Sulfone-mediated synthesis of substituted furans on solid support

Elena A. Arvanitis, Donald Craig,* and Andreas P. Timm

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, U.K.
E-mail: d.craig@ic.ac.uk

Dedicated with respect and friendship to Professor James R. Bull on the occasion of his retirement from the Mally Chair of Organic Chemistry at the University of Cape Town

Abstract

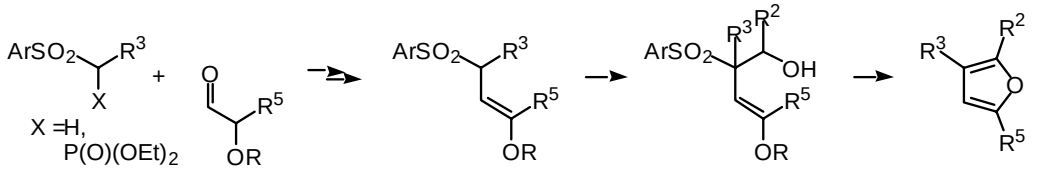
The polymer-supported synthesis of 2,5-disubstituted furans using a traceless linker strategy is described. Deprotonation of a Merrifield resin-bound methyl aryl sulfone followed by reaction with diethyl chlorophosphate furnishes a phosphonate, the lithio-derivative of which reacts *in situ* with α-methoxyaldehydes to yield vinylsulfones. Base-mediated isomerisation to the allylsulfones followed by reaction of the derived anions with aldehydes gives alcohols; trifluoroacetic acid treatment provides 2,5-disubstituted furans with concomitant cleavage from the solid support.

Keywords: Sulfone, traceless linker, furan, enol ether, carbanion

Introduction

One of the central thrusts of solid-phase synthesis involves the design of reaction sequences which allow the 'traceless' cleavage of the product from the polymeric material on which it was elaborated.[1] Reactions which have been adapted to serve this purpose are inter- and intramolecular addition–elimination sequences,[2] Wittig reactions,[3] desilylation,[4] reductive desulfurisation[5] and ring-closing olefin metathesis,[6] and methods have been developed also which provide the opportunity for a further diversification step involving C–C bond formation to be carried out during the cleavage reaction.[7] Despite the rich and varied solution-phase chemistry of sulfone carbanions, there have been relatively few reports concerned with the deployment of these reactive intermediates on the solid phase[8] and we were keen to adapt some of the sulfone chemistry developed in our own laboratory for use on solid support. The goals of our study at the outset were twofold: (i) to realise a sulfone carbanion-mediated, solid-supported synthesis of furans using the traceless linker strategy, and (ii) to gain some insights into the accessibility and usefulness of such highly reactive, basic carbanionic species in this potentially demanding

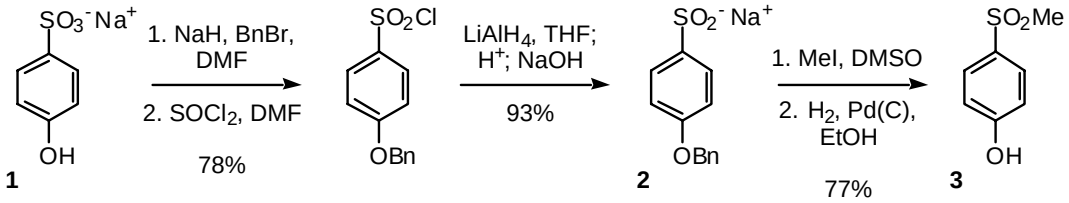
reaction medium. We had shown previously that readily-available lithiated alkoxyallyl aryl sulfones could be combined with aldehydes to give alcohols, which upon acid treatment underwent cyclisation with loss of arylsulfinic acid and concomitant aromatisation to give substituted furans (Scheme 1).[9] We reasoned that if the sulfone moiety could be harnessed both to provide attachment to the solid phase and to serve as an anion-stabilising and leaving group, then the proposed traceless linker strategy would be viable. This paper reports our findings.



Scheme 1. Solution-phase synthesis of substituted furans.[9]

Results and Discussion

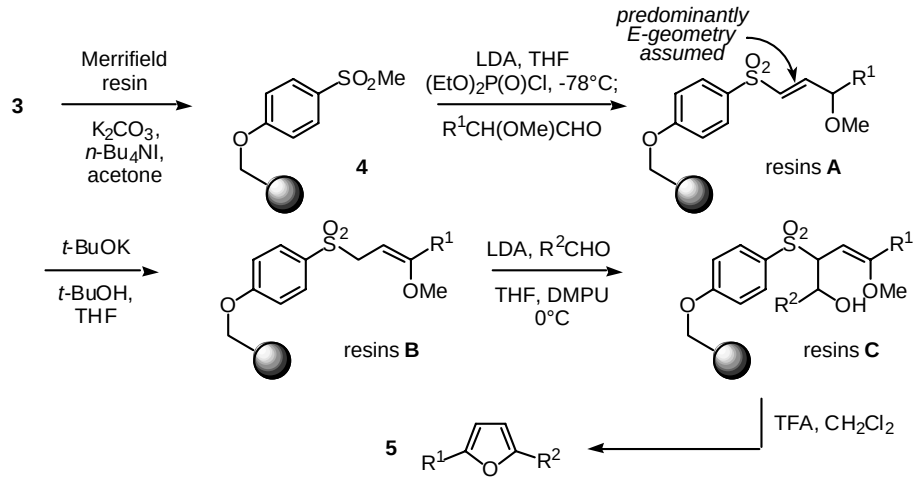
In order to modify our methodology for use on solid phase we elected to attach the aryl methyl sulfone to Merrifield resin using an ether linkage. We were keen to minimise the number of synthetic operations carried out on solid support prior to deploying the furan-forming sequences, and to this end (4-hydroxyphenylsulfonyl)methane was synthesised in solution-phase from commercially available[10] 4-hydroxyphenylsulfonic acid sodium salt **1** in five steps according to the sequence depicted in Scheme 2. Thus, formation of the disodium salt of **1** followed by *in-situ* monobenzylation gave the corresponding ether. This was converted in almost quantitative yield into the sulfonyl chloride,[11] which was subjected to reduction with lithium aluminium hydride; acidification of the reaction mixture and extraction into 2M aqueous NaOH gave the desired *para*-substituted sodium phenylsulfinate **2**, again in excellent yield. Finally, *S*-methylation and hydrogenolytic removal of the benzyl group gave (4-hydroxyphenylsulfonyl)methane **3**[12] in 56% overall yield from **1**.



Scheme 2. Synthesis of (4-hydroxyphenylsulfonyl)methane.

In order to carry out the furan-forming sequence using a polystyrene support, compound **3** was attached directly to Merrifield resin to give the corresponding resin-bound

(arylsulfonyl)methane **4**. This reaction was conveniently followed by tlc monitoring of the disappearance of (4-hydroxyphenylsulfonyl)methane from the liquid phase of the reaction mixture. The resulting resin was characterised by elemental combustion analysis, which indicated a loading of *ca.* 97% of available sites based on the cited assay, and by single-bead reflectance infrared spectroscopy, which showed the characteristic S=O symmetric and asymmetric stretching vibrational modes. Deprotonation of this resin with LDA followed by addition of diethyl chlorophosphate to the dark orange-coloured resin suspension caused a colour change to dark yellow, indicative of the formation of the carbanionic species stabilised by the sulfonyl and phosphonyl groups. Addition of 2-methoxyaldehydes[9] followed by work-up gave modified resins (resins **A**; see Experimental section), which were isolated and subsequently treated with potassium *tert*-butoxide in THF to effect isomerisation to the alkoxyallyl aryl sulfones supported on resin (resins **B**). Initially, hydroxyalkylation was effected as in the previous solution-phase studies, by the addition of strong base at low temperature to resins **B** pre-swollen in THF, followed by quenching of the anions by the addition of aldehydes R^2CHO. It was found subsequently that the reactions could be carried out at 0°C without any diminution in yield. Optimum conversion to hydroxyalkylated resins **C** was observed when DMPU was included in the reaction medium. Lastly, treatment of resins **C** with two equivalents of trifluoroacetic acid[13] in dichloromethane at ambient temperature effected the formation and release into solution of 2,5-disubstituted furans **5**; no purification other than simple removal of solvents under reduced pressure was necessary. The sequence was deployed in the preparation of a small library of 2,5-disubstituted furans. Different R^1 substituents were introduced by varying the 2-methoxyaldehydes used in the Horner–Wadsworth–Emmons reaction; commercially available aldehydes R^2CHO were used in the hydroxyalkylation step. The overall yield of furans based on the calculated initial loading of the Merrifield resin ranged from 13-32% (Scheme 3, Table).



Scheme 3. Solid-phase synthesis of 2,5-disubstituted furans **5**.

Table 1. Synthesis of a 14-member library of 2,5-disubstituted furans **5**

Entry	R^1	R^2	Yield of furan (%)
a	C_6H_{13}	$C_{11}H_{23}$	22
b	C_6H_{13}	$CH_2CH(CH_3)_2$	27
c	C_6H_{13}	3-pyridyl[a]	13
d	C_6H_{13}	4-pyridyl[a]	13
e	C_6H_{13}	$4\text{-}NCC_6H_4$	16
f	*cyclo*-C_6H_{11}	$CH_2CH(CH_3)_2$	20
g	*cyclo*-C_6H_{11}	$4\text{-}ClC_6H_4$	23
h	*cyclo*-C_6H_{11}	$4\text{-}BrC_6H_4$	20
i	*cyclo*-C_6H_{11}	3-pyridyl[a]	17
j	Ph	$C_{11}H_{23}$	26
k	Ph	$CH_2CH(CH_3)_2$	28
l	$4\text{-}BrC_6H_4$	C_6H_{13}	20
m	$4\text{-}BrC_6H_4$	$C_{11}H_{23}$	25
n	$4\text{-}BrC_6H_4$	$CH_2CH(CH_3)_2$	32

In summary, we have shown that the (4-alkoxyphenylsulfonyl)alkyl groups serve as effective active linkers in the traceless synthesis of 2,5-disubstituted furans, and that relatively basic and highly nucleophilic sulfone-stabilised carbanions are viable entities when immobilised on Merrifield resin.

Experimental Section

General Procedures. ^1H Nmr spectra were recorded in $CDCl_3$ on either Jeol GX-270Q, Bruker WM-250 or Bruker DRX-300 spectrometers, using residual isotopic solvent ($CHCl_3$, δ_H = 7.26 ppm) as an internal reference. The infrared spectrum was recorded using a Graseby Specac diffuse reflectance kit. Accurate masses were determined using the VG Autospec Q instrument at Imperial College. The elemental combustion analysis was performed by the University of North London microanalytical laboratory. Analytical thin layer chromatography (tlc) was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light and/or iodine. Standard solvents were distilled under dried nitrogen: Et_2O and THF from sodium-benzophenone ketyl, CH_2Cl_2 from phosphorus pentoxide, MeCN from calcium hydride. Petrol refers to petroleum ether bp 40-60°C which was distilled prior to use; EtOAc was also distilled before use. Other solvents and reagents were obtained from commercial sources and purified where necessary according to standard procedures.[14]

Preparation of 4-benzyloxyphenylsulfonic acid, sodium salt. To NaH (4.14 g of a 60% suspension in mineral oil, 103.5 mmol, 1.2 equiv) under nitrogen with stirring was added *via* cannula a solution of 4-hydroxyphenylsulfonic acid, sodium salt dihydrate 20 g, 86.3 mmol) in anhydrous DMF (250 ml). Benzyl bromide (12.3 ml. 103.5 mmol, 1.2 equiv) was added and the reaction mixture stirred at rt overnight prior to quenching by the addition of EtOAc. The mixture was filtered under suction and the residue washed with EtOAc and Et_2O to give 4-benzyloxyphenylsulfonic acid, sodium salt (19.7 g, 80%) as a lustrous, colourless solid; mp >300°C; ν_{max} (Nujol) 3060, 1598, 1456, 1378, 1237, 1174, 1139, 1054, 1011, 835 cm^{-1}; δ_H (270 MHz, D_2O) 7.65 (2H, d, J 9.0 Hz, C_6H_4 *o*- to SO_3), 7.55-7.35 (5H, m, Ph), 7.15 (2H, d, J 9.0 Hz, C_6H_4 *o*- to OBn), 5.20 (s, 2H, $PhCH_2O$); *m*/*z* (FAB^-) 263, 219, 208, 192, 173, 162, 85, 77, 65, 45.

Preparation of 4-benzyloxyphenylsulfonyl chloride.[11] To a suspension of 4-benzyloxyphenylsulfonic acid, sodium salt (20.2 g, 70.5 mmol) in DMF (160 ml) at rt was added thionyl chloride (6.7 mol, 91.6 mmol, 1.3 equiv). After 5 min the mixture was poured onto ice and the mixture stirred for 5 min. The mixture was filtered under suction and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 4-benzyloxyphenylsulfonyl chloride (19.5 g, 98%) as a colourless solid; mp 92-94°C; ν_{max} (film) 3100, 1586, 1572, 1455, 1361, 1263, 1187, 1166, 1116, 1083, 835 cm^{-1}; δ_H (270 MHz, DMSO-d_6) 7.54 (2H, d, J 8.5 Hz, C_6H_4 *o*- to SO_2Cl), 7.51-7.31 (5H, m, Ph), 6.96 (2H, d, J 8.5 Hz, C_6H_4 *o*- to OBn), 5.13 (s, 2H, $PhCH_2O$); *m*/*z* (EI) 285, 284, 282, 250, 249, 247, 92, 91, 89, 65, 63, 62, 52, 51, 49 (Found: $[M]^+$, 282.0117. $C_{13}H_{11}ClO_3S$ requires $[M]^+$, 282.0120).

Preparation of 4-benzyloxyphenylsulfinic acid, sodium salt. To a stirred solution of 4-benzyloxyphenylsulfonyl chloride (19.5 g, 68.9 mmol) in THF (150 ml) at –20°C under nitrogen was added $LiAlH_4$ (39.6 ml of a 1M solution in THF, 39.6 mmol, 0.57 equiv). The resulting thick white suspension was stirred at –20°C during 3 h and then carefully quenched by the addition of 2M aqueous HCl (150 ml). The organic phase was separated and extracted with 2M aqueous NaOH (100 ml). Solid NaCl was added to the aqueous layer and the resulting precipitate collected by filtration and washed with Et_2O to give 4-benzyloxyphenylsulfinic acid, sodium salt (17.4 g, 93%) as a lustrous, colourless solid; mp >200°C; ν_{max} (film) 3100, 1584, 1460, 1378, 1244, 1175, 1047, 1009, 978 cm^{-1}; δ_H (270 MHz, DMSO-d_6) 7.47-7.35 (7H, m, Ph and C_6H_4 *o*- to SO_2), 6.95 (2H, d, J 8.5 Hz, C_6H_4 *o*- to OBn), 5.11 (s, 2H, $PhCH_2O$); *m*/*z* (FAB^-) 517, 418, 247, 170, 156.

Preparation of (4-hydroxyphenylsulfonyl)methane. To a stirred suspension of 4-benzyloxyphenylsulfinic acid, sodium salt (28.5 g, 105 mmol) in DMSO (135 ml) at rt was added MeI (8.51 ml, 137 mmol, 1.3 equiv). After 16 h the suspension was diluted with H_2O (200 ml) and filtered. The residue was washed with additional H_2O (3 x 100 ml) and petrol (5 x 100 ml). The resulting colourless solid was dried under reduced pressure to give (4-benzyloxyphenylsulfonyl)methane (21.5 g); mp 134°C. This material was dissolved in EtOH (1500 ml) and the solution added *via* cannula to 5% Pd on activated carbon (10 g) under nitrogen. The flask was purged with hydrogen and the suspension stirred under a hydrogen

atmosphere overnight, and then filtered through Celite. Removal of the solvent under reduced pressure yielded (4-hydroxyphenylsulfonyl)methane (13.9 g, 77% from 4-benzyloxyphenylsulfinic acid, sodium salt) as a colourless solid; mp 92-94°C; δ_H (300 MHz) 7.79 (2H, d, J 9.0 Hz, C_6H_4 *o*- to SO_2), 6.98 (2H, d, J 9.0 Hz, C_6H_4 *o*- to OH), 3.08 (3H, s, Me).

Alkylation of (4-hydroxyphenylsulfonyl)methane with Merrifield resin. Merrifield resin (chloromethylated polystyrene, crosslinked with 1% divinylbenzene, 1.08 mmol g^{-1} Cl from Sigma, 18.5 g, 20 mmol) was suspended in dry acetone (80 ml). After 10 min a solution of (4-hydroxyphenylsulfonyl)methane (3.44 g, 20 mmol) K_2CO_3 (2.76 g, 20 mmol, 1 equiv) and tetra-*n*-butylammonium iodide (0.74 g, 2 mmol, 0.1 equiv) in acetone (80 ml) was added, and the reaction mixture heated under reflux for 48 h. Further K_2CO_3 (0.276 g, 2 mmol, 0.1 equiv) and tetra-*n*-butylammonium iodide (0.074 g, 0.2 mmol) were added and heating was continued for 12 h, after which time tlc analysis revealed the absence of (4-hydroxyphenylsulfonyl)methane in solution. The reaction mixture was filtered under suction. The resin was washed with 50% aqueous THF (200 ml), 50% ethanol–diethyl ether (200 ml) and finally diethyl ether (400 ml), and dried under vacuum to give 20.8 g resin-bound (arylsulfonyl)methane; ν_{max} (single bead reflectance) *inter alia* 1315, 1141 cm^{-1} (Found: S, 2.89%. 97% loading @ 1.08 mmol g^{-1} requires S, 2.97%).

Typical procedure for solid-phase synthesis of 2,5-disubstituted furans

Stage A

To a solution of diisopropylamine (2.78 ml, 19.8 mmol, 2.2 equiv) in THF (10 ml) under N_2 at –78°C was added *n*-butyllithium (7.92 ml of a 2.5M solution in hexanes, 19.8 mmol, 2.2 equiv) and the mixture stirred for 15 min. The resulting solution was added dropwise to a magnetically stirred suspension of resin-bound (arylsulfonyl)methane (9.36 g, 9 mmol, 1 equiv) in THF (100 ml) at –78°C. The orange reaction mixture was stirred for one hour and diethyl chlorophosphate (9 mmol, 1,55 g, 1.3 ml, 1 equiv) was added. The now yellow suspension was stirred for 1 h and a solution of 2-methoxyoctanal[9] (18 mmol, 2.86 g, 2 equiv) in THF (10 ml) was added. After stirring for 3 h the reaction mixture was quenched with 50% aqueous THF (5 ml) and filtered under suction. The resin was washed with 50% aqueous THF (200 ml), 50% ethanol–diethyl ether (200 ml) and finally diethyl ether (200 ml). Drying under vacuum gave 10.26 g resin **A**.

Stage B

To a suspension of resin **A** (9.69 g, 8.5 mmol) in a mixture of THF (80 ml) and *tert*-butanol (8 ml, 85 mmol, 10 equiv). was added potassium *tert*-butoxide (8.5 mmol, 0.954 g, 1 equiv) and the resultant orange reaction mixture stirred at rt for 22 h. Acetic acid (8.5 ml of a 1M solution in THF, 8.5 mmol) was added and the mixture filtered under suction. The resin was washed with 50% aqueous THF (200 ml), 50% ethanol–diethyl ether (200 ml) and finally diethyl ether (200 ml). Drying under vacuum gave 9.4 g resin **B**.

Stage C

To a suspension of resin **B** (0.332 g, 0.3 mmol) in a mixture of THF (3 ml) and DMPU (1 ml) at 0°C was added *n*-butyllithium (0.36 ml of a 2.5M solution in hexanes, 0.9 mmol, 3 equiv) and the orange reaction mixture stirred for 30 min. Dodecanal (0.2 ml, 0.9 mmol, 3 equiv) was added and stirring continued for 2 h. The yellow reaction mixture was quenched with 50% aqueous THF and filtered under suction. The resin was washed with 50% aqueous THF (40 ml), 50% ethanol–diethyl ether (40 ml) and finally diethyl ether (40 ml). After drying under vacuum 0.332 g resin **C** was obtained.

Stage D

To a suspension of resin **C** (0.332 g, 0.3 mmol) in dichloromethane (4 ml) at rt was added trifluoroacetic acid (0.04 ml, 0.6 mmol, 2 equiv). The reaction mixture was stirred for 2 h and then filtered under suction. The filtrate was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure to yield 5-hexyl-2-undecylfuran (20.5 mg, 0.067 mmol, 22% over five steps from (4-hydroxyphenylsulfonyl)methane).

1H Nmr and ms data for furans

5-Hexyl-2-undecylfuran (5a). δ_H (270 MHz) 5.85 (2H, s, ArH), 2.57 (2H, t, J 7.5 Hz, CH_2 α- to Ar), 2.46 (2H, t, J 7.5 Hz, CH_2 α- to Ar), 1.60 (4H, m, 2 x CH_2 β- to Ar), 1.27 (28H, m, all other CH_2), 0.89 (6H, m, 2 x Me); *m*/*z* (EI) 307 $[MH]^+$ (Found: $[MH]^+$, 307.3010. $C_{21}H_{38}O$ requires $[MH]^+$, 307.3001).

2-Hexyl-5-(2-methylpropyl)furan[9] (5b). δ_H (270 MHz) 5.86 (2H, s, ArH), 2.58 (2H, t, J 7.5 Hz, C*H*$_2$C$_5$H$_{11}$), 2.45 (2H, d, J 7.5 Hz, C*H*$_2$CHMe$_2$), 1.94 (1H, m, C*H*Me$_2$), 1.62 (2H, quintet, J 7.5 Hz, $CH_2CH_2(CH_2)_3Me$), 1.32 (6H, m, $Ar(CH_2)_2(CH_2)_3Me$), 0.94 (6H, d, J 7.5 Hz, CH*Me*$_2$), 0.90 (3H, t, J 7 Hz, $(CH_2)_5$*Me*).

5-Hexyl-2-(3-pyridyl)furan (5c). δ_H (270 MHz) 8.92 (1H, m, pyridine H-6), 8.47 (1H, m, pyridine H-2), 7.90 (1H, d, J 8 Hz, pyridine H-4), 7.31 (1H, m, pyridine H-5), 6.66 (1H, d, J 3.5 Hz, furan H-3), 6.11 (1H, d, J 3.5 Hz, furan H-4), 2.71 (2H, t, J 7.5 Hz, $CH_2(CH_2)_4Me$), 1.71 (2H, quintet, J 7.5 Hz, $CH_2CH_2(CH_2)_3Me$), 1.36 (6H, m, $(CH_2)_2(CH_2)_3Me$), 0.90 (3H, m, $(CH_2)_5$*Me*); *m*/*z* (EI) 230 $[MH]^+$ (Found: $[MH]^+$, 230.1554. $C_{15}H_{19}NO$ requires $[MH]^+$, 230.1545).

5-Hexyl-2-(4-pyridyl)furan (5d). δ_H (270 MHz) 8.59 (2H, m, pyridine H-2 + H-6), 7.49 (2H, m, pyridine H-3 + H-5), 6.81 (1H, d, J 3.5 Hz, furan H-3), 6.14 (1H, d, J 3.5 Hz, furan H-4), 2.71 (2H, t, J 7.5 Hz, $CH_2(CH_2)_4Me$), 1.71 (2H, quintet, J 7.5 Hz, $CH_2CH_2(CH_2)_3Me$), 1.36 (6H, m, $(CH_2)_2(CH_2)_3Me$), 0.92 (3H, t, J 7.5 Hz, $(CH_2)_5$*Me*); *m*/*z* (EI) 230 $[MH]^+$ (Found: $[MH]^+$, 230.1553. $C_{15}H_{19}NO$ requires $[MH]^+$, 230.1545).

2-(4-Cyanophenyl)-5-hexylfuran (5e). δ_H (300 MHz) 7.70 (2H, d, J 8.5 Hz, cyanophenyl H-3 + H-5), 7.64 (2H, d, J 8.5 Hz, cyanophenyl H-2 + H-6), 6.73 (1H, d, J 3.5 Hz, furan H-3), 6.14 (1H, d, J 3.5 Hz, furan H-4), 2.71 (2H, t, J 7.5 Hz, $CH_2(CH_2)_4Me$), 1.71 (2H, quintet, J 7.5 Hz, $CH_2CH_2(CH_2)_3Me$), 1.35 (6H, m, $(CH_2)_2(CH_2)_3Me$), 0.91 (3H, t, J 6.5 Hz, $(CH_2)_5$*Me*); *m*/*z* (CI) 271 $[MNH_4]^+$ (Found: $[MNH_4]^+$, 271.1817. $C_{17}H_{19}NO$ requires $[MNH_4]^+$, 271.1810).

2-Cyclohexyl-5-(2-methylpropyl)furan (5f). δ_H (270 MHz) 5.87 (1H, d, J 3 Hz, ArH), 5.83 (1H, d, J 3 Hz, ArH), 2.58 (1H, m, cyclohexyl H-1), 2.45 (2H, d, J 7 Hz, C*H*$_2$CHMe$_2$), 2.03 (2H, m, cyclohexyl), 1.94 (1H, m, C*H*Me$_2$), 1.79-1.25 (8H, m, cyclohexyl), 0.94 (6H, d, J 7.5 Hz, CH*Me*$_2$); *m*/*z* (EI) 207 $[MH]^+$ (Found: $[MH]^+$, 207.1739. $C_{14}H_{22}O$ requires $[MH]^+$, 207.1749).

2-(4-Chlorophenyl)-5-cyclohexylfuran (5g). δ_H (300 MHz) 7.57 (2H, dd, J 8.5, 2 Hz, chlorophenyl H-3 + H-5), 7.33 (2H, dd, J 8.5, 2 Hz, chlorophenyl H-2 + H-6), 6.55 (1H, d, J 3.5 Hz, furan H-3), 6.05 (1H, d, J 3.5 Hz, furan H-4), 2.69 (1H, m, cyclohexyl H-1), 2.09-1.45 (10H, m, cyclohexyl); *m*/*z* (EI; for ^{35}Cl species) 261 $[MH]^+$ (Found: $[MH]^+$, 261.1042. $C_{16}H_{17}{}^{35}ClO$ requires $[MH]^+$, 261.1046).

2-(4-Bromophenyl)-5-cyclohexylfuran (5h). δ_H (270 MHz) 7.50 (4H, m, BrC_6H_4), 6.57 (1H, d, J 3.5 Hz, furan H-3), 6.05 (1H, d, J 3.5 Hz, furan H-4), 2.69 (1H, m, cyclohexyl H-1), 2.09-1.34 (10H, m, cyclohexyl); *m*/*z* (EI; for ^{81}Br species) 307 $[MH]^+$ (Found: $[MH]^+$, 307.0528. $C_{16}H_{17}{}^{81}BrO$ requires $[MH]^+$, 307.0521).

5-Cyclohexyl-2-(3-pyridyl)furan (5i). δ_H (270 MHz) 8.91 (1H, m, pyridine H-6), 8.47 (1H, m, pyridine H-2), 7.90 (1H, d, J 8 Hz, pyridine H-4), 7.30 (1H, m, pyridine H-5), 6.66 (1H, d, J 3.5 Hz, furan H-3), 6.08 (1H, d, J 3.5 Hz, furan H-4), 2.70 (1H, m, cyclohexyl H-1), 2.11-1.39 (10H, cyclohexyl); *m*/*z* (EI) 228 $[MH]^+$ (Found: $[MH]^+$, 230.1370. $C_{15}H_{17}NO$ requires $[MH]^+$, 228.1388).

2-Phenyl-5-undecylfuran (5j). δ_H (270 MHz) 7.66 (2H, d, J 7.5 Hz, phenyl H-2), 7.38 (2H, t, J 7.5 Hz, phenyl H-3), 7.24 (1H, t, J 7.5 Hz, phenyl H-4), 6.58 (1H, d, J 3 Hz, furan H-3), 6.08 (1H, d, J 3.5 Hz, furan H-4), 2.71 (2H, t, J 7.5 Hz, C*H*$_2$(CH$_2$)$_9$Me), 1.71 (2H, quintet, J 7.5 Hz, CH$_2$C*H*$_2$(CH$_2$)$_8$Me), 1.36-1.26 (16H, m, (CH$_2$)$_2$(C*H*$_2$)$_8$Me), 0.90 (3H, d, J 6.5 Hz, (CH$_2$)$_{11}$*Me*); *m*/*z* (EI) 299 $[MH]^+$ (Found: $[MH]^+$, 299.2383. $C_{21}H_{30}O$ requires $[MH]^+$, 299.2375).

5-(2-Methylpropyl)-2-phenylfuran (5k). δ_H (270 MHz) 7.66 (2H, d, J 7.5 Hz, phenyl H-2), 7.39 (2h, t, J 7.5 Hz, phenyl H-3), 7.24 (1H, t, J 7.5 Hz, phenyl H-4), 6.58 (1H, d, J 3 Hz, furan H-3), 6.10 (1H, d, J 3.5 Hz, furan H-4), 2.58 (2H, d, J 7 Hz, CH$_2$), 2.06, (1H, m, C*H*Me$_2$), 1.01 (6H, d, J 6.5 Hz, CH*Me*$_2$); *m*/*z* (EI) 201 $[MH]^+$ (Found: $[MH]^+$, 201.1285. $C_{14}H_{16}O$ requires $[MH]^+$, 201.1279).

2-(4-Bromophenyl)-5-hexylfuran (5l). δ_H (270 MHz) 7.50 (4H, m, bromophenyl), 6.57 (1H, d, J 3 Hz, furan H-3), 6.08 (1H, d, J 3 Hz, furan H-4), 2.71 (2H, t, J 7.5 Hz, C*H*$_2$(CH$_2$)$_4$Me), 1.70 (2H, quintet, J 7.5 Hz, CH$_2$C*H*$_2$(CH$_2$)$_3$Me), 1.34 (6H, m, (CH$_2$)$_2$(C*H*$_2$)$_3$Me), 0.92 (3H, t, J 6.5 Hz, (CH$_2$)$_5$*Me*); *m*/*z* (EI; for ^{81}Br species) 309 $[MH]^+$ (Found: $[MH]^+$, 309.0685. $C_{16}H_{19}{}^{81}BrO$ requires $[MH]^+$, 309.0677).

2-(4-Bromophenyl)-5-undecylfuran (5m). δ_H (270 MHz) 7.50 (4H, m, bromophenyl), 6.57 (1H, d, J 3 Hz, furan H-3), 6.08 (1H, d, J 3 Hz, furan H-4), 2.68 (2H, t, J 7.5 Hz, C*H*$_2$(CH$_2$)$_9$Me), 1.70 (2H, quintet, J 7.5 Hz, CH$_2$C*H*$_2$(CH$_2$)$_8$Me), 1.30 (16H, m, (CH$_2$)$_2$(C*H*$_2$)$_8$Me), 0.90 (3H, t, J 6.5 Hz, (CH$_2$)$_{11}$*Me*); *m*/*z* (EI; for ^{81}Br species) 379 $[MH]^+$ (Found: $[MH]^+$, 379.1442. $C_{16}H_{19}{}^{81}BrO$ requires $[MH]^+$, 379.1460).

2-(4-Bromophenyl)-5-(2-methylpropyl)furan (5n). δ_H (270 MHz) 7.50 (4H, m, bromophenyl), 6.57 (1H, d, J 3 Hz, furan H-3), 6.09 (1H, d, J 3 Hz, furan H-4), 2.56 (2H, t, J 7.5 Hz, C*H*$_2$), 2.03

(2H, m, C*H*Me_2) 0.99 (6H, d, J 6.5 Hz, CH*Me*$_2$); *m*/*z* (EI; for ^{81}Br species) 281 $[MH]^+$ (Found: $[MH]^+$, 281.0360. $C_{14}H_{15}{}^{81}BrO$ requires $[MH]^+$, 281.0364).

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References and Notes

1. For a discussion of linkers, including their definition, see the following reviews: (a) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (b) Comely A. C.; Gibson, S. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1012.
2. (a) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973. (b) Whitehouse, D. L.; Nelson K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett.* **1997**, *38*, 7139. (c) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667. (d) Gordon, D. W.; Steele, J. *BioMed. Chem. Lett.* **1995**, *5*, 47.
3. (a) Johnson, C. R.; Zhang, B. *Tetrahedron Lett*. **1995**, *36*, 9253. (b) Hughes, I. *Tetrahedron Lett*. **1996**, *37*, 7595. (c) Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc*. **1998**, *120*, 5132.
4. (a) Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem* **1997**, *62*, 6102. (b) Newlander, K. A.; Chenera, B.; Veber, D. F.; Yim, N. C. F.; Moore, M. L. *J. Org. Chem.* **1997**, *62*, 6726. (c) Hone, N. D.; Davies S. G.; Devereux, N. J.; Taylor, S. L.; Baxter, A. D. *Tetrahedron Lett.* **1998**, *39*, 897.
5. (a) Jung, K. W.; Zhao, X.; Janda, K. D. *Tetrahedron Lett.* **1996**, *37*, 6491. (b) Zhao, X.; Jung, K. W.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 977. (c) Zhao, X.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 5437.
6. (a) Van Marseveen, J. H.; den Hartog, J. A. J.; Engelen, V.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249. (b) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143.
7. Craig, D.; Robson, M. J.; Shaw, S. J. *Synlett* **1998**, 1381.
8. (a) Cheng, W.-C.; Halm, C.; Evarts, J. B.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1999**, *64*, 8557. (b) Halm, C.; Evarts, J; Kurth, M. J. *Tetrahedron Lett.* **1997**, *38*, 7709. (c) Cheng, W.-C.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2001**, *66*, 5528. (d) Cheng, W.-C.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 4387.
9. Craig, D.; Etheridge, C. J. *Tetrahedron* **1996**, *52*, 15289.
10. Aldrich Chemical Co.
11. Toja, E.; Gorini, C.; Zirotti, C.; Barzaghi, F.; Galliani, G. *J. Med. Chem.* **1991**, *26*, 403.
12. Compound **3** is now commercially available (Acros Organics).
13. Inferior yields for this transformation were obtained using H_2SO_4 in chloroform, TMSI in acetonitrile, $BF_3{\cdot}OEt_2$ in dichloromethane and $SnCl_4$ in dichloromethane.
14. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd Edn; Pergamon: Oxford, 1988.