. ^{13}C nmr spectra of (4a-c), (5a) and (5b)[a]

	(4a)	(4b)	(4c)	(5a) (1st isomer)	(5a) (2nd isomer)	(5b)[b]
C-2	123.60	124.50	117.06	111.54	111.82	112.80/112.50
C-4	77.08	76.98	76.39	78.45	78.88	78.36/78.30
C-5	76.58	76.57	76.05	77.66	77.54	78.13/78.07
				69.87	70.30	70.23/70.12
	69.89	69.66	69.83	70.19	70.01	20.09
Pr^i	21.64	21.65	21.62	21.54	21.73	20.05
	21.52	21.72	21.68	21.41	21.51	
				21.26	21.31	-
OEt	14.94	15.02	14.94	-	-	-
	59.40	58.41	60.37	-	-	-
CO	168.24	168.37	168.41	167.47	167.96	168.25
	168.35	168.67	168.56	167.29	167.69	168.05
	126.54	-	-	126.39	126.61	-
Ph	128.10	-	-	128.01	127.96	-
	129.36	-	-	129.36	129.44	-
	136.53	-	-	136.30	135.83	-
CH_3	-	22.20	-	-	-	21.64
C-2'				172.12	172.31	172.43/172.35
C-3'				123.71	123.70	123.56/123.41
C-4'				151.14	151.78	152.78/151.91
C-5'				85.81	85.79	85.92/85.42

[a] Spectra recorded in $CDCl_3$ solution. [b] Mixture of 2 diastereoisomers.

Experimental

Infrared spectra were recorded on a Pye Unicam SP1050 spectrometer. Ultraviolet spectra were recorded on a Philips PU8720 scanning spectrometer. ^1H nmr spectra were recorded on a Bruker 250WM spectrometer at 250 MHz and, where indicated, a Hitachi Perkin-Elmer R24B spectrometer at 60 MHz. The high field spectra were recorded using Bruker spectrometers at 360 and 400 MHz. ^{13}C nmr spectra were recorded on a Bruker 250WM spectrometer at 62.5 MHz. All spectra used tetramethylsilane as the internal standard, and were run in deuterated chloroform, unless otherwise stated. The mass spectra were recorded on a VG-12-250 low resolution quadruple mass spectrometer, whilst accurate mass measurements were obtained on a ZAB-E, high resolution, double focusing mass spectrometer. Melting points were recorded on an Electrothermal digital melting point apparatus, and are uncorrected. Optical rotation values were obtained from a Perkin-Elmer 141 polarimeter, using a sodium lamp at 589 nm.

Analytical hplc work was carried out using a Milton Roy 3100 SpectroMonitor, 3100 constaMetric pump, CI-4100 integrator, and an Apex DP 5 μm column. Thin layer chromatography was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates. Flash chromatography was performed with sililca gel (Merck 9385, Kieselgel 60, 230-400 mesh). Small scale purifications were conducted on a chromatotron 7924 using 1mm, 2mm or 4mm plates prepared from silica gel (Merck 7749, Kieselgel 50 F_{254} gipshaltig).

Table 5. ^{1}H nmr spectra of (8a-c), (9a,b) and (10)-(16).[a]

	(8a)[b] (JHz)	(8b)[b] (JHz)	(8c) (JHz)	(9a) (JHz)	(9b) (JHz)	(10a) (JHz)
H-4	5.06m	(2.84dq(6.0,4.3) (3.93dq(6.0,7.6)	4.25m	5.17dd(6.87,7.85)	5.00m	5.32dd(6.86,7.74)
H-5	3.95m	(3.77d(4.3)	4.58d(5.4)	4.00dd(6.87,8.30)	4.04dd(7.19,9.08)	4.10dd(6.86,8.10)
	4.39m	(4.67d(7.6)		4.54dd(7.85,8.30)	4.41dd(7.82,9.08)	4.62dd(7.74,8.10)
Me(Ts)	2.15s/2.17s	2.25s/2.32s	2.32s/2.34s	2.23s	2.18s	2.18s
OMe	3.25s/3.28s	3.29s	3.74s	-	-	3.60s
Ar-H	6.82-7.79m	7.08-7.81m	6.89-7.82m	6.72-6.81m	6.64-6.70m	6.41-6.68m
				6.92-7.86m	6.84-7.85m	6.93-7.80m
CH_3-C_4	-	1.37d(6.0)	0.90d(6.7)	-	-	-
		1.78d(6.0)	1.00d(6.9)			
H-3'	-	-	-	6.16dd(2.08,5.79)	6.35dd(2.01,5.78)	5.15d(2.62)
H-4'	-	-	-	7.14dd(1.56,5.79)	8.08dd(1.58,5.78)	-
H-5'	-	-	-	6.77dd(1.56,2.08)	6.62dd(1.58,2.01)	6.52s

	(11d) (JHz)	(12c) (JHz)	(13) (JHz)	(14) (JHz)	(15) (JHz)	(16) (JHz)
H-4	3.58dq(9.10,5.98)	3.60dq(9.03,5.97)	3.65dd(9.15,5.95)	3.58dd(9.18,5.95)	4.42dd(8.75,7.25)	5.02m
H-5	5.00d(9.10)	4.97d(9.03)	5.02d(9.15)	4.89d(9.18)	3.62m	3.57m
					4.22dd(7.25,8.75)	4.51m
Me(Ts)	2.31s	2.28s	2.31s	2.32s	2.31s	2.21s
OMe	-	3.50s	-	-	3.86s,3.90s	3.71s,3.88s
Ar-H	6.83-6.95m	6.78-6.92m	6.81-6.95m	6.87ABq(8.30)	6.69-7.78m	6.73-7.51m
	7.30-7.59m	7.18-7.53m	7.06-7.60m	7.25-7.51m		
CH_3-C_4	1.59d(5.98)	1.58d(5.97)	1.58d(5.95)	1.50d(5.95)		-
-						
H-3'	6.12dd(2.03,5.82)	5.06d(0.70)	2.45dd(2.67,18.40)	2.02dd(1.75,17.95)	2.81dd(9.72,18.10)	2.92dd(8.11,17.92)
			3.12dd(10.45,18.40)	2.83dd(9.25,17.95)	3.08dd(0.87,18.10)	2.27m
H-4'	7.28dd(1.48,5.82)	-	3.44ddd(2.20,2.67,10.45)	2.38m	2.71d(9.72)	2.40m
H-5'	6.64dd(1.48,2.03)	6.33d(0.70)	6.06d(2.20)	5.62d(1.46)	6.31d(0.87)	6.32d(1.72)
CH_3-C_4'	-	-	-	1.52d(6.89)	-	-
CH_2-C_4'	-	-	-	-	-	2.56m

[a] Spectra recorded in $CDCl_3$ solution. [b] Mixture of 2 diastereoisomers.

Table 6. ^{13}C nmr spectra of (8a,b), (9a,b) and (10)-(16).[a,b]

	(8a)[c]	(8b)[c]	(9a)	(9b)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
C-2	113.17	114.49	98.12	99.01	98.62	96.24	97.04	99.33	99.24	104.59	102.48
	113.53	105.83									
C-4	62.12	62.16	63.65	63.98	63.96	61.16	61.01	60.60	59.31	64.20	64.29
	63.95	68.22									
C-5	71.29	85.16	73.39	74.86	75.98	87.42	87.86	87.27	86.19	73.43	74.42
	71.35	88.09									
CH_3(Ts)	20.96	18.64	21.29	21.23	21.22	21.43	21.35	21.40	20.40	21.56	21.26
	-	21.64									
OMe	50.98	49.25	-	-	59.54	-	59.55	-	-	55.87	55.57
	50.32	52.22								56.00	55.88
CH_3-C_4	-	14.26	-	-	-	17.24	17.14	17.08	20.02	-	-
	-	14.37									
C-2'	-	-	172.73	172.37	172.20	172.73	172.02	177.29	177.85	175.96	177.15
C-3'	-	-	86.27	85.36	82.33	87.98	82.16	37.58	28.65	32.86	35.02
C-4'	-	-	152.61	152.50	179.49	152.82	179.34	42.28	30.17	45.75	38.15
C-5'	-	-	122.73	124.47	90.10	123.44	90.36	90.28	88.85	80.30	85.20
CH_3-C_4'	-	-	-	-	-	-	-	-	15.95	-	-
CH_2-C_4'	-	-	-	-	-	-	-	-	-	73.51	40.80

a) Spectra recorded in $CDCl_3$ solution.
b) Aromatic Carbon atoms not listed.
c) Mixture of 2 diastereoisomers.

Preparation of diisopropyl (4*R*, 5*R*)-2-ethoxy-2-phenyl-2,3-dioxolan-4,5-dicarboxylate (4a).

A mixture of diisopropyl L-tartrate (11.7g, 60mmol), triethyl orthobenzoate[18] (56g, 250mmol, 5 mol equiv.) and a catalyic amount of concentrated H_2SO_4 was heated at 130°C for 3 hours under nitrogen. Anhydrous K_2CO_3 was added to neutralize the acid and the solution was filtered under nitrogen. The resulting mixture was fractionally distilled to give (4a) as a yellowish oil (14.64g, 80%), b.p. 148°C/0/01 mmHg; (Found: C, 62.28; H, 7.15. $C_{19}H_{26}O_7$ requires C, 62.31; H, 7.18%); *m/z* (EI) 321 (M-OEt) and (CI) 367 (M+H). See Tables 3 and 4 for ^1H and ^{13}C nmr data.

Preparation of diisopropyl (4*R*, 5*R*)-2-ethoxy-2-methyl-1,3-dioxolan-4,5-dicarboxylate (4b).

A mixture of diisopropyl L-tartrate (13g, 55mmol), triethyl orthoacetate (44.55g, 275mmol, 5 mol equiv.) and a catalytic amount of concentrated H_2SO_4 was heated at 130°C for 3 hours under nitrogen. Anhydrous K_2CO_3 was added to neutralize the acid and the solution was filtered under nitrogen. The resulting mixture was fractionally distilled to give (4b) as a colourless liquid (16.05g, 96%), b.p. 112°C/0.01 mmHg; (Found: C, 55.35; H, 7.99. $C_{14}H_{24}O_7$ requires C, 55.25; H, 7.94%); *m/z* (EI) 259 (M-OEt) and (CI) 305 (M+H). See Tables 3 and 4 for ^1H and ^{13}C nmr data.

Preparation of diisopropyl (4*R*, 5*R*)-2-ethoxy-1,3-dioxolan-4,5-dicarboxylate (4c).

A mixture of diisopropyl L-tartrate (15g, 64 mmol), triethyl orthoformate (47.36g, 320mmol, 5 mol equiv.) and a catalytic amount of concentrated H_2SO_4 was heated at 130°C for 3 hours under nitrogen. Anhydrous K_2CO_3 was added to neutralize the acid and the solution was filtered under nitrogen. The resulting mixture was fractionally distilled to give (4c) as a yellowish oil (18.9g, 88%), b.p. 100-104°C/0.01 mmHg; (Found : C, 53.85; H, 7.71. $C_{13}H_{22}O_7$ requires C, 53.79; H, 7.63%); *m/z* (EI) 245 (M-OEt) and (CI) 291 (M+H). See Tables 3 and 4 for ^1H and ^{13}C nmr data.

Preparation of 2-Trimethylsilyloxyfuran (1)[19].

A mixture of triethylamine (7.82g, 77.2mmol) and trimethylchlorosilane (8.11g, 74mmol) was added to pre-cooled (0°C) 2(5*H*)-furanone (6g, 71mmol) under nitrogen. The reaction mixture was allowed to stay at room temperature for 24h. After this time fractional distillation under reduced pressure afforded (1) with a small amount of triethylammonium chloride, which was removed by redistillation (9.11g, 82%), b.p. 44-46°C/15 mmHg (lit. 34.35°C/10 mmHg). ^1H nmr ($CDCl_3$) 6.60br, 6.00t(J=3.0Hz), 4.90dd (J=1.0, 3.0Hz), 0.27s.

Preparation of 2-Trimethylsilyloxy-4-methoxyfuran (2)[20,4].

Methyl tetronate (5.7g, 50mmol) in dry THF (100ml) was added to a stirred solution of n-butyllithium (20ml of a 2.5 M solution in hexane, 50mmol) in THF (200ml), under nitrogen at -78°C, over 5 min. The solution was stirred for a further 20 min, then used directly in the subsequent reaction.

To the solution of methyl 5-lithiotetronate (50mmol) was added trimethylchlorosilane (9.23g, 85mmol) in dry THF (10ml) over 3-4 min. through a cooled double ended needle. The reaction mixture was stirred for a further 1h at -78°C, then the solution was allowed to warm to room temperature. After stirring for 1h, the solvent was evaporated under reduced pressure in the absence of moisture. Dry pentane (120ml) was added and the precipitated lithium chloride was removed by filtration under nitrogen. Evaporation of the filtrate, followed by fractional distillation, gave the product (8.10g, 87%), b.p. 84°C/15 mmHg. The product was kept under nitrogen and never exposed to moisture. ^1H nmr ($CDCl_3$) 6.19d(J=2.0Hz), 4.72d(J=2.0Hz), 3.31s, 0.27s.

Preparation of (-)-(4*R*, 5*R*, 5'*S*)-and (+)-(4*R*, 5*R*, 5'*R*)-diisopropyl-2-(2'-oxo-2',5'-dihydro-5'-furyl)-2-phenyl-1,3-dioxolan-4,5-dicarboxylate (5a).

Anhydrous $ZnCl_2$ (1.08g, 8mmol) was loaded into a bent tube which was kept in drying pistol (105°C) overnight and cooled to room temperature under nitrogen, before being connected to the reaction flask. (4a) (3g, 8mmol) was dissolved in dry CH_2Cl_2 (20ml) and the anhydrous $ZnCl_2$ was introduced. The solution was cooled to -78°C and pre-cooled 2-trimethylsilyloxyfuran (2.42g, 16mmol, 2 mol equiv.), dissolved in dry CH_2Cl_2 (10ml), was added *via* a double ended needle. After stirring the reaction mixture at -78°C for 7 hours, anhydrous K_2CO_3 was added, the solution was filtered under nitrogen and evaporated, to afford a yellow gum. Purification by flash chromatography

on neutral silica (Et_2O/petroleum spirit) afforded (**5a**) as a white solid (1.78g, 55%). ^1H nmr indicated two isomers in a 35:65 ratio, and these were subsequently separated by fractional crystallisation using Et_2O and Et_2O-petroleum spirit.

1st isomer: m.p. 112°C. $[\alpha]_D^{20}$: -63.4 (c=0.858, $CHCl_3$); (Found: C, 62.39; H, 6.10. $C_{21}H_{24}O_8$ requires C, 62.37; H, 5.94%); IR (KBr): 1760 (C=O), (C=C) 1615 cm^{-1} ; See Tables 3 and 4 for ^1H and ^{13}C nmr data. *m/z* (EI) 321(78), 237(71), 105(100%). *m/z* (CI) 422 ($M+NH_4$, 27), 405 (M+H, 3%). HRMS 422.1815 ($M+NH_4$). $C_{21}H_{24}O_8$ requires 422.1815.

2nd isomer: m.p. 80°C. $[\alpha]_D^{20}$: +55.8 (c=0.634, $CHCl_3$); (Found: C, 62.32; H, 5.92. $C_{21}H_{24}O_8$ requires C, 62.37; H, 5.94%); IR (KBr): 1770 (C=O), 1605 (C=C)cm^{-1}; See Tables 3 and 4 for ^1H and ^{13}C nmr data. *m/z* (EI) 321(73), 237(53), 105(100%). *m/z* (CI) 422 ($M+NH_4$, 81), 405 (M+H, 9%). HRMS 422.1815 ($M+NH_4$). $C_{21}H_{24}O_8$ requires 422.1815.

Preparation of (4*R*, 5*R*, 5'*RS*)-diisopropyl-2-(2'-oxo-2',5'-dihydro-5'-furyl)-2-methyl-1,3-dioxolan-4,5-dicarboxylate (5b).

Anhydrous $ZnCl_2$ (0.544g, 4mmol) was loaded into a bent tube which was kept in drying pistol (105°C) overnight and cooled to room temperature under nitrogen, before being connected to the reaction flask. (**4b**) (1.216g, 4mmol) was dissolved in dry CH_2Cl_2 (10ml) and the anhydrous $ZnCl_2$ was introduced. The solution was cooled to -78°C and pre-cooled 2-trimethylsilyloxyfuran (1.248g, 8mmol, 2 mol equiv.), dissolved in dry CH_2Cl_2 (10 ml), was added *via* a double ended needle. After stirring the reaction mixture at -78°C for 7 hours, anhydrous K_2CO_3 was added, the solution was filtered under nitrogen and evaporated, to afford yellow gum. Purification by flash chromatography on neutral silica (Et_2O/petroleum spirit) afforded (**5b**) as a white solid. (0.534g, 39%). ^1H nmr indicated that (**5b**) was a mixture of two isomers (43:57 ratio). m.p. 68-70°C. (Found: C, 56.21; H, 6.52. $C_{16}H_{22}O_8$ requires C, 56.14; H, 6.43%); IR (KBr): 1775 (C=O), 1600 (C=C) cm^{-1} ; See Tables 3 and 4 for ^1H and ^{13}C nmr data. *m/z* (EI) 259(35), 217(13), 175(37%). *m/z* (CI) 360 ($M+NH_4$, 63), 343 (M+H, 11%). HRMS 360.1660 ($M+NH_4$). $C_{16}H_{22}O_8$ requires 360.1661.

Preparation of (-)-N-tosyl-2-(*R*)-phenylglycinol (7a).[21]

To a solution of (-)-(*R*)-phenylglycinol (**6a**)[22] (3.68g, 26.8mmol) and triethylamine (4.1ml, 30mmol) in CH_2Cl_2 (30ml), *p*-toluenesulfonyl chloride (5.71g, 30mmol), dissolved in CH_2Cl_2 (20ml) was added at 0°C and the solution stirred for 24h at this temperature. The reaction mixture was diluted with CH_2Cl_2 (60ml), washed with 2N aq. H_2SO_4, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised from Et_2O to give white crystals (6.38g, 82%). m.p.103-104°C; $[\alpha]_D^{20}$: -85.5 (c=1.052, $CHCl_3$); *m/z* (CI) 292 (M+H), 309 ($M+NH_4$). HRMS 309.1273 ($M+NH_4$). $C_{15}H_{17}NSO_3$ requires 309.1273. IR (KBr): 3485 (OH), 3310 (NH), 1320 and 1160 (NH), 1320 and 1160 (SO_2) cm^{-1}. ^1H nmr ($CDCl_3$) 7.04-7.59m(ArH), 6.14d(J=7.2Hz, NH), 4.44dd(J=5.8, 7.2Hz, CH), 3.70d(J=5.8Hz, CH), 3.02br (OH), 2.32s (Ts). ^{13}C nmr ($CDCl_3$) 21.43(Ts), 59.78(C1), 6607(C2), 126.89, 127.09, 127.65, 128.41, 129.36, 137.09, 137.53, 132.17(arom).

Preparation of (2*R*, 4*R*)-2-methoxy-2,4-diphenyl-3-(4-methylbenzenesulfonyl-1,3-oxazolidine (8a).

Method:A

To a mixture of N-tosyl-phenylglycinol (**7a**) (5.1g, 17.5mmol) and trimethyl orthobenzoate[18] (3.64g, 51.4mmol) in xylene (80ml), a catalytic amount of *p*-toluenesulfonic acid was added. The reaction mixture was refluxed for 4 days with a soxhlet apparatus, filled with solid $LiAlH_4$ or 4A molecular sieves, placed between the flask and the reflux condenser. Solid K_2CO_3 was added, the solution filtered and solvent evaporated under reduced pressure. The resulting mixture was purified by flash chromatography on silica to give a colourless gum (5.72g, 80%).

Method:B

N-Tosyl-phenylglycinol (**7a**) (1.06g, 3.76mmol) was dissolved in trimethyl orthobenzoate[18] (40g, 220mmol) and methanesulfonic acid (0.036g, 0.376mmol) was added. The reaction mixture was stirred for 24 hours at room temperature, and for 2h at 130°C. Solid K_2CO_3 was added and the

solution filtered with the exclusion of moisture. Excess trimethyl orthobenzoate was recovered by fractional distillation and residue was purified by flash chromatography on silica (EtOAc/petroleum spirit) to give a colourless gum (1.3g, 85%). IR (neat): 1360 and 1160 cm^{-1} (SO_2). See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* 409 (M^+, 3), 378 (M-OMe, 100), 118(48), 105(33), 91(97%). HRMS 409.1360 (M^+). $C_{23}H_{23}NSO_4$ requires 409.1361.

Preparation of N-tosyl-(1*R*, 2*R*)-norpseudoephedrine (7b).

To a suspension of (-)-(1*R*,2*R*)-norpseudoephedrine (**6b**) hydrochloride (1.82g, 15mmol) and triethylamine (4.5, 33mmol) in CH_2Cl_2 (40ml) at 0°, *p*-toluenesulfonyl chloride (3.15g, 16.5mmol), dissolved in CH_2Cl_2 (25ml) was slowly added the stirring continued for 14 hours. After aqueous work-up (60ml of water, followed by 60ml of saturated aq. NaCl), the organic phase was dried with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was crystallised from CH_2Cl_2/Et_2O to give the product (3.58g, 78%). m.p. 118-120°C (lit. 119°C); $[\alpha]_D^{20}$: -39.9 (c=1.013, $CHCl_3$). HRMS 306.1164 (M+H). $C_{16}H_{19}NSO_3$ requires 306.1164. IR(KBr): 3490 (OH), 1315 and 1150 (SO_2) cm^{-1} . ^1H nmr ($CDCl_3$) 7.17-7.64m(ArH), 5.34d(J=7.7Hz, NH), 4.43dd(J=6.6, 3.1Hz, PhC*H*), 3.39m(MeC*H*), 3.20d(J=3.1Hz, OH), 2.38s(Ts), 0.90d(J=6.6Hz, Me). ^{13}C nmr ($CDCl_3$) 21.49(Ts), 17.84(Me), 55.72(C1), 76.92(C2), 126.74, 126.97, 127.91, 128.31, 129.65, 137.29, 140.41, 143.26(arom).

Preparation of (2*RS*,4*R*,5*R*)-2-methoxy-2,5-diphenyl-3-(4-methylbenzenesulfonyl)-4-methyl-1,3-oxazolidine (8b).

Method:A

To a mixture of N-tosyl-norpseudoephedrine (**7b**) (5g, 16mmol) and trimethyl orthobenzoate[18] (3.45g, 19mmol) in xylene (80ml), a catalytic amount of *p*-toluenesulfonic acid was added. The reaction mixture was refluxed for 3 days with a Soxhlet apparatus, filled with solid $LiAlH_4$ or 4A molecular sieves, placed between the flask and reflux condenser. Solid K_2CO_3 was added, the solution filtered, and the solvent evaporated under reduced pressure. The resulting mixture was purified by flash chromatography to give a white gum (4.80g, 71%).

Method:B

N-Tosyl-norpseudoephedrine (**7b**) (2.06g, 6.75mmol) was dissolved in trimethyl orthobenzoate[18] (85g, 0.467mol) and methanesulfonic acid (0.09g, 0.945mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. Solid K_2CO_3 was added and the solution filtered with the exclusion of moisture. Excess trimethyl orthobenzoate was recovered by fractional distillation and the residue was purified by flash chromatography (Et_2O/petroleum spirit) to give a white gum (2.25g, 79%). IR (film): 1355 and 1160 cm^{-1}. See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 392(M-OMe, 53), 288(7), 155(18), 132(100), 105(24), 91(24%). HRMS 392.1320 (M-OMe). $C_{23}H_{22}NSO_3$ requires 392.1320.

Preparation of N-tosyl-(1*R*,2*S*)-norephedrine (7c).[13]

To a solution of L-norephedrine (**6c**) (10g, 6.6mmol) and triethylamine (7.08g, 70mmol, 9.8ml) in dry ether (300ml), p-toluenesulphonyl chloride (17.35g, 90mmol) was added the the reaction mixture was refluxed for 30 min. The precipitated solid was filtered off, the solution poured onto crushed ice and acidified with dil. HCl. The organic phase was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil (19.24g). Purification by flash chromatography on silica (200g) followed by recrystallisation from ether-petroleum ether gave white crystals (14.7g, 73%), m.p. 87-89° (lit.[13], m.p. 86-88°). ^1H nmr ($CDCl_3$) 7.16-7.78m(ArH), 5.53d(J=8.4Hz, NH), 4.80d(J=3.0Hz, PhC*H*), 3.50-3.54m(MeC*H*), 3.35br(OH), 2.37s(Ts), 0.79d(J=6.8Hz, Me). ^{13}C nmr ($CDCl_3$) 21.49(Ts), 14.14(Me), 55.04(C1), 75.69(C2), 126.03, 127.00, 127.91, 128.21, 129.74, 137.65, 140.41, 143.41(arom).

Preparation of (2*RS*,4*R*,5*S*)-2-methoxy-2,5-diphenyl-3-(4-methylbenzenesulfonyl)-4-methyl-1,3-oxazolidine (8c).

To a solution of N-tosyl-norephedrine (**7c**) (0.5g, 1.72mmol) in dry benzene (12.5ml) was added trimethyl orthobenzoate[18] (0.9ml, 5.23mmol) and a bypassed dropping funnel fitted with 4Å molecular sieves was interposed between the flask and the reflux condenser. After 30 min refluxing pyridinium

tosylate (133mg, 0.53mmol) dissolved in CH_2Cl_2 (1ml) was added and the resulting mixture was refluxed for 5h. The solution was cooled and the solvent evaporated under reduced pressure. Flash chromatography of the crude product gave only 16% of desired product (**8c**), which could not be fully characterised because of impurities. See Tables 5 and 6 for ^1H and ^{13}C nmr data.

Preparation of (-)-(2*S*,4*R*,5'*R*)- and (-)-(2*S*,4*R*,5'*S*)-2-(2'-oxo-2',5'-dihydro-5'-furyl)-2,5-diphenyl-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (9a) and (9b).

1,3-Oxazolidine (**8a**) (7.50g, 18.3mmol) was dissolved in dry CH_2Cl_2 (20ml) and 2-trimethylsilyloxyfuran (5.72g, 36.67mmol, 2 equiv.) was added using a syringe. The solution was cooled down to -78°C and pre-cooled $BF_3.Et_2O$ (5.20g, 36.67mmol, 2 equiv.) in dry CH_2Cl_2 (10ml) was introduced *via* a double-ended needle, The reaction mixture was then stirred at -78°C for 4 hours, when solid K_2CO_3 was added. The solution was filtered under nitrogen and the solvent evaporated. Purification of the residue by flash chromatography on neutral silica (EtOAc/petroleum spirit) afforded (**9a**) and (**9b**) (ratio 1:2) (5.23g, 62%).

(**9a**): m.p. 88°C. $[\alpha]_D^{20}$ = -12.7 (c=1.018, $CHCl_3$); (Found : C, 67.60; H, 4.95; N, 2.98. $C_{26}H_{23}O_5NS$ requires C, 67.67; H, 5.01; N, 3.03%); IR (KBr): 1755 (C=O), 1600 (C=C) cm^{-1} . See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 378(23), 274(12), 155(44), 118(18), 105(32), 91(100%). *m/z* (CI) 479($M+NH_4$, 100), 461(M+H, 19%). HRMS 479.1641($M+NH_4$). $C_{26}H_{23}NSO_5$ requires 479.1641.

(**9b**): $[\alpha]_D^{20}$ = -102.9 (c=1.02, $CHCl_3$); (Found C, 67.63; H, 4.98; N, 3.02. $C_{26}H_{23}O_5NS$ requires C, 67.67; H, 5.01; N, 3.03%); IR (neat) : 1745 (C=O), 1590 (C=C) cm^{-1} . See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 378(8), 274(19), 155(28), 118(52), 105(36), 91(100%). *m/z* (EI) 378(8), 274(19), 155(28), 118(52), 105(36), 91(100%). *m/z* (CI) 479($M+NH_4$, 48), 462(M+H, 10%). HRMS 479.1641 ($M+NH_4$). $C_{26}H_{23}NSO_5$ requires 479.1641.

Preparation of (-)-(2*R*, 4*R*, 5'*S*)-2-(2'-oxo-4'-methoxy-2',5'-dihydro-5'-furyl)-2,5-diphenyl-3-(4-methylbenzenesulfonyl)-1,3-oxazolidine (10a).

1,3-Oxazolidine (**8a**) (0.424g, 1.03mmol) was dissolved in dry CH_2Cl_2 (2ml) and 2-trimethylsilyloxy-4-methoxyfuran (0.3831g, 2.06mmol, 2 equiv.) was added using a syringe. The solution was cooled to -78°C and pre-cooled $BF_3.Et_2O$ (0.2933g, 2.06mmol, 2 equiv.) in dry CH_2Cl_2(10ml) was introduced *via* a double-ended needle, The reaction mixture was then stirred at -78°C for 3.5h. After this time solid K_2CO_3 was added, the solution was filtered under nitrogen and solvent evaporated. Purification of the residue by flash chromatography on neutral silica (EtOAc/petroleum spirit) afforded (**10a**) as a colourless foam (0.189g, 37.5%). IR (KBr): 1745 (C=O), 1620 (C=C) cm^{-1} ; (Found: C, 65.88; H, 5.03; N, 2.79. $C_{27}H_{25}O_6NS$ requires C, 65.98; H, 5.12; N, 2.84%); $[\alpha]_D^{20}$ = -23.95 (c=1.002, $CHCl_3$). See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 378(17), 274(13), 155(35), 118(15), 105(22), 91(100%). *m/z* (CI) 509($M+NH_4$, 43), 492(M+H, 8%). HRMS 509.1750 ($M + NH_4$). $C_{27}H_{25}NSO_6$ requires 509.1751.

Preparation of (-)-(2*R*,4*R*,5*R*,5'*S*)-2-(2'-oxo-2',5'-dihydro-5'-furyl)-2,5-diphenyl-3-(4-methylbenzenesulfonyl)-4-methyl-1,3-oxazolidine (11d).

1,3-Oxazolidine (**8b**) (5.47g, 12.93mmol) was dissolved in dry CH_2Cl_2 (20ml) and 2-trimethylsilyloxyfuran (4.034g, 25.86mmol, 2 equiv.) was added using a syringe. The solution was cooled to -78°C for 3h and pre-cooled $BF_3.Et_2O$ (3.66g, 25.86mmol, 2 equiv.) in dry CH_2Cl_2 (10ml) was introduced *via* a double-ended needle. After this time solid K_2CO_3 was added, the solution was filtered under nitrogen and solvent evaporated. Purification of the residue by flash chromatography on neutral silica (EtOAc/petroleum spirit) and subsequent crystallisation afforded (**11d**) as colourless crystals (3.02g, 49.2%). m.p. 145-147°C. IR (KBr): 1760 (C=O), 1605 (C=C) cm^{-1} ; (Found : C, 67.68; H, 5.06; N, 2.71. $C_{27}H_{25}O_5NS$ requires C, 68.16; H, 5.29; N, 2.90%); $[\alpha]_D^{20}$ = -129.3 (c=1.03, $CHCl_3$); See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 392(22), 288(18), 155(31), 132(34), 105(100), 91(77%). *m/z* (CI) 493($M+NH_4$, 39), 476(M+H, 4%). HRMS 493.1797 ($M+NH_4$). $C_{27}H_{25}NSO_5$ requires 493.1797.

Preparation of (-)-2*R*,4*R*,5*R*,5'*R*)-2-(2'-oxo-4'-methoxy-2',5'-dihydro-5'furyl)-2,5-diphenyl-3-(4-methylbenzenesulfonyl)-4-methyl-1,3-oxazolidine (12c).

1,3-Oxazolidine (**8b**) (0.5513g, 1.3mmol) was dissolved in dry CH_2Cl_2 (2ml) and 2-trimethylsilyloxy-4-methoxyfuran (0.4836g, 2.6mmol, 2 equiv.) was added using a syringe. The solution was cooled down to -78°C and pre-cooled $BF_3.Et_2O$ (0.369g, 2.6mmol, 2 equiv.) in dry CH_2Cl_2 (1ml) was introduced *via* a double-ended needle. The reaction mixture was then stirred at -78°C for 3h. After this time solid K_2CO_3 was added, the solution was filtered under nitrogen and solvent evaporated. Purification of the residue by flash chromatography on neutral silica (EtOAc/petroleum spirit) and subsequent crystallisation afforded (**12c**) as a colourless foam (0.3203g, 48.8%). IR (KBr) : 1760 (C=O), 1635 (C=C) cm^{-1} ; (Found: C, 66.12; H, 5.30; N, 2.70. $C_{28}H_{27}O_6NS$ requires C, 66.53; H, 5.37; N, 2.76%); $[\alpha]_D^{20}$ = -93.62 (c=0.998, $CHCl_3$). See Tables 5 and 6 for ^1H +and ^{13}C nmr data. *m/z* (EI) 392(37), 288(3), 155(40), 105(100), 91(68%). *m/z* (CI) 523($M+NH_4$, 45), 506(M+H, 4%). HRMS 523.190 ($M+NH_4$). $C_{28}H_{27}NSO_6$ requires 523.1901.

Preparation of Ph_2CuLi.

From CuI

To a stirred suspension of CuI (0.599g, 3.14mmol) in dry ether (8ml), phenyllithium (6.28mmol, 3.48ml, 1.8M solution in hexane) was added dropwise at -20°C under nitrogen. The solution was stirred for 20 min. at this temperature, then used directly for the conjugate addition reaction.

From Me_2SCuBr.

To a colourless solution of $Me_2S.CuBr$ (1.297g, 6.32mmol) in Me_2S (8ml) and dry ether (8ml), phenyllithium (7.01ml, 12.62mmol, 1.8M solution in hexane) was added dropwise at -20°C. The solution was stirred for 20 min. at this temperature, then used directly for the conjugate addition reaction.

Preparation of (13).

To the green solution of lithium diphenylcuprate (6.32mmol, 5 mol equiv.), pre-cooled (**11d**) (0.6g, 1.263mmol) in dry THF (4ml) was added at -78°C. The reaction mixture was allowed to warm to room temperature over 4h, and then quenched by adding saturated NH_4Cl (5ml). The resulting mixture was filtered on celite and the aqueous phase extracted with CH_2Cl_2 (3 x 10ml). The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc/petroleum spirit) to afford (**13**) as a colourless foam (0.223g, 32%). $[\alpha]_D^{20}$ = + 19.53 (c = 0.998, $CHCl_3$); (Found: C, 71.14; H, 5.59; N, 2.48. $C_{33}H_{31}O_5SN$ requires C, 71.59; H, 5.64; N, 2.52%); IR (neat): 1775 cm^{-1} (γ-lactone). See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 392(86), 288(44), 155(57), 105(100), 91(91%). *m/z* (CI) 571 ($M+NH_4$, 15%). HRMS 571.227 ($M+NH_4$). $C_{33}H_{31}NSO_5$ requires 571.2271.

Preparation of (14).

To a suspension of CuI (0.844g, 4.435mmol) in dry Et_2O (8ml), methyllithium (11.90ml, 8.87mmol, 0.745M solution in hexane) was added dropwise at -20°C. The solution was stirred for 20 min. at this temperature, then used directly for the subsequent addition reaction.

To a solution of (**11d**) (0.421g, 0.887mmol) in dry THF (8ml), freshly distilled $BF_3.Et_2O$ (0.629g, 4.35mmol) was added at -100°C, and stirred for 15 min. at this temperature. This solution was transferred to a pre-cooled suspension of CuMe at -100°C. The reaction mixture was stirred for 7.5h, while it was warmed to room temperature, and then quenched by adding saturated NH_4Cl (5ml). The resulting mixture was filtered on celite and aqueous phase extracted with CH_2Cl_2 (3 x 10ml). The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc/petroleum spirit) to afford (**14**) as a colourless foam (0.089g, 20.5%). $[\alpha]_D^{20}$ = -5.41 (c = 0.998, $CHCl_3$); (Found: C, 68.08; H, 5.82; N, 2.79. $C_{28}H_{29}O_5SN$ requires C, 68.41; H, 5.94; N, 2.84%); IR (neat): 1760 cm^{-1} (γ-lactone). See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 392(83), 288(12), 155(32), 105(100), 91(72%). *m/z* (CI) 509 ($M+NH_4$, 15%). HRMS 509.2110 ($M+NH_4$). $C_{28}H_{29}NSO_5$ requires 509.2110.

Preparation of (15).

3,4-Dimethoxybenzaldehyde bis(phenylthio)acetal (0.3312g, 0.9mmol) was dissolved in dry THF (5ml), under a nitrogen atmosphere, and taken down to -78°C. To this was added, *via* syringe, n-BuLi (0.55ml of 1.05M, 1.08mmol, 1.2 equiv.). Stirring was continued at -78°C for 2h. After this time, pre-cooled (**9a**) (0.539g, 1.17mmol, 1.3 equiv.), dissolved in dry THF (2ml), was added *via* a double-ended needle to the orange solution. Stirring was continued at -78°C for 2h before quenching by adding aqueous NaCl (2ml). The reaction was allowed to warm to room temperature before extracting with CH_2Cl_2 (2 x 20ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated, yielding a yellow foam. Purification of this by flash chromatography on silica (EtOAc/Petroleum spirit) afforded (**15**) as a colourless foam (0.581g, 78%). $[\alpha]_D^{20}$ = -6.45 (c = 0.604, $CHCl_3$); (Found: C, 67.89; H, 5.01; N, 1.60. $C_{47}H_{43}O_7S_3N$ requires C, 68.09; H, 5.10; N, 1.68%); IR (neat): 1750 cm^{-1} (γ-lactone). See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 720 (M-SPh, 100), 612 (M-SPh-PhSH, 12), 378 (41%). *m/z* (FAB) 852 (M+Na, 9%). HRMS 852.2094 (M+Na). $C_{47}H_{43}NS_3O_7$ requires 852.2094.

Preparation of (16).

The addition product (**15**) (0.2045g, 0.2469mmol) was dissolved in MeOH (50ml), and $NiCl_2.6H_2O$ (1.373g, 4.938mmol, 20 mol equiv.) was added. The stirred green solution was taken down to 0°C and $NaBH_4$ (0.5604g, 14.84mmol, 60 mol equiv.) was added carefully, in order to minimise the effervescence produced. The black suspension was then removed from the ice bath and thoroughly stirred for 1.5h at room temperature. After this time, water (10ml) was added and the mixture was passed through a short celite column to remove the nickel salts. Water (30ml) was added to the resulting solution and diethyl ether (3 x 30ml) used for the extraction. The combined organic layers were dried ($MgSO_4$), filtered and evaporated, yielding a yellow foam. Purification of this by flash chromatography on silica (EtOAc/petroleum spirit) afforded (**16**) as a colourless foam (0.108g, 72%). $[\alpha]_D^{20}$ = -13.62 (c = 0.756, $CHCl_3$); (Found: C, 68.35; H, 5.62; N, 2.24. $C_{35}H_{35}O_7SN$ requires C, 68.44; H, 5.70; N, 2.28%); IR (neat): 1770 cm^{-1} (γ-lactone). See Tables 5 and 6 for ^1H and ^{13}C nmr data. *m/z* (EI) 378(65), 91(77%). *m/z* (CI) 631 ($M+NH_4$, 100), 458 (M-Ts, 47%). HRMS 631.248 ($M+NH_4$). $C_{35}H_{35}NSO_7$ requires 631.2481.

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