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Conversion of γ-substituted bicyclo[2.2.1] (*Z*)-vinylsulfones to the corresponding (*E*)-allylsulfones

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Abstract—The preparation of bicyclo[2.2.1] (*E*)-allylsulfones starting from the corresponding (*Z*)-vinylsulfones is described. Starting from 2,3-bis(phenylsulfonyl)norbornadiene **1**, the Michael addition of organometallic reagents followed by the base catalyzed isomerization affords (*E*)-allylsulfones in high yields. The procedure allows to obtain vinylidenic norbornenes which are characteristic nuclei of valuable biologically active compounds.

The synthesis of alkenes is a relevant field in organic chemistry. The double bond is one of the most versatile functional groups in organic synthesis, founding widespread application in a series of synthetic transformations such as epoxidation, dihydroxylation, hydroformylation, metathesis, cross-coupling, conjugated additions, polymerization and so forth. The growing interest towards synthons or building blocks containing this functionality has prompted the development of a variety of alkenylation methods;[1] among these, one of the most used engages the Wittig reaction of carbonyl compounds or related reactions.[2] However, both the steric demand as well as the structural rigidity of reactants can make the condensation-type reactions inefficient. Bridged polycyclic compounds are particularly sensitive to these effects, nevertheless, a number of valuable biologically active compounds are characterized by a bridged polycyclic skeleton bearing alkenyl substituents at the exocyclic position, such as the odour and fragrance compounds related to santalol and Dupical® (Fig. 1). The main constituents of natural sandalwood oil have been synthesized starting from enantiopure 3-methyl-2-norbornanones transforming the carbonyl function to a vinylidenic group by means of Wittig-type reactions.[3] Despite all the synthetic attempts devoted to the preparation of santalols in either enantiomerically pure or racemic form, no industrial viable process has yet been found. Therefore the perfumers have to mainly rely on cheaper synthetic substitutes.

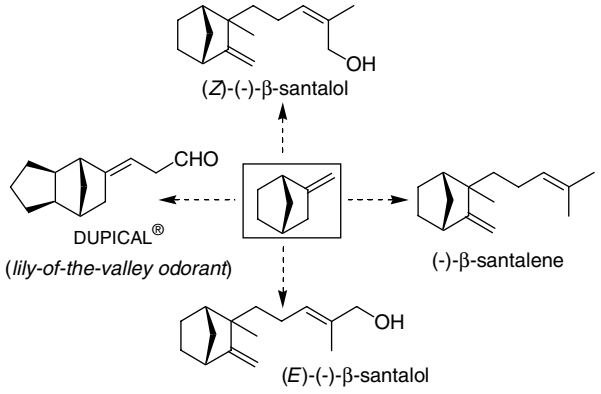

Figure 1.

Therefore, in connection with our interest on new synthetic strategies useful to achieve intermediates of odours and fragrances related to santalol, we have developed an efficient and inexpensive way to prepare γ-substituted bicyclo[2.2.1]allylarylsulfones containing an exocyclic double bond linked to the bridged skeleton at position 3 (Scheme 1).

We have previously reported on the reactivity of 2,3-bis(phenylsulfonyl)norbornadiene **1** towards Grignard

Keywords: Polycyclic alkenes; Vinylsulfones; Allylsulfones; Alkene isomerization; Grignard reagents.
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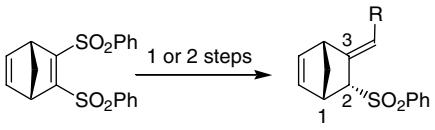
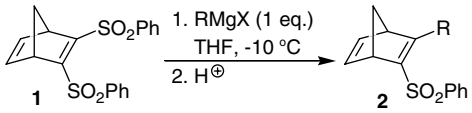
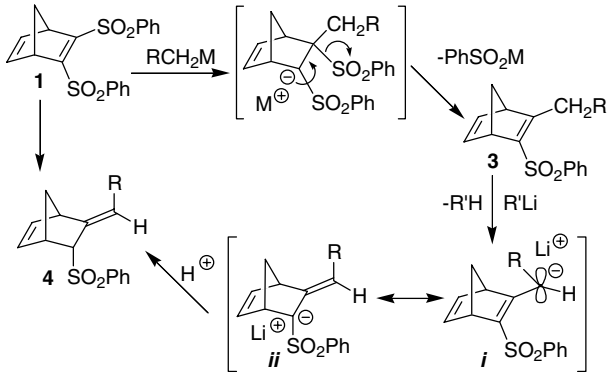


Scheme 1.



Scheme 2.



Scheme 3.

reagents (Scheme 2).[4] The reaction products are 3-aryl- and 3-alkyl-2-phenylsulfonylnorbornadienes **2**.

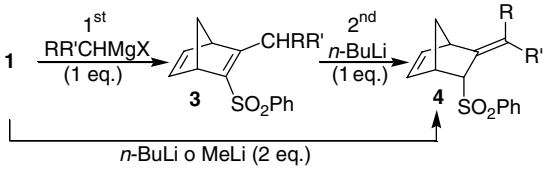
This Michael-type conjugated addition occurs through an addition–elimination mechanism analogously to what we have observed in the case of nucleophiles centred on heteroatoms (O, S and N).[5] Having a convenient access to vinylsulfones of structure **3** containing two active hydrogen atoms in the exocyclic γ-position, we have envisaged, based on the known chemistry of arylsulfonyl stabilized carbanions,[6,7] converting vinylsulfones **3** to the corresponding allylsulfones **4** by a base-induced γ-deprotonation process. The strategy is based on the formation of a stabilized allylic anion species **i** (Scheme 3) α to the phenylsulfonyl group (mesomer **ii**). The transformation is totally regioselective, converting γ-substituted (*Z*)-vinylsulfones to the corresponding allylsulfones of (*E*) stereochemistry. The transformation, occurring through a reaction pathway sterically controlled by the $PhSO_2$-group, exclusively furnishes *endo* oriented phenylsulfonyl isomers. This chemistry constitutes a straightforward tool for endocyclic to exocyclic isomerization of a C=C double bond of substituted norbornadienic systems.

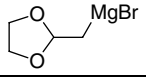
Both the nucleophilic and basic Grignard and organolithium reagents have been carefully evaluated. An optimized two-step route involving the sequential use of RMgX as the alkylating reagent, and of *n*-BuLi as base was pursued. According to our procedures,[4] a series of 3-alkyl-2-phenylsulfonyl norbornadienes, possessing different steric requirements has been prepared by reaction between **1** and a suitable Grignard reagent (RMgX). Compounds **3a**–**g** (Table 1) have been treated with an equivalent amount of *n*-BuLi at −20 °C. After 24 h at room temperature the reaction cleanly furnishes the corresponding 3-alkenyl **4a**–**g** derivatives. In all the cases, flash chromatography of the crude reaction mixtures (eluant: *n*-hexane/Et_2O in a 7/3 ratio) gave chemically pure compounds in very high yields (Table 1).

It is noted that, starting from **1**, the synthetic process could be realized in a single step by using two equivalents of organolithium reagent (*n*-BuLi or MeLi) (Table 1, runs 2 and 5). Alternatively, under similar reaction conditions, the use of Grignard reagents as base gave poorer results, furnishing complex reaction mixtures.

Previously, Otera et al. observed the isomerization of acyclic vinylsulfones to the corresponding allylsulfones as a side reaction during the synthesis of acetylenes from vinylsulfones.[6] Successively, Inomata et al. have reported the conversion of linear (*E*)- and (*Z*)-vinylsulfones to the corresponding allylsulfones under mild basic

Table 1. Alkylation-base induced isomerization of compound **1**



#	R	R′	Reagent	Yield (%) first step	Yield (%) second step	*endo*/*exo* Ratio
1	H	H	MeMgBr	82 (**3a**)	98 (**4a**)	75/25
2	H	H	MeLi	—	98 (**4a**)	75/25
3	Me	H	EtMgBr	85 (**3b**)	95 (**4b**)	100/0
4	Me	Me	*i*-PrMgCl	60 (**3c**)	Traces (**4c**)	100/0
5	*n*-Pr	H	*n*-BuLi	—	92 (**4d**)	100/0
6	Ph	H	BnMgCl	72 (**3e**)	89 (**4e**)	100/0
7	Allyl	H	AllylMgCl	91 (**3f**)	65 (**4f**)	100/0
8		H		78 (**3g**)	10 (**4g**)	100/0

conditions (DBU).[7] Moreover, they have found that (*E*)-vinylsulfones preferentially afford (*Z*)-allylsulfones as kinetically-controlled products, while (*Z*)-vinylsulfones give (*E*)-allylsulfones exclusively. These results were rationalized invoking the concept of *conformational acidity* (as a sort of kinetic acidity) related to a '*syn*-effect' (as shown in Scheme 4), which was explained in terms of 6π-electron homoaromaticity, σ-orbital interactions, dipole–dipole interactions and chelation.

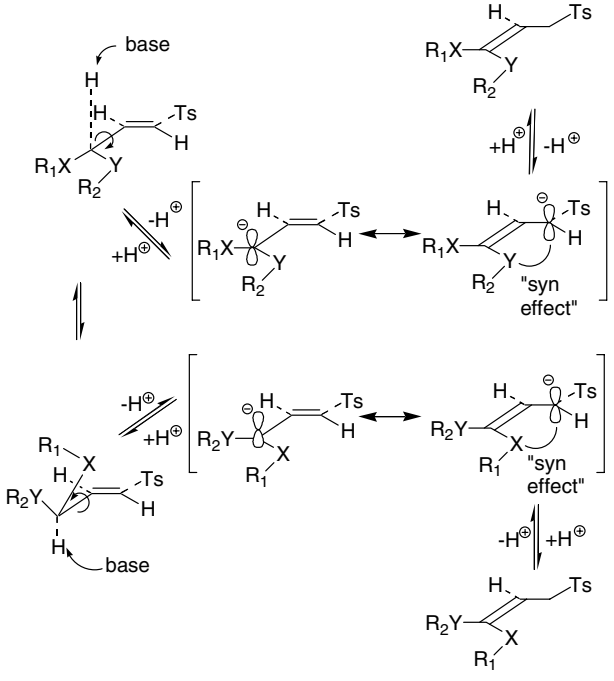
In the case of polycyclic derivatives **3** only the (*E*)-isomer can be obtained because of the hindered rotation around the RC–C=C single bond (Fig. 2) due to steric reasons.

In fact, the stabilization of the negative charge exerted by the phenylsulfonyl group at the position α (Scheme 3, mesomer **ii**) requires a suitable interaction between three pure p orbitals arranged in an almost parallel situation. Under these circumstances the substituents at the γ exocyclic position lie orthogonal to the pure p orbital, therefore obliging one of the substituents to occupy a position subjected to steric interactions with the phenylsulfonyl group. As expected, even the slight modification introduced at the exocyclic position γ to the phenylsulfonyl group, by the substitution of one of the hydrogen atoms with an alkyl group, inhibits the deprotonation processes because of the difficulties to arrange the phenylsulfonyl group and the internal substituent of the alkyl moiety in a suitable position. This effect was also observed in the case of the isopropyl derivative **3c** (Table 1, run 4) (Fig. 3) and the dioxolanic derivative **3g** (Table 1, run 8) making it difficult to achieve tetrasubstituted olefin by this route.

As recently described by Knochel and co-workers,[8] in the case of 2-phenyl-3-alkylbicyclo[2.2.1]hept-2,5-dienes the phenyl substituent can exert a stereoelectronic effect similar to those aforementioned for the $PhSO_2$-group.

The structures of compounds **4a**–**g** have been assigned by NMR spectroscopy (NOESY, HMQC and HMBC). In this regard, the case of **3f** is representative (Fig. 4). The presence of a vicinal coupling between H_2 and H_1 is helpful to recognize the *exo* configuration of H_2. Moreover the NOESY map shows a number of diagnostic interactions: among these, particularly significant are those between H_2 and the vinylic exocyclic proton Hd, as well as between Ha and H_4 as the proposed structure requires.[9]

In conclusion, it is possible to consider the vinylsulfone functionality as a masked carbonyl function. Taking into account this assumption and having interest in the preparation of optically active alkenyl substituted bis(phenylsulfonyl) norbornadienes, we have explored the possibility to access this class of compounds through an enantioselective addition of Et_2Zn catalyzed by enantiopure aminoalcohols. Therefore, in a preliminary experiment, a THF sample of **1** was treated with Et_2Zn in the presence of optically pure (−)-ephedrine under the classical conditions adopted for the aminoalcohol catalyzed Et_2Zn addition to carbonyl compounds. We have observed after 24 h that the reaction affords the optically active 3-ethyl-2-phenylsulfonylnorbornadiene [20% ee (HPLC): Chiralpak OT(+) (Daicel), MeOH 100%, 5 °C].



Scheme 4.

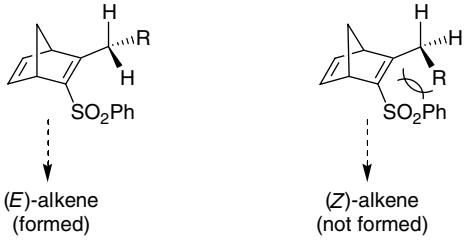


Figure 2.

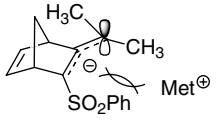


Figure 3.

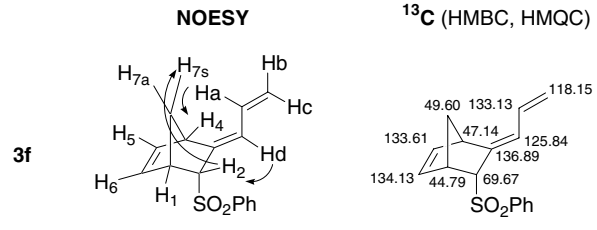


Figure 4.

Acknowledgements

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9. Compound *endo*-**4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (d_b, 1H, $J = 8.8$ Hz, H_{7syn}), 1.64 (dt, 1H, $J = 8.8$, 2.0 Hz, H_{7anti}), 3.04 (s_b, 1H, H_4), 3.29 (s_b, 1H, H_1), 4.20 (q, 1H, $J = 2.4$ Hz, H_{2exo}), 5.25 (d, 1H, $J = 2.0$ Hz, =CH*H*), 5.32 (d, 1H, $J = 1.6$ Hz, =C*H*H), 6.05 (dd, 1H, $J = 5.6$, 2.8 Hz, H_5), 6.13 (dd, 1H, $J = 5.6$, 3.2 Hz, H_6), 7.52–7.67, 7.87–7.94 (series of m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$, 1C atom omitted): δ 45.45, 49.81, 52.29, 69.00, 110.01, 128.71, 128.95, 133.07, 133.54, 135.08, 143.15. Compound *exo*-**4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (dq, 1H, $J = 9.2$, 1.6 Hz, H_{7syn}), 2.01–2.05 (m, 1H, H_{7anti}), 3.17 (s_b, 1H, H_1), 3.28 (s_b, 1H, H_4), 3.49 (q, 1H, $J = 2.0$, H_{2endo}), 5.11 (d, 1H, $J = 1.6$ Hz, =CH*H*), 5.26 (dt, 1H, $J = 2.0$, 0.8 Hz, =C*H*H), 6.09 (dd, 1H, $J = 5.6$, 3.2 Hz, H_6), 6.28 (dd, 1H, $J = 5.6$, 3.2 Hz, H_5), 7.52–7.69, 7.87–7.97 (series of m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.75, 46.29, 50.66, 67.46, 111.13, 128.69, 128.89, 129.12, 133.61, 135.57, 139.93, 142.82. Compound **4e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, 1H, $J = 8.7$ Hz, H_{7syn}), 1.66 (d, 1H, $J = 8.7$ Hz, H_{7anti}), 3.12 (s_b, 1H, H_1), 3.80 (s_b, 1H, H_4), 4.37 (*t*, 1H, $J = 3.0$ Hz, H_{2exo}), 6.08 (dd, 1H, $J = 5.3$, 2.6 Hz, H_6), 6.18 (dd, 1H, $J = 5.3$, 2.9 Hz, H_5), 6.97 (s, 1H, =C*H*Ph), 7.24–7.98 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.66, 48.01, 50.18, 69.92, 125.74, 127.06, 128.23, 128.34, 128.86, 128.98, 133.60, 134.05, 134.17, 136.62, 137.32, 139.32. Compound **4f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, 1H, $J = 8.4$ Hz, H_{7syn}), 1.66 (dt, 1H, $J = 8.6$, 2.0 Hz, H_{7anti}), 3.03 (s_b, 1H, H_1), 3.73 (s_b, 1H, H_4), 4.25 (s_b, 1H, H_{6exo}), 5.13 (dd, 1H, $J = 10.4$, 2.4 Hz, H_b), 5.25 (dd, 1H, $J = 16.8$, 2.4 Hz, H_c), 6.01 (dd, 1H, $J = 5.2$, 2.4 Hz, H_6), 6.05 (dd, 1H, $J = 5.2$, 3.2 Hz, H_5), 6.49 (d, 1H, $J = 10.4$ Hz, H_d), 6.54 (dt, 1H, $J = 16.8$, 10.8 Hz, H_a), 7.50–7.75, 7.79–8.01 (series of m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.91, 47.14, 49.60, 69.67, 118.15, 125.84, 128.77, 128.93, 133.13, 133.59, 133.61, 134.13, 136.89, 139.42.