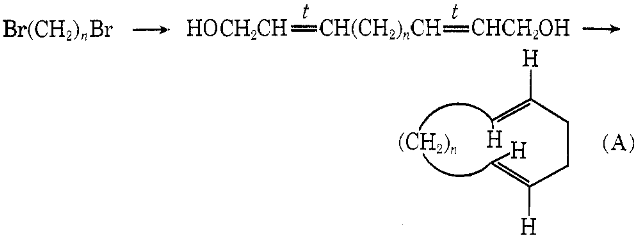
Useful New Organometallic Reagents for the Synthesis of Allylic Alcohols by Nucleophilic Vinylation

Summary: *trans*-1-Tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl ether (**1**), available in one step from propargyl tetrahydropyranyl ether, allows the generation of the vinylic nucleophiles **2** and **5**; these reagents can be used for the extension of chains, the addition of a vinylic appendage by conjugate addition to an enone, or for ring formation.

Sir: For some time it has been clear that a method for the nucleophilic introduction of the *trans*-CH═CHCH$_2$OH unit would be of considerable utility in synthesis. For example, such a process could allow the expeditious synthesis of medium-large rings from 1,*n*-dihalides by sequence A

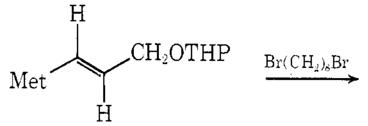


$$\mathrm{Br(CH_2)_nBr} \longrightarrow \mathrm{HOCH_2CH\overset{t}{=}CH(CH_2)_nCH\overset{t}{=}CHCH_2OH} \longrightarrow$$

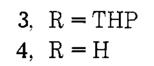
(A)

using the previously discovered cyclization of bis allylic halides under the influence of nickel carbonyl,[1] or the introduction of a highly functionalized appendage by conjugate addition to α,β-enones.[2,3] We report here on a readily available organometallic reagent, *trans*-1-tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl ether (**1**),[4] which allows the realization of this methodology. Applications are presented to chain extension, ring appendage introduction, and ring formation operations, including a new synthetic route to the biologically interesting 11-deoxyprostaglandins.

The vinyltin reagent **1** was readily prepared from propargyl tetrahydropyranyl ether.[5,6] Reaction of **1** with 1 equiv of *n*-butyllithium in tetrahydrofuran (THF) at −78° for 1 hr resulted in complete formation of the lithium reagent **2**.



1, Met = n-Bu$_3$Sn
2, Met = Li
5, Met = Cu—C≡CC$_3$H$_7$

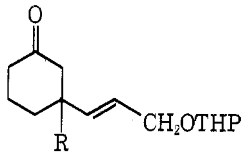


$$\mathrm{ROCH_2CH\overset{t}{=}CH(CH_2)_8CH\overset{t}{=}CHCH_2OR}$$

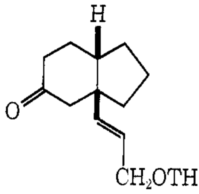
3, R = THP
4, R = H

The effectiveness of **2** as a nucleophilic vinylating agent was demonstrated by reaction with 1,8-dibromooctane to afford the THP ether **3** in 85% isolated yield. From **3** the diol **4** and cyclotetradeca-1,5-diene (trans,trans) can be obtained in high yield according to scheme A.[1]

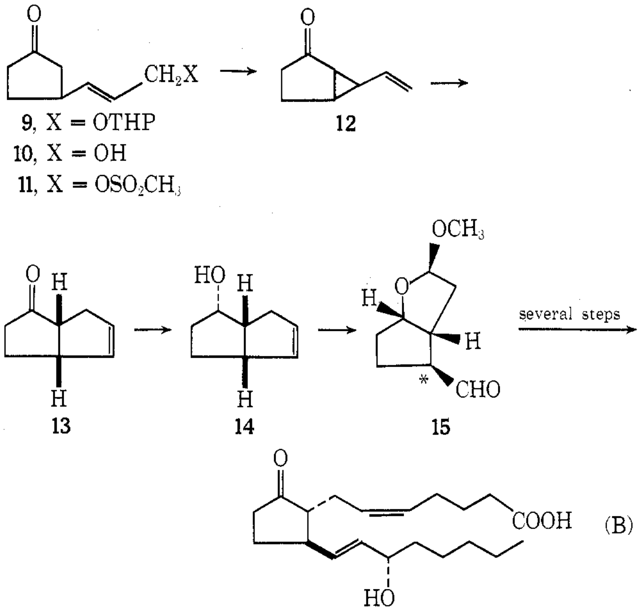
Reaction of the lithio derivative **2** in THF with 1 equiv of 1-pentynylcopper[7] (−78°, 60 min; −50°, 10 min) afforded a red-orange, soluble mixed Gilman (cuprate) reagent **5** which has proven to be a highly reactive and useful intermediate for synthesis. Using only 1.05–1.1 equiv of this reagent, the conjugate adducts **6–8** were obtained from the corresponding α,β-enones as indicated (conditions, yield). In addition, the vinylated product **9** was prepared from 2-cyclopentenone (reaction at −78 to −50° for ~2 hr, isolated yield 80%). These intermediates have been converted in a variety of ways to useful and otherwise less accessible compounds. An illustration of such utility is provided herein for the adduct **9** which can be converted to 11-deoxyprostaglandin E$_2$ (**16**) as shown in sequence B. The allylic alcohol



6, R = H (−78° for 75 min, 85%)
7, R = CH$_3$ (−78 to −20° for 2 hr, 84%)



8, (−78 to −20° for 1.5hr, 71%)



9, X = OTHP
10, X = OH
11, X = OSO$_2$CH$_3$
12
13
14
15
16

10, obtained by hydrolysis of the tetrahydropyranyl ether **9**, was converted to the allylic mesylate **11**. Reaction of **11** at 0° for 5 min with potassium *tert*-butoxide in THF gave the vinylcyclopropane **12** in nearly quantitative yield (carbonyl, 1730 cm^{-1}). Thermolysis of **12** by evaporation at 0.2-mm pressure through a 33-cm column heated to 600° (packed with chips of leaded potash glass) afforded ketone **13**.[8] Reduction of this bicyclic ketone with sodium borohydride in methanol at −40° afforded alcohol **14** stereospecifically. Treatment of **14** with osmium tetroxide-sodium metaperiodate effected fission of the double bond. The resulting material when treated with methanol containing a catalytic amount of boron trifluoride etherate afforded the aldehyde **15** and the epimer at C* (65% yield from **14**). Exposure of the mixture of epimeric aldehydes [^{1}H NMR peaks (CDCl$_3$) due to CHO at δ 9.68 and 9.58] to 1,5-diazabicyclo[5.4.0]undec-5-ene (1 equiv) in methylene chloride (12 hr at 25°) converted it to a single isomer (δ 9.58), the more stable **15**.[9] The transformation of **15** to 11-deoxyprostaglandin E$_2$ is readily effected as described previously.[10]

The simple preparation of reagent **1** and its use for both direct displacement (via the lithium derivative) and conjugate addition (via the copper derivative) under very mild conditions makes this the method of choice for the introduction of a trans allylic alcohol group to a wide variety of molecules.[11]

References and Notes

(1) (a) E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **86**, 1641 (1964); (b) E. J. Corey and M. F. Semmelhack, *Tetrahedron Lett.*, 6237 (1966); (c) E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.*, **89**, 2757 (1967); (d) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967); (e) E. J. Corey and H. A. Kirst, *ibid.*, **94**, 667 (1972).

(2) (a) Although metallic acetylides derived from propargyl tetrahydropyranyl ether have been used for such processes (e.g., ref 1c), they suffer from the disadvantage of giving only moderate to poor yields in S_N2 alkylation [see E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968), and also J. A. Katzenellenbogen, Ph.D. thesis, Harvard University]. Further, such acetylenic derivatives are not suitable for cuprate mediated conjugated addition to α,β-enones (see ref 2b). (b) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).

(3) For conjugate addition of unsubstituted vinyl, see E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, **93**, 7318 (1971).

(4) For a related previous study in the organotin field, see E. J. Corey and R. H. Wollenberg, *J. Am. Chem. Soc.*, **96**, 5581 (1974).

(5) The following procedure was used. A neat mixture of 42.5 g (71.3 mmol) of bis(tri-*n*-butyltin) oxide (Alfa Products, Ventron Corp.) and 9.50 g of polymethylhydrogen siloxane (Aldrich Chemical Co.) was stirred at room temperature under argon for 30 min and then treated with 14.0 g (100 mmol) of propargyl tetrahydropyranyl ether and 100 mg of azobisisobutyronitrile. The mixture was stirred at 80° for 2 hr and distilled directly from the reaction vessel to afford 38 g (89%) of **1** (bp 140–142° at 0.1 mm) as a colorless oil. NMR studies showed that the hydrostannation reaction occurs only by terminal addition to the acetylenic bond and that the reaction mixture consists of mostly the cis isomer of **1** below 80°, consistent with previous results [see A. J. Leusink, H. A. Budding, and J. W. Marsman, *J. Organomet. Chem.*, **9**, 285 (1967)]. However, at temperatures above 80° (e.g., during distillation) isomerization to the trans isomer takes place. All organometallic reactions were carried out under an inert (argon) atmosphere.

(6) Satisfactory ir, ^{1}H NMR, and mass spectral data were obtained on all products cited herein.

(7) See ref 2b for a description of selective transfer from such alkynyl-containing Gilman reagents.

(8) For references to other vinylcyclopropane rearrangements, see B. M. Trost, *Acc. Chem. Res.*, **7**, 85 (1974); W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963); L. Skattebøl, *Tetrahedron*, **23**, 1107 (1967); C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc.*, **82**, 1007 (1960); L. A. Paquette, R. P. Henzel, and R. F. Eizember, *J. Org. Chem.*, **38**, 3257 (1973).

(9) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971).

(10) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

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