

**HIGHLY STEREOSELECTIVE SYNTHESIS OF BICYCLO[2.1.1]HEXENES-5-d
BY TRANSMETALLATION OF A TETRA-ALKYL TIN.**

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Abstract: Synthesis of the title compounds is achieved by a transmetallation reaction that appears to involve regio- and stereochemical control by chelation with a neighboring hydroxyl function.

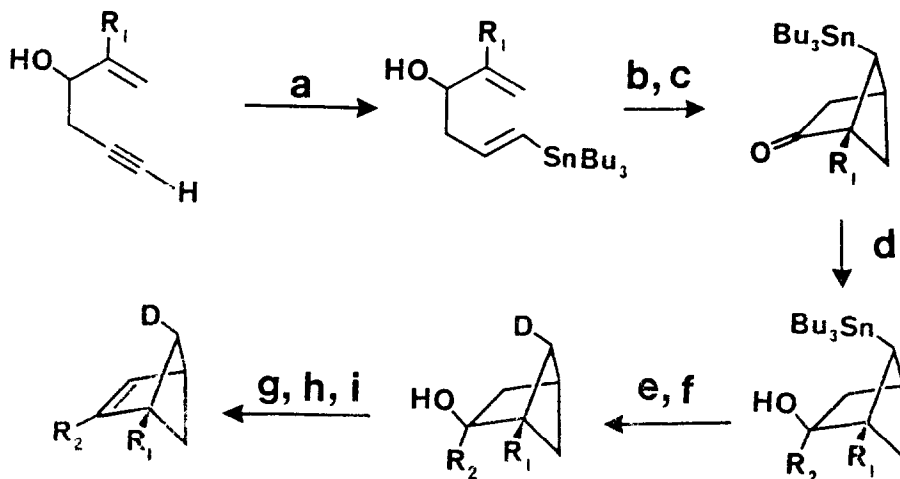
The use of deuterium and tritium labels is a time-honored strategy for elucidation of mechanisms in organic chemistry. Unfortunately the synthesis of the labeled reactants can be quite difficult, especially when the heavy isotope must be introduced stereoselectively. In this communication we describe the syntheses of both stereoisomers of bicyclo[2.1.1]hex-2-ene-5-d and two phenyl-substituted analogues.

The most significant step in each of these syntheses is the transmetallation and quenching of a tetra-alkyl tin with high stereoselectivity. It had previously been thought that transmetallation of tetra-alkyl tin compounds with alkyl lithiums would give complex equilibrium mixtures¹. We show that this need not always be true, and we speculate about the factors that might be involved in determining both the regio- and stereoselectivity of the reaction in the present case.

The syntheses of the *endo* stereoisomers of bicyclo[2.1.1]hex-2-ene-5-d and its 1- and 2-phenyl derivatives are summarized in Scheme 1². The *exo* stereoisomers were obtained by exchange of the acetylenic hydrogen with D₂O under basic conditions, and by substituting H₂O for D₂O in the quench of the alkyl lithium. In each case the photocycloaddition³ that yielded the bicyclo[2.1.1]-hexanone derivative was quite stereoselective (typically 75:25). The preferred stereoisomer was assumed to be *endo* since the subsequent addition reactions to the carbonyl function were completely stereoselective. It is hard to imagine that the tributyl tin group would have exerted such stereochemical control if it had been *exo* to the carbonyl function. The stereochemistry of deuterium incorporation was determined by NMR using shift reagents on the bicyclo[2.1.1]-

hexanones. The stereochemistry so deduced is consistent with the expected^a overall retention of configuration for the transmetalation, quenching sequence.

The stereoselectivity of deuterium incorporation was determined by integration of the ²H NMR spectrum. For both phenyl-substituted bicyclo[2.1.1]hexenes the stereoselectivity was near 100%. The two stereoisomers were examined, and in neither case could any of the undesired isomer be detected (from the signal to noise ratio one can estimate that 0.5% would have been readily detectable). For the parent hydrocarbon the stereoselectivity was 97.8±0.4%. Since some difficulty was encountered in separation of the stereoisomeric tin compounds in this case, it is possible that the apparently lower stereoselectivity here is an artifact caused by contamination of reactant with a small amount of the epimer.



Scheme Ia,b

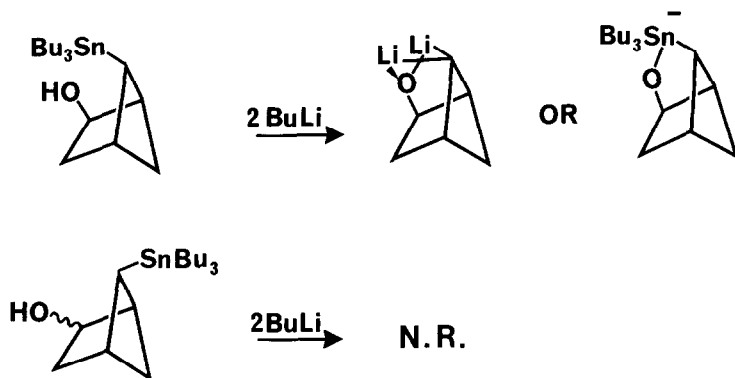
^aReagents: $R_1 = R_2 = H$: (a) Bu_3SnH/h ; (b) H_2CrO_4 ; (c) h ; (d) $NaBH_4$; (e) 2 eq. $nBuLi$, -78 to 0 °C; (f) D_2O ; (g) pyridinium dichromate; (h) $TsNHNH_2$; (i) $MeLi$

$R_1 = Ph$, $R_2 = H$: (a) Bu_3SnH/h ; (b) $Me(CO)_2Cl/py$; (c) h ; (d) $NaBH_4$; (e) 2 eq. $nBuLi$, -78 to 0 °C; (f) D_2O ; (g) pyridinium dichromate; (h) $TsNHNH_2$; (i) $MeLi$

$R_1 = H$, $R_2 = Ph$: (a) Bu_3SnH/h ; (b) H_2CrO_4 ; (c) h ; (d) $PhMgBr$; (e) 2 eq. $nBuLi$, -78 to 0 °C; (f) D_2O ; (g) NaH ; (g) CS_2 ; (i) MeI, Δ .

^bYields $R_1 = R_2 = H$: (a) 77%; (b)+(c) 63%; (d) 81%; (e)+(f) 78%; (g)+(h)+(i) 30%
 $R_1 = Ph$, $R_2 = H$: (a) 86%; (b)+(c) 58%; (d) 73%; (e)+(f) 94%; (g)+(h)+(i) 34%
 $R_1 = H$, $R_2 = Ph$: (a) 77%; (b)+(c) 63%; (d) 70%; (e)+(f) 80%; (g)+(h)+(i) 55%

It is interesting to speculate about the factors that make cleavage of the secondary C-Sn bond preferred in the transmetalation reaction, and those that cause high retention of configuration in the resulting alkyl lithium. It is possible that the strain in the bicyclo[2.1.1]hexyl ring system makes a carbanion at C5 relatively stable because of higher σ character in the orbital bearing the pair of electrons. It seems less plausible that the ring strain could create a sufficient inversion barrier in the carbanion to explain the high stereoselectivity of the reaction. An intriguing alternative explanation for both the regio- and stereoselectivity of the transmetalation is that the syn alkoxy group on C2 acts as a chelating ligand for the lithium (or, perhaps, for a tin ate complex⁴). In support of this idea is the observation that 5-exo-1-phenyl-5(tributylstannyl)bicyclo[2.1.1]hexan-2-ol, prepared as a mixture of epimers at C2 from the minor isomeric product of the photocycloaddition, failed to react with n-butyl lithium under conditions that allowed facile transmetalation of the endo isomer. (Obviously, we would have been unable to detect degenerate substitution of the n-butyl groups).



We note with interest that if the chelation explanation is correct, it might be possible to use a suitably disposed hydroxyl group to direct the regio- and stereoselectivity of tetra-alkyl tin transmetalation in a quite general way. Obviously, the resulting alkyl lithium could react with a variety of carbon electrophiles in addition to the D₂O or H₂O used here.

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References and Notes.

(1) Seyferth, D.; Weiner, M. A. J. Am. Chem. Soc. **1962**, 84, 361. Exceptions are known when the carbon of the Sn-C bond to be cleaved is incorporated in a cyclopropyl ring (reference 4b) or has an attached alkoxy function (Still, W. C. J. Am. Chem. Soc. **1978**, 100, 1481).

(2) The new compounds gave satisfactory analytical data for C and H, and spectra (^1H and ^{13}C NMR, IR) that were in accord with the proposed structures.

(3) Bond, F. T.; Jones, H. C.; Scerbo, L. Tetrahedron Lett. **1965**, 4685. Gibson, T. W.; Erman, W. F. J. Org. Chem. **1972**, 37, 1148. Agosta, W. C.; Wolff, S. Ibid. **1980**, 45, 3139. Gibson, T. W. Ibid. **1981**, 46, 1073.

(4)(a) Still, W. C.; Srekumar, C. J. Am. Chem. Soc. **1980**, 102, 1201. (b) Corey, E. J.; Eckrich, T. M. Tetrahedron Lett. **1984**, 25, 2415.

(5) We thank Professors Hans Reich and Robert Boeckman for suggesting this possibility.

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