Pheromone Synthesis *via* Organoboranes: A stereoselective Synthesis of (*E*)-1,3-Alkenynes *via* Thexylchloroborane-Dimethyl Sulfide

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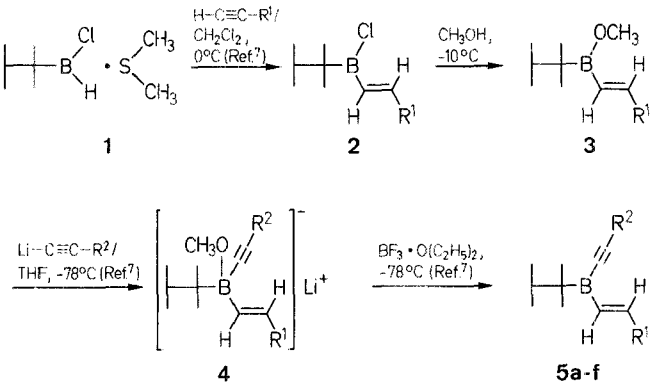
Treatment of thexylalkenylalkynylboranes with iodine in the presence of potassium methoxide produces (*E*)-1,3-enynes in good yield (58–82%) and excellent stereochemical purities (≥ 95%). The methodology was successfully applied to the synthesis of (5*Z*,7*E*)-5,7-dodecadien-1-ol, the sex pheromone of the forest tent caterpillar (*Malacosoma disstria*).

Synthetic applications[2-9] of thexylchloroborane-dimethyl sulfide (**1**), a new versatile hydroborating agent, have been explored in the past several years. It provides an easy access to thexylalkylchloroboranes[2] and to thexylalkenylchloroboranes[2]. Recently we reported[7] the synthesis of thexylalkenylalkynylboranes (**5**), organoboranes with three different types of organic groups, based on this hydroborating agent (Scheme **A**).

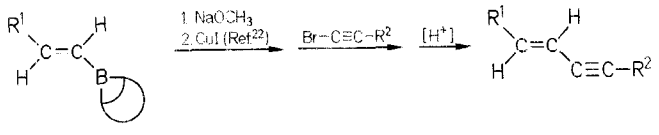


Scheme **A**

Many insect pheromones contain a conjugated *cis*, *trans*-diene grouping[10-14]. Because conjugated enynes are readily converted to the corresponding conjugated *cis*, *trans*-dienes by a simple hydroboration-protonolysis sequence[15,16], the stereospecific synthesis of conjugated enynes is a highly desirable goal.

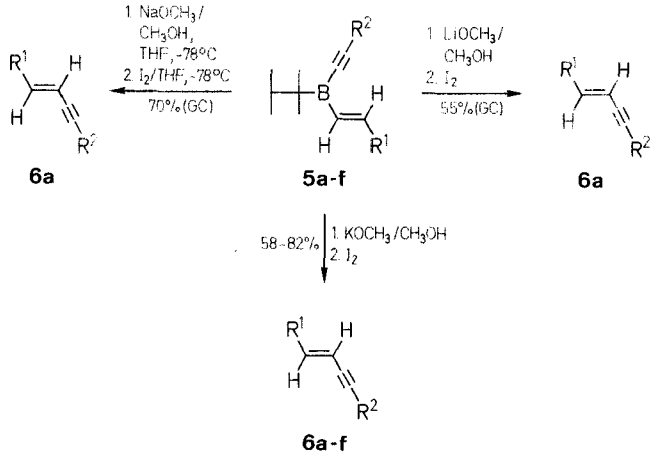
Several complex, low yield procedures have been described for the synthesis of conjugated enynes[17]. Some of these require the prior stereoselective synthesis of alkenyl halides[18]. E. Negishi and coworkers developed a highly stereoselective (≥ 99%) synthesis of conjugated enynes and utilized the procedure for the synthesis of two insect pheromones[19,20]. Suzuki et al synthesized the conjugated *trans*-enynes utilizing the palladium-catalyzed reaction of 1-alkenylboranes with 1-halo-1-alkynes[21]

Recently we reported a novel procedure for the synthesis of conjugated *trans*-enynes[22] which involves cross-coupling of 1-halo-1-alkynes with alkenyl copper intermediates generated from the *B*-alkenyl-9-BBN derivatives (Scheme **B**).

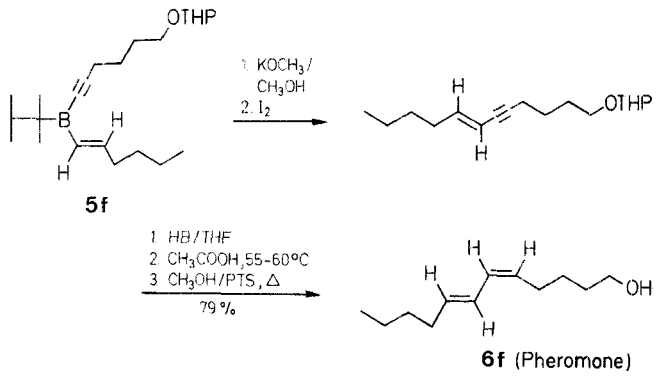


Scheme **B**

In a continuation of our studies[2,4,8,9] on the applications of thexylchloroborane-dimethyl sulfide (**1**) for organic transformations, we herein report a highly stereoselective synthesis of (*E*)-1,3-enynes utilizing thexylalkenylalkynylboranes (**5**) (Scheme **C**). This methodology has successfully been applied to synthesize (5*Z*,7*E*)-5,7-dodecadien-1-ol[23], a sex pheromone of the forest tent caterpillar (*Malacosoma disstria*).



Scheme **C**



THP = tetrahydropyranyl
HB = hydroboration
PTS = *p*-toluenesulfonic acid

Scheme **D**

1-Alkynes were hydroborated with thexylchloroborane-dimethyl sulfide **1** to provide the corresponding thexylalkenylchloroboranes **2**. Subsequent treatment with methanol resulted in the formation of the corresponding thexylalkenylborinates **3**. These borinate esters were reacted with alkynyllithium reagents to generate the corresponding "ate" complexes **4**, readily converted by 1.33 equiv of borontrifluoride-etherate[24] to the desired thexylalkenylalkynylboranes **5**. The low migratory aptitude[3-9] of the thexyl group led us to explore the possibilities of employing **5** for the stereoselective synthesis of (*E*)-1,3-enynes. Iodination of these thexylalkenylalkynylboranes **5** in the presence of potassium methoxide in methanol at −78 °C for 3 h produced (*E*)-1,3-enynes **6** in high yields (Table). We observed that the use of lithium methoxide and sodium methoxide gave reduced yields of **6** (Scheme **C**). Each enyne thus obtained was shown by GC analysis to be at least 95% isomerically pure. The corresponding *cis*-isomers[25] were also prepared. Both isomers separate cleanly on a 10% SE-30 column[26]. The *trans* geometry of the double bond in conjugated 1,3-enynes was established by ^{1}H-NMR (J_{trans} = 16 Hz) and ^{13}C-NMR[27] spectral data. Thexyl migrated products were not detected.

(5*Z*,7*E*)-5,7-Dodecadien-1-ol (**6f**) the pheromone of the forest tent caterpillar (*Malacosoma disstria*) has been synthesized in 95% isomeric purity by employing the same methodology. The resulting (*E*)-1,3-enyne (**5f**) was hydroborated[16] and protonolyzed[16] to obtain **6f** (Scheme **D**).

In summatry we now have a convenient method for the synthesis of (*E*)-1,3-enynes **6** *via* thexylchloroborane-dimethyl sulfide (**1**). The procedure appears general and its simplicity should make it quite valuable for such syntheses. The present procedure for preparing (*E*)-1,3-enynes does not offer any significant advantage over earlier methods[21,22]. However, it does provide an alternative synthetic route and extends the applicability of thexylchloroborane-dimethyl sulfide (**1**) in organic syntheses, a major objective of our present program. The methodology has successfully been applied for the synthesis of (5*Z*,7*E*)-5,7-dodecadien-1-ol (**6f**), a pheromone of the forest tent caterpillar (*Malacosoma disstria*).

All glassware used for the experiments were thoroughly dried in an oven and cooled under a stream of nitrogen. The alkynes (from Farchan Acetylenes) were converted into alkynyllithium by the action of *n*-butyllithium. The special experimental techniques used in handling air- and moisture-sensitive materials are described elsewhere[28]. All boiling points are uncorrected. The GC analyses were carried out an a Varian 1200 gas chromatograph (column 12 ft × 1/8 in packed with 10% SE-30 on Chromosorb W AW

Table. Stereoselective Synthesis of (*E*)-1,3-Enynes *via* Thexylchloroborane-Dimethyl Sulfide[a]

Alkyne for Hydroboration by **1**	Alkyne for Alkynyllithium	Product[b] No.	R^1	R^2	Yield[c] [%]	b.p. [°C]/torr	Lit. b.p. [°C]/torr	n_D^{20}
1-Hexyne	1-Octyne	**6a**	*n*-C_4H_9	*n*-C_6H_{13}	(82)	–	–	–
1-Hexyne	1-Hexyne	**6b**	*n*-C_4H_9	*n*-C_4H_9	70	78–80/1.6	–	1.4660
1-Octyne	Cyclohexylethyne	**6c**	*n*-C_6H_{13}	*c*-C_6H_{11}	73	86–88/0.01	–	1.4930
1-Pentyne	1-Decyne	**6d**	*n*-C_3H_7	*n*-C_8H_{17}	68	76–78/0.01	–	1.4675
1-Decyne	*t*-Butylacetylene	**6e**	*n*-C_8H_{17}	*t*-$C(CH_3)_3$	68	68–70/0.01	–	1.4585
1-Hexyne	5-Hexyn-1-ol	**6f**	*n*-C_4H_9	*n*-C_4H_9O	58	82–84/0.08	90–91/0.5[23]	1.4724[d]

[a] All reactions were carried out on a 20-mmol scale.
[b] The structures were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectra.
[c] Yields of pure (> 95% isomeric purity by GC) products isolated by distillation, based on 1-alkyne used; values in parentheses indicate GC yields.
[d] Lit.[23], n_D^{20} = 1.4865.

DMCS, temperature 50–250 °C programmed 10 °C/min, carrier gas nitrogen). ^{1}H-NMR spectra (δ, relative to TMS) were recorded on a Varian T-60 spectrometer. Both ^{13}C (δ, relative to TMS) and ^{11}B (δ, relative to borontrifluoride-etherate) NMR spectra were recorded on a Varian FT-80A spectrometer equipped with a broadband probe and a Hewlett-Packard 3335 A frequency synthesizer. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer.

(*E*)-5-Dodecen-7-yne (6b); Typical Procedure:

A dry, 100-ml, round-bottom flask equipped with a sidearm capped with a rubber septum, magnetic stirring bar and a connecting tube attached to a mercury bubbler is flushed with nitrogen. To a 1.64 molar solution of thexylchloroborane-dimethyl sulfide (**1**) in dichloromethane (12.20 ml, 20 mmol) in the above flask is added 1-hexyne (2.30 ml, 20 mmol) at 0 °C under nitrogen. The mixture is stirred for 2 h at 0 °C. Then the reaction mixture is cooled to −10 °C and methanol (1.60 ml, 40 mmol) is added. Stirring is continued for 0.25 h at −10 °C. Solvents are removed under reduced pressure. To the resulting thexylalkenylmethoxyborane in tetrahydrofuran (20 ml) at 0 °C is added hexynyllithium (20 mmol), prepared from 1-hexyne (2.30 ml, 20 mmol) and *n*-butyllithium (7.80 ml, 20 mmol, 2.56 molar) at 0 °C in tretrahydrofuran and the mixture is immediately cooled to −78 °C. After 0.5 h, boron-trifluoride etherate (3.30 ml, 26.60 mmol) is added dropwise at −78 °C and stirred for an additional 0.5 h at −78 °C. The reaction mixture is then allowed to warm up to room temperature while the solvents are removed under reduced pressure. Pentane (20 ml) is added to the white solid and the mixture stirred for 15 min. The pentane solution is decanted, the solid is washed with pentane (2 × 20 ml), and the pentane solutions are combined. The pentane is removed under vacuum and the resulting thexylalkenyl-alkynylborane (4.68 g, 18 mmol, ^{11}B-NMR δ = +63.00 ppm) is dissolved in tetrahydrofuran (20 ml). To the reaction mixture is added a 1.84 molar solution of potassium methoxide in methanol (29.3 ml, 54 mmol) dropwise at 0 °C and the mixture is stirred for 0.25 h at 0 °C. It is then cooled to −78 °C and a solution of iodine (4.58 g, 18 mmol) in tetrahydrofuran (20 ml) is added dropwise at −78 °C with vigorous stirring. Stirring is continued for 3 h at −78 °C. Any excess iodine present is decolorized by adding an aqueous solution of sodium thiosulfate. The flask is then brought to room temperature and the reaction mixture is extracted with *n*-pentane (3 × 50 ml). The organic layer is washed with 3 normal sodium hydroxide solution (2 × 20 ml), followed by washing with water (2 × 50 ml) and dried with anhydrous potassium carbonate. The solvent is removed on a rotovapor and the residue is purified by high vacuum distillation to afford (*E*)-5-dodecen-7-yne (**6b**); yield: 2.30 g (70%); b.p. 78–80 °C/1.6 torr; n_D^{20} = 1.4660; GC purity: >95%.

IR (neat): ν = 2217 (C≡C), 957 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 6.0 (m, 1 H), 5.40 (d, 1 H, J = 16 Hz), 2.30–2.03 (m, 4 H), 1.60–1.23 (m, 8 H), 1.0–0.80 ppm (m, 6 H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 143.19, 109,98 (C=C); 88.62, 79,27 (C≡C), 32.63, 31.01, 30.89, 22.15, 21.99, 19.04, 13.79, 13.55 ppm (alkyl C).

(5*Z*,7*E*)-5,7-Dodecadien-1-ol (6f) (Pheromone):

The compound **5f** (7.2 g, 20 mmol) is dissolved in tetrahydrofuran (10 ml). To this mixture is added a solution of disiamylborane (22 mmol) in tetrahydrofuran at −5 to 0 °C. The reaction mixture is stirred at 0 °C for 2 h, then diluted with glacial acetic acid (5 ml) and maintained at 55–60 °C for 5 h. After the protonolysis, the reaction mixture is made basic by adding a 6 molar aqueous solution of sodium hydroxide (20 ml). The disiamylborinate formed is oxidized at 35–40 °C with 30% hydrogen peroxide (5 ml). After stirring the reaction mixture at room temperature for 0.5 h, sodium chloride is added to saturate the solution and the upper phase formed is separated. The aqueous phase is extracted with *n*-pentane (2 × 20 ml) and the combined extract is dried with magnesium sulfate. The product obtained after removal of pentane is refluxed with a catalytic amount of *p*-toluenesulfonic acid in methanol (20 ml). Distillation of the product gives (5*Z*,7*E*)-5,7-dodecadien-1-ol (6f), a pheromone, yield: 2.8 g (79%); b.p. 82–84 °C/0.08 torr; n_D^{20} = 1.4724; 95% isomeric purity by GC analysis (Lit.[23], b.p. 90–91 °C/0.05 torr, n_D^{25} = 1.4865).

IR (neat): ν = 3333 (—OH), 1667, 1626, 844 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 6.6–5.1 (m, 4 H); 4.0 (br s, 1 H); 3.5 (m, 2 H); 2.20 (m, 4 H); 1.6–1.2 (m, 8 H); 1.1–0.8 ppm (m, 3 H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 134.33, 129.09, 128.91, 125.54 (C=C); 61.89 (CH_2—OH); 32.40, 32.04, 31.61, 27.28, 25.83, 22.09, 13.67 ppm (alkyl C).

MS: m/e = M^+, 182.

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