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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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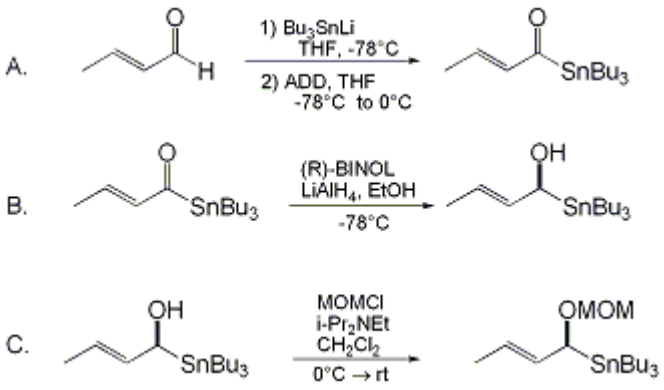
SYNTHESIS OF (S,E)-1-(METHOXYMETHOXY)-1-TRIBUTYLSTANNYL-2-BUTENE

[Stannane, tributyl[1-(methoxymethoxy)-2-butenyl]-, [S-(E)]-]



Submitted by James A. Marshall, Albert W. Garofalo, and Kevin W. Hinkle[1] .
Checked by Peter Belica and Steven Wolff.

1. Procedure

Caution! Many organotin compounds are highly toxic. All operations should be conducted in an efficient fume hood. Gloves and appropriate eye protection should be worn while performing these experiments.

A. A 500-mL, one-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar (Note 1), rubber septum and nitrogen inlet. The flask is charged with anhydrous tetrahydrofuran (THF) (150 mL) followed by diisopropylamine (4.60 mL, 32.8 mmol). The solution is stirred at 0°C and BuLi is added (2.5 M solution in hexane, 12.2 mL, 30.4 mmol). After 15 min, tributyltin hydride (7.70 mL, 27.8 mmol, (Note 2)) is added and the resulting yellow solution is stirred for 20 min. The solution is cooled to −78°C by means of a dry ice-acetone bath and crotonaldehyde (2.10 mL, 25.3 mmol, (Note 2)) is added. After 30 min a solution of 1,1'-(azodicarbonyl)dipiperidine (ADD) (8.31 g, 32.9 mmol, (Note 2)) in THF (65 mL) is added by means of a cannula. The resulting dark red reaction mixture is warmed to 0°C and stirred for 1 hr (Note 3). The reaction is then quenched with 100 mL of aqueous saturated ammonium chloride solution (Note 4) and extracted with two 100-mL portions of ether . The aqueous phase is saturated with sodium chloride and extracted with 100 mL of ether . The organic extracts are combined, dried over magnesium sulfate , filtered, and the solution is concentrated by rotary evaporation to a volume of 100 mL (Note 5). The orange solution is separated from a yellow precipitate by means of a cannula into a 2-L, two-necked, round-bottomed flask equipped with an overhead stirrer and containing 1 L of vigorously stirring hexane (Note 2) under a nitrogen atmosphere (Note 6). The resulting mixture is filtered through a glass-fritted funnel and the solvent is removed by rotary evaporation to afford the crude acyl stannane as a clear orange oil. This oil is dissolved in 65 mL of THF and immediately subjected to reduction with 2,2'-dihydroxy-1,1'-binaphthyl-lithium aluminum hydride (BINAL-H) (Part B).

Because of the lability of the acyl stannane it is important to have a freshly prepared solution of BINAL-H at −78°C ready for addition of the acyl stannane. This is best achieved by starting the following reduction procedure just prior to the acyl stannane sequence.

B. A 500-mL, two-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar (Note 1), condenser, rubber septum and nitrogen inlet. The flask is charged with a suspension of lithium aluminum hydride ($LiAlH_4$) powder (2.13 g, 53.4 mmol) in 110 mL of anhydrous THF. The

suspension is stirred at room temperature and a solution of ethanol (EtOH) (3.13 mL, 53.4 mmol, (Note 7)) in 10 mL of THF is added dropwise over a period of 15 min with vigorous evolution of hydrogen gas. The mixture is stirred for 20 min and a solution of (R)-1,1'-bi-2-naphthol (16.0 g, 55.8 mmol, (Note 8)) in 60 mL of THF is added over 1 hr by means of a cannula. The resulting cloudy, milky solution is refluxed for 2 hr (Note 9). The solution is cooled to −78°C in a dry ice-acetone bath and a solution of the acyl stannane in 65 mL of THF (Part A) is added over 45 min by means of a cannula. The reaction mixture is stirred for 16 hr (Note 10) as the bath slowly warms to room temperature. The reaction is quenched by the careful addition of 100 mL of aqueous saturated ammonium chloride solution and diluted with 100 mL of water and 200 mL of ether . The layers are separated and the aqueous layer is acidified by the addition of 200 mL of 1.0 M hydrochloric acid (HCl) and extracted with two 200-mL portions of ether . The organic layers are combined and washed with 200 mL of aqueous saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and the solvent is removed by rotary evaporation. Hexane (100 mL) is added and distilled from the solution by rotary evaporation to ensure complete removal of residual ether and THF (Note 11). The solid yellow residue is triturated with 200 mL of hexane and filtered. Solvent is removed from the filtrate by rotary evaporation and the yellow oil is again triturated with 200 mL of hexane and filtered (Note 12). Solvent is again distilled from the filtrate by rotary evaporation to afford 8.97 g of crude hydroxy stannane as a yellow oil (Note 13).

While the α-hydroxy stannane is not as labile as the acyl stannane precursor, it should generally be converted to the ether derivative immediately after isolation.

C. The hydroxy stannane is dissolved in 100 mL of anhydrous methylene chloride in a 250-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar. The yellow solution is stirred at 0°C and diisopropylethylamine (i-Pr_2NEt) (8.80 mL, 50.5 mmol) is added, followed by chloromethyl methyl ether (2.90 mL, 38.2 mmol). After 5 hr the reaction is quenched with 100 mL of aqueous saturated ammonium chloride solution. The layers are separated and the aqueous layer is extracted with two 100-mL portions of ether . The organic layers are combined, dried over magnesium sulfate, filtered, and the solvent is distilled by rotary evaporation. The residue is purified by column chromatography on silica gel (Note 14). Elution with hexane followed by EtOAc-hexane (1:9) affords 4.1-5 g (40-49% yield) of (S,E)-1-methoxymethyl)-1-tributylstannyl-2-butene (Note 15).

2. Notes

1. All apparatus was dried by alternately evacuating the flask while heating with a flame and venting in dry nitrogen gas.
2. Tributyltin hydride, 97%, crotonaldehyde, 99%, 1,1'-(azodicarbonyl)dipiperidine, 99%, and lithium aluminum hydride, 95%, were purchased from Aldrich Chemical Company, Inc. Hexane refers to a distilled, isomeric mixture of C_6H_{14}.
3. A viscous oil may form which makes stirring difficult. If this occurs, the flask is removed from the bath and shaken by hand until stirring can be resumed.
4. The reaction is monitored by TLC (silica gel; 1:9 EtOAc-hexane). The TLC plate is developed by dipping into a 0.02 M solution of phosphomolybdic acid in EtOH. The initially formed hydroxy stannane (R_f = 0.52) will stain blue without heating. The acyl stannane (R_f = 0.69) is observed by charring the plate.
5. Because of the air sensitive nature of the acyl stannane, the flask is vented with argon after removal of solvent.
6. A large volume of hexane is required to precipitate fully residual ADD and its reduction product. Alternatively the ether extracts may be concentrated to dryness and triturated with 250 mL of hexane .
7. The ethanol is distilled from calcium hydride and stored over molecular sieves.
8. Incomplete reduction of the acyl stannane is observed when fewer equivalents of BINAL-H are employed.
9. It was discovered by J. C. Saddler and co-workers at Upjohn that for reproducible results it was necessary to reflux the mixture of binaphthol, $LiAlH_4$, and EtOH before performing the reduction. Enantioselective reduction of the acyl stannane can also be effected with Chirald, albeit with slightly diminished enantioselectivity.[2]
10. The reduction is generally complete within a few hours and may be monitored by TLC (Note 4). As

stated in the procedure section, the submitters recommend that the hydroxy stannane not be stored after isolation. It can, however, be kept in the reaction mixture overnight.
11. The ensuing trituration is most efficient when residual ether and THF are completely removed.
12. Because of a slight solubility of the binaphthol in the crude hydroxy stannane mixture, two triturations are required. The binaphthol is recrystallized as previously described.[3] Generally >90% of purified binaphthol is recovered.
13. The checkers found that the residue after removal of solvent contained water, which they removed azeotropically with toluene. Subsequent incomplete removal of the toluene led to amounts of stannane greater than theoretical.
14. The crude product was chromatographed on a silica gel column (ca. 150 g) using 300 mL of hexane followed by EtOAc-hexane (1:9 v/v) until complete elution. Because of a slight impurity, the early and late fractions of this separation were yellow; the middle fractions were colorless.
15. The following physical data were recorded: $[\alpha]_D^{25}$ −62.6 (CH_2Cl_2, *c* 2.3), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (m, 15 H), 1.31 (m, 6 H), 1.50 (m, 6 H), 1.68 (d, 3 H, J = 6.2), 3.33 (s, 3 H), 4.56 (m, 1 H), 4.49, 4.67 (ABq, 2 H, J = 6.6), 5.39 (dq, 1 H, J = 15.4, 6.2), 5.58 (dd, 1 H, J = 15.4, 7.7) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 8.9, 13.5, 17.5, 27.3, 29.0, 55.2, 72.4, 95.0, 119.9, 132.5 . Anal. Calcd for $C_{18}H_{38}O_2Sn$: C, 53.35; H, 9.45. Found: C, 53.63; H, 9.28. The rotation corresponds to an enantiomeric excess of greater than 90% as previously reported.[2]

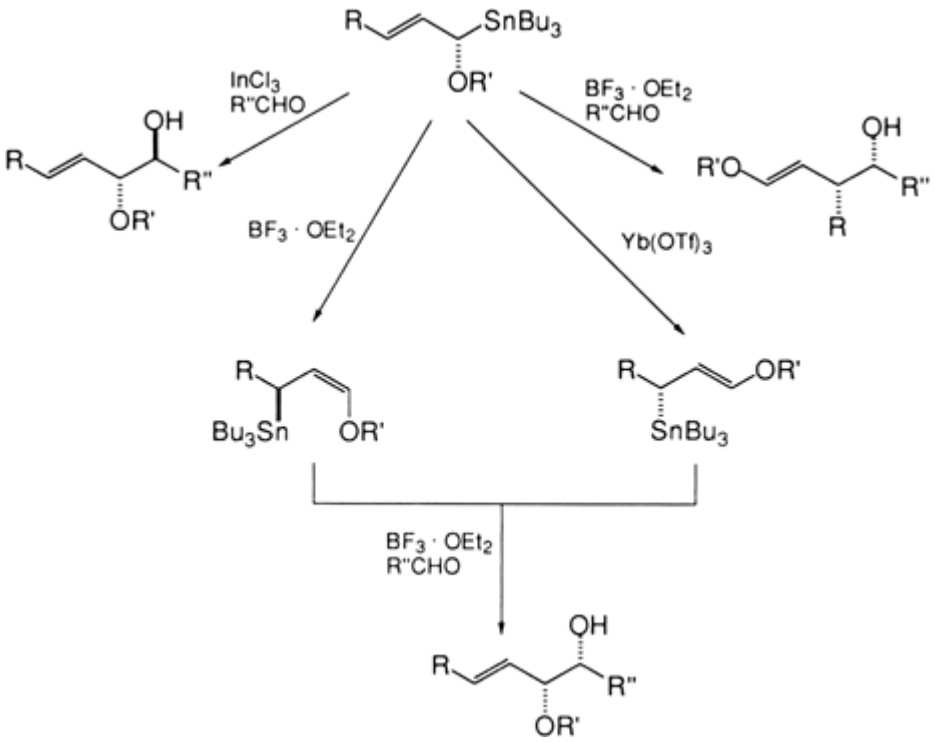
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

Chiral α-alkoxyallylic stannanes [O-MOM, O-BOM (benzyloxymethyl)], as well as their α-siloxy (O-TBS) analogues, are useful reagents for chain homologation (Figure 1). The title compound has been used for the synthesis of carbohydrate homologues, cembranes, and macrolide precursors.[4] [5,6] [7] The reagents are readily prepared and can be stored for extended periods with no apparent decomposition or racemization. The preparation of chiral α-siloxy allylic stannanes parallels the above procedure with the substitution of appropriate silylating agents in Part C. These stannanes undergo highly selective Lewis-acid promoted additions to aldehydes to give syn $S_{E'}$ addition products.[2]

Figure 1



These reagents are also useful for the preparation of 1,2-diols. Upon exposure to Lewis acids such as boron trifluoride etherate ($BF_3{\cdot}OEt_2$), the α-alkoxy and α-siloxyallyl stannanes undergo a stereospecific, intermolecular 1,3-isomerization to give γ-alkoxy- and γ-siloxy allylic stannanes.[3,8,9] When tert-butyldimethylsilyl trifluoromethanesulfonate is substituted for chloromethyl methyl ether in the above procedure, the isomeric γ-siloxy allylic stannane can be obtained directly with no loss of enantioselectivity.[8] These stannanes can then be added to various aldehydes to give monoprotected 1,2-diols with high diastereoselectivity.[10]

References and Notes

1. Department of Chemistry, University of Virginia, Charlottesville, VA 22901.
2. Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.
3. (R)-1,1'-Bi-2-naphthol was prepared by resolution employing the N-benzylammonium chloride salt of (−)-cinchonidine to form separable diastereomeric clathrate complexes. Hu, Q-S.; Vitharama, D.; Pu, L. *Tetrahedron: Asymmetry* **1995**, *6*, 2123.
4. Marshall, J. A. *Chemtracts: Org. Chem.* **1992**, *5*, 75;
5. Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
6. Marshall, J. A.; Seletsky, B. M.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 3413;
7. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 105.
8. Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1992**, *57*, 7158.
9. Isomerization of α-silyloxy and α-alkoxyallyl stannanes using either $BF_3{\cdot}OEt_2$ or lithium perchlorate ($LiClO_4$) affords (Z)-γ-siloxy- and γ-alkoxyallylic stannanes. Treatment with Yb $(OTf)_3$ affords mixtures of (Z)- and (E)-γ-siloxy- and γ-alkoxyallylic stannanes. See: Marshall, J. A.; Jablonowski, J. A.; Elliott, L. M. *J. Org. Chem.* **1995**, *60*, 2662.
10. While these reagents have largely been used to form syn-1,2-diols (see Refs. [3], [4] [5], and [6] [7]), recently methodology has been developed that allows access to anti-1,2-diols with similar diastereoselectivity. See: Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S,E)-1-(Methoxymethoxy)-1-tributylstannyl-2-butene:
Stannane, tributyl[1-(methoxymethoxy)-2-butenyl]-, [S-(E)]- (12); (131433-64-2)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Tributyltin hydride:
Stannane, tributyl- (8,9); (688-73-3)

Crotonaldehyde:
Crotonaldehyde, (E)- (8);
2-Butenal, (E)- (9); (123-73-9)

1,1'-(Azodicarbonyl)dipiperidine [ADD]:
Diimide, bis(piperidinocarbonyl)- (8);
Piperidine, 1,1'-(azodicarbonyl)bis- (9); (10465-81-3)

Lithium aluminum hydride:
Aluminate(1−), tetrahydro-, lithium (8);
Aluminate(1−), tetrahydro-, lithium, (T-4)- (9); (16853-85-3)

(R)-(+)-1,1'-Bi-2-naphthol:
[1,1'-Binaphthalene]-2,2'-diol, (R)-(+)- (8);
[1,1'-Binaphthalene]-2,2'-diol, (R)- (9); (18531-94-7)

Phosphomolybdic acid:
Molybdophosphoric acid ($H_3PMo_{12}O_{40}$), hydrate (9); (51429-74-4)

Chloromethyl methyl ether CANCER SUSPECT AGENT:
Ether, chloromethyl methyl (8);
Methane, chloromethoxy- (9); (107-30-2)

Chirald:
Benzenethanol, α-[2-(dimethylamino)-1-methylethyl]-α-phenyl-, [S-(R,R)]- (9); (38345-66-3)