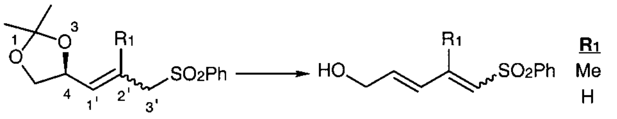
Stereoselective Synthesis of 1-Hydroxymethyl-4-phenylsulfonylbutadienes

Julio G. Urones, Isidro S. Marcos, Narciso M. Garrido, P. Basabe, Angel J. Bastida, Sonia G. San Feliciano, David Díez* and Jonathan M. Goodman[#]
Dpto. de Química Orgánica, Universidad de Salamanca. Plaza de los Caídos 1–5, 37008 Salamanca, SPAIN.
[#] Dept. of Chemistry. Lensfield Road, Cambridge, CB2 1EW, U.K.

Received 28 September 1998

Abstract: Stereoselective syntheses of 1-hydroxymethyl-4-phenylsulfonylbutadienes were achieved from unsaturated sulfones which were easily obtained from D-Mannitol.

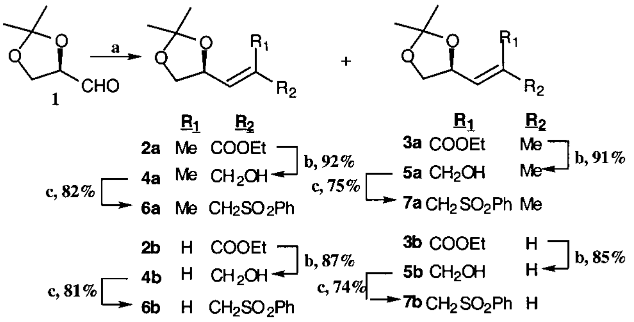
Vinyl sulfones, sulfides and sulfoxides are very useful compounds in organic synthesis and have recently been the object of several studies.[1] More complex molecules, like arylsulfonyl-1,3-dienes, have attracted considerable interest due to their usage as synthons in a variety of reactions,[2] for example cycloadditions with normal and inverse electron demand.[3] In the same way, conjugated unsaturated alcohols are an interesting class of compounds not only because of their occurrence in nature, but from a synthetic point of view. Due to our interest in the chemisty of unsaturated sulfones,[4] we investigated the following reaction of β,γ-unsaturated sulfones. (Scheme 1).



Scheme 1

This reaction permits us to obtain conjugated unsaturated alcohols and α,β,-γ,δ-unsaturated sulfones in a very simple way with excellent control of the selectivity.

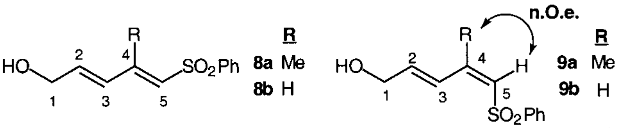
Following known procedures, the aldehyde **1** was synthesized from D-Mannitol.[5] The Wittig reaction of **1** led to the esters **2** and **3** in a ratio 95:5 (Scheme 2). The reduction of both with DIBAL[6] gave the alcohols **4** and **5**. These were treated separately and sequencially with mesyl chloride[7] and sodium phenylsulfinate[8] in DMF to give in high yield sulfones **6** or **7**, accordingly. With these sulfones in hand, we procceded to prepare the 1,3 butadienes.



a) $Ph_3P=C(CH_3)COOEt$, 90% or $Ph_3P=CHCOOEt$, 95%
b) DIBAL, c) i. MsCl, Et_3N; ii. $NaSO_2Ph$

Scheme 2

Treatment of the sulfone **6a** with *n*-BuLi or LDA gave dienes **8a** and **9a** in good yield 82 and 70% respectively in the same ratio 25:75[9] (Scheme 3). The elimination could be explained by the release of acetone as the driving force.

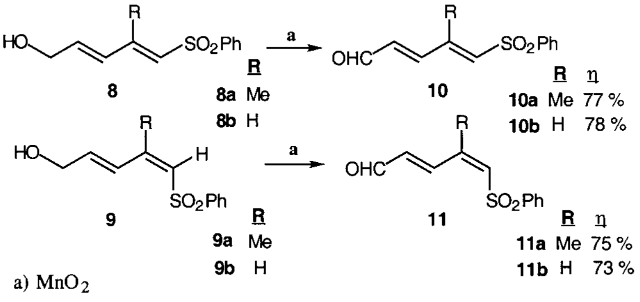


	8a	9a
6a	25	75
7a	85	15

	8b	9b
6b	100	0
7b	100	0

Scheme 3

The stereochemistry of the double bonds was assigned by NMR methods. Compound **9a** showed a n.O.e between the methyl on C-4 and H-5, in agreement with a *Z* geometry at $\Delta^{4,5}$ and, therefore, an *E* geometry for the same double bond in compound **8a**. Oxidation of alcohols **8a** and **9a** to aldehydes **10a** and **11a** with MnO_2,[10] allowed the determination of an *E*-geometry for $\Delta^{2,3}$, according to the coupling constant value between H-2 and H-3 of J = 16.1 Hz in both aldehydes. (Scheme 4).



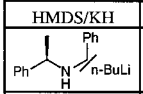
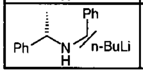
a) MnO_2

Scheme 4

When compound **7a** was submitted to the same conditions with *n*-BuLi or LDA, 80 and 75% yield respectively, the same compounds **8a** and **9a** were obtained but with a larger and opposite stereoselectivity of 85/15 in this case in favour of **8a**.

In order to increase the selectivity in this reaction when **6a** is used as the starting sulfone, different bases were studied as can be seen in Table.

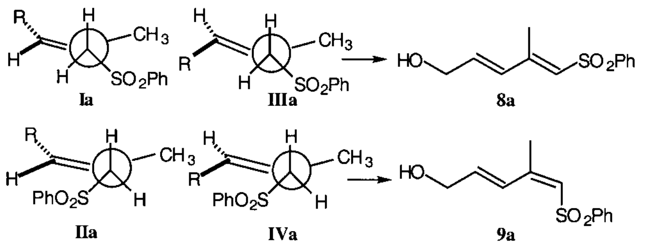
Table

Base	Eq.Base	Solvent	T/^{0}C	8a/9a	Time/h	Yield
n-BuLi	1.2	THF	-78^{0}C	25/75	1	82%
LDA	2.2	THF	-78^{0}C	25/75	1	70%
NaH	2.2	THF	-78^{0}C	25/75	1	50%
KH	2.2	THF	-78^{0}C	25/75	1	45%
HMDS/KH	3.0	THF	0^{0}C	**5/95**	1	70%
	2.2	THF	-78^{0}C	10/90	1	80%
	2.2	THF	-78^{0}C	10/90	1	80%

As can be seen the best results are found using HMDS, presumably due to greater steric congestion. Different bases with pair matched and mismatched were used, but failed to improve the stereoselectivity of the double bond formation.

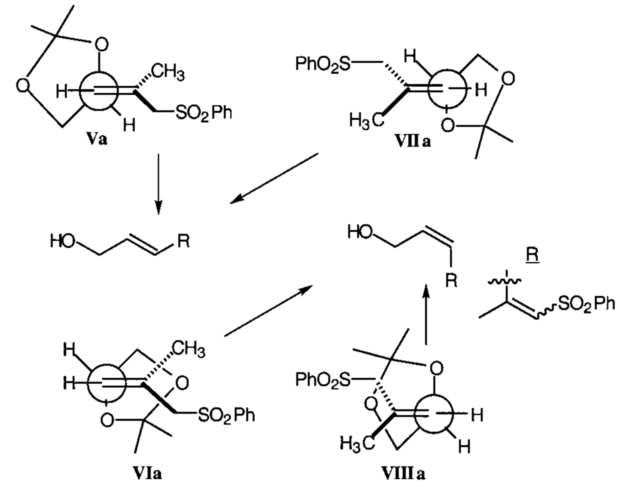
This reaction has been extended to other protecting groups of the 1,2 diol functionality. The acetone ketal of **6a**, was removed and changed for cyclohexanone ketal, methoxy ethers, acetates and *tert*-butyldimethylsilyl derivatives. All these compounds when treated with *n*-BuLi gave aproximately the same yields and ratio in selectivity of dienes **8a** and **9a**.

These results can be understood by the assumption that the preferred conformations of transition states, which are responsible in the reaction, are **Ia** and **IIa** for compound **6a** and **IIIa** and **IVa** for compound **7a**. In Scheme 5 the Newman projection for $C_{3'}$-$C_{2'}$ of **6a** and **7a** has been represented. As can be seen, the steric congestion is a bit higher in **Ia** than in **IIa**, in agreement with the experimental result of 25:75 ratio for compounds **8a** and **9a**. In the case of the conformers of **7a**, **IVa** is more crowded than **IIIa** due to steric repulsion between the groups and this explains the observed stereoselectivity and the ratio in this case 85:15 in favour of **8a**.



Scheme 5

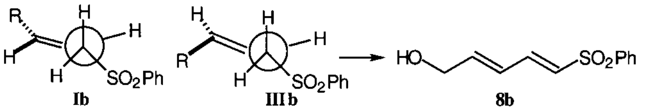
To study the stereoselectivity observed in the second double bond, the transition states for **6a** and **7a** are represented on Scheme 6. They are **Va** and **VIa** for the former and **VIIa** and **VIIIa** for the latter. As can be observed, the conformers **VIa** and **VIIIa** are crowded, this explainins why an *E* geometry was obtained for Δ^1 in both compounds.



Scheme 6

On the other hand, we have tried to explain the observed experimental results carring out molecular modeling calculations. The theoretical study was done with the MacroModel Program[11], version 6.0, using the MM2* force field[12]. After a full conformational search of starting materials **6a** and **7a** with Monte Carlo Search was completed, the torsion angles were constrained so that both the breaking C-H bond (0° and 180°) and the breaking C-O bond were lined up with Π orbitals of the double bond (90°) based on the Hammond Postulate. Relative energy values of the rotameric transition states thus obtained are consistent with experimental results, so the transition state with lowest energy was expected to lead to the major product on each case. This gives confidence that similar calculations might be used to predict the results of related reactions.

Compounds **6b** and **7b** only led to **8b** by treatment with *n*-BuLi under the same conditions in 85 and 80% yield respectively (Scheme 3). These results can be explained in a similar manner as previously. The more favoured transition states would be **Ib** and **IIIb** which would lead to the same stereochemistry for $\Delta^{4,5}$. The stereochemistry of the double bond between C2-C3 can be explained by the same reasons as in the case above. Thus, a new way of obtaining α,β-γ,δ-unsaturated sulfones with good control over the double bond geometry has been obatined (Scheme 7).



Scheme 7

Further studies of the extension of this methodology to the synthesis of related compounds will be reported in due course.

Acknowledgments. The authors thank the CICYT, Junta Castilla y Leon (SA 44-96) and M.E.C. for financial support and Dr. D. Craig for helpful discussions.

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(9) Representative data for selected compounds; **8a**: ^{1}H-NMR ($CDCl_3$) δ: 8.00-7.90 (2H, m, Ar), 7.70-7.90 (3H, m, Ar), 6.4-6.2 (3H, m, H_2, H_3 and H_5), 4.3 (2H, m, CH_2OH), 2.25 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 149.0 (C_4), 143.2 (C*ipso*), 137.0 (C_5), 133.0 (C*para*), 131.4 (C_3), 129.4 (C_2), 129.2 (C*meta*), 127.2 (C*ortho*), 62.9 (CH_2OH), 13.3 (Me). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; Found: C, 60.35; H, 5.99.

9a: ^{1}H-NMR ($CDCl_3$) δ: 7.90-7.80 (2H, m, Ar), 7.70-7.50 (3H, m, Ar), 6.20-6.40 (2H, m, H_2 and H_3), 6.10 (1H, s, H_5), 4.28 (2H, m, CH_2OH), 1.94 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 147.7 (C_4), 142.4 (C*ipso*), 138.7 (C_5), 133.7 (C*para)*, 129.2 (C*meta*), 127.2 C*ortho*), 127.0 (C_2), 124.5 (C_3), 63.2 (CH_2OH), 20.7 (Me). IR $\upsilon_{cm}{}^{-1}$: 3600-3200, 2990-2870, 1300, 1150, 700. Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; Found: C, 60.29; H, 6.01.

8b: ^{1}H-NMR ($CDCl_3$) δ: 7.88 (2H, m, Ar), 7.53 (3H, m, Ar), 7.30 (1H, m, Ar), 6.4-6.2 (3H, m), 4.25 (3H, s, CH_2OH). ^{13}C-NMR ($CDCl_3$) δ: 144.8 (C_4), 141.9 (C_5), 140.7 (C*ipso*), 133.4 (C*para*), 129.3 (C*meta*), 129.0 (C_3), 127.4 (C*ortho*), 124.9 (C_2), 62.1 (C_1). IR $\upsilon_{cm}{}^{-1}$: 3511, 2930, 2870, 1647, 1595, 1447, 1306, 1144, 999, 920, 828. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 60.40; H, 5.84; Found: C, 60.28; H, 5.77.

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