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TOTAL SYNTHESIS OF (-)-PERIPLANONE-B, THE SEX PHEROMONE OF THE AMERICAN COCKROACH

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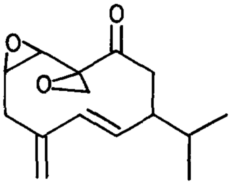
Abstract: The total synthesis of (-)-periplanone-B, the sex excitant pheromone of the American cockroach, *Periplaneta americana* is accomplished starting from (+)-limonene.

Periplanone-B, the extraordinarily potent sex attractant and sex excitant pheromone of the American cockroach, *Periplaneta americana*, was first characterized spectroscopically by Persoons et al.[1] as i (stereochemistry unknown) in 1975 after some 25 years of extensive efforts by several research groups[2] since its discovery.[3] The relative stereochemistry of (±)-periplanone-B was determined through Still's first and elegant total synthesis[4] and its absolute configuration as shown in 1 was deduced by chiroptical studies of a resolved synthetic intermediate.[5] Recently the second total synthesis of (±)-1 was announced by Schreiber and Santini.[6]



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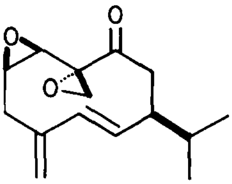

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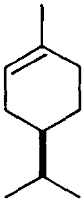

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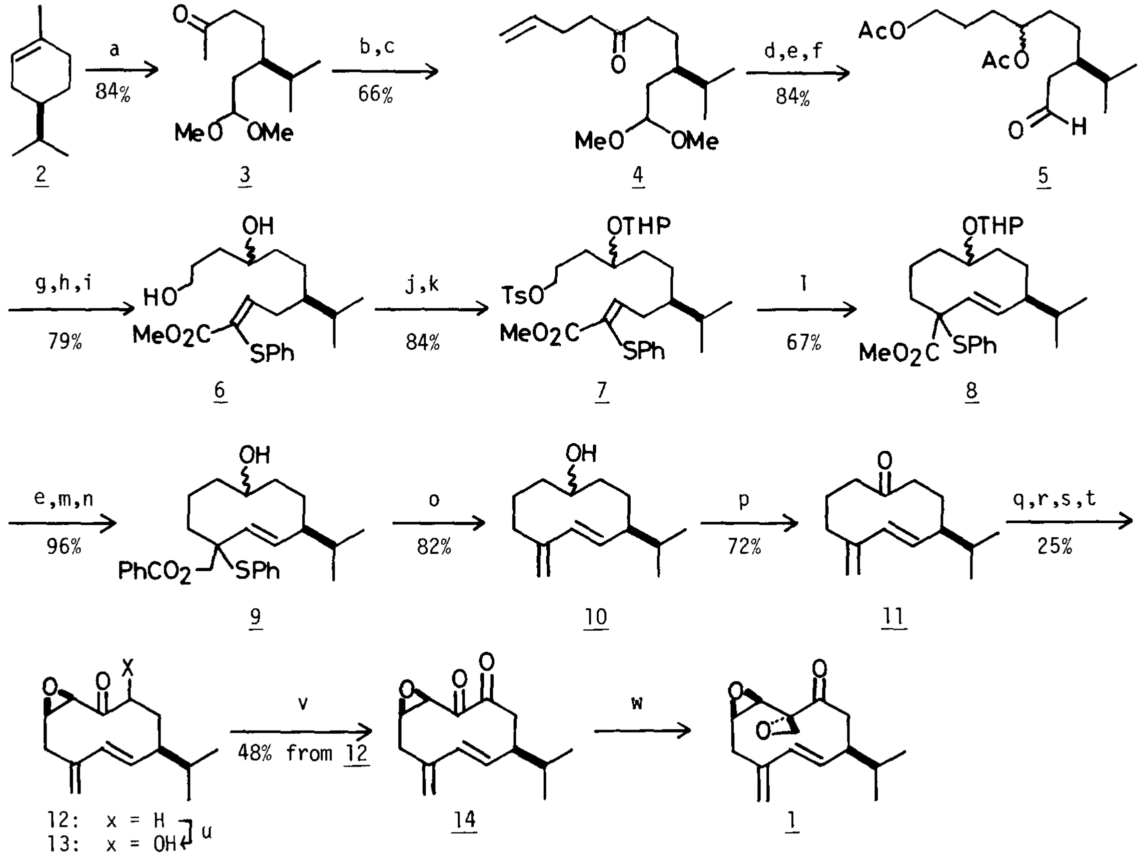
In connection with our continuing interest in the synthesis of medium-ring systems and optically active pheromones, we started our investigation to afford a substantial amount of 1 in optically active form. Herein, we report a total synthesis of (-)-periplanone-B 1 starting from (+)-dihydrolimonene 2 readily available in a large quantity.[7] The key steps in our synthesis are intramolecular alkylation of a substituted α-phenylthioacrylate[8] to provide the (E)-cyclodecene derivative 8 and reductive elimination[9] of vicinal phenylthio-benzoate 9 to furnish the diene system.

Ozonolysis of (+)-dihydrolimonene was followed by a reductive workup with Me_2S-*p*-TsOH-MeOH to give a keto acetal 3 (~300 g scale, 84%).[10] Methoxycarbonylation of 3 with NaH-$CO(OMe)_2$ in refluxing dioxane and succesive quenching of the enolate with allyl bromide gave an olefinic keto ester, which was decarbomethoxylated by heating with KOH in aqueous MeOH to give an olefinic ketone 4 (66% from 3). Lemieux-Johnson oxidation[11] of 4 with OsO_4-$NaIO_4$, $LiAlH_4$ reduction, acetlyation and subsequent workup with 6N HCl gave an aldehyde 5 (84%). Condensation of 5 with an anion of $PhSCH_2CO_2Me$, followed by dehydration with Ac_2O-AcONa and methanolysis of the acetate with MeONa-MeOH provided a diol ester 6 (79%). The diol 6 was selectively monotosylated with *p*-TsCl, DMAP and Et_3N in CH_2Cl_2 at -15 °C to give an unstable monotosylate[12] whose secondary OH was protected with a tetrahydropyranyl group (DHP, PPTS[13]) to give 7, the precursor for cyclization (84%).



a) O_3, MeOH, -60 °C; Me_2S, *p*-TsOH. b) $(MeO)_2CO$, NaH, dioxane, reflux, 24 h; $CH_2 = CHCH_2Br$ reflux 2 h. c) 5% KOH in 40% MeOH aq., 90 °C / 2 h. d) OsO_4-$NaIO_4$, Et_2O-H_2O, rt / 3.5 h. e) $LiAlH_4$, Et_2O. f) Ac_2O, Py. workup with 6N HCl. g) LDA, $PhSCH_2CO_2Me$, THF, -78 °C, 10 min. h) Ac_2O, AcONa 130 °C, 30 min. i) 1% MeONa-MeOH, reflux, 20 min. j) TsCl, DMAP, Et_3N, CH_2Cl_2 -10-- -15 °C, 4 h. k) DHP, PPTS, CH_2Cl_2. l) $NaN(TMS)_2$, DME, reflux, 50 min. m) PhCOCl, DMAP, Py, rt, 1 day. n) Dowex $50W(H^+)$, MeOH, 40 °C. o) Na-$C_{10}H_8$, THF, -78 °C, 5 min. p) PCC-NaOAc, CH_2Cl_2. q) $LiN(TMS)_2$, $PhSSO_2Ph$, -10 °C, 15 min. r) $NaIO_4$-MeOH, rt, 24 h. s) $CaCO_3$, toluene, reflux, 4 h. t) t-BuOOH, KH, THF, rt / 1 h. u) $LiN(TMS)_2$, THF, 30 min→MoO_5.HMPA.Py, -70 °C, 5 min. v) PCC, Molecular sieves 3A , CH_2Cl_2, rt, 5 h. w) Me_2S=CH_2, DMSO-THF, 0 °C / 10 min.

Cyclization was effected by addition of 7 in DME over 50 min to a solution of NaN(TMS)$_2$ (1.2 eq.) in DME at reflux temperature to give a cyclodecene ester 8 (67%). Reduction of 8 with LiAlH$_4$, followed by benzoylation and subsequent hydrolysis of the THP group [Dowex 50W(H$^+$)-MeOH, 40 °C] gave the alcohol 9 (96%). The second key step, the reductive elimination of a vicinal phenylthiobenzoate, was examined under several conditions. For example, using 4% Na-Hg as a reducing reagent,[14] the reaction was extremely slow at -20 °C. On the other hand, treatment of 9 with metallic lithium in liquid ammonia[9] gave a 1:1 mixture of the desired dienol 10 and its dihydro derivative, an overreduction product, even though the reaction was complete within 5 min at -78 °C. The best result was obtained by using sodium naphthalenide in THF at -78 °C for 5 min[9] to give 10 in 82% yield as a sole product. Oxidation with PCC-NaOAc[16] gave the dienone 11 (72%), the Schreiber's intermediate for the synthesis of (±)-1, in optically active form: $[\alpha]_D^{22}$ -362.0° (c = 1.22, *n*-hexane).

Transformation of (-)-11 to (-)-1 was carried out in a similar manner to that reported by Schreiber[6] with several modifications. Thus, introduction of a double bond at the C_2-C_3 position was executed by regioselective phenylsulfenylation [LiN(TMS)$_2$, PhSSO$_2$Ph], oxidation (NaIO$_4$, MeOH) and subsequent pyrolytic elimination (CaCO$_3$, toluene). The resulting trienone was epoxidized smoothly with *t*-BuOOH-KH to give the epoxy ketone 12 predominantly (25% from 11). Stereoselective hydroxylation of 12 with Mimoun's reagent[16] in the presence of LiN(TMS)$_2$ gave the ketol 13 as a sole product(75%). Oxidation of 13 with PCC-molecular sieves 3A[17] afforded the α-diketone 14. Finally, monoepoxydation of 14 with dimethylsulfonium methylide gave crystalline (-)-periplanone-B 1, mp. 47--50°, $[\alpha]_D^{22}$ -667° (c = 0.13, *n*-hexane), whose spectral data (IR, 500 MHz ^{1}H-NMR, MS) were identical with those reported.[18] In a preliminary behavioral test, the synthetic (-)-1 caused the characteristic sexual excitement against male American cockroaches clearly.

In summary, the total synthesis of (-)-periplanone-B was accomplished in 24 steps from (+)-dihydrolimonene. An improved procedure to increase the overall yield and to obtain sufficient amount of chiral 1 for the biological study is now in progress and will be reported in full account.

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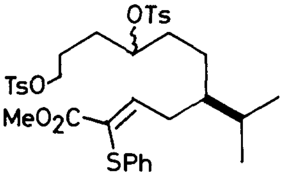

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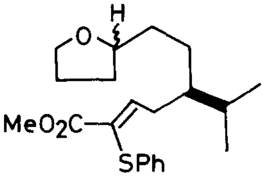

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