Sulfone directed alkylative bridge cleavage of oxabicyclic vinyl sulfones with organolithium reagents (1)

Oxabiciclo vinil sulfonas: Rotura alquilante directa del puente con reactivos organolíticos

ARJONA, O. and PLUMET. J.
Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain.

ABSTRACT

An efficient regio- and stereocontrolled methodology for the alkylative bridge cleavage of oxabicyclic vinyl sulfones is described. A range of 7-oxabicyclic[2.2.1.]heptenyl and 8-oxabicyclic [3.2.1.]octenyl sulfones has been found to undergo an overall *syn* S_N2' opening when treated with a wide variety of organolithium reagents and lithium aluminum hydride. In this manner, highly functionalized cyclohexenyl and cycloheptenyl sulfones, versatile synthetic intermediates, are now available in high yields. The complete stereoselectivity encountered in the *exo* conjugate addition may be explained by chelation of the organometallic reagent with the oxygen bridge and steric factors. Furthermore, less-strained substrates allow for complete control of the addition and elimination stages.

Key words: Oxabicyclic compounds. Syn S_N2'. Exo conjugate addition.

RESUMEN

Se describe una interesante rotura alquilante regio-y estereocontrolada del puente de oxabiciclo vinil sulfonas. Las 7-oxabiciclo[2.2.1] heptenil y 8-oxabiciclo [3.2.1.] octenil sulfonas sufren aperturas syn S_N2' cuando se tratan con una amplia variedad de reactivos organolíticos e hiduro de litio y aluminio. De esta forma, se obtienen ciclohexenil y cicloheptenil sulfonas, altamente funcionalizadas, que son intermedios sintéticos versátiles. La completa estereoselectividad encontrada en la adición conjugada exo puede explicarse en base a la quelación del reactivo organometálico con el oxígeno puente.

Palabras clave: Compuestos oxabiciclicos. Syn S_N2'. Adición conjugada exo.

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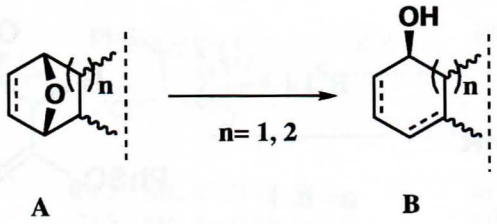
INTRODUCTION

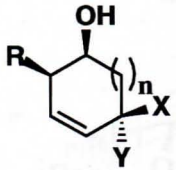
Oxabicyclic compounds are valuable intermediates (2) for the synthesis of a variety of molecules of biological interest (3). Recent advances in asymmetric Diels-Alder processes (4), enzymatic (5) and chemical (6) resolutions should render these intermediates even more attractive to organic chemists and encourage the search for new regio- and stereocontrolled functionalizations of these substrates. A crucial transformation in many syntheses employing oxabicyclic intermediates **A** (Scheme I) has been the cleavage of the oxygen bridge to produce functionalized cyclohexane or cycloheptane derivatives **B**. To this end, many groups have developed different solutions including β-eliminations of suitable derivatives (7), treatment with strong acids (8), reductive elimination of *endo* functionalities such as Cl or SO_2Ph (9), fragmentation (10) and hydrolytic conditions (11). However, all these methods have failed in several cases (9, 12) and none of the above protocols allow for the construction of carbon-carbon bonds throughout the bridge cleavage step. Thus, the rigid bicyclic structures, powerful elements for stereo- and regiocontrol, are not utilized for this crucial transformation.

Several years ago we reported a new regio- and stereoselective cleavage of the oxygen bridge of simple oxanorbornenic alcohols **4** and **5** with organolithium reagents to produce cyclohexenediols **10** (13) (Scheme I). While this methodology, coupled with our procedures to prepare *endo* **4** or *exo* **5** substrates (14) was later found to be quite general (15), the inherent lack of regiocontrol became apparent at an early stage; namely, regiocontrolled conditions to prepare isomeric cyclohexenols **14** could not be found. In fact, either protection of the free alcohol, **7**, or separation of the free alcohol from the reactive center by a methylene bridge, **9**, resulted in dramatic losses of regioselectivity. The same behavior was observed in the case of 8-oxabicyclo[3.2.1.]octenyl carbinols **6** and **8** (16a). Thus, the reaction of **6** with *t*-BuLi affords compound **11** regioselectively whereas in the case of **8**, a *ca.* equimolecular mixture of regioisomeric hydroxycycloheptenes **13** and **15** was obtained. These limitations and our interest in the development of regiospecific methodology to achieve the alkylative bridge cleavage towards either isomer (**12-13** or **14-15**) was a matter of intensive research in our laboratory.

The introduction of an electron withdrawing substituent on the double bond was envisaged to be an appealing and straightforward solution to this problem. In this manner, the regiochemistry of the process should be readily controlled and furthermore the synthetic potential of the opening products would be increased substantially. A phenylsulfonyl functionality (Scheme II) appeared particularly attractive at this stage since the required substrates **C** and **E** should be readily available from a variety of oxabicyclic compounds (17) (see below) and the synthetic versatility of vinyl sulfones is well documented (18, 19). It was

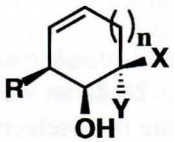
Scheme I





1 X= CN, Y= OAc, n= 1
2 X= Y= O, n= 1
3 X= Y= O, n= 2
4 X= H, alkyl, vinyl, aryl, Y= OH, n= 1
5 X= OH, Y= alkyl, vinyl, aryl, n= 1
6 X= Me, Y= OH, n= 2
7 X= Me, Y= OBn, n= 1
8 X= Me, Y= OBn, n= 2
9 X= H, Y= CH_2OH, n= 1

10 X= H, alkyl, vinyl, aryl, Y= OH, R= Me, *n*-Bu, Ph, etc., n= 1
11 X= Me, Y= OH, R= *t*-Bu, n= 2
12 X= Me, Y= OBn, R= *n*-Bu, n= 1
13 X= Me, Y= OBn, R= *t*-Bu, n= 2

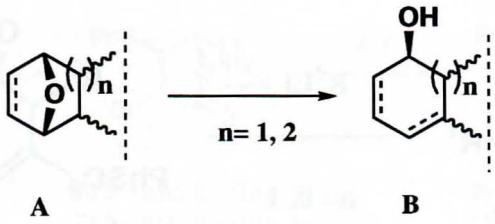


14 X= Me, Y= OBn R= *n*-BuLi, n= 1
15 X= Me, Y=OBn, R= *t*-BuLi, n= 2

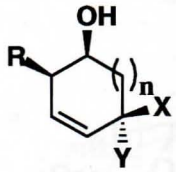
expected that conjugate addition of an organolithium reagent (R^3Li) to vinyl sulfones **C** and **E** would generate an α-sulfonyl carbanion which would undergo ß-elimination giving rise to adducts **D** and **F** respectively.

In this paper we report a full account of our efforts in this field (16) which have resulted in an efficient regio- and stereocontrolled methodology to achieve the alkylative bridge cleavage of oxabicyclic vinyl sulfones to produce substituted hydroxycyclohexenyl or cycloheptenyl vinyl sulfones.

Scheme I

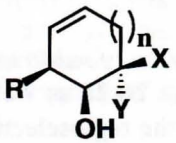


A **B**



1 X= CN, Y= OAc, n= 1
2 X= Y= O, n= 1
3 X= Y= O, n= 2
4 X= H, alkyl, vinyl, aryl, Y= OH, n= 1
5 X= OH, Y= alkyl, vinyl, aryl, n= 1
6 X= Me, Y= OH, n= 2
7 X= Me, Y= OBn, n= 1
8 X= Me, Y= OBn, n= 2
9 X= H, Y= CH_2OH, n= 1

10 X= H, alkyl, vinyl, aryl, Y= OH, R= Me, *n*-Bu, Ph, etc., n= 1
11 X= Me, Y= OH, R= *t*-Bu, n= 2
12 X= Me, Y= OBn, R= *n*-Bu, n= 1
13 X= Me, Y= OBn, R= *t*-Bu, n= 2



14 X= Me, Y= OBn R= *n*-BuLi, n= 1
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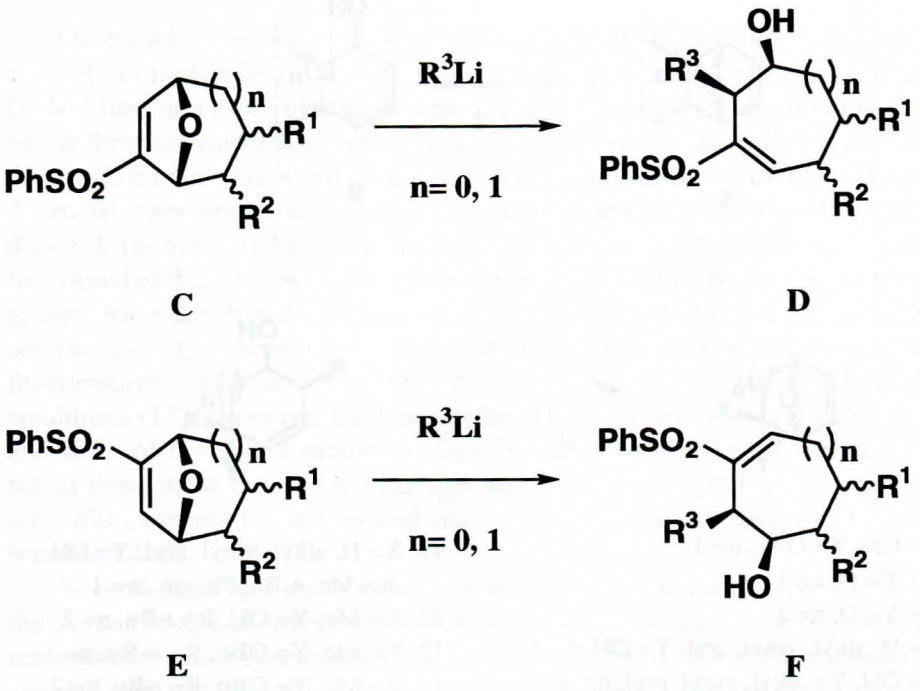
Scheme II

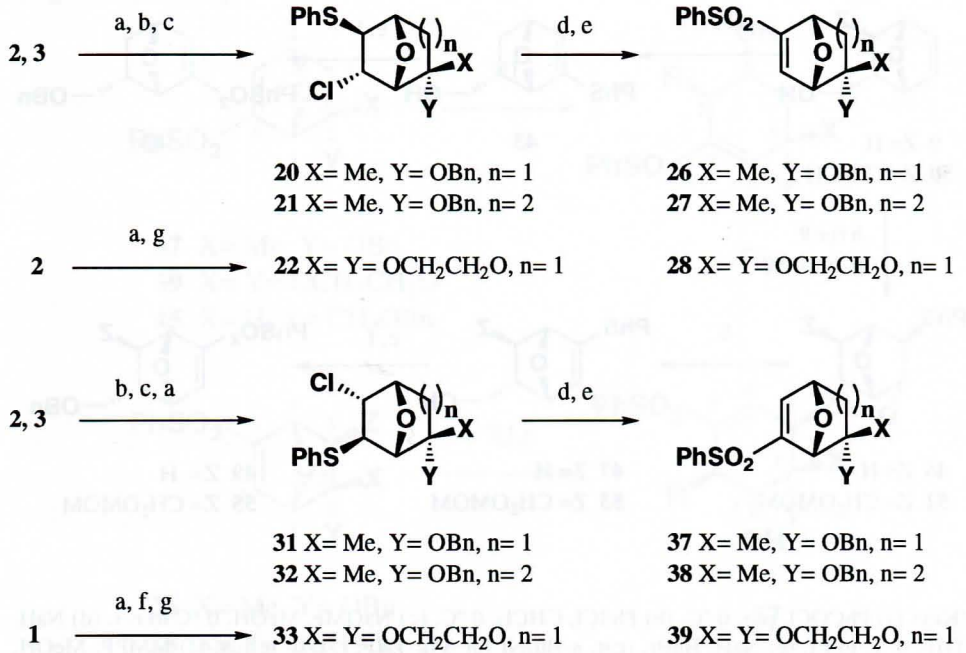


RESULTS AND DISCUSSION

Preparation of substrates. Scheme III outlines the synthetic routes to obtain vinyl sulfones **26-28** as well as their regioisomers **37-39**. The key step of these syntheses is the regioselective addition of sulfenyl halides under kinetic control to bicyclic substrates, such as **1** and **2**, controlled by remote substitution on C-2 (17). Thus, addition of phenylsulfenyl chloride to ketones **2** and **3** followed by functional group manipulations affords chlorosulfides **20**, **21** and **22** (20). Alternatively, cyanoacetoxy derivative **1** and the *endo*-benzyl ethers (resulting from reaction of MeMgBr with **2** and **3** (14, 16a) and subsequent benzylation) give rise to regioisomeric chlorosulfides **31**, **32** and **33**, presumably under steric control (17). Subsequent oxidation and elimination complete the sequence (21).

In order to extend the scope of the methodology, we prepared substrates **45**, **49** and **55** as shown in Scheme IV (see experimental section). Oxanorbornene methanol **9** was benzoylated and PhSCl was added with complete steric control (22). Removal of the benzoate group and treatment with sodium hydride, interestingly, resulted in smooth formation of vinyl sulfide **43** (23). Standard benzylation and oxidation afforded **45**. Alternatively, tricyclic sulfide **46** (22) was treated with an excess of *n*-BuLi in an effort to test the applicability of our strain-directed

Scheme III[a]



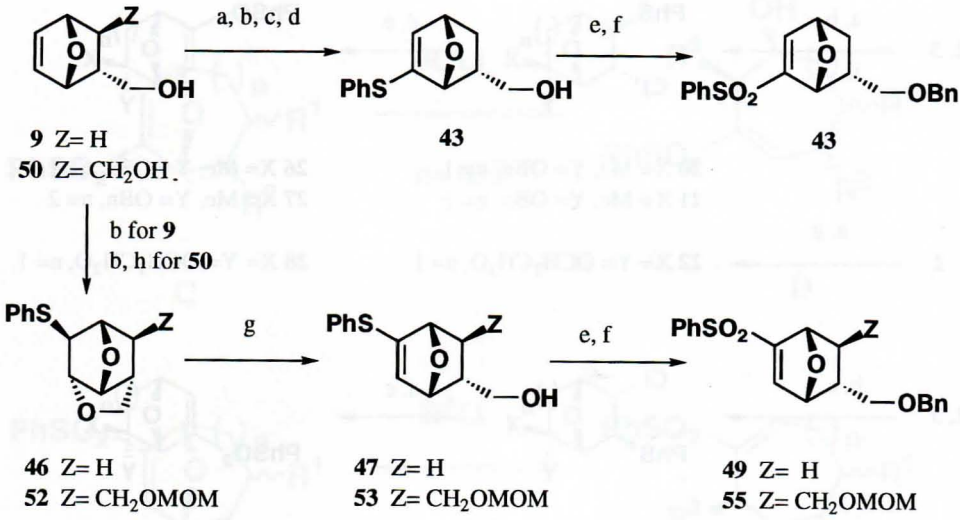
[a]**Key:** (a) PhSCl, $CHCl_3$ or CH_3CN, 0 °C. (b) MeMgBr, Et_2O 0 °C. (c) NaH, BnBr, (cat. *n*-Bu_4NI for **21** and **32**= THF, 0 °C to reflux. (d) *m*CPBA, K_2CO_3, 0 °C to r.t. for **26, 28, 37** and **39**; MMPP; MeOH, 0 °C to r. t. for **27** and **38**. (e) DBU, CH_2Cl_2, 0 °C. (f) 1. NaOMe, MeOH. 2. aq CH_2O, 0 °C to r.t. (g) Ethyleneglycol, *p*-TsOH, C_6H_6, reflux. **Overall yields, 26**: 26% from **2**; **27**: 54% from **3**; **28**: 62% from **2**; **37**: 33% from **5; 38:** 64% from **3**; **39**: see reference 21.

ß-eliminations (24) to this case, to afford an excellent yield of vinyl sulfide **47**. Vinyl sulfone **49** was prepared as above. On the other hand, diol **50** (25) was converted to the highly substituted and differentially protected vinyl sulfone **55** using an analogous synthetic route, i. e., formation of the tricyclic sulfide, strained-directed ring opening and functional group manipulations.

Alkylative Bridge Cleavage

7-Oxabicyclo[2.2.1.]heptenes systems. In view of previous efforts involving S_N2' additions of organometallic reagents to cyclic vinyl sulfones (26, 27), we selected Grignard, cuprate and organolithium reagents for our study. Preliminary experiments with methyl Grignard and cuprate reagents did not

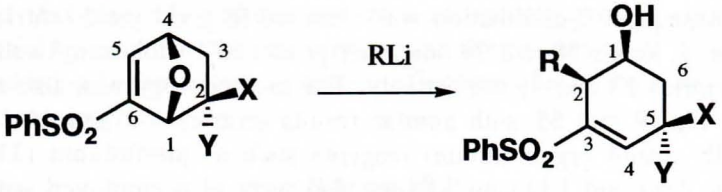
Scheme IV[a]



[a]**Key:** (a) PhCOCl, pyr, 0 °C. (b) PhSCl, $CHCl_3$, 0 °C. (c) NaOMe, MeOH, 0 °C to r. t. (d) NaH, THF, 0 °C to r.t. (e) NaH, BnBr, (cat. *n*-Bu_4NI for **55**), THF, r. t. to reflux. (f) MMPP; MeOH, 0 °C to r. t. (g) *n*-BuLi, THF, –78 °C. (h) $CH_2(OMe)_2$, *p*-TsOH, CH_2Cl_2, reflux. **Overall yields, 45**: 61% from **9**; **49**: 58% from **46**; **55**: 37% from **50**.

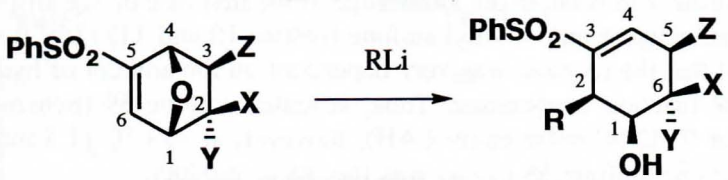
produce the desired transformation. Accordingly, we examined the reaction between **37** and an excess of MeLi (3 equiv, –78 °C, THF, 10 min) and an excellent yield of **56a** was obtained. Encouraged by this smooth transformation, we explored other organolithium reagents and these results are gathered in Table I. In clear contrast to MeLi, the reaction between **37** and *n*-BuLi (2 equiv, THF) was remarkably slow, even at 0 °C, and, more importantly, the isolated yield of **56b** were very low and variable amounts of other by-products, tentatively characterized as desulfonylated **37** and **56b**, were also produced. After considerable experimentation, we found that the use of toluene, a less coordinating solvent (28) afforded excellent yields of alkylative opening product **56b** (entry 2). Similarly, PhLi and vinyllithium (29) (2 equiv) gave excellent yields of **56c** and **56d** respectively (entries 3 and 4). While we do not fully understand the differences found between MeLi and *n*-BuLi in THF, the crucial effect of the use of toluene for the latter is noteworthy (30).

Table I.—S_N2' Opening Reactions of 7-Oxanorbornenic Vinyl Sulfones with Organolitium Reagents and $LiAlH_4$



37 X= Me, Y= OBn
39 X= Y= OCH_2CH_2O
45 X= H, Y= CH_2OBn

56



26 X= Me, Y= OBn
28 X= Y= OCH_2CH_2O
49 X= Z= H, Y= CH_2OBn
55 X=H, Y= CH_2OBn, Z= CH_2OMOM

57

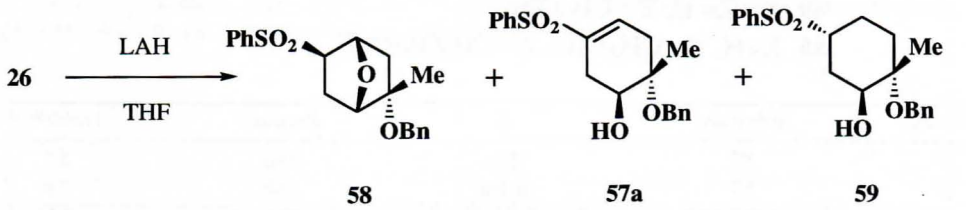
Entry	*Substrate*	*R*	*Product*	*Yield(%)*[a]
1[b]	37	Me	56a	87
2[c]	37	n-Bu	56b	78
3[c]	37	Ph	56c	86
4[c]	37	Vinyl	56d	95
5[b]	39	Me	56e	85
6[c]	45	Me	56f	81
7[d]	45	n-Bu	56g	78
8[d]	45	Allyl	56h	64
9[d]	45	2-Propenyl	56i	67
10[b]	39	H[e]	56j	62
11[b]	26	H[e]	57a	65
12[b]	26	Me	57b	80
13[b]	28	Me	57c	75
14[b]	49	Me	57d	82
15[d,f]	49	1-Hexynyl	57e	74
16[d]	49	2-Furyl	57f	69
17[b]	55	Me	57g	88

NOTES: [a]Unoptimized yields of pure products. [b]In THF, –78 °C. [c]In Toluene, –78 °C. [d]In a mixture Tol/Et_2O, 1:1, –78 °C. [e]LiAlH4. [f]0 °C.

To explore the anticipated regiocontrolled bridge opening, vinyl sulfone **26** was treated with MeLi, and adduct **57b** resulting from nucleophilic addition to C-6 and subsequent ß-elimination was obtained in good yield (entries 11 and 12). Similarly, ketals **28** and **39** smoothly produced cyclohexenyl sulfones **57c** and **56e** (entries 13 and 5) respectively. The methodology was also applied to substrates **45**, **49** and **55** with similar results (entries 6-9 and 14-17). Other synthetically useful organolithium reagents such as allyllithium (31, 32), 2-furyllithium (33) and 1-hexynyllithium (34) were also employed with similar results.

In order to extend the scope of this methodology, the reactions between oxanorbornenic sulfones **26** and **39** and lithium aluminum hydride (4 molar equiv, –78 °C) were studied. Thus, fair yields of cyclohexenyl sulfones **57a** and **56j** were realized in what, to our knowledge, is the first case of S_N2' displacements of a hydride reagent onto a vinyl sulfone (entries 10 and 11) (35). It should be mentioned that the reaction was very dependent on the amount of hydride used and on the reaction temperature. Thus, saturated sulfone **59** (Scheme V) was obtained at 0 °C (4 molar equiv LAH); however, at –78 °C (1.5 molar equiv LAH), bicyclic sulfone **58** (49%) was the major product.

Scheme V



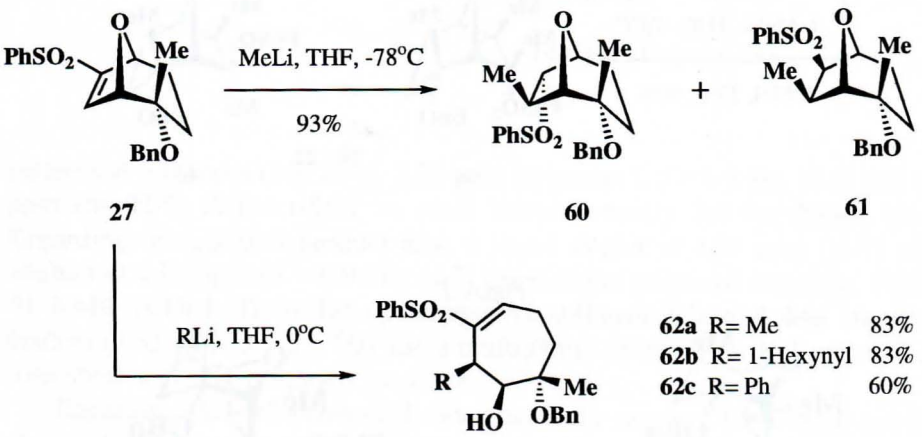
58 **57a** **59**

The regio- and stereochemistry of these products were readily established by spectroscopic techniques, particularly by ^{1}H NMR with the aid of selective decouplings and DNOE experiments. For instance, **56a** and **57b** presented quite different splitting patterns for the vinylic protons (**56a**, d, J = 1.3 Hz; **57b**, ddd, J = 5.4, 3.0, 2.4 Hz). In addition, H-1 exhibits a trans diaxial coupling (12.6 Hz) in **56a** and an equatorial-axial coupling (3.7 Hz) in **57b**. The large homoallylic coupling found for **57b** ($J_{2,5ax}$ = 3.0 Hz) is also noteworthy.

8-Oxabicyclo[3.2.1.]octenesystems. The extension of this methodology to 8-oxabicyclic[3.2.1.]octene sulfones **27** and **38** was explored in order to assess the influence of a less strained oxygen bridge in the overall S_N2' process. Additionally, the synthetic potential of the resulting products (not easily available highly functionalized cycloheptenes) was particularly attractive (36). In this context,

and in sharp contrast with [2.2.1.] systems, the reaction of **27** with MeLi (1.1 equiv, THF, –78 °C) gave a *ca.* 50:50 mixture of conjugate addition products **60** and **61** (Scheme VI) without any trace of opening product. However, we were pleased to discover that just carrying out the reaction at 0 °C allowed for a facile addition/ß-elimination sequence affording **62a** in excellent yield as a single diastereomer.

Scheme VI



On the other hand, a single addition product **63** was obtained from **38** and MeLi at –78 °C, under a variety of reaction conditions (Tol or THF; 1-3 equiv of MeLi), after quenching with aq. NH_4Cl or D_2O the stereoselectively generated *endo*-lithiosulfonyl derivative (Scheme VII). This selectivity may be attributed to steric interactions about the *endo* face in the diastereomeric carbanion (Figure I, **A**) and/or coordination with the *endo*-benzyloxy moiety at C-2 (Figure I, **B**) which results in retention of the carbanion configuration when small electrophiles are added. However, trapping with MeI led to a 78:22 mixture of **64** and **65**, being the major product the one arising from inversion due to steric hindrance to electrophilic *endo* attack (37).

Since the ring opening of regioisomeric sulfone **38**, could not be achieved at 0 °C (a mixture of **63a** and **66a** in 86:14 ratio was obtained, Scheme VIII) we envisaged to take advantage of the known compatibility of organometallic reagents and strong Lewis acids at low temperatures (38). Thus, after complete addition of MeLi to **38** in toluene at –78 °C (TLC), 3.0 equiv of $BF_3{\cdot}OEt_2$ were added to trigger the opening and **66a** was smoothly obtained in good yield. Alternatively, the system $MeLi{\cdot}BF_3$ at –78 °C directly effected the same epoxidic cleavage (39). Not surprisingly, the presence of a less coordinating solvent

Scheme VII

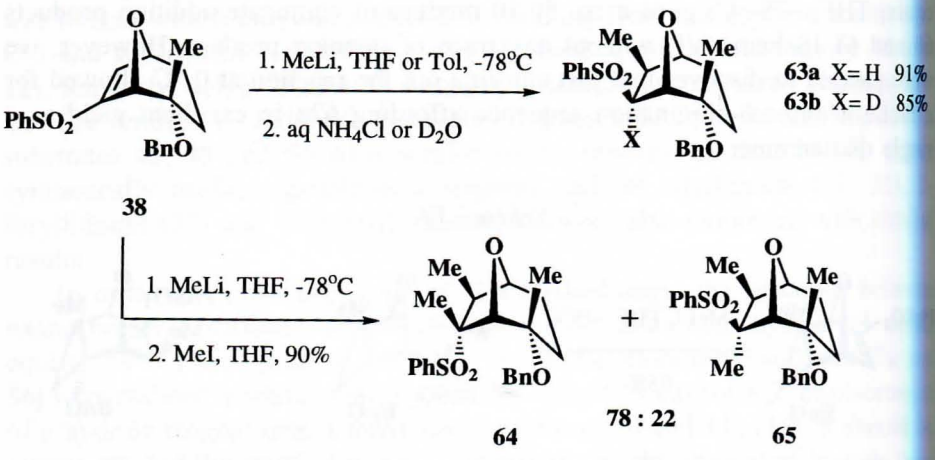
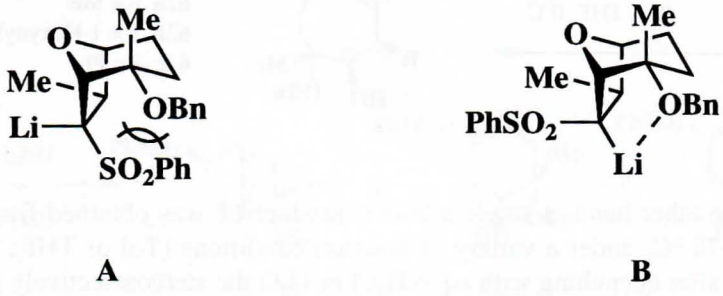


Figure I

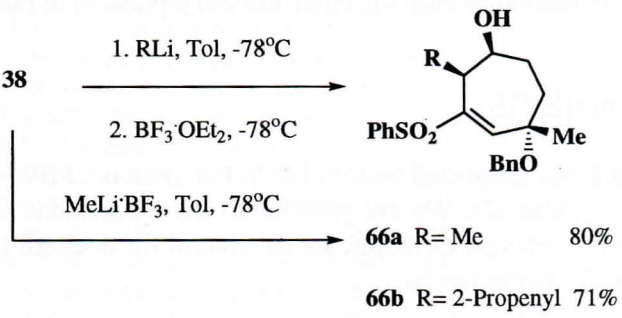


(toluene) instead of THF was again required for these transformations (40), where in this latter case, MeLi is possibly undergoing a direct addition to an oxabicycle-boron trifluoride complex.

The desired hydroxycycloheptenyl sulfones could also be prepared with a variety of organolithium reagents with different electronic characteristics (Schemes VI and VIII) in order to secure the generality of the process. The possibility of obtaining an S_N2' displacement with concomitant opening of a not highly strained oxygen bridge using 1-alkynyllithium reagents (**62b**) is remarkable.

The structure and stereochemistry of these products were also determined by spectroscopic methods (^{1}H NMR, selective decouplings and DNOE techniques). Thus, ^{1}H NMR analyses of pure addition products showed a broad singlet at 3.79 ppm (H-1) and a doublet at 3.75 ppm (J = 9.1 Hz, H-6) for **61**, indicating an *endo* stereochemistry for H-6 and H-7. On the contrary, **60** exhibits splitting

Scheme VIII



patterns at 3.60 ppm (brs, H-1), 3.32 ppm (apparent t, J = 6.8 Hz, H-6) and 4.50 ppm (m, H-5) that confirm an *endo* stereochemistry for the $PhSO_2$ group. Regarding the addition product **63a**, a broad singlet at 4.15 ppm (H-1) and a doublet at 4.11 ppm (J = 9.9 Hz, H-7) ensured the proposed structure. Finally, ^1H NMR ($CDCl_3$+D_2O) for cycloheptenyl sulfones **62a** and **66a** showed a doublet (3.52 ppm, J = 2.5 Hz) and a multiplet (3.66 ppm) for H-1 respectively, consistent with the proposed structure.

Regarding the stereochemical outcome of the process, the overall *syn* S_N2' observed is in good agreement with previous knowledge in the literature for epoxy vinyl sulfones (26d, 39b), and may be attributed to direct addition *via* chelation of the organometallic reagent with the oxygen bridge. The *syn* relative stereochemistry for the bridge opening of [3.2.1.] systems was unequivocally confirmed based on the previous assignment of addition products **60**, **61** and **63** (41). For these substrates the Lewis acid or temperature-controlled conditions for the b-elimination are crucial to the success of the process. In both cases, the beneficial effects of toluene may support the hypothesis of chelation. Nevertheless, the influence of steric control directing the approach of the nucleophile cannot be ruled out due to the bicyclic character of our substrates (15, 16).

CONCLUSIONS

A new and general methodology to effect the regio- and stereocontrolled S_N2' alkylation and reduction of oxabicyclic vinyl sulfones with concomitant cleavage of the oxygen bridge has been developed. The scope of the methodology has been defined and, in this manner, highly functionalized cyclohexenyl and cycloheptenyl sulfones bearing up to four contiguous chiral centers are produced in high yields. The diastereoselective nature of these procedures indicates that enantiomerically pure cleavage products should be readily available from the

corresponding Diels-Alder adducts (4-6). The application of this methodology to the synthesis of natural products is being currently pursued in our laboratories.

ACKNOWLEDGMENTS

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