Use of Organoboranes in the Synthesis of Pheromones: A Convenient Synthesis of (Z)-6-Heneicosen-11-one and (Z)-5-Undecen-2-one, Pheromones from the Douglas Fir Tussock Moth and the Bontebok, Respectively

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Treatment of thexyborane with a halomagnesiumdialkylcuprate afforded the corresponding (B-alkyl)thexylborane in favourable yields. A second reaction with a halomagnesiumdialkylcuprate produced the totally mixed (B-alkyl)(B-alkenyl)thexylborane. Subsequent treatment with sodium cyanide and benzoyl chloride followed by alkaline peroxide yielded an unsaturated ketone. In this way, (Z)-6-heneicosen-11-one, a sex pheromone of the Douglas Fir Tussock Moth, and (Z)-5-undecen-2-one, a pheromone from the pedestal gland of the Bontebok, were prepared.

The development of a general method for the synthesis of unsaturated ketones is a major point of interest in organic synthesis and a variety of methods have been reported. In a continuation of our studies on the reaction of diorgano-
cuprates with organoboranes 1-4 we herein report the synthesis of unsaturated ketones using mixed (alkyl)(alkenyl)thexylboranes. This methodology has successfully been applied to synthesize (Z)-6-heneico-
sen-11-one (1, n = 3, R = C_{12}H_{25}) the active sex phero-
monne of the Douglas Fir Tussock Moth 5 and (Z)-5-unde-
cen-2-one (1, n = 2, R = Me) a pheromone from the pede-
sl gland of the Bontebok. 6

1, 2-Migrations of an organic group from boron to an acceptor atom are most important in organic synthesis. 7 For ionic reactions, migration is initiated by nucleophilic attack of an electron-rich species upon the electron-deficient borane, the charge separated complex so formed stabilising itself by intramolecular migration. Such a mechanism is displayed in the reaction of cyanide ion with trisubstituted boranes. The generated trisubstituted cy-
anonoborate, when warmed with benzoyl chloride in tetra-
hydrofuran followed by peroxide oxidation, produced

suitably substituted ketones. 8 The low migratory apti-
tude 3 of the thexy group led us to explore this strategy for the synthesis of the two pheromones.

For the preparation of the pheromone (Z)-6-Heneico-
sen-11-one (1, n = 3, R = C_{12}H_{25}), the immediate or-
organoborane precursor is (B-decyl)(B-(dec-4-enzyme)thexylborane (2, n = 3, R = C_{12}H_{25}) prepared from the mono-
substituted thexylborane 3 (R = C_{12}H_{25}) and the diale-
nylhalomagnesium cuprate 4 (n = 3) (Scheme 1).

The homochromonaphene cuprate 4 (n = 3) is prepared starting from 3-chloropropanol (Scheme 2, n = 3).

\[ \text{Li}^{+} \text{CuClCClH}_{11}, (\text{Bu})_{2} \text{N}^{+} \text{Br} \]

\[ \text{THF, 0°C to r.t.} \]

\[ \text{Cl(CH}_{3} \text{O)} \text{OH} \rightarrow \text{Cl(CH}_{3} \text{O)} \text{OTs} \]

\[ \text{73 - 76%} \]

\[ \text{5} \]

Thus 3-chloropropanol was tosylated with toluene-4-
sulfonyl chloride and cold pyridine, and the product was

subsequently treated with one equivalent of 1-hep-

tyn-1-lylium under phase-transfer conditions. 9 The
coloralkyne 6 was reduced by borane-dimethyl sulfide in

THF 10 which, after protonation with glacial acetic

cid, afforded the corresponding (Z)-chloroalene 7. The

Grignard was then readily prepared using activated magnesium in diethyl ether and this was treated with 0.5

equivalent of cuprous iodide to produce the halomagne-
sium cuprate 4 (n = 3). An ethereal solution of 4 (n = 3)

was reacted with the mixed thexylborane 3 (R = C_{12}H_{25})

at -80°C and the reaction was allowed to warm to room

temperature. At -40°C the reaction mixture gradually

darkened, and after 2 h at room temperature a greyish-

black heterogeneous suspension, presumably a cop-

per-magnesium halide adduct, remained.

Initial problems were encountered with the formation of

the cyanoborate since all magnesium salts had to be

removed before this could be prepared. Filtering the

etheral solution of the mixed thexylborane through

Celite or anhydrous sodium sulfate under nitrogen

failed
Table 1. Yields, Properties and Spectroscopic Data for Compounds 5, 6 and 7

<table>
<thead>
<tr>
<th>Prod- n</th>
<th>Yield (%)</th>
<th>bp (°C/ mmHg)</th>
<th>¹H NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>¹³C NMR (CDCl₃/TMS)</th>
<th>IR (near) νmax (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>3 76</td>
<td>184/5</td>
<td>2.1 (m, 2H, CH₂CH₂CH₂), 2.5 (s, 3H, ArCH₃), 3.6 (t, 2H, CH₂Cl), 4.2 (t, 2H, CH₂OSO₂), 7.4 (d, 2H, J = 8, ArH), 7.8 (d, 2H, J = 8, ArH)</td>
<td>13.7 (CH₂), 18.6 (CH₂Cl), 21.2 (CH₂Cl), 25 (CH₂), 28 (CH₂CH₂Cl), 31.3 (CH₂CH₂CH₂), 43.8 (CH₂Cl), 77 (CH₂CC=C), 81.5 (C=CCH₂)</td>
<td>9000, 2220, 1450, 1118, 760, 675, 655</td>
</tr>
<tr>
<td>5b</td>
<td>2 73</td>
<td>156/0.3</td>
<td>2.5 (s, 3H, ArCH₃), 3.6 (t, 2H, CH₂Cl), 4.2 (t, 2H, CH₂SO₂), 7.4 (d, 2H, J = 8, ArH), 7.8 (d, 2H, J = 8, ArH)</td>
<td>13.7 (CH₂), 18.6 (CH₂Cl), 21.2 (CH₂Cl), 25 (CH₂), 28 (CH₂CH₂Cl), 31.3 (CH₂CH₂CH₂), 43.8 (CH₂Cl), 77 (CH₂CC=C), 81.5 (C=CCH₂)</td>
<td>9000, 2220, 1450, 1118, 760, 675, 655</td>
</tr>
<tr>
<td>6a</td>
<td>3 78</td>
<td>135/24</td>
<td>0.85 (t, 3H, CH₃C=), 1.2–1.4 [m, 6H (CH₂₂)], 1.9 (m, 2H, CH₂CH₂CH₂), 2.1 (m, 2H, CH₂C=C), 2.3 (m, 2H, CH₂CH₂CH₂), 3.6 (t, 2H, CH₂Cl)</td>
<td>13.7 (CH₂), 18.6 (CH₂Cl), 21.2 (CH₂Cl), 25 (CH₂), 28 (CH₂CH₂Cl), 31.3 (CH₂CH₂CH₂), 43.8 (CH₂Cl), 77 (CH₂CC=C), 81.5 (C=CCH₂)</td>
<td>9000, 2220, 1450, 1118, 760, 675, 655</td>
</tr>
<tr>
<td>6b</td>
<td>2 76</td>
<td>100/16</td>
<td>0.85 (t, 3H, CH₃C=), 1.2–1.4 [m, 6H (CH₂₂)], 2.1–2.3 (dt, 4H, CH₃C=CCH₂), 3.6 (t, 2H, CH₂Cl)</td>
<td>13.7 (CH₂), 18.6 (CH₂Cl), 21.2 (CH₂Cl), 25 (CH₂), 28 (CH₂CH₂Cl), 31.3 (CH₂CH₂CH₂), 43.8 (CH₂Cl), 77 (CH₂CC=C), 81.5 (C=CCH₂)</td>
<td>9000, 2220, 1450, 1118, 760, 675, 655</td>
</tr>
<tr>
<td>7a</td>
<td>3 75</td>
<td>103/16</td>
<td>0.85 (t, 3H, CH₃C=), 1.2–1.4 [m, 4H (CH₂₂)], 1.5 (m, 2H, CH₂CH₂CH₂), 1.8 (m, 2H, CH₂CH₂CH₂), 2.0–2.2 (dq, 4H, CH₂CH₂CH₂), 3.45 (t, 2H, CH₂Cl), 5.2–5.5 (m, 2H, CH=CH₂)</td>
<td>13.7 (CH₂), 22.8 (CH₂CH₂Cl), 27.8 (CH=CH₂CH₂Cl), 30.7 (CH₂CH₂Cl), 32.6 (CH₂CH₂CH₂), 37.6 (CH=CH₂CH₂Cl), 40.1 (CH=CH₂CH₂Cl), 45.1 (CH₂Cl), 129.8 (CH=CH₂Cl), 131.6 (CH=C)</td>
<td>9000, 2220, 1450, 1118, 760, 675, 655</td>
</tr>
<tr>
<td>7b</td>
<td>2 75</td>
<td>88/16</td>
<td>0.85 (t, 3H, CH₃C=), 1.2–1.4 [m, 6H (CH₂₂)], 2.0–2.2 (4H, dq, CH₂CH₂CH₂CH₂), 3.5 (t, 2H, CH₂Cl), 5.2–5.5 (m, 2H, CH=CH₂)</td>
<td>13.7 (CH₂), 22.8–40.1 (CH₂), 45.1 (CH₂Cl), 129.8 (CH=CH₂Cl), 131.6 (CH=C)</td>
<td>9000, 2220, 1450, 1118, 760, 675, 655</td>
</tr>
</tbody>
</table>

* Lit⁵⁻¹³³°C/0.2 mmHg

Table 2. Yields and Spectroscopic Data for Phenomerone 1

<table>
<thead>
<tr>
<th>Prod- n</th>
<th>Yield (%)</th>
<th>¹H NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>¹³C NMR (CDCl₃/TMS)</th>
<th>IR (near) νmax (cm⁻¹)</th>
<th>MS (70 eV) m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>C₁₀H₁₁₂</td>
<td>83</td>
<td>0.9 (t, 6H, 2 × CH₃), 1.3 [m, 22H, (CH₂₂)₂], 1.9 (m, 4H, CH₂CH₂CH₂), 2.4 (t, 4H, J = 7, CH₂COCH₂), 5.3 (m, 2H, CH=CH)⁵</td>
<td>13.8–44.1 (alkyl C), 128, 131 (C=C), 205 (C=O)</td>
<td>3000, 2920, 2850, 1715, 1455, 1370, 1125, 1080</td>
</tr>
<tr>
<td>1b</td>
<td>Me</td>
<td>77</td>
<td>0.85 (t, 3H, J = 6.3, CH₃CH₂), 1.1–1.6 [m, 6H, (CH₂₂)₂], 1.9 (m, 4H, CH₂CH₂CH₂), 2.1 (s, 3H, CH₃CO), 2.4 (t, 2H, J = 7, CH₂CO), 5.2–5.6 (m, 2H, CH=CH)⁶</td>
<td>14.1, 21.7, 22.5, 27.2, 29.3, 31.5, 43.7 (alkyl C), 127.6, 131.1 (C=C), 205.1 (C=O)</td>
<td>168 (M⁺) 23, 57 (36), 43 (100)</td>
</tr>
</tbody>
</table>

* Satisfactory microanalyses obtained: C, H ± 0.3%.

to remove these salts completely. Instead the ether was evaporated, the residue taken up into dry hexane and then the suspension passed through a short column of silica gel. The hexane solution was concentrated, the residue dissolved in dry THF and the product treated successively with sodium cyanide, benzyl chloride and basic hydrogen peroxide.⁸ The product (Z)-6-henicosen-11-one (I) was purified by flash chromatography¹¹ and gave an NMR spectrum almost identical to that of an authentic sample.¹²

The preparation of the thexylborene 3 (R = C₁₀H₂₁) was achieved in a similar fashion to that just described. Didecyclopropennagnesium bromide, prepared from 0.5 equivalent of copper(I) iodide with the Grignard of 1-bromodecane, was added to an ethereal solution of thexylborene (from diborane and 2,3-dimethylbut-2-ene¹³) at −80°C and the mixture was allowed to warm to room temperature. At −40°C the mixture darkened resulting in a greyish-black heterogeneous suspension after 2 h. This solution was then carefully decanted through a double-ended needle into the ethereal solution of 4 (n = 3) at −80°C.

A similar general synthetic strategy as described above was followed for the preparation of the biologically active ketone of the pedal gland of the Bontebok, (Z)-5-Undecen-2-one (I, n = 2, R = Me). The immediate organoborane precursor (Scheme 1) is (B-methyl)[B-(non-3-enyl)]hexasylborene (2, n = 2, R = Me), prepared from the monosubstituted thexylborene 3 (R = CH₃) and the allylhalomagnesiumcuprate 6 (n = 2). This cuprate is, in turn, prepared from 2-chloropropanol (Scheme 2, n = 2). Tosylation of 2-chloropropanol with tolue-4-sulfonyl chloride in cold (5°C) pyridine was followed by treating the product with one equivalent of 1-heptyn-1-ylithium under phase-transfer conditions. The subsequent chloroalkyne 6 was reduced with borane-dimethyl sulfide in THF and, after protonation, the chloroalkene 7 was converted into the Grignard using activated magnesium in dry diethyl ether. Cuprate 4 (n = 2) was then formed by decanting the Grignard
solution onto 0.5 equivalents of anhydrous copper(I) iodide.

When B-methylthexylborane (3, R = Me) was reacted with an ethereal solution of 4 (n = 2) at −80 ºC and the mixture was allowed to reach room temperature, the corresponding totally mixed thexylborane 2 (n = 2, R = CH₃) was produced in a favourable yield. As in the previous case, the reaction mixture darkened considerably at about −40 ºC with, however, a concomitant evolution of gas. After 2 h at room temperature, a greyish-black heterogeneous suspension containing a copper–magnesium halide adduct resulted.

Again these magnesium salts were removed by filtering a hexane suspension of 2 (n = 2, R = Me) through silica gel, removing the solvent and taking the residue up into THF. This was then treated with sodium cyanide, benzoyl chloride and basic hydrogen peroxide to form (Z)-5-undecen-2-one (1, n = 2, R = Me) identified from NMR spectra by comparison with an authentic sample.³

B-Methylthexylborane (3, R = Me) can be easily prepared via the general procedure of treating an ethereal solution of dimethylcoppermagnesium bromide with thexylborane³ at −80 ºC then allowing the solution to warm to room temperature. The resulting heterogeneous solution was carefully decanted onto the ethereal solution of 4 (n = 2) at −80 ºC.

From a previous study in these laboratories,³ it was established that the method described above is only suitable for aliphatic ketones thus making this method most pertinent for the syntheses under investigation. This argument is supported by considering the mechanism. Firstly there is an initial oxidative addition of the organocuprate to the electron-deficient boron atom of the thexylborane forming a copper(III) intermediate¹⁴ (Scheme 3). This copper species collapses through reductive elimination, producing a B-alkyl substituted thexylborane hydride and the corresponding alkylcopper. Borohydrides of this nature are well known as reducing agents and a powerful source of hydride ions¹⁵ and it is believed that the H⁺ reduces the alkylcopper to produce an alkylhydridocuprate. This thermally decomposes¹⁶ to yield an alkane and a black copper–magnesium complex. The fact that a second black suspension occurred after the addition of the second dialkylcuprate indicates a second reduction via hydride and the formation of the totally mixed thexylorganoborane 2 (R = Me or C₁₆H₂₁, n = 2 or 3) (Scheme 1).

The present procedure does not offer any significant advantage over earlier methods¹⁷,¹⁸ but it does, however, provide an alternative synthetic route and extends the applicability of the reaction of organocuprates with organoboranes in organic synthesis, a major objective of our present program. The methodology has successfully been applied for the synthesis of both the pheromones (Z)-6-eneicosen-11-one of the Douglas Fir Tussock moth and (Z)-5-undecen-2-one from the Bontebok.

Et₂O, hexane and THF were distilled from CaH₂ or lithium aluminium hydride under N₂ prior to use. Other solvents and liquid reagents were purified by standard procedures.¹⁹ All glassware, syrings and needles were oven dried, assembled hot and allowed to cool under dry nitrogen. Solvents and air-sensitive materials were transferred by syringes and the manipulation of boron reagents followed according to known procedures.²⁰ Butyllithium in hexane was a commercial product (Merck) and was standardised using 2,2-bipyridyl as indicator.²¹ All Grignard reagents were prepared by known methods²² and standardised using 2,2-biquinolyl as indicator. Copper(I) iodide (Merck) was continuously extracted with THF in a Soxhlet apparatus (48 h) and dried in vacuum over H₂SO₄ at 20 ºC.

Chloroalkyl 4-Toluene sulphonates (5); General Procedure: Toluene-4-sulfonyl chloride (2.2 g, 11.5 mmol) was added to a stirred solution of chlororoolkan-1-tol (10 mmol) in pyridine (6.0 mL) kept at 55 ºC (3 h). CH₂Cl₂ (35 mL) was added and the mixture was washed successively with 2 M HCl (10 mL), water (10 mL) and 10% aq NaHCO₃ (10 mL). The organic layer was dried, evaporated and purified by flash chromatography¹¹ to yield colourless oils. Yields, properties and spectral data are shown in Table 1.

Chloroalkynes (6); General Procedure: A dry 100 mL flask equipped with a magnetic stirrer and septum inlet was flushed with N₂. The flask was charged with the chloroalkyl 4-toluene sulphonate 5 (10 mmol), dry THF (20 mL) and tert-butylammonium bromide (3.22 g, 10 mmol) and the mixture was cooled to 0 ºC. 1-Heptynyllithium (10 mmol) prepared by the addition of butyllithium (3.6 mL, 2.8 M) to 1-heptyne (1.3 mL, 10 mmol) in THF (20 mL) was then added via a double-ended needle. The mixture was stirred at 0 ºC (1 h) then allowed to reach r.t. overnight. The solvent was removed, water was added to the residue and the solution was extracted into Et₂O. The organic layer was washed with saturated aq NaCl then dried (MgSO₄), filtered and the solvents were evaporated under reduced pressure. The products were purified by flash chromatography¹¹ to afford oils. Yields, properties and spectral data are shown in Table 1.

(Z)-Chloroalkenes (7); General Procedure: A dry, 50 mL round-bottomed flask equipped with a magnetic stirrer and septum inlet was flushed with nitrogen. The flask was charged with the chloroalkyne (10.0 mmol) and dry THF (20 mL), cooled to 0 ºC and then treated dropwise with borane-dimethyl sulphide (Aldrich, 2 M solution, 5.0 mL, 10.0 mmol). The mixture was stirred (4 h, 0 ºC) followed by heating (60 ºC, 1 h) with glacial AcOH (15 mL). After being cooled and neutralised, the product was extracted into Et₂O. The organic layer was dried and evaporated and the residue distilled under reduced pressure. The products were further purified by flash chromatography¹¹ to afford oils. Yields, properties and spectral data are shown in Table 1.

(B-Alkyl)thexylborane (3): The corresponding alkylmagnesium bromide prepared from 1-bromooalkane (10.0 mmol) and activated magnesium (240 mg,
10.0 mmol) in refluxing Et₂O (30 mL)] (2.08 M, 10.0 mmol) was added to copper(I) iodide (950 mg, 5.0 mmol) in dry Et₂O (20 mL) at −30°C. The solution was stirred at this temperature (1 h) then cooled to −78°C and the xyleneborane (1.6 M, 6.3 mL, 10.0 mmol) [prepared according to reference 13] was added. The mixture was allowed to warm to r.t. and at −40°C a grey-black colloidal suspension of copper began to form. After stirring at 20°C for 2 h, GLC analysis of the supernatant solution showed the presence of (Z-alkynyl)(alkoxy)borane (84%).

(B-alkynyl)(Z-alkenyl)alkylpropylborane (2):
An ethereal solution of 1(alkenyl)magnesium chloride (1.9 M, 10.0 mmol) [prepared from the action of activated magnesium (240 mg, 10.0 mmol) on (Z)-1-chloroalkene (10.0 mmol) in Et₂O] was added to copper(I) iodide (950 mg, 5.0 mmol) in dry Et₂O (10.0 mL). The mixture was cooled to −80°C and then treated with a solution of borane 3 by decanting the latter through a double-ended needle. The mixture was allowed to reach r.t., solvents were removed under reduced pressure and the residue taken up in dry hexane (35 mL). This solution was passed through a silica gel column (10 × 1 cm), the column was washed with hexane (2 × 20 mL), and the hexane solutions were combined and evaporated under reduced pressure. The crude organoborane was obtained as a viscous oil and was used without further purification (80%).

Pheromones 1:
The aforesaid crude organoborane (9.0 mmol) was dissolved in dry THF (25 mL), treated with powdered sodium cyanide (10.0 mmol, 490 mg) and warmed up to 45°C (1 h). Benzoyl chloride (12 mmol, 1.7 g) was then added carefully and the reaction mixture kept at 45°C (12 h). The flask was cooled to 0°C andaq NaOH (5 M, 20 mL) and hydrogen peroxide (30%, 20 mL) were added simultaneously. When the initial vigorous reaction subsided, the cooling bath was removed. The oxidation was completed by stirring for 3 h at 50°C, after which the mixture was extracted into Et₂O. The organic layer was dried and evaporated under reduced pressure to give the desired material (83%). Spectral data are shown in Table 2.

(9) Whiteley, C. G.; unpublished results.