The stereochemistry of addition of allyl sulfone carbanions to aldehydes. Formation of dihydrofurans [1]

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This paper is dedicated in friendship and with best wishes to Prof. Albert Padwa on the occasion of his 65th birthday

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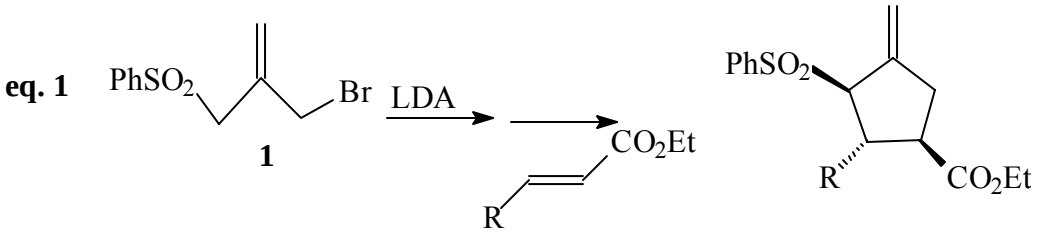
Abstract
The reaction of the mono-anion of the bromoallyl sulfone **1** with aldehydes **2** was examined with the aim of obtaining selectively substituted tetrahydrofurans. At –100ºC *syn*- and *anti*- open chain adducts **3** and **4** were isolated together with a low yield of 4-methylene-2,3-disubstituted tetrahydrofuran **5**. In the presence of HMPA or at higher temperature the reaction led to formation of 2,5-dihydrofurans **6**. The stereochemical results are consistent with initial addition of **1** to the aldehyde involving Li ion chelation.

Keywords: Dihydrofurans, Michael additions, allyl sulfones, Li chelation

Introduction

Recently we have shown [2,3] that 2-(bromomethyl)-3-phenylsulfonyl-1-propene **1** reacts with one molar equivalent of LDA to generate a lithiated α-allylsulfone carbanion that is stable at low temperature and undergoes regioselective and stereoselective additions via the α-carbon to Michael acceptors such as unsaturated esters, ketones, sulfones and nitro compounds, followed by cyclization to methylene-cyclopentenes. For instance, in the case of unsaturated esters, the primary Michael adduct was not even isolable at –78ºC and the incipient carbanion immediately underwent intramolecular reaction with the allylic bromide to afford stereoselectively substituted methylenecyclopentane derivatives (eq. 1).[2] The high stereoselectivity in the product can be rationalized on the basis of Li-ion chelation by the sulfone and the ester function during addition.

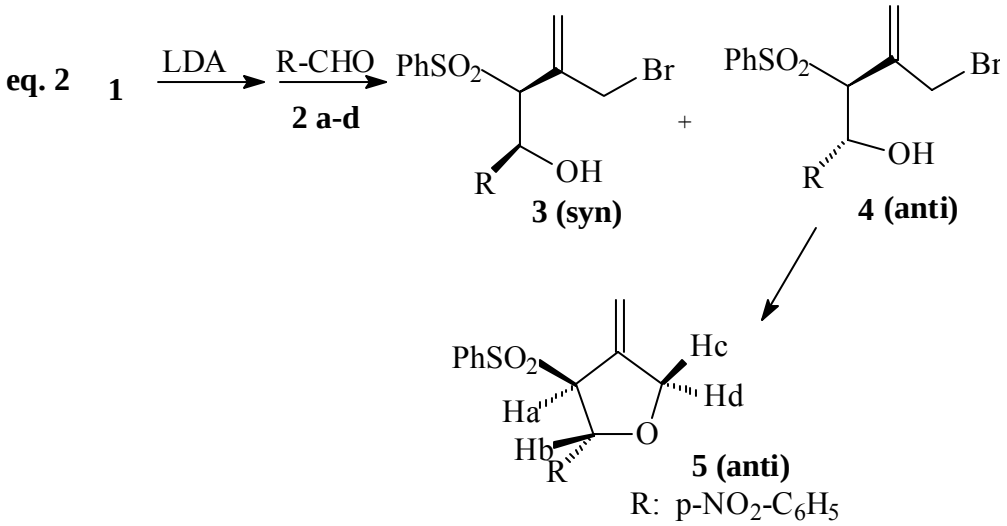
The addition of lithiated **1** to the C=N of sulfinimines proceeded less stereoselectively and led with double bond rearrangement to 2-arylpyrrolines.[3c]



In view of general interest in formation of stereoselectively substituted tetrahydrofurans, such as the naturally occurring polyether antibiotics,[4] we investigated the reaction of **1** with aldehydes as a potential entry into substituted tetrahydrofurans. We report here our findings, using the mono-lithio derivative of the bromoallyl sulfone **1** and of the hydroxyallylsulfone **8** in reactions with aldehydes **2**.

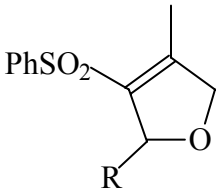
Results and Discussion

The bromoallylsulfone **1** was deprotonated using 1.1 equiv. of LDA in THF at –100ºC. The monolithio derivative thus generated was treated with *p*-nitrobenzaldehyde **2d** at the same temperature and quenched after 30 min with HOAc to give a mixture of two open chain *syn*- and *anti*- isomers,[5] **3** and **4**, as well as the *trans*- 2,3-disubstituted-4-methylenetetrahydrofuran **5** (see eq. 2 and Table 1, entry 2).

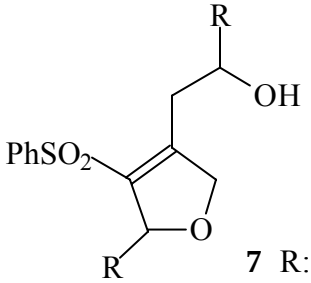


The *syn*- and *anti*- isomers **3** and **4** were separated by flash-column chromatography and their structures in the preferred conformation were assigned as **3A** and **4A**, respectively, on the basis of NMR data. Similarly, the structure assignment of **5** is based on NMR (see discussion below). Addition of LiBr to the reaction mixture did not alter the results: however, addition of a solvating agent (TMEDA or especially HMPA) at –100ºC did change the ratio of products and led to

isolation of the dihydrofuran **6d**, with the *syn* isomer **3** remaining unchanged (see Table 1). In two cases,[7] a Michael adduct of the anion derived from product **5** to the aldehyde **2d**, was isolated in *ca*. 5% yield.



6 a-d



7 R: p-NO_2-C_6H_5

Reaction at higher temperature (-40ºC) for a longer period of time (3 h) in the absence of HMPA afforded the *syn*- isomer **3** together with rearranged dihydrofuran **6d**. When the monolithio derivative of **1** was treated with aldehyde **2d** followed by HMPA in excess, and allowed to react at –40ºC for 3 h, the only product isolated was the dihydrofuran **6d** (see Table 1).

Table 1. Products **3–6** from reaction of **1** with 1.1 eq. of LDA followed by *p*-nitrobenzaldehyde, **2d**

Entry	Conditions	**3**, Yield (%)	**4**, Yield (%)	**5**, Yield (%)	**6**, Yield (%)
1	0.5h, -100ºC	51	22	12	-
2	0.5h, -100ºC, LiBr	51	22	12	-
3[a]	1h, -100ºC, TMEDA	50	8	8	15
4[a]	1h, -100ºC, HMPA	50	-	-	27
5	3h, -40ºC	50	-	-	25
6	3h, -40ºC, HMPA	-	-	-	48

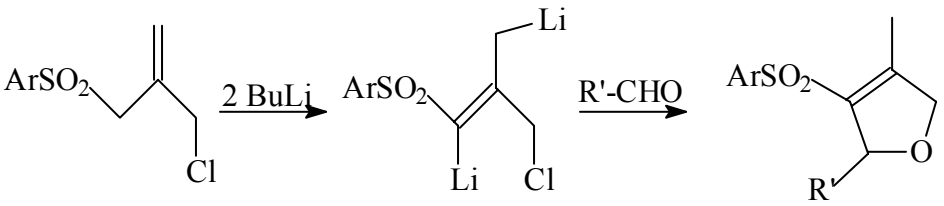
In this manner, several aliphatic and aromatic aldehydes **2a**–**d** were converted to the dihydrofurans **6a–d** by means of the monolithio- derivative of **1** at –40ºC in the presence of HMPA, in good yields (see Table 2).

Table 2. Dihydrofurans **6** from reaction of **1** with LDA and aldehydes **2** (**a–d**) in the presence of HMPA at –40ºC

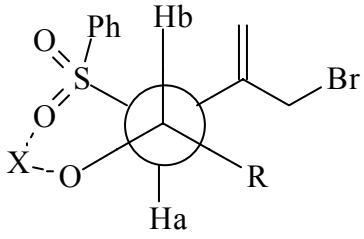
2	**R**	**6**, Yield (%)
a	$CH_3(CH_2)_2$-	63
b	$CH_3(CH_2)_4$-	52
c	*p*-Tolyl-	85
d	*p*-Nitrophenyl-	48

While this work was in progress, Najera *et al*.[6] reported the formation of the dianion of the chloro analog of **1** using 2 equiv. of BuLi and DMPU and its reaction with alkyl halides and aldehydes (eq. 3). With alkyl halides, dialkylation took place. Allowing the reaction with aldehydes to proceed to room temperature, led to dihydrofuran analogs of **6,** while the reaction with propanal and quenching at –40ºC gave a mixture of **6** and open-chain diastereomeric adducts. However, no separation of the latter, or their stereochemical elucidation, was reported.

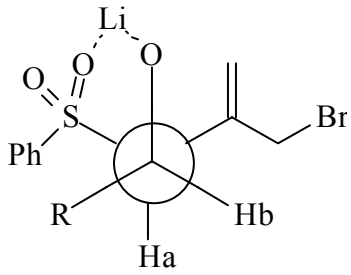
eq. 3



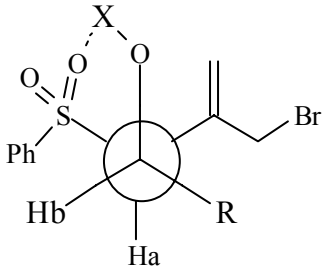
Our stereochemical results are best explained via the "cyclic model" in which the lithio allylsulfone carbanion reacts by an α-carbon attack on the aldehyde leading to a chelated intermediate. As can be seen, the *syn*-chelated structure **3B** (likely as a chair conformer of a 6-membered ring with two equatorial groups) should be favored over *syn*- **3C** or over *anti*- **4A** [7] because of gauche interactions; this explains why the *syn* product predominates.



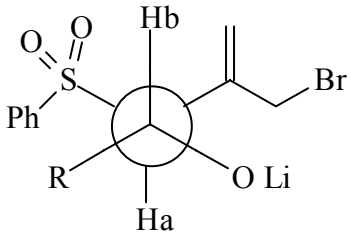
3A syn, X=H
3B syn, X=Li



3C syn



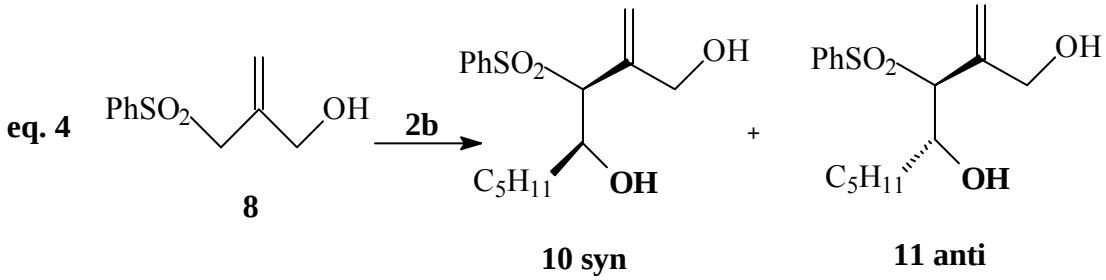
4A anti, X=H
4B anti, X=Li



4C anti

When chelation of the Li cation with sulfone- and alcohol- oxygens is disrupted, as in the presence of HMPA, rotation can occur to **3C** and **4B**, respectively,[7] conformers needed for subsequent cyclization. In this case, it is the *anti*- isomer in its anionic form (**4B** or **4C**) which is expected to ring-close to a tetrahydrofuran **5**, while steric hindrance inherent in vicinally *cis*-disubstituted five-membered rings should raise the transition state energy for the cyclization of *syn*- **3C**. Indeed, only cyclization of the *anti*- isomer to the *trans*- tetrahydrofuran **5** was observed at –100ºC (Table 1, entry 4). At higher temperature and in the presence of HMPA and base, ring closure of both diastereomers took place followed by isomerisation to the dihydrofuran **6**, as well as side reactions. The above series of events is consistent with the products which we had observed in the reaction of **1** with ω-nitrostyrene, in which the *anti*- adduct ring-closed more readily (to the *trans*- substituted cyclopentane) than did the *syn*- isomer.[3b]

It was hoped that chelation to the hydroxyallylsulfone **8** might lead to higher stereoselectivity during the addition to the carbonyl group by complexation, as shown in **9**. In fact, the hydroxyallylsulfone **8** had been shown to add regio- and stereoselectively to nitro-olefins.[8] Hence, we also examined the condensation of the Li derivative of **8** with hexanal **2b**. In this case, however, two diastereomers **10** (*syn*-) and **11** (*anti*-) were formed in essentially equal amounts and addition of TMEDA did not change the results. Apparently, in this system chelation of the Li cation from the aldehyde to the sulfone or the hydroxy group are either not important, or more likely, equal.



Structure assignment

The configurational assignment of **3A** as the *syn*- isomer is based on a value of 9 Hz for the coupling constant between H_a and H_b indicating an *anti*- relationship. In the second isomer **4A** the corresponding coupling constant is 2.5 Hz, consistent with a *gauche* orientation of H_a and H_b. In both isomers the hydroxylic proton exhibits a doublet with coupling to H_b of 2 Hz. This phenomenon is known in cases where the exchange rate of the hydroxylic proton is very low and may be due to hydrogen bonding. The determination of configuration of the *trans*- substituted tetrahydrofuran **5** is also based on a 4 Hz coupling between H_a and H_b. Although configurational assignment in 5-membered rings based on NMR should be made with caution in cyclopentanes that are rather flat, *trans*- vicinal hydrogens usually show a small coupling constant of 2–4 Hz (dihedral angle near 120º) while *cis*- vicinal hydrogens exhibit a larger coupling constant of 8–11 Hz (dihedral angle closer to 0º). In the case of **5** the assumption that the ring is rather flat is well

founded since (a) there is an sp^2 hybridized center in the ring, (b) the 5-membered ring contains an oxygen atom, (c) each of the vinylic protons shows three similar allylic couplings (with H_a, H_c, H_d). This is consistent with having C_3, C_4, C_5 in nearly the same plane. More convincing is the NOE (2%) observed in **5** between H_a and the *ortho*- hydrogens of the *cis*- *p*-nitrophenyl ring, as well as between H_a and H_d and between H_b and H_c.

In conclusion, the lithio allylsulfone carbanion derived from **1** added stereoselectively to aldehydes to produce preferentially the *syn*- adduct at low temperature (–100ºC). This is best explained by a chelated intermediate **3B**, while at higher temperature and in the presence of HMPA, ring-closure and finally isomerisation to the dihydrofuran **6** took place. There was no stereochemical preference in the addition of hydroxysulfone **8** to aldehyde **2b**.

Experimental Section

General anhydrous experimental techniques and analytical measurements were as previously described.[8]

General procedure for the reaction of 1 with *p*-nitrobenzaldehyde (2d); Formation of 3–7

To a stirred solution of LDA (prepared from 0.14 mL (1 mmol) of diisopropylamine and 0.64 mL of n-BuLi (0.92 mmol, 1.475 *N* in hexane) in 4 mL of THF) was added dropwise at –100ºC a solution of **1** (200 mg, 0.72 mmol) in 1 mL of THF. After stirring for 10 min at the above temperature, *p*-nitrobenzaldehyde (121 mg, 0.08 mmol) in 1 mL of THF was added dropwise. After 15 min, at –100ºC, the reaction mixture was quenched with aqueous (20%) AcOH, poured into water, and extracted with CH_2Cl_2. The extracts were washed successively with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatographic purification of the residue (ether/petroleum ether, 1:2) gave compounds **3–7**, as viscous oils. Yields are reported in Table 1.

2-Bromomethyl-4-(*p*-nitrophenyl)-3-benzenesulfonyl-1-buten-4-ol (*syn*) (3). ^{1}H NMR δ 8.18–8.08 (m, 2H), 7.94–7.85 (m, 2H), 7.76–7.48 (m 5H), 5.53–5.40 (m, 3H), 4.60 (d, J = 2 Hz, 1H), 4.13 (dd, J = 9, 1 Hz, 1H), 3.46 (dd, J = 11, 1Hz, 1H), 3.21 (dd, J = 11, 1H). ^{13}C NMR δ 147.9 (s), 145.9 (s), 137.1 (s), 135.1 (s), 134.5 (d), 129.6 (d), 129.1 (d), 128.9 (d), 124.3 (t), 123.3 (d), 73.3 (d), 72.3 (d), 36.1 (t). M.S. (CH_4/CI) m/e (%): 443, 445 (MH^+, 84, 100), 363 (MH^+ –HBr, 11); HRMS: calcd. ($C_{17}H_{17}NO_5SBr$, MH^+) 427.9990, 426.0010, found 427.9410, 425.9447.

2-Bromomethyl-4-(*p*-nitrophenyl)-3-benzenesulfonyl-1-buten-4-ol (*anti*) (4). ^{1}H NMR δ 8.20–8.11 (m, 2H), 7.95–7.84 (m, 2H), 7.75–7.67 (m, 1H), 7.63–7.43 (m, 4H), 6.11 (s, 1H), 5.83 (BS, 1H), 5.67 (s, 1H), 3.95 (dd, J = 2.5, 1Hz, 1H), 3.83 (d, J = 2 Hz, 1H), 3.49 (dd, J = 11, 1 Hz, 1H), 3.18 (dd, J = 11, 1Hz, 1H). ^{13}C NMR δ 147.6 (s), 146.0 (s), 136.7 (s), 134.5 (d), 132.1 (s), 129.2 (d), 129.1 (t), 127.2 (d), 126.1 (d), 123.4 (d), 70.9 (d), 69.8 (d), 37.3 (t). M.S. (ammonia/CI) m/e (%): 443, 445 ($(NH_3+MH)^+$, 50, 58), 363 (NH_3+MH^+ –HBr, 100), 316 (NH_3+MH^+–HBr–HNO_2, 13).

4-Methylene-*trans*-2-(*p*-nitrophenyl)-3-benzenesulfonyltetrahydrofuran (5). ^{1}H NMR δ 8.23–8.14 (m, 2H), 7.98–7.90 (m, 2H), 7.77–7.69 (m, 1H), 7.66–7.56 (m, 2H), 7.51–7.43 (m, 2H), 5.72 (d, J = 4 Hz, 1H), 5.32 (dt, J = 13, 1 Hz), 4.35 (dq, J = 13, 2Hz, 1H) 4.09–4.02 (m, 1H). ^{13}C NMR δ 149.1 (s), 147.6 (s), 139.4 (s), 136.5 (s), 134.4 (d), 129.7 (d), 129.2 (d), 126.5 (d), 123.8 (d), 114.3 (t), 80.0 (d), 72.3 (t). M.S. (iso-butane/CI) m/e (%): 346 (MH^+, 21), 203 (M^+-HSO_2Ph, 100).

2-(*p*-Nitrophenyl)-3-benzenesulfonyl-4-(1'-*p*-nitrophenyl-2'-ethyl-1'-ol)-2,5-dihydrofuran (7). ^{1}H NMR δ 8.32–8.24 (m, 2H), 8.15–7.99 (m, 2H), 7.72–7.63 (m, 2H), 7.50–7.48 (m, 2H), 7.44–7.37 (m, 2H), 7.30–6.63 (m, 4H), 5.91 (dd, J = 5.7, 3.7 Hz, 1H), 5.22 (dt, J = 7.4, 5.5 Hz, 1H), 5.00 (dd, J = 15.5, 5.5 Hz, 1H), 4.89 (dd, J = 15.5, 3 Hz, 1H), 3.24–3.14 (m, 3H). ^{13}C NMR δ 152.0 (s), 150.5 (s), 148.1 (s), 147.7 (s), 145.6 (s), 139.6 (s), 136.5 (s), 133.9 (d), 129.1 (d), 128.8 (d), 127.2 (d), 126.3 (d), 124.0 (d), 123.4 (d), 87.6 (d), 79.2 (t), 72.1 (d), 35.6 (t). M.S. (ammonia/CI) m/e (%): 514 (MNH_4^+, 100), 449 (M^+-HNO_2, 52), 419 (MH^+-Ph, 46), 373 (MNH_4^+-SO_2Ph, 5).

General procedure for the reaction of aldehydes (2a–d) with 1-benzenesulfonyl-2-methylene-3-bromopropane (1); preparation of compounds (6a–d)

To a stirred solution of LDA (prepared from 0.07 mL (0.5 mmol) of diisopropylamine and 0.32 mL of n-BuLi (0.46 mmol, 1.475*N* in hexane) in 2 mL of THF) was added dropwise at –100ºC a solution of **1** (100 mg, 0.36 mmol) in 0.5 mL of THF. After stirring for 10 min at the above temperature, the aldehyde **2 (a–d)** (0.4 mmol) in 0.5 mL of THF was added dropwise. After addition of the aldehyde, a mixture of HMPA (0.5 mL) and THF (0.4 mL) was added dropwise at –100ºC. The mixture was stirred for an additional 3 h at –40ºC and then quenched with aqueous AcOH (20%), poured into water, and extracted with CH_2Cl_2. The extracts were washed successively with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatographic purification of the residue (petroleum ether/ether, 2:1) gave the desired product **(6a–d)**.

4-Methyl-3-benzenesulfonyl-2-propyl-2,5-dihydrofuran (6a) was obtained from **1** and butyraldehyde **(2a)** as a viscous liquid (60 mg, 0.23 mmol, 63%). ^{1}H NMR δ 7.94–7.83 (m, 2H), 7.70–7.51 (m, 3H), 4.99–4.85 (m, 1H), 4.67 (dd, J = 14, 5 Hz, 1H), 4.54 (dd, J = 14, 3 Hz, 1H), 2.15 (s, 3H) 1.86–1.46 (m, 2H), 1.39–1.12 (m, 2H) 0.85 (t, J = 7 Hz, 3H). ^{13}C NMR δ 150.7 (s), 141.3 (s), 133.9 (s), 133.5 (d), 129.2 (d), 127.2 (d), 86.7 (d), 78.9 (t), 36.9 (t), 17.8 (t), 13.8 (q), 11.3 (q). M.S. (EI) m/e (%): 267 (MH^+, 100), 223 (MH^+–C_3H_8, 99) 141 (SO_2Ph^+, 37), 125 (SO_2Ph^+–O, 57), 77 (Ph^+, 78); HRMS calcd. ($C_{14}H_{19}O_3S$, MH+) 267.1054, found 267.0881.

4-Methyl-2-pentyl-3-benzenesulfonyl-2,5-dihydrofuran (6b) was obtained from **1** and hexanal **(2b)** as a viscous liquid (55 mg, 0.19 mg, 52%). ^{1}H NMR δ 7.94–7.83 (m, 2H), 7.69–7.50 (m, 3H) 5.00–4.87 (m. 1H), 4.67 (dd, J = 16, 5 Hz, 1H), 4.55 (dd, J = 16, 4 Hz, 1H), 2.15 (s, 3H) 1.92–1.04 (m, 8H), 0.84 (t, J = 6 Hz, 3H). ^{13}C NMR δ 150.7 (s), 141.3 (s), 133.7 (s), 133.4 (d), 129.2 (d), 127.1 (d), 86.8 (d), 78.8 (t), 34.7 (t), 31.5 (t), 24.1 (t), 22.5 (t), 13.9 (q), 11.2 (q). M.S.

(EI) m/e (%): 295 (MH^+, 97), 223 (MH^+-C_5H_{12}, 100) 141 (SO_2Ph^+, 28) 125 (SO_2Ph^+–O, 23), 77 (Ph^+, 76); HRMS calcd. ($C_{16}H_{23}O_3S$, MH^+) 295.1367, found 295.1274.

4-Methyl-3-benzenesulfonyl-2-(*p*-tolyl)-2,5-dihydrofuran (6c) was obtained from **1** and *p*-tolyl-benzaldehyde (**2c**) as a white solid (96.4 mg, 0.306 mmol, 85%, m.p. 123.7ºC). ^{1}H NMR δ 7.51–7.39 (m, 1H), 7.32–7.17 (m, 4H), 6.99–6.89 (m, 4H), 5.93–5.87 (m, 1H), 4.88 (dd, J = 15, 5.5 Hz, 1H), 4.78 (dd, J = 15, 3.5 Hz, 1H), 2.29 (s, 6H). ^{13}C NMR δ 150.5 (s), 141.0 (s), 138.4 (s), 136.0 (s), 135.7 (d), 128.9 (d), 128.6 (d), 127.9 (d), 127.3 (d), 89.0 (d), 79.7 (t), 21.2 (q), 11.4 (q). M.S. (iso-butane/CI) m/e (%): 332 (MH_2O^+, 6) 315 (MH^+, 13) 297 (MH^+–H_2O), 8), 223 (M^+–$C_7H_7^+$, 100), 173 (M^+–SO_2Ph^+, 2).

4-Methyl-3-benzenesulfonyl-2-(*p*-nitrophenyl)-2,5-dihydrofuran (6d) was obtained from **1** and *p*-nitrobenzaldehyde **(2d)** as a yellow solid (60 mg, 0.173 mmol, 48%, m.p. 224.2ºC). ^{1}H NMR δ 8.02–7.94 (m, 2H), 7.51–7.19 (m, 7H), 6.05–5.97 (m, 1H), 4.96 (dd, J = 15, 5 Hz, 1H), 4.85 (dd, J = 15, 4 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR δ 151.8 (s), 148.0 (s), 146.0 (s), 140.7 (s), 134.4 (s), 133.3 (d), 128.8 (d), 127.0 (d), 123.3 (d), 87.9 (d), 80.1 (t), 11.4 (q). M.S. (iso-butane/CI) m/e (%): 346 (MH^+, 100), 323 (MH^+–H_2O), 58), 223 (M^+–NO_2Ph^+, 47), 204 (M^+–SO_2Ph^+, 62), 158 (M^+-SO_2Ph^+-NO_2Ph^+, 9); HRMS calcd ($C_{17}H_{16}NO_5S$, MH^+) 346.0749, found 346.0738.

General procedure for the reaction of hexanal (2b) with 1-benezenesulfonyl-2-methylene-3-hydroxypropane (8); preparation of compounds (10–11)

To a stirred solution of LDA (prepared from 0.17 mL (1.2 mmol) of diisopropylamine and 0.94 mL of n-BuLi (1.2 mmol, 1.475N in hexane) in 4 mL of THF) was added dropwise at –100ºC a solution of **8** (100 mg, 0.48 mmol) in 1 mL of THF. After stirring for 10 min at the above temperature, the hexanal **2b** (58 mg, 0.58 mmol) in 0.5 mL of THF was added dropwise. The mixture was stirred for an additional 1 h at –100ºC and then quenched and extracted as described for **6(a–d)**. Chromatographic purification of the residue (petroleum ether / ethyl acetate, 1:1) gave products **10** and **11** (66 mg, 0.21 mmol, 44%) (10:11 = 1.28:1) as a viscous oil (inseparable mixture).

2-Methylene-3-(benzenesulfonyl)nonane-1,4-diol (10, *syn*) a and (11, *anti*) b. ^{1}H NMR δ 7.91–7.83 (m, 2Ha, 2Hb), 7.72–7.48 (m, 3Ha, 3Hb), 5.47 (s, 1Hb), 5.40 (s, 1Ha), 5.36 (s, 1Hb), 5.03 (s, 1Ha), 4.93–4.46 (m, 3Ha, 3Hb), 3.85 (d, J = 9 Hz, 1Hb), 3.75 (d, J = 2 Hz, 1Ha), 3.68–3.59 (m, 1Ha, 1Hb), 2.91 (t, J = 6 Hz, 1Hb), 2.35 (t, J = 6 Hz, 1Ha), 1.66–1.13 (m, 8Ha, 8Hb), 0.94–0.79 (m, 3Ha, 3Hb). ^{13}C NMR δ 139.5 (s, a), 137.7 (s, b), 137.5 (s, b), 137.1 (s, a), 134.0 (d, b), 133.9 (d, a), 129.1 (d, b), 129.0 (d, a), 128.9 (d, a), 128.7 (d, b), 123.9 (t, b), 119.5 (t, a), 73.2 (d, a), 72.4 (d, b), 70.3 (d, a), 68.5 (d, b), 65.6 (t, a), 65.3 (t, b), 34.5 (t, b), 34.3 (t, a), 31.5 (t, a), 31.4 (t, b), 25.3 (t, b), 24.7 (t, a), 22.5 (t, a), 22.4 (t, b), 13.9 (q, a, b). M.S. (CH_4/CI) m/e (%): 313 (MH^+, 32), 295 (MH^+-H_2O, 100), 277 (MH^+-$2H_2O$, 8), 195 (M^+-H_2O $C_6H_{12}O$, 10); HRMS: calcd. ($C_{16}H_{25}O_4S$, MH^+) 313.1473, found 313.1378.

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References and Notes

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7. We are ignoring conformations in which the *p*-nitrophenyl group (R) is *gauche* to the two large groups ($PhSO_2$ and allyl bromide).
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