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HIGHLY STEREOSELECTIVE SYNTHESIS OF EXOCYCLIC ALKENES VIA CYCLIALKYLATION[1]

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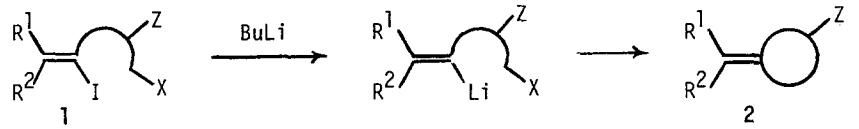
SUMMARY: Treatment of stereodefined ω-halo-2-iodoalkene derivatives (**1**), prepared via stereoselective addition reactions of alkynes, with either n-BuLi (1 equiv) or t-BuLi (2 equiv) can produce exocyclic alkenes whose isomeric purity is essentially 100%.

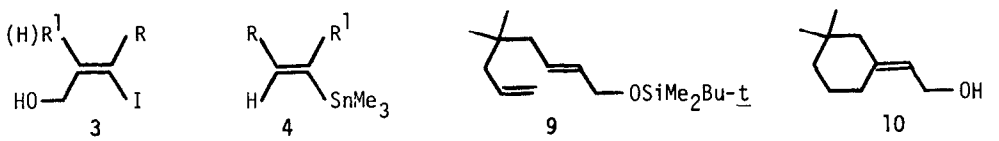
We have recently reported a cyclialkylation reaction of alkenyllithiums to produce cycloalkenes.[3] The favorable results prompted us to apply the reaction to the synthesis of exocyclic alkenes (eq 1).



1 2 (1)

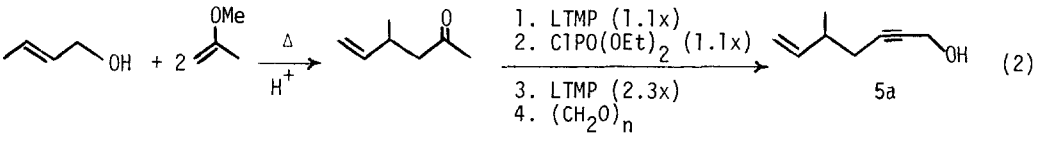
Herein we demonstrate, for the first time, that the BuLi-induced cyclialkylation reaction of ω-halo-2-iodoalkenes (**1**) can proceed with strict retention of configuration leading to the formation of stereochemically pure compounds in high yields. Although conversion of ω-sulfonyloxy-1-alkynes into stereodefined exocyclic alkenylsilanes was recently reported,[4] the cyclization yields were disappointing (30-46%).

The preparation of alkenyl iodides represented by **1** in a completely stereo- and regio-controlled manner is at present a nontrivial synthetic task. To our knowledge, virtually no such compounds have previously been synthesized. However, there are several addition reactions of alkynes that are, in principle, adaptable for this purpose. Hydrometallation[5a] carbometallation[5b] of propargyl alcohols producing **3** look particularly promising, since they allow the preparation of highly functional tri- and tetrasubstituted alkenes in a completely stereo- and regioselective manner. Also attractive is the reaction of alkynylborates with trialkyltin chlorides, e.g., Me_3SnCl, followed by sequential treatment with n-BuLi, $CuBr\text{-}SMe_2$, and MeOH, which converts terminal alkynes into **4** in a highly stereo- and regioselective manner.[6]



3 4 9 10

Propargyl alcohols **5a**, **5b**, and **5c** were prepared as follows. The Claisen rearragnement of (E)-crotyl isopropenyl ether afforded 4-methyl-5-hexen-2-one in 74% yield, which was then sequentially treated with 1.1 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP), 1.0 equiv of $ClPO(OEt)_2$, 2.3 equiv of LTMP,[7] and 2.3 equiv of paraformaldehyde to give **5a** in 52% yield (eq 2). Its regioisomer **5b** was prepared in 77% yield by sequential treatment with 2.5 equiv of lithium diisopropylamide (LDA) and paraformaldehyde (3.2 equiv) of 5-chloro-2-methyl-1,5-hexadiene, which in turn was prepared in 75% yield by the reaction of methallylmagnesium chloride with 2,3-dichloropropene in THF-ether.[8] Quenching the alkynyllithium intermediate with acetone (3.4 equiv) in place of paraformaldehyde afforded the corresponding acetone adduct in 90% yield which, on treatment with 3% of KOH at 110°C,[9] gave 2-methyl-1-hexene-5-yne (**6**) in 96% yield (eq 3). 4,4-Dimethyl-6-hexen-2-one, prepared in 87% yield by the reaction of mesityl oxide with allyltrimethylsilane catalyzed by $TiCl_4$,[10] was subjected to sequential treatment with LDA (1.1 equiv), $ClPO(OEt)_2$ (1.1 equiv), LDA (2.3 equiv),[7] and paraformaldehyde (2.3 equiv) to give **5c** in 81% yield (eq 4).



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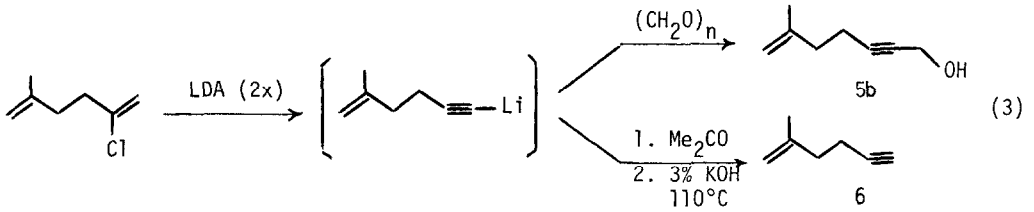

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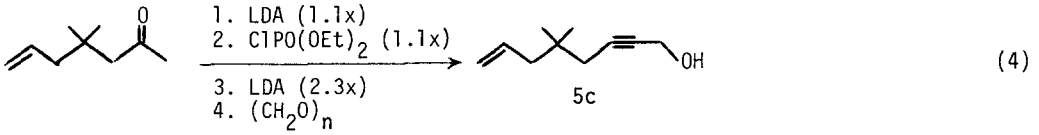
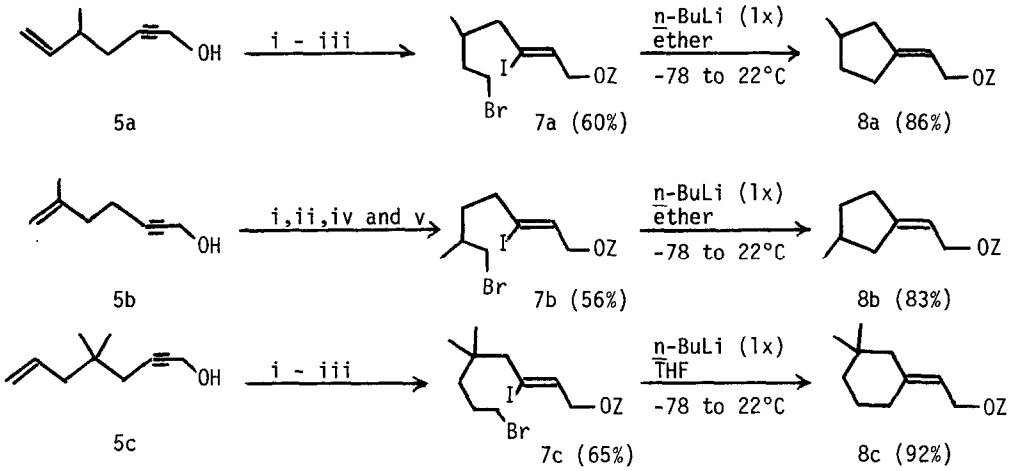


(4)

Conversion of **5a** and **5c** into **7a** and **7c**, respectively, was carried out in 60-65% yields by sequential treatment of **5a** and **5c** with (i) $LiAlH_4$-NaOMe followed by I_2, (ii) t-$BuMe_2SiCl$, NEt_3, 4-dimethylaminopyridine (DMAP),[11] and (iii) i-Bu_3Al (2.0 equiv) Cl_2ZrCp_2 (0.3 equiv) followed by NBS (6.6 equiv).[12] Conversion of **5b** into **7b**, on the other hand, required replacement of the step (iii) shown above with (iv) 9-borabicyclo[3.3.1]nonane (9-BBN) (1.3 equiv) followed by $NaOH-H_2O_2$ and (v) LDA, $MeSO_2Cl$, and then LiBr[13] (Scheme 1).

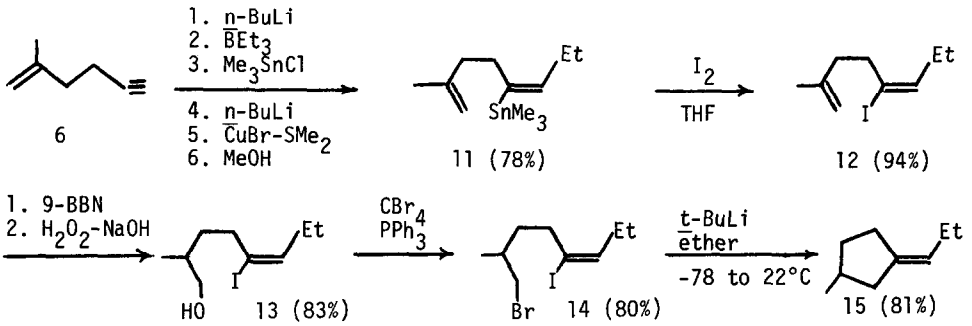
Scheme 1



Z = $SiMe_2Bu$-t

The use of t-BuLi (2 equiv) in place of n-BuLi (1 equiv) in the conversion of **7c** into **8c** resulted in the formation of a byproduct **9** in 40% yield along with a 60% yield of **8c**. The extent of formation **9** observed with n-BuLi was only 2%, while no elimination was observed in the preparation of **8a** and **8b**. Examination by ^{13}C and ^{1}H NMR indicated that all these cyclic products were stereo- and regiochemically homogeneous.[14] These results clearly indicate that the cyclialkylation of alkenyllithiums can proceed with strict retention of stereochemistry. Treatment of **8c** with n-Bu_4NF in THF provided the E isomer (**10**)[15] of a sex pheromone of boll weevil[16] in 97% yield.

Sequential treatment of enyne **6** with 1.0 equiv of n-BuLi, 1.0 equiv of BEt_3, Me_3SnCl (1.0 equiv), n-BuLi (1.0 equiv), CuBr-SMe_2 (1.1 equiv), and MeOH[6b] afforded **11** in 78% yield, which was then treated with I_2 (1.2 equiv) in THF to give **12** in 94% yield. Hydroboration of **12** with 9-BBN followed by oxidation with H_2O_2-NaOH gave **13** in 83% yield, which was converted into **14** in 80% yield by treatment with CBr_4 (2.0 equiv)-PPh_3 (2.0 equiv).[17] Conversion of **14** into **15**,[18] which was isomerically >99% pure, was achieved in 81% yield by treatment of **14** with 2 equiv of t-BuLi in ether (-78 to 22°C over 1 h) (eq 5).



The results presented herein provide a novel addition to the rapidly growing list of highly selective methods for preparing exocyclic alkenes.[19]

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(14) **8a:** ^{13}C NMR ($CDCl_3$) -5.12, 18.42, 19.64, 26.02, 28.28, 34.02, 34.42, 42.21, 61.46, 120.13, 144.79. **8b:** ^{13}C NMR ($CDCl_3$) -5.09, 18.42, 20.06, 26.02, 33.05, 34.14, 34.63, 37.43, 61.67, 120.22, 144.77. **8c:** ^{13}C NMR ($CDCl_3$) -4.82, 14.24, 18.55, 23.30, 26.19, 28.60, 32.98, 39.75, 50.36, 59.72, 123.28, 139.30.

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