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# NEW STEREOSPECIFIC SYNTHESES OF PHEROMONE BOMBYKOL AND ITS THREE GEOMETRICAL ISOMERS

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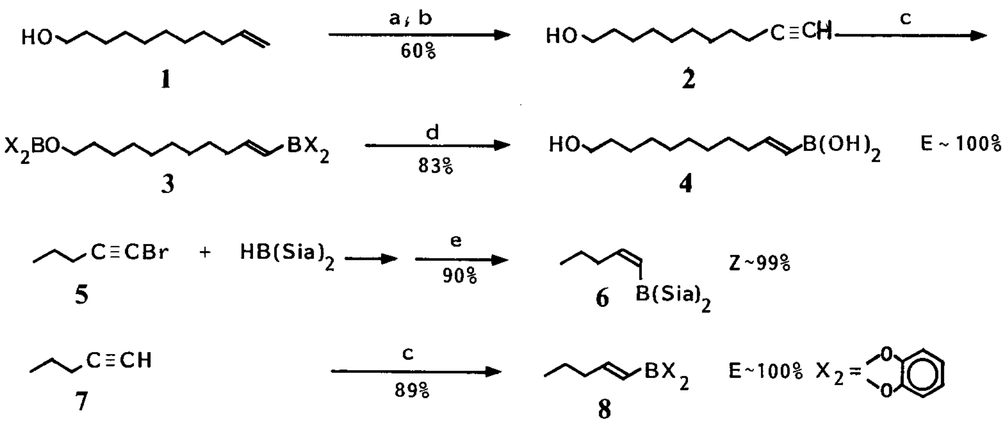
Abstract: We describe stereospecific syntheses of pheromone, bombykol and the three geometrical isomers by means of the palladium-catalyzed cross-coupling between an appropriate alkenylborane and an alkenyl halide in the presence of a base.

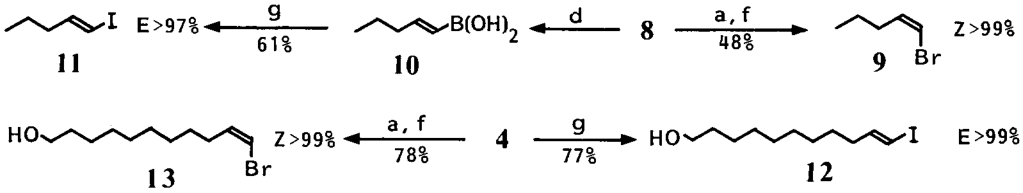
Bombykol is a well-known pheromone, first isolated from Bombyx Mori L and its structure clarified by Butenandt and his colleagues.1,2) The first syntheses of bombykol and the three geometrical isomers by employing the Wittig reaction were achieved by Butenandt and his colleagues3) as well as by Truscheit and Eiter.4) Since then, new syntheses of bombykol by two groups of investigators have been reported.5,6) In this paper we wish to report new stereospecific syntheses of bombykol and its three geometrical isomers by use of the palladium-catalyzed cross-coupling reaction between an alkenylborane and an appropriate alkenyl halide in the presence of a base. We described this method in our previous papers,7) and we believe that the present results show that the method developed by us is a powerful and reliable one for the stereospecific syntheses of conjugated dienes using alkenylboranes.

The 11-Hydroxy-1-undecenylboronic acid (4), (Z)-1-pentenyldisiamylborane (6), and (E)-1-pentenyl-1,3,2-benzodioxaborole (8) required for this coupling were newly prepared by the hydroboration of the appropriate acetylenic precursors as shown in Scheme 1. Thus, bromination at -10°~0°C, of 1-undecen-11-ol (1), prepared by the reduction of commercially available methyl 11-undecenoate with $LiAlH_4$ gave 10,11-dibromoundecan-1-ol in a nearly quantitative yield. Its dehydrobromination with $NaNH_2$8) in liquid ammonia afforded 11-hydroxy-1-undecyne (2) as a viscous oil in a 60% yield. This acetylenic alcohol (2), without protecting the hydroxy group, was subjected to hydroboration with 1,3,2-benzodioxaborole to afford a borole (3) which was immediately hydrolyzed at room temperature to give (4), an amorphous solid. The yield of 4 from 2 was 83%. Borane (6) (99% isomeric purity by $^1H$ n.m.r.) was then prepared by hydroboration of 1-bromo-1-pentyne (5)10) with disiamylborane in a 90% yield according to the literature procedure.11)

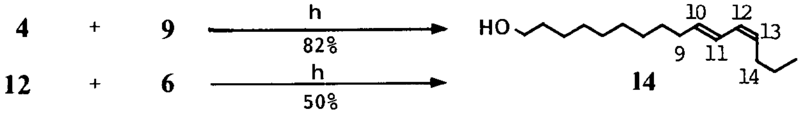
Scheme 1



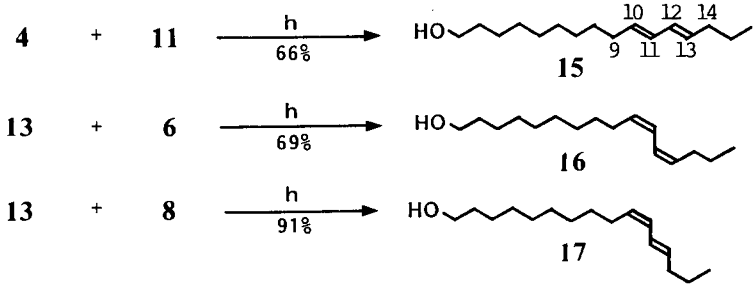
Scheme 2



Scheme 3



Scheme 4



a, $Br_2$ b, $NaNH_2/NH_3$ c, $HBX_2$ d, $H_2O$ e, t-BuLi f, NaOMe g, $NaOH/I_2$ h, $PdL_4$/NaOEt/benzene

Furthermore, borole (8) was prepared by hydroboration$^{9)}$ of 1-pentyne (7) with 1,3,2-benzodioxaborole in a 89% isolated yield. The geometry of the olefinic protons was confirmed by the $^1$H n.m.r. spectrum.

On the other hand, the four alkenyl halides, (Z)-1-pentenyl bromide (9), (E)-1-pentenyl iodide (11), (E)-11-hydroxy-1-undecenyl iodide (12), and (Z)-11-hydroxy-1-undecenyl bromide (13) were prepared by stereospecific halogenolysis of (4) and (8) according to the described procedure.$^{12\sim14)}$ Thus, the treatment of (8) with $Br_2$ followed by $CH_3ONa$ in MeOH resulted in the replacement of borane by $Br_2$ with an inversion of configuration$^{12)}$ and gave (9) with an isomeric purity of over 99% (g.l.c.) (a 48% yield). Hydrolysis of borole (8) with $H_2O$ into an amorphous (E)-1-pentenylboronic acid (10) and the treatment of it with NaOH followed by $I_2$ according to the procedure by Brown et al.$^{14)}$ resulted in the replacement of boronic acid by $I_2$ with the retention of configuration to afford (11) in a 61% yield. The geometry of the olefinic protons was confirmed by the $^1$H n.m.r. spcetrum. Analysis of the iodide (11) by g.l.c. indicated that the isomeric purity was 97%. Analogously, using the procedure described above, iodide (12) and bromide (13) were readily prepared by stereospecific halogenolysis of boronic acid (4) with $I_2$ and with $Br_2$ in 77% and 78% yields respectively. The isomeric purity of (12) and (13) analyzed by g.l.c. exceeded 99%.

## The Cross-Coupling Reactions

A mixture of (4) and (9) in benzene containing $Pd(PPh_3)_4$ and EtONa was heated under reflux for 2.5 h in an atmosphere of $N_2$. An excess of boronic acid was then removed by oxidation with 30% $H_2O_2$ and NaOH. A normal work-up and distillation of the crude product (a 82% g.l.c. yield) by using a Kugelrohr gave an analytically pure bombykol (14) (Scheme 3). The coupling constants of the olefinic protons in the $^1$H n.m.r. (400 MHz), which showed no signals other than those due to bombykol, are shown in Table 1. An alternative synthesis of bombykol by cross-coupling between eleven-carbon alkenyl-halide (12) and five-carbon alkenyl borane (6) in benzene containing $Pd(PPh_3)_4$ and EtONa gave bombykol in 50% g.l.c. yield (Scheme 3).

The cross-coupling of (4) with (11) under the conditions similar to the synthesis of bombykol and the distillation of the product by using a Kugelrohr gave (10E,12E)-hexadecadien-1-ol (15) in a 53% isolated yield (Scheme 4). Syntheses of the remaining two geometrical isomers of bombykol were accomplished by the stereospecific coupling of an eleven-carbon alkenyl halide and a five-carbon alkenyl borane; bromide (13) and borane (6) in benzene were subjected to the coupling reaction in the presence of $Pd(PPh_3)_4$ and EtONa to yield (10Z,12Z)-hexadecadien-1-ol (16) in a 59% isolated yield (Scheme 4). Similarly, the cross-coupling of bromide (13) with borole (8) gave (10Z,12E)-hexadecadien-1-ol (17) in a 77% isolated yield (Scheme 4). The coupling constants of olefinic protons of the three geometrical isomers of bombykol, (15), (16) and (17) are shown in Table 1.

## Table 1

Chemical shifts(δ) and coupling constants(Hz) of the olefinic protons of bombykol and the three geometrical isomers ($CDCl_3$-TMS, 400 MHz)

| compd. | 10-H | 11-H | 12-H | 13-H |
|---|---|---|---|---|
| 10*E*,12*Z*<br>(bombykol) | 5.65<br>dt(15 and 6.8)<br>$J_{9\text{-H},10\text{-H}}=6.8$<br>$J_{10\text{-H},11\text{-H}}=15$ | 6.30<br>dd(15 and 11)<br>$J_{11\text{-H},12\text{-H}}=11$ | 5.96<br>dd(11 and 11)<br>$J_{12\text{-H},13\text{-H}}=11$ | 5.30<br>dt(11 and 7.3)<br>$J_{13\text{-H},14\text{-H}}=7.3$ |
| 10*Z*,12*Z* | 5.42<br>dt(9.3 and 7.6)<br>$J_{9\text{-H},10\text{-H}}=7.6$<br>$J_{10\text{-H},11\text{-H}}=9.3$ | 6.26<br>d(9.3) | 6.26<br>d(9.3) | 5.42<br>dt(9.3 and 7.6)<br>$J_{12\text{-H},13\text{-H}}=9.3$<br>$J_{13\text{-H},14\text{-H}}=7.6$ |
| 10*Z*,12*E* | 5.30<br>dt(11 and 7.5)<br>$J_{9\text{-H},10\text{-H}}=7.5$<br>$J_{10\text{-H},11\text{-H}}=11$ | 5.95<br>dd(11 and 11)<br>$J_{11\text{-H},12\text{-H}}=11$ | 6.30<br>dd(11 and 15)<br>$J_{12\text{-H},13\text{-H}}=15$ | 5.66<br>dt(7.3 and 15)<br>$J_{13\text{-H},14\text{-H}}=7.3$ |
| 10*E*,12*E* | 5.56 or 5.57<br>dt(6.8 and 14.2 or 6.8 and 11.7)<br>$J_{9\text{-H},10\text{-H}}=6.8$<br>$J_{10\text{-H},11\text{-H}}=11.7$ or 14.2 | 5.98 or 6.01<br>dd(6.8 and 11.7 or 6.8 and 14.2)<br>$J_{11\text{-H},12\text{-H}}=6.8$ | 5.98 or 6.01<br>dd(6.8 and 11.7 or 6.8 and 14.2)<br>$J_{12\text{-H},13\text{-H}}=11.7$ or 14.2 | 5.56 or 5.57<br>dt(6.8 and 14.2 or 6.8 and 11.7)<br>$J_{13\text{-H},14\text{-H}}=6.8$ |

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