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REGIO- AND STEREOSPECIFIC SYNTHESIS OF SUBSTITUTED CYCLOHEXENEDIOLS FROM 7-OXABICYCLO[2.2.1]HEPT-5-EN-2-OLS AND ORGANOLITHIUM REAGENTS

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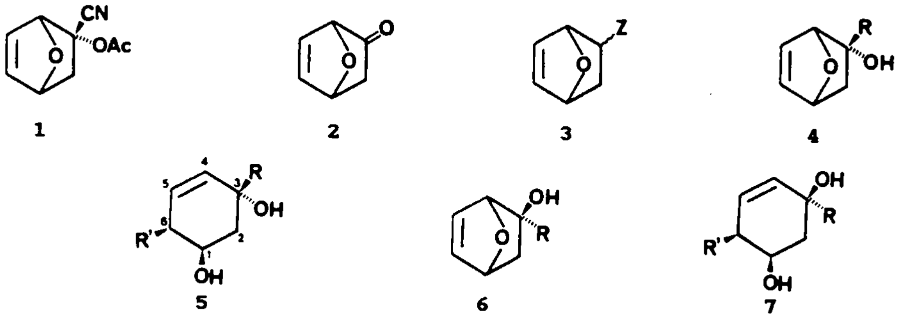
Summary: The bridge opening reactions of 7-oxabicyclo[2.2.1]hept-5-en-2-ols, **4** and **6** with organolithium reagents proceed with complete regio- and stereoselectivity to produce highly functionalized cyclohexene derivatives **5** and **7**, respectively.

7-Oxabicyclo[2.2.1]heptane derivatives[1] are important starting materials for syntheses of natural products and derivatives of biological interest[2]; oxanorbornenic substrates **1** and **2** (Scheme I), are particularly attractive synthetic intermediates[3] since they are now readily available even optically pure[4]. Within this field, the question of effecting the regioselective opening of the oxygen bridge without concomitant aromatization, to produce functionalized cyclohexenols is a problem of current interest. A relatively general solution proceeds by a base induced β-elimination of the heteroatom bridge in derivatives of **2**[3d], or in derivatives of **3** (Z = CO_2Me[5], Z = SO_2Ph[6]). Strongly acidic conditions have also been used successfully in some cases[7]. Another approach involves the reductive elimination of an *endo* functionality (Cl, SO_2Ph)[8]; this method has been utilized with limited success[9,10]. In this report we describe a new regioselective cleavage of the oxygen bridge of 7-oxanorbornenic substrates based upon the serendipitous observation that the reaction between *endo* alcohol **4c** (R = *n*-Bu) and an excess of *n*-butyllithium produces a good yield of cyclohexenediol **5c** (R = R′ = *n*-Bu).

The reaction between 7-oxanorbornenone **2** and organolithium and Grignard reagents yields the expected *endo* alcohols, **4**, with high selectivity[11]. However, when the reaction between **2** and 3 equivalents of *n*-BuLi (Et_2O, 0°C) was studied, low yields of the expected *endo* alcohol **4c** were obtained. A detailed study of this reaction allowed for the isolation of a good yield of the unexpected cyclohexenediol **5c** (R = R′ = *n*-Bu), whose structure was established by ^{13}C and ^{1}H NMR spectroscopy[12]. The regio- and stereochemistry of this adduct is supported by the observed coupling constants values for the carbinol proton (11.5 and 4.2 Hz with the adjacent methylene, and 5.3 Hz with the adjacent methine). While there are two isolated reports in the literature involving the addition of alkyllithiums to 1,4-dihydronaphthalene -1,4-*endo*-oxide with concurrent bridge opening[13], to the best of our knowledge, the reaction of organolithiums with simple oxanorbornenic systems and especially, the complete regioselectivity encountered by us are unprecedented in the literature.

Scheme I



The above results prompted us to further explore this unexpected process and the results obtained are summarized in Table I. First of all, it was established that alcohols **4** are intermediates in the bridge opening (entry 3). Thus, the reaction of pure **4c** with 3 equivalents of *n*-BuLi, produced **5c** in comparable yields to those obtained before. Several *endo* carbinols were then subjected to the reaction conditions (entries 1, 2 and 4) and good yields of the corresponding adducts were realized. Similar results were obtained for phenyllithium and methyllithium which afforded good yields of cyclohexenediols **5e** and **5f**.

Table I. Ring Opening Reactions of 7-Oxanorbornenic Alcohols 4 and 6 with Organolithium Reagents.

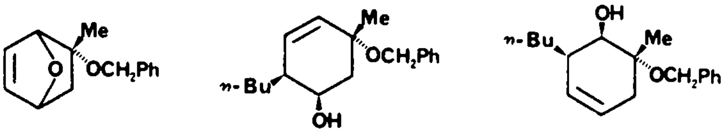
Entry	Substrate	R	R'Li	Product	Yield[a](%)
1	**4a**	H	*n*-Bu	**5a**	70
2	**4b**	Me	*n*-Bu	**5b**	78
3	**4c**	*n*-Bu	*n*-Bu	**5c**	80
4	**4d**	$-CH=CH_2$	*n*-Bu	**5d**	70
5[b]	**4b**	Me	Ph	**5e**	70
6[b,c]	**4b**	Me	Me	**5f**	60
7[b]	**6a**	Me	*n*-Bu	**7a**	75

[a] Isolated yields of pure products. These yields have not been optimized. [b] A large excess of organolithium reagent was employed (5-9 equiv.) at room temperature. [c] Reaction time 4 days.

The high regio- and stereoselectivity of the process were found to be independent of the stereochemistry of the carbinol center (entry 7). However, the reaction between *exo* alcohol **6a**, prepared from **2** and Me_2CuLi[11], and *n*-BuLi required slightly harsher conditions (5 equivalents *n*-BuLi, Et_2O, 25°C).

While at the time we do not have a good understanding of the origin of this surprising regioselectivity[14], a free alcohol functionality on C-2 was instrumental in determining the outcome of the process. Indeed, the reaction of benzyl ether **8** with *n*-BuLi afforded a 2:1 mixture of regioisomeric opening products **9** and **10** (Scheme II).

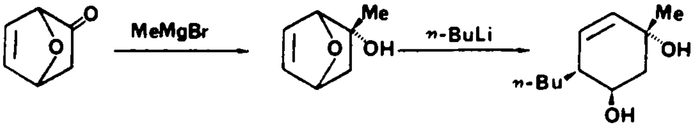
Scheme II



8 **9** **10**

The preparation of enantiomerically pure cyclohexenediols **5** was also addressed. For this purpose, optically active 7-oxanorbornenone (+)-**2**[4b] was treated with MeMgBr to produce (+)-**4b** [ee ≥ 99%[15], $[\alpha]_{578}^{28}$ +91 (c 6.85 mg/mL, $CHCl_3$)] which in turn provided enantiomerically pure (+)-**5b** [ee ≥ 99%[15], $[\alpha]_{578}^{28}$ +161 (c 5.72 mg/mL, $CHCl_3$)], upon reaction with *n*-BuLi (Scheme III).

Scheme III



(+)-**2** (+)-**4b** (+)-**5b**

In summary the highly regio- and stereoselective bridge opening reaction between the readily available 7-oxabicyclo [2.2.1]hept-5-en-2-ols[11] and organolithium reagents, allows for the synthesis of highly functionalized cyclohexene derivatives. The clarification of the precise origin of the unusual regioselectivity encountered, as well as the scope and synthetic potential of this methodology are currently being explored in our laboratories.

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(14) This observation may be tentatively attributed to an electrostatic repulsion or to a modification of the coefficients of the M.O. of the substrate induced by the presence of the alkoxide. However, more data is necessary to advance an explanation for the observed regioselectivity.

(15) The optical purity of (+)-**4b** and (+)-**5b** was determined by high field ^{1}H NMR with the aid of the chiral shift reagent Eu(hfc)$_3$ in conditions which produced clear splittings when the racemic materials were employed.

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