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NOTE

Exploration of Dicaranyl Methyl Borate for Asymmetric Epoxidation- Synthesis of Pheromone Intermediates

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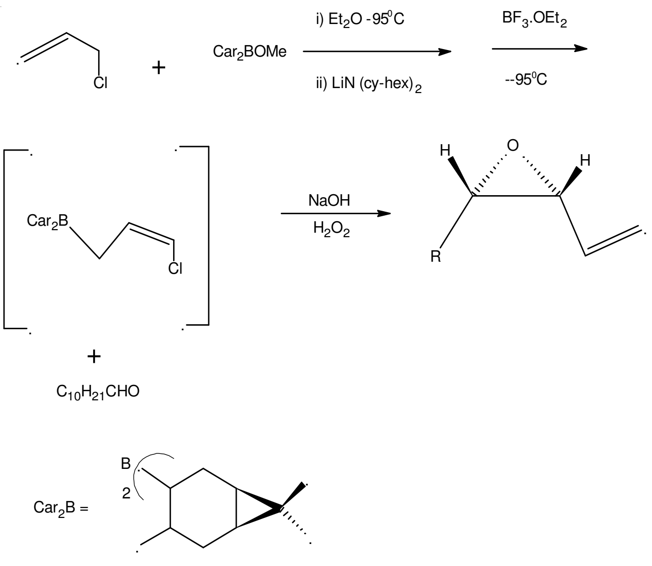
A novel method to generate chiral *cis*-epoxide, an intermediate for the synthesis of disparlure pheromone was explored. Under *in situ* condition, reaction between allyl chloride and (-)β-methoxydicaranylborane in the presence of LiN(cy-hex)$_2$ (DCHA) and diethyl ether yielded an ate complex, [(α-chloroallyl)lithium]. This ate complex on further reaction with (BF_3.OEt) at -95 ºC resulted in the formation of a reagent [(Z)-γ-chloroallylBcar^2]. The reagent thus formed on further chloroallylboration using an aldehyde, followed by elimination of chiral auxiliary provided syn-α-chlorohydrins in high ee (> 95 %). Base induced cyclization of chlorohydrins furnished chiral *cis*-vinylepoxides. (-)β-methoxydicaranylborane showed better results than (-)β-methoxydiisopinocamphenyl borane and was also economical. This methodology was further experimented for pheromone synthesis. By this process we have successfully synthesized the key intermediate of Disparlure cost effectively.

Key Words: Chiral *cis*-epoxide, (-)β-Methoxydicaranylborane, ate complex, Chloroallylboration, Syn-α-chlorohydrins.

The importance of chirality in chemical communication system of insects has led to many approaches to the synthesis of chiral pheromones[1]. Pheromones are usually obtained in µg to mg quantities, which are insufficient for the determination of their absolute configuration as well as for the biological studies to examine practicality in the field[2]. Pheromone synthesis is therefore important in order to establish the structure of a new pheromone and also to provide for sufficient quantities to carry out extensive biological tests[3,4]. Pheromones are usually low molecular weight organic compounds with stereospecific center(s) and/or double bond(s). It is therefore necessary to employ efficient carbon-carbon bond forming reactions and enantioselective reactions to synthesize pheromones. The chiral epoxides are very good intermediates in pheromone synthesis. The systematic exploration of pheromone synthesis with asymmetric centers are very important, since these compounds are bio-active in nature. The synthetic route to pheromones are tedious process involving sharpless epoxidation, enzymatic reactions and chiral borane reagents[5]. Borane reagents are more emphasized on synthetic reactions due to its versatility. Nevertheless, borane reagents yield chiral products with high ee. DIP-Cl, DIP-OMe are well known chiral borane reagents, reported. Although these reagents provide satisfactory results[6], their utility are still limited due to the cost and availability. (-)β-Methoxydicaranyl-borane can serve as good alternative. This paper is an attempt to explore the synthetic utility of (-)β-methoxydicaranylborane in comparison with DIP-Cl & DIP-OMe. In this context, we have successfully synthesized the key intermediate of (+) disparlure using (-)β-methoxydicaranylborane. The scheme is given below.



Scheme-I

All reagents and solvents were purchased from Sigma-Aldrich and were used as supplied. Thin-layer chromatography was performed on 0.25 mm pre coated silica gel 60 F254 aluminum sheets and column chromatography on silica gel 60 (0.063-0.2 mm) as well as silica gel 60 (< 0.063 mm), products of Merck & Co. (Darmstadt, Germany).

Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl. Dicyclohexylamine [(cy-hex)$_2$NH] was freshly distilled from CaH_2 prior to use. Allyl chloride was freshly distilled over P_2O_5 prior to use. Undecanyl aldehyde was distilled prior to use. δ-3-Carene was purchased from Aldrich and used without purification. Moisture- and air-sensitive reactions were conducted under nitrogen in vacuum-dried glassware. A nitrogen glove bag was used to weigh moisture-sensitive compounds. Syringes and cannulas were used to transfer air-sensitive reagents. All boiling points and melting points were uncorrected. The IR spectra were scanned with a Perkin-Elmer 783 spectrophotometer and only the pertinent values are expressed, in cm^{-1}. The ^1H NMR spectra were recorded, with a Bruker (500 MHz) spectrometer, with TMS as internal standard. $CDCl_3$ was used as the solvent. The chemical shift (d) and coupling constant (*J*) values were expressed in ppm and Hz only. The GLC analyses were carried out on a Shimadzu GC-7A chromatograph fitted with a flame ionization detector and glass packed column for routine analysis and a capillary column for the determination of isomeric compositions. The mass spectra (EI) were recorded at 70 eV with a Shimadzu GC-MS QP-1000A spectrometer. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

Synthesis of dicaranyl methylborate: To a stirred and cooled (-10 ºC) δ-3-carene (2.6 g, 20 mmol) in THF, 1 mL of BMS was injected. The reaction was then warmed to room temperature and allowed to go for 2 h. After the completion of reaction, quantitative amount of dry methanol was added and stirred for 1 h. The excess solvent was then distilled out, the product was isolated as a white solid, which was stable in nitrogen atmosphere.

***Cis*-(3R, 4R)-3,4-epoxy-1-tetradecene**: To a stirred and cooled (-95 ºC) mixture of Car_2BOMe (11.5 mmol) and allyl chloride (15 mmol) in anhydrous ether (50 mL) was added a solution of LiN(cy-hex)$_2$ (15 mmol) in THF (25 mL). After being stirred for 1 h, $BF_3.OEt_2$ (30 mmol) and undecanyl aldehyde (11.5 mmol) were added sequentially. The reaction was continued at -95 ºC for 4 h. Solvents were removed *in vacuo* at room temperature and the residue was triturated with *n*-hexane (40 mL) and allowed to settle (12 h). The supernatant was transferred to another predried flask by cannula. The residue was further treated with hexane (2_30 mL) and the hexane extracts were combined. Removal of hexane *in vacuo* furnished a semisolid.

Oxidation of boron intermediate. The residue obtained from chloroallylboration reaction was dissolved in THF (20 mL) with stirring and cooled to 0 ºC. Then, 3 M NaOH (12 mL) and 30 % H_2O_2 (12 mL) were sequentially added. The reaction mixture was allowed to warm to room temperature (14 h). Standard workup followed by flash chromatography yielded a colourless liquid (1.43 g, 71 % yield).

[R]23 D +21.09 (*c*) 8.81, CH_2Cl_2); ^{13}C NMR ($CDCl_3$, ppm) 132.78, 120.13, 58.79, 57.17, 31.90,29.58, 29.53, 29.42,29.30, 27.75, 26.29, 22.66, 14.04. ^1H NMR ($CDCl_3$, ppm) 5.69 (ddd, *J*) 17.2,10.4,7.2 Hz, 1H), 5.46 (ddd, *J*) 17.2,1, 1 Hz, 1H), 5.34 (ddd, *J*) 10.2, 1, 1 Hz, 1H), 3.39 (dd, *J*) 7.2, 4.3 Hz, 1H), 3.06 (m, 1H), 1.58-1.26 (m, 18H), 0.87 (t, *J*) 6.8 Hz, 3H) ^1H NMR ($CDCl_3$, ppm) 5.69 (ddd, *J*) 17.2, 10.4, 2 Hz, 1H), 5.46 (ddd, *J*) 17.2, 1, 1 Hz, 1H), 5.34 (ddd, *J*) 10.2, 1, 1 Hz, 1H), 3.39 (dd, *J*) 7.2, 4.3 Hz, 1H), 3.06 (m, 1H), 1.58-1.26 (m,18H), 0.87 (t, *J*) 6.8 Hz, 3H).

Asymmetric allylboranes react with aldehyde to produce chiral homoallylic alcohols which can be converted to chiral epoxides[7-9]. This reaction had attained considerable importance in the art of stereoselective synthesis of highly sophisticated, conformationally non-rigid systems. β-Allyl dicaranyl boranes have been made from dicaranyl borane methoxides. This reagent provided high ee for most of the aldehyde. The homo allyl alcohol formed can be converted to the corresponding epoxide by treatment with a base. These epoxides are very good intermediates in pheromone synthesis. Dicaranyl borane methoxide provides an excellent way to make asymmetric epoxide in greater ee, than even DIP-OMe and also it is more cost effective. The gypsy moth, Lymantria dispar, uses a chiral epoxide, (+)-(7R, 8S)-2-methyl-7,8-epoxyoctadecane, (+)-disparlure, as its main sex attractant. In this work, we have successfully synthesized the key intermediate of disparlure with > 95 % ee using dicaranyl borane methoxide as chiral auxiliary.

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