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Asymmetric Synthesis of 5-Hexadecanolide, Pheromone of the Queen of the Oriental Hornet, *Vespa Orientalis*

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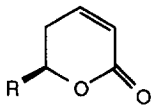
Abstract: An efficient asymmetric synthesis of 5-hexadecanolide from a chiral epoxide is described. Both the enantiomeric forms of the chiral epoxide are easily available from mannitol and ascorbic acid. The key step in the synthesis is the formation of δ-lactone from δ-hydroxy acetal using m-CPBA and $BF_3{\cdot}OEt_2$.

Enantiopure 6-substituted 5,6-dihydro-2*H*-pyran-2-ones **1** (α,β-unsaturated δ-lactones) are important structural subunits of several natural products.[1] They are responsible for a wide variety of biological activities, such as plant growth inhibition, insect antifeedal, antifungal, and antitumor properties. These pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers, and fruits. The short chain alkyl homologues are volatile and important aroma compounds in food and beverages. Besides all these important properties, they are key synthons for several biologically important molecules. The saturated analogues such as (*S*)-**2** and its enantiomer have been identified as insect pheromones. There are many approaches to these, and, some of them are quite cumbersome.[2] In this paper, we report synthesis of enantiomerically pure pheromones **2** using a simple and flexible approach which provides an handle to synthesize saturated and unsaturated δ-lactones in optically pure form.



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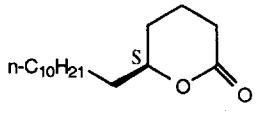
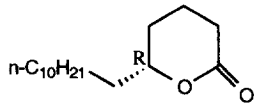


(*S*)-**2**

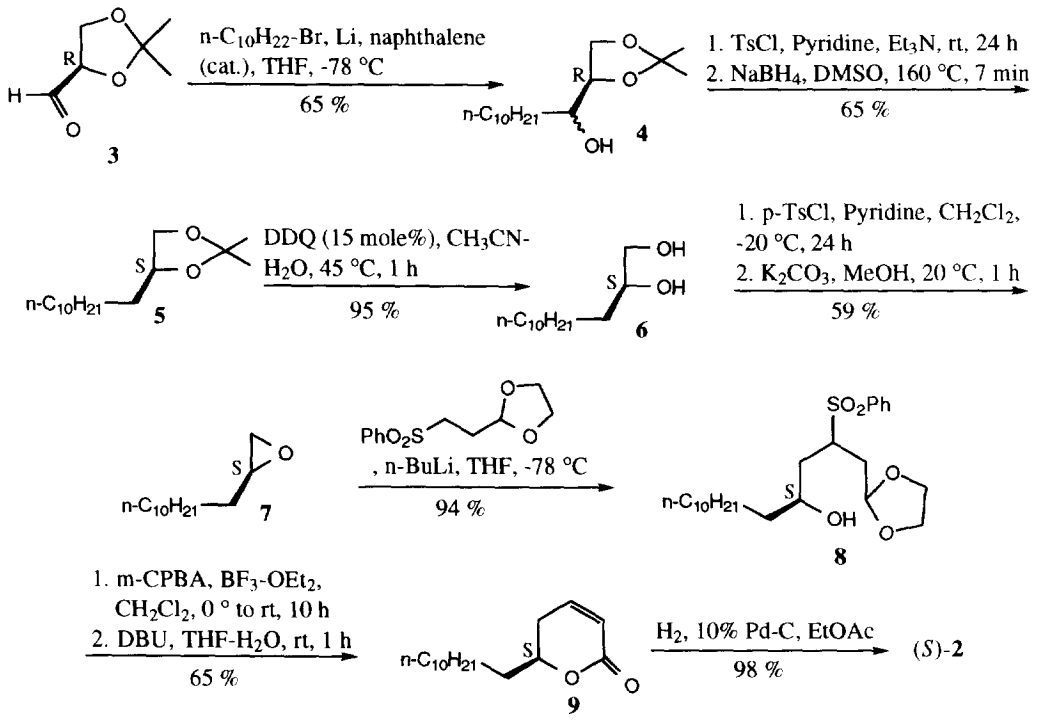


(*R*)-**2**

Close inspection of the target structure (*S*)-**2** indicates that the chiral center in the molecule can be elaborated from (*R*)-isopropylidene glyceraldehyde **3** which can easily be synthesized[3] from oxidative cleavage of readily available 1,2:5,6-di-O-isopropylidene-D-mannitol. The (*R*)-acetonide **3**[3], thus synthesized from mannitol, was treated with 1-bromodecane in the presence of lithium and naphthalene[4] to furnish the addition product **4** in 65% yield. The alcohol **4** was expected to be a mixture of diastereomers (Cram and *anti*-Cram products), but, it was inconsequential in the synthesis as the hydroxyl group would be removed at the latter step. Deoxygenation of the hydroxyl group in the **4** was carried out by reduction of the corresponding tosylate

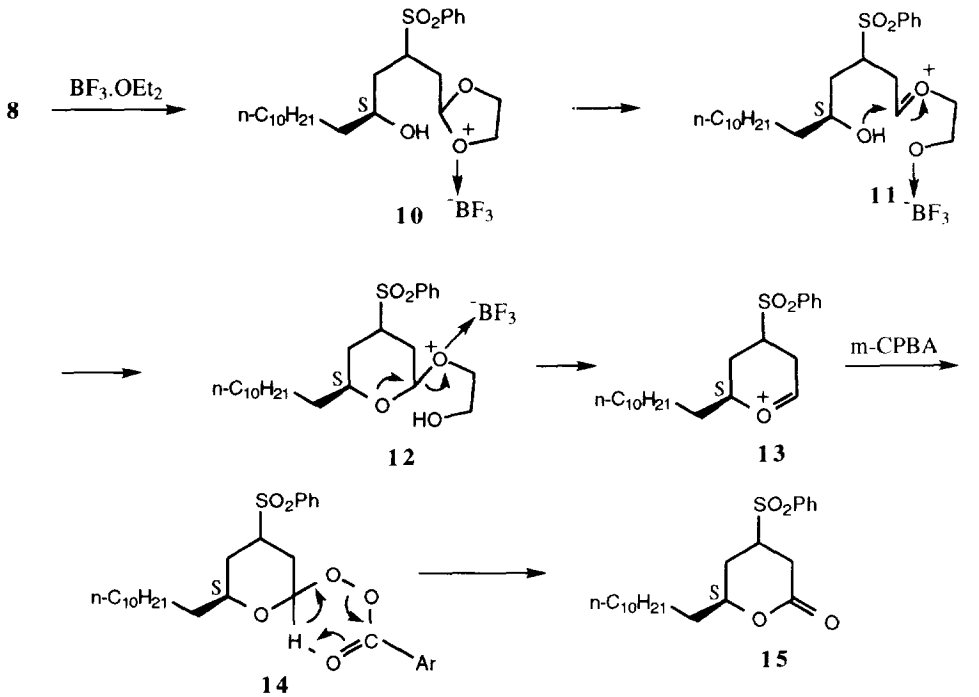
with $NaBH_4$ in DMSO at 160 °C for a very short time. The acetonide **5** was converted to a chiral epoxide **7** in three steps: (a). DDQ[5] induced deprotection of the acetonide **5** into diol **6**, (b). regioselective conversion of primary alcohol into tosylate, and (c). ring closure of the tosylate to the epoxide **7**.

Elaboration to unsaturated δ-lactone unit on the epoxide **7** was done in the following way: The epoxide **7** was opened with sulphone reagent[6] to provide hydroxy acetal **8** which, on treatment with BF_3-OEt_2 and m-CPBA (under dry condition), gave a mixture of sulphone δ-lactone **15** and unsaturated δ-lactone **9** in the ratio 9:1. The minor compound **9** is formed due to Lewis acid induced desulphonation of the sulphone lactone **15** first formed.[7] Since the unsaturated lactone **9** is the next required compound in the synthesis, the crude mixture, without purification, was treated with DBU in order to have complete conversion into unsaturated δ-lactone **9**.[8] Hydrogenation of the double bond in the **9** provided the pheromone (*S*)-**2** in enantiopure form (Scheme I).



Scheme I

The key step in the synthesis is direct conversion of **8** into δ-lactone. Although the reaction is known[9] for the conversion of lactol ethers to lactone, conversion of the type **8** to **9**, to the best of our knowledge, is unprecedented. The mechanistic aspect of the reaction is proposed in scheme II. The Lewis acid opens the acetal group of **8** into oxonium ion **13** which is susceptible to attack from the peracid used in the reaction. The intermediate **14**, thus formed, rearranges to the lactone **15** *via* a six-membered transition state.



Scheme II

The strategy described in this paper is flexible and a variety of δ-lactone of the type **1** can be synthesized in enantiopure form. Following the same approach, (*R*)-**2** antipode of the pheromone can be synthesized from (*S*)-isopropylidene glyceraldehyde (*S*)-**3** which is easily available[10] from L-ascorbic acid.

Experimental Section

^{1}H NMR spectra were recorded on Jeol and Brucker, as mentioned in the experimentals, using TMS as internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on Perkin-Elmer 580 and 1320 spectrometers. Optical rotations were taken on Rudolph Autopol-II automatic polarimeter.

Routine monitoring of reactions was performed using silica gel-G obtained from Acme. All the chromatographic separations were done by using silica gel (Acme's, 60-120 mesh). Petroleum ether used was of boiling range 60-80 °C. Reactions, which needed anhydrous conditions, were run under an atmosphere of dry nitrogen or argon using flame-dried glasswares. The organic extracts were dried over anhydrous sodium sulphate. Evaporation of solvents was performed at reduced pressure, using a Büchi rotary evaporator. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitogen. Dimethylsulphoxide (DMSO) was distilled over CaH_2 at reduced pressure. Pyridine was distilled over CaH_2 at atmospheric

pressure. The water content of m-CPBA was removed in the following way: The m-CPBA was taken in CH_2Cl_2. The organic layer was washed with brine and stored over *anhydrous* Na_2SO_4 for 30 min before use.

(2*S*)-(+)-1,2-(Isopropylidenedioxy)-tridecan-3(*R*,*S*)-ol 4: A catalytic amount of naphthalene (100 mg, 0.78 mmol) was added to lithium (300 mg, 42.8 mmol) which was cut into small pieces and immersed in THF (10 mL). The mixture was stirred at rt for 30 min, and then, cooled to -78 °C. A solution of (*R*)-2,3-O-isopropylideneglyceraldehyde (1.0 g, 7.6 mmol) and bromodecane (2.1 g, 9.5 mmol) in 1 ml THF was added via a syringe pump over a period of 6 h. After the addition was complete, the reaction mixture was further stirred at the same temperature for 8 h, and then warmed to 0 °C. It was filtered through a small plug of cotton in order to remove unreacted lithium pieces. The filtrate was concentrated on rotary evaporator. The crude mixture was taken in ether and washed with water, brine, and dried. The solvent was removed and the crude was chromatographed to give pure alcohol **4** (1.34 g, 65% yield) as a liquid; R_f 0.19 (EtOAc in Petroleum ether, 95:5); $[\alpha]^{25}_D$ + 1.0° (*c* 1.05, THF); IR (film) 3440, 1055 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ0.90 (t, J = 5 Hz, 3H), 1.10 - 1.73 (m, 24H), 2.0 (bs, 1H, -OH), 3.54 - 4.10 (m, 4H). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.59; H, 11.76. Found: C, 70.68; H, 11.86.

(2*S*)-(1,2)-(Isopropylidenedioxy)-tridecane 5: Solid p-tosyl chloride (1.4 g, 7.34 mmol) was added in two portions to a solution of the alcohol **4** (1.0 g, 3.67 mmol) in pyridine (5 ml) at rt. Then, triethylamine (750 µl, 7.42 mmol) was added and the solution was stirred at the same temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with 5% cold aq. HCl, aq. $NaHCO_3$, water, and brine. The organic layer was dried and concentrated on rotary evaporator. The crude tosylate (1.5 g), thus obtained, was taken in DMSO (10 ml), and to this solution, $NaBH_4$ (1.14 g, 30 mmol) was added in one portion (exothermic). The flask containing this mixture was directly dipped in a preheated oil bath (160 °C) and the reaction mixture was vigorously stirred at the same temperature for 7 min. The reaction mixture was cooled, diluted with water, and extracted with ether. The organic layer was washed with brine and dried. Solvent removal and purification over silica gel gave the acetonide **5** (600 mg, 65% yield) as a liquid; R_f 0.46 (EtOAc in Petroleum ether, 4 : 96); $[\alpha]^{25}_D$ + 10.5° (*c* 1.62, THF); IR (film) 1060 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ0.88 (t, J = 5 Hz, 3H), 1.30 (bs, 26H), 3.12 - 3.58 (m. 1H), 3.56 - 4.12 (m, 2H).

(*S*)-(-)-1,2-Dihydroxytridecane 6: The acetonide **5** (500 mg, 1.95 mmol) was treated with DDQ (67 mg, 0.29 mmol) in acetonitrile/water (20 mL, 9 : 1) at 45 °C for 1 h. The solvent was removed and the diol was purified by column chromatography to give 400 mg (95% yield) of the diol **6**[2a] as a semisolid; R_f 0.18 (EtOAc in Petroleum ether, 1 : 4); $[\alpha]^{25}_D$ - 10.4° (*c* 2.12, MeOH); IR (film) 3320 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ0.9 (t, J = 5 Hz, 3H), 1.3 (s, 20H), 2.48 (bs, 2H), 3.5 - 3.9 (m, 3H).

(*S*)-Tridecene Oxide 7: To a mixture of diol **6** (400 mg, 1.85 mmol) and pyridine (3 mL) was added a solution of p-tosyl chloride (350 mg, 1.85 mmol) in CH_2Cl_2 (2 mL) dropwise at -30 °C. The mixture was stirred for 5 h and then allowed to warm to -20 °C and stirred at the same temperature for 12 h. The reaction mixture was taken in 50 mL EtOAc, washed with cold dil HCl, saturated aq. sodium bicarbonate solution, water, and brine. Solvent removal and purification over silica gel gave pure mono tosylate (430 mg) which was dissolved in dry methanol (5 mL) and treated with anhydrous K_2CO_3 at rt for 1 h. Most of the methanol was

removed in vacuo and the crude was taken in methylene chloride and washed with water, brine, and dried. Solvent was removed and the crude mixture was purified over silica gel to give pure epoxide **7**[2a] (216 mg, 59% yield) as a colourless liquid; R_f 0.63 (EtOAc in pet-ether, 3:97); $[\alpha]^{25}_D$ - 11.0° (*c* 1.0, THF), lit.[11] $[\alpha]^{25}_D$ - 12.1° (*c* 1.3, THF); ^{1}H NMR (80 MHz, $CDCl_3$) δ0.87 (t, J = 5 Hz, 3H), 1.28 (bs, 20 H), 2.45 (dd, J = 8.7, 3.0 Hz, 1H), 2.75 (t, J = 10 Hz, 1H), 2.90 (m, 1H).

2-(4'-(*S*)-hydroxy-2'-phenylsulphonyl)-pentadecyl-1,3-dioxolane 8: n-BuLi (1.59 mmol) was added to a solution of sulphone acetal (385 mg, 1.59 mmol) in THF (10 mL) at -78 °C and stirred for 30 min at the same temperature. The epoxide **7** (210 mg, 1.06 mmol) solution in 2 mL THF was added and stirred for 8 h (-78 °C to 0 °C). Most of the THF was removed on rotavap. The crude was taken in EtOAc, washed with water, brine, and dried. The solvent was removed and the crude mixture was chromatographed over silica gel to afford **8** (440 mg, 94% yield); R_f 0.10 (EtOAc in petroleum ether, 1:4); $[\alpha]^{25}_D$ + 11.9° (*c* 2.6, THF); IR (film): 3480, 1440, 1300, 1150, 1070, 1030 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ0.90 (t, J = 5 Hz, 3H), 1.36 (bs, 20H), 1.93 (m, 2H), 2.0 (bs, 1H, OH), 3.34 - 3.77 (m, 1H), 3.93 (bs, 4H), 4.3 - 4.8 (m, 1H), 5.06 (t, J = 5 Hz, 1H), 7.83 (m, 3H), 8.13 (m, 2H).

(*S*)-6-Undecyl-5,6-dihydro-2*H*-pyran-2-one 9: A solution of **8** (250 mg, 0.56 mmol) in 4 mL CH_2Cl_2 was treated with $BF_3.OEt_2$ (80 mg, 0.56 mmol) followed by dry m-CPBA (1.3 equiv.; as a solution in CH_2Cl_2) at 0 °C. The reaction mixture was stirred for 12 h (0 °C to rt). The reaction mixture was diluted with some more CH_2Cl_2 and washed with aq $NaHCO_3$ solution, water, and brine. It was dried, solvent was removed, and the crude mixture was filtered over a small plug of silica gel to give a mixture of sulphone lactone and unsaturated lactone (168 mg) which was taken in THF:H_2O (10:1, 5 mL) and treated with DBU (190 mg, 1.25 mmol) at rt for 1 h. Most of the solvent was removed on rotavap and the residue was taken in EtOAc, washed with water, brine, and dried. Solvent removal and purification over silica gel gave pure unsaturated lactone **7** (94 mg, 65% yield) as a colourless liquid; R_f 0.62 (EtOAc in petroleum ether, 1:4); $[\alpha]^{25}_D$ + 78.7° (*c* 1.0, THF); IR (film): 3060, 1720, 1040 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ0.88 (t, J = 5 Hz, 3H), 1.32 (bs, 20H), 2.10 - 2.47 (m, 2H), 4.33 (m, 1H), 5.86 (dt, J = 10, 1.5 Hz, 1H), 6.76 (dt, J = 10, 4 Hz, 1H); UV: λ^{CHCl_3} 235.5 nm; MS (Fab, m/z): 253 (M^++1). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.19; H, 11.11. Found: C, 76.02; H, 11.26.

(*S*)-6-Undecyl-3,4,5,6-tetrahydropyran-2-one 2: A solution of unsaturated lactone **9** (60 mg, 0.24 mmol) in EtOAc (1 mL) was hydrogenated (rt, 12 h) in the presence of a small amount of 10% Pd/C using H_2 balloon. It was filtered, solvent removed, and the crude was chromatographed over silica gel to provide pure product (*S*)-**2**[2a,11] (56 mg, 98% yield) as a liquid; R_f 0.26 (EtOAc in petroleum ether, 1:9); $[\alpha]^{25}_D$ - 40.2° (*c* 1.5, THF), lit[11] $[\alpha]^{25}_D$ - 43.0° (*c* 0.74, THF); IR (film): 1740, 1240, 1050 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ0.88 (t, J = 5 Hz, 3H), 1.13-2.1 (m, 24H), 2.20 - 2.63 (m, 2H), 3.93 - 4.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.0, 18.5, 22.6, 24.9, 27.8, 29.3, 29.4, 29.6, 31.9, 35.8, 80.5, 171.; MS (Fab, m/z): 255 (M^++1).

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