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Regio- and Stereocontrolled Alkylative Ring Opening of Unsymmetrical 8-Oxabicyclo[3.2.1]octene Systems. Synthesis of Highly Substituted Hydroxycycloheptenyl Sulfones.

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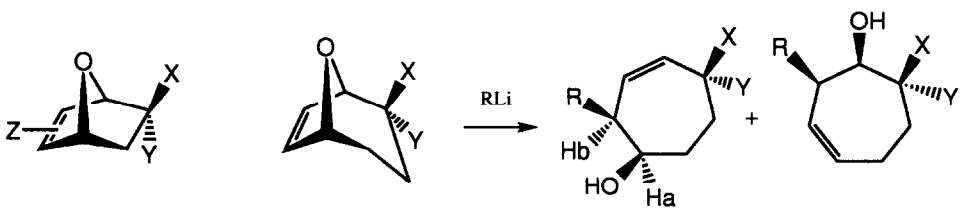
Key words: Nucleophilic Ring Opening; Conjugate Additions; Vinyl Sulfones; Hydroxycycloheptenyl Derivatives.

Abstract: *The organolithium mediated bridge opening of unsymmetrically substituted 8-oxabicyclo[3.2.1]octene derivatives* ***6, 7****, proceeds with complete regio- and stereoselectivity to afford highly functionalized hydroxycycloheptenyl sulfones* ***10, 12*** *in high yields. It was also found possible to control the conjugate addition/β-elimination sequence towards the synthesis of adducts* ***8, 9, 11****.*

The ring opening of oxabicyclic systems constitutes a crucial transformation in many organic synthetic methodologies[1,2] in order to obtain compounds with known relative stereochemistry. In previous papers we have developed satisfactory procedures for totally regio- and stereoselective alkylative bridge cleavage of 7-oxabicyclo[2.2.1]heptene systems **1** using an unprotected hydroxyl group[3] or a phenyl sulfonyl group[4] as an element of regiocontrol. Despite several recent reports by Lautens[5] that establish the nucleophilic ring opening of related *meso* oxabyciclic [2.2.1] and [3.2.1] compounds[6], only substitution at the bridgehead position allows for regioselective bridge cleavage using alkyllithium reagents exclusively[7]. Thus, the extension of our investigations of these reactions to unsymmetrical, simple, 8-oxabicyclo[3.2.1]octene alcohols **2b-c** and vinyl sulfones **6, 7** would be a desirable, not yet explored, goal because: i) the regioselectivity in the reaction of **2b** with organolithium reagents was a matter of concern with respect to **1a**[3] due to the distance of the *endo* alkoxide from the π-system[8,9]; and ii) the presence of a less strained oxygen bridge could introduce important modifications in the β-elimination process when vinyl sulfones are used to guide the incoming nucleophile.



1a X = H, alkyl, vinyl, aryl
Y = OH; Z = H

1b, c X = Me; Y = OBn;
Z = $PhSO_2$

2a X = Y = O

2b X = Me; Y = OH

2c X = Me; Y = OBn

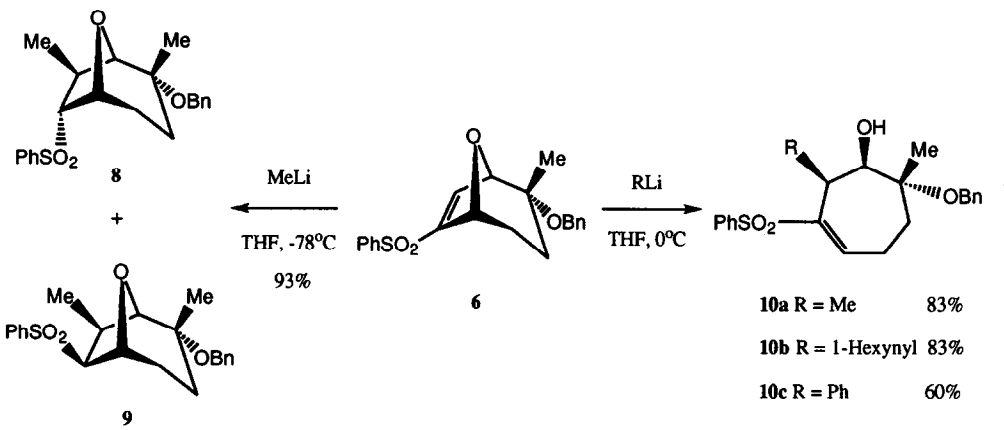
3b R = *n*-Bu

4b R = *t*-Bu

4c R = *t*-Bu

5c R = *t*-Bu

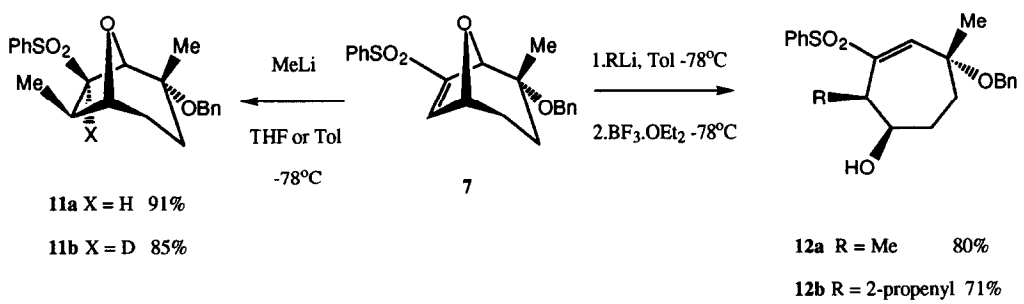
In this context, reaction of carbinol **2b**, prepared from **2a**[10] (MeMgBr, Et_2O, 0°C, 100%) with a variety of alkyllithum reagents was examined. After disapointing results when a large excess of MeLi, PhLi, or *n*-BuLi was used[11], reaction with 8.0 equivalents of *t*-BuLi (Et_2O, 0°C to r.t., 20h, 84%)[12] cleanly afforded **4b** in a regio and stereospecific fashion towards product derived from *exo* attack at C-6 position[13]. No other products could be detected within the detection limit of 300 MHz ^1H NMR. Again, the presence of an alkoxide group was crucial for this unprecedent selectivity because benzylation of **2b** (NaH, BnBr, cat. *n*-Bu_4NI, THF 97%) and reaction with 5.0 equivalents of *t*-BuLi under the same conditions smoothly produced a 58:42 mixture of regioisomeric cycloheptenols **4c** and **5c** in 92% overall yield[12,13].



Scheme 1

As for [2.2.1] systems, a straightforward solution to this inherent lack of regiocontrol was the introduction of a phenyl sulfonyl functionality on the double bond since the versatility of vinyl sulfones is well documented[14,15] and the synthetic potential of the ring opening products would be increased substantially[16,17]. Moreover, the required substrates **6,7** were readily available from **2a**[18] in excellent yields. In sharp contrast with [2.2.1] systems[4] treatment of **6** with 1.0 equivalents of MeLi in THF at -78°C for 10 min. led to the isolation of a 1:1 mixture of addition products **8** and **9**[12] without any trace of opening product after quenching with aqueous NH_4Cl (Scheme 1)[19].

To our delight, increasing the temperature to 0°C allowed for the addition/β-elimination reaction affording **10a** in excellent yield as a single diastereomer[12,20]. The isolation of **8** and **9** serve as well to confirm



Scheme 2

unequivocally the *syn* relative stereochemistry of this S_N2' reaction because the assignment of relative stereochemistry in seven membered rings is not a trivial problem due to its conformational flexibility.

It was also found that **7** undergoes stereoselective *exo* addition at -78°C yielding **11a** as a single diastereoisomer probably due to steric factors and/or coordination of the *endo*-lithio intermediate with the *endo*-benzyloxy substituent (Scheme 2). This intermediate led to **11b** after addition of D_2O. However, as only a mixture of **11a** and **12a** in a 6:1 ratio respectively was obtained under the same opening conditions mentioned, we envisaged to take advantage of the compatibility of organometallic reagents and strong Lewis acids at low temperatures[21] to complete this epoxidic opening[22]. Thus, after addition of 3.0 equivalents of MeLi to **7** in Toluene at -78°C (as shown by TLC), 3 equivalents of $BF_3.OEt_2$ were added and **12a** was obtained with total conversion and high yield. The desired hydroxycycloheptenyl sufones could be prepared with a variety of organolithium reagents[12] with different electronic characteristics (Schemes 1 and 2) in order to secure the generality of the process. The possibility of obtaining these S_N2' displacements using 1-hexynyllithium is specially remarkable.

In summary, new and highly functionalized cycloheptenyl vinyl sulfones are now readily available via S_N2' reactions. Further transformations of these valuable substrates are currently being explored in our laboratories.

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11. No reaction occurs and starting material was fully recovered upon standing for 24 h in the presence of 5.0 equiv. of MeLi or PhLi (Et_2O, 0°C to r.t.). Surprisingly, treatment of **2b** with *n*-BuLi (8.0 equiv., Et_2O, 0°C to r.t., 8 h) gave a complex mixture where **3b** could be isolated in only 25% yield. In sharp contrast with Lautens's results (see ref. 6b and 9) no improvement but only minor conversion was obtained when using TMEDA as co-solvent.
12. All new products had satisfactory spectral and analytical data.
13. The *syn* relative stereochemistry between R and OH groups in **4b** was established using ^1H NMR (homonuclear decoupling experiments), since J_{HaHb}= 0 Hz and the value for similar systems that exhibit *anti* relationship (Lautens, M.; DiFelice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817-6820) are fairly different. Additionally, MM calculations (PC Model 4-3) indicates a J_{HaHb} for the syn arrangement of 0.8 Hz.
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18. **6** and **7** were synthesised in 50-60% overall yield from **2a** using well established methodology. See: Black, K.A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341-5348. Detailed procedures for these transformations will be reported in due course.
19. It should be noted that no addition product to related [2.2.1] systems[4], derived from α-lithio sulfonyl carbanions, could be previously isolated.
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