Tetrahedron Letters, Vol.31, No.42, pp 5993-5996, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

FORMATION OF A TRANS-BICYCLO[3.3.0]OCTANE BY TANDEM ANIONIC CYCLIZATION: EVIDENCE FOR THE HIGHLY STEREOSELECTIVE IRREVERSIBLE NATURE OF 5-HEXEN-1-YLLITHIUM CYCLIZATIONS

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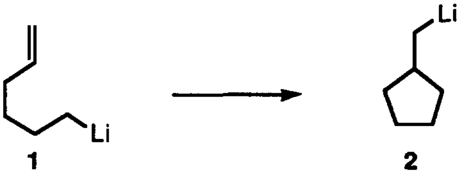
Summary: Tandem anionic cyclization of 4-ethenyl-6-hepten-1-yllithium (**7**), prepared from the corresponding iodide (**6**) by low - temperature lithium - iodine exchange, occurs rapidly at room temperature in the presence of TMEDA to give (trans-3-bicyclo[3.3.0]octyl)methyllithium (**9**). Hydrolysis of the reaction mixture delivers 3-methyl-trans-bicyclo[3.3.0]octane in 87% yield.

The regiospecific 5-exo-trig cyclization[1] of 5-hexen-1-yllithium (**1**) to (cyclopentyl)methyllithium (**2**) has been used to advantage for the preparation of a variety of cyclopentylmethyl - containing products.[2-7]

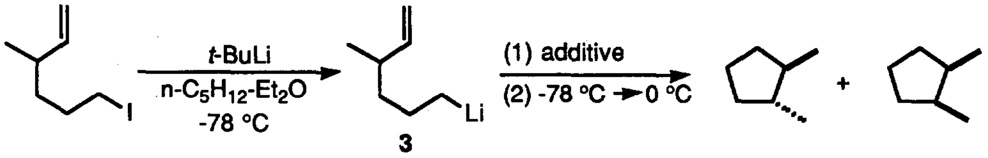


Consideration of the bonding changes attendant to isomerization of **1** to **2** suggests that the cyclization is a highly exothermic process: a σ-bond (bond energy ca. 88 kcal/mol) is generated at the expense of a π-bond (π-bond energy ca. 60 kcal/mol). In view of the potential synthetic utility of this anionic route to functionalized carbocycles, it was of interest to determine if the thermodynamically favorable isomerization could be exploited to prepare relatively unstable molecular frameworks via effectively irreversible cyclization of a suitably constituted 5-hexen-1-yllithium. The results detailed below indicate that this is indeed the case.

The impetus for the present study was provided by the observation that cyclizations of olefinic alkyllithiums are apparently more stereoselective than the widely studied 5-exo-trig isomerizations of 5-hexen-1-yl radicals.[7,8] We have recently reported,[2] as summarized in **Scheme I**, that 4-methyl-5-hexen-1-yllithium (**3**), derived from the corresponding iodide by lithium-iodine exchange, undergoes a highly trans-selective cyclization at room temperature to give, following hydrolysis, an approximately 13:1 mixture of trans- and cis-1,2-dimethylcyclopentane in 82% yield. Addition of N,N,N',N'-tetramethylethylenediamine (TMEDA) to the hexenyllithium solution serves to facilitate the cyclization but it has little effect on the high stereoselectivity of the isomerization.

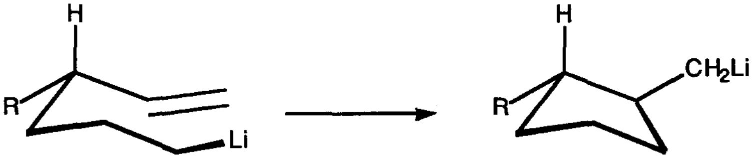
The stereochemical outcome of this and related cyclizations of 5-hexen-1-yllithiums is conveniently accommodated by a transition state model, **4**→ **5**, that involves ring formation from a chair-like transition state

Scheme I



no additive:	93%	6.8%
TMEDA:	80%	7.2%

in which a substituent preferentially occupies a pseudo-equatorial position. Consideration of this result suggests that it should be possible to construct a trans-fused bicyclo[3.3.0]octane by tandem cyclization of a 5-hexen-1-yllithium bearing an allyl group at C(4) (**4**, R=allyl) provided that the cyclizations are effectively irreversible.

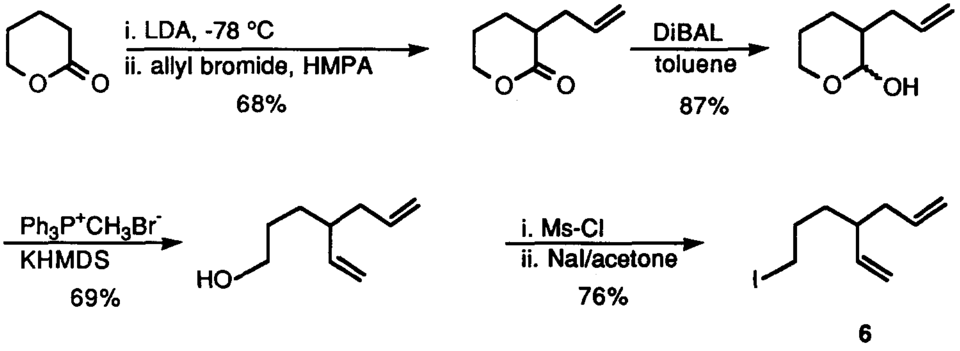


4 **5**

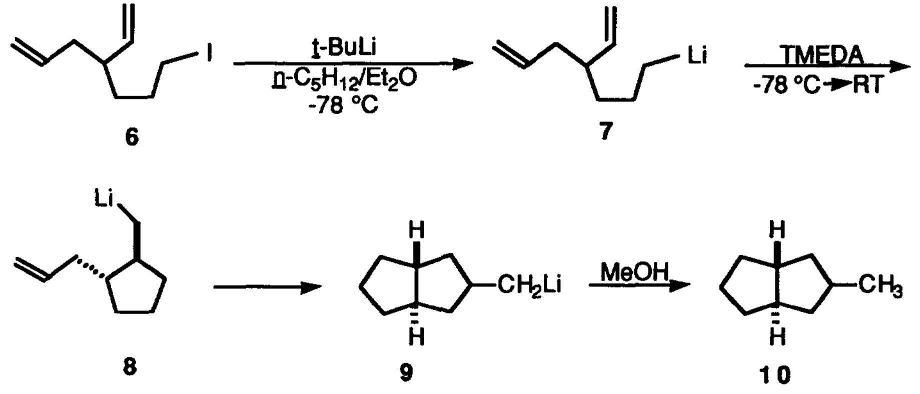
In an effort to test this hypothesis, we prepared 7-iodo-4-ethenyl-1-heptene (**6**) in a straightforward manner[9] (**Scheme II**) and investigated the tandem cyclization of the diolefinic alkyllithium derived by lithium-iodine exchange. Treatment of an approximately 0.1 M solution of **6** in n-pentane - diethyl ether (3:2 by volume) at -78 °C with 2.2 molar equivalents of tert-butyllithium (t-BuLi) following our general protocol[10] serves to cleanly generate 4-ethenyl-6-hepten-1-yllithium, **7**, in virtually quantitative yield as demonstrated by the fact that quench of such a reaction mixture with methanol at -78 °C affords 3-propyl-1,5-hexadiene in virtually quantitative yield. Addition of 2.2 equivalents of dry, deoxygenated TMEDA to the cold (-78 °C) solution of **7** in n-pentane - diethyl ether, followed by removal of the cooling bath initiates tandem cyclization (**Scheme III, 7→8→9**). The reaction mixture was allowed to warm and stand at ambient temperature for 1 h prior to quench with deoxygenated methanol. Analysis of the product mixture revealed that 3-methyl-trans-bicyclo[3.3.0]octane (**10**) had been formed in 87% yield[11] (**Scheme III**). The balance of the reaction mixture consisted of diene (7%), isomeric 1-allyl-2-methylcyclopentanes (3%), and a small amount (ca. 3%) of 3-methyl-cis-bicyclo[3.3.0]octane. The trans-bicyclo[3.3.0]octane, **10** , was easily isolated by washing the reaction mixture with concentrated sulfuric acid to remove olefinic impurities and its structure was confirmed by the observation of nine separate resonances in the ^{13}C NMR spectrum of a $CDCl_3$ solution of **10**: 54.96 (CH), 52.73 (CH), 39.26 (CH), 36.87 (CH_2), 34.80 (CH_2), 29.59 (CH_2), 26.47 (CH_2), 26.45(CH_2), 23.59 (CH_3).

The virtually exclusive formation of a *trans*-fused bicyclo[3.3.0]octane upon tandem cyclization of **7** is noteworthy in several respects. The *trans*-ring fusion engenders considerable strain in the bicyclo[3.3.0]octane skeleton, as evidenced by the fact that the parent *trans*-bicyclo[3.3.0]octane is some 6.1-6.4 kcal/mol less stable than its *cis*-isomer,[12] and the ease with which the second isomerizaion proceeds (**Scheme III, 8→ 9**) is a rather dramatic indication of the favorable thermodynamics associated with such cyclizations. The results also demonstrate that the 5-exo-trig cyclizations are effectively irreversible since equilibration of the 5-hexen-1-yllithiums and (cyclopentyl)methyllithiums would invariably lead to a product mixture rich in *cis*-fused 3-methylbicyclo[3.3.0]octane. In summary, the facile generation of **9** illustrates the utility of anionic bicycization for the preparation of molecular frameworks that are not readily accesible by radical mediated strategies.[8, 13] We are in the process of extending the scope of this tandem anionic cyclization for the preparation of relatively inaccessible functionalized *trans*-bicyclo[3.3.0]octanes by trapping of **9** with a variety of electrophiles and will report the results of these studies in due course.

Scheme II



Scheme III



Acknowledgment. This work was supported by the Department of Higher Education under Grant 90-630.

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(Received in USA 31 May 1990; accepted 18 July 1990)