COMMUNICATIONS TO THE EDITOR

Synthesis of Hydroazulenic Intermediates

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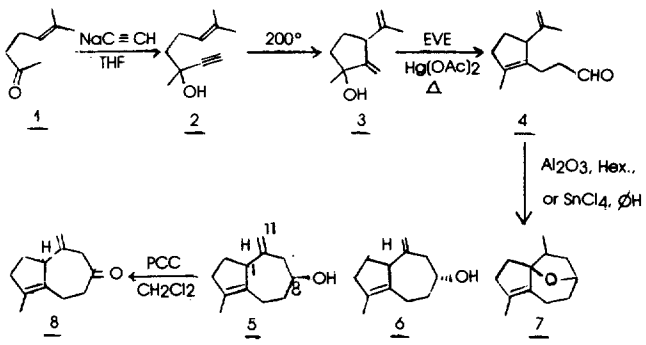
Synthesis of hydroazulenic sesquiterpenes has been the goal of much recent activities[1]. General methods for the synthesis of the hydroazulene skeleton are few compared to the much-studied hydronaphthalene system, and stereochemical control about the flexible nucleus still presents formidable problems to synthetic chemists. Only handful of chiral synthesis of hydroazulenic natural products have been reported. In this communication, we wish to report a short synthesis of hydroazulenic intermediates, which was easily adapted for the chiral synthesis from (+)-limonene. The key olefin-aldehyde reaction[2] to form seven-membered ring was found to be effectively catalyzed by acidic alumina.



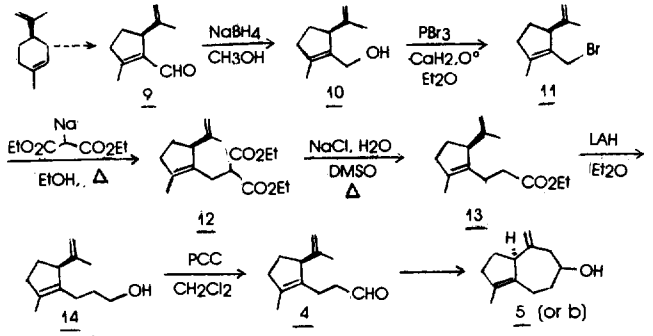
Scheme 1

Commercially available 6-methyl-5-hepten-2-one(**1**) was reacted in THF with sodium acetylide to form dehydrolinalool(**2**) in 98% yield(Scheme 1). When a neat sample of **2** containing a catalytic amount of 1,8-bis(dimethylamino)-naphthalene was heated at 200° (sealed tube reaction) for 2 hours almost quantitative yield of diastereomeric mixture of cyclic products **3** was obtained[3]. Reaction of **3** with 5 equivalents of ethyl vinyl ether and 0.1 equivalent of mercuric acetate under reflux for 5 days resulted in the formation of the aldehyde **4** in 50~60% yield[4].

* Dedicated to Professor Nung Min Yoon on the occasion of his 60th birthday.

Facile formation of hydroazulenic ring system was achieved when **4** was loaded on an acidic alumina column[5] in hexane. The major alcohol was eluted in ethyl acetate in 62~75% yield along with the minor alcohol in 10~15% yield. The major alcohol exhibited nmr signals at δ 4.87 and 5.05(AB_q, J = 2 Hz, 11-H_2), δ 3.97(broad, 8-H), and δ 3.37(broad, 1-H), whereas the minor alcohol was characterized by the signals at δ 4.89(broad singlet, 11-H_2) and δ 3.67(broad, 8-H). The cyclization was also effected by treating a solution of **4** in dry benzene with stannic chloride at room temperature for 10 min[6]. This way, 65~75% yield of the major alcohol was obtained along with a trace amount (<2%) of the minor alcohol and ~6% yield of a tricyclic ether **7**, which exhibited nmr signals at δ 0.88(doublet, J = 7 Hz, 11-H_3) and δ 4.35(broad, 8-H). Oxidation of the major alcohol with pyridinium chlorochromate in dichloromethane(buffered with solid sodium acetate) afforded the corresponding ketone **8** in 93% yield, which was reconverted to the mixture (~8:7) of the major and minor alcohols with lithium aluminum hydride in ether. The structure of the major and minor alcohols can be represented as **5** or **6**, but it is difficult to make clear distinction at this stage.

Monocyclic aldehyde **9**[7], obtained from (+)-limonene, served as the starting material in the chiral version of the syn-



Scheme 2

thesis (Scheme 2). Thus, the primary bromide **11** was obtained after sodium borohydride reduction of **9**($[\alpha]_D^{20} = +61.5°$, neat) and reaction of the resulting primary alcohol **10** with calcium hydride and phosphorus tribromide in ether at 0° for 7 hours. The crude bromide **11** was reacted with diethyl sodiomalonate in refluxing ethanol for 3 hours to produce the diester **12** in 73% yield.

Monoester **13** was obtained in 76% yield when **12** was heated in DMSO containing water and sodium chloride at 170° for 12 hours[8]. Conversion of **13**($[\alpha]_D^{20} = +97°$, C = 0.1, $CHCl_3$) to the alcohol **14** was achieved in 80% yield with lithium aluminum hydride reduction in ether and the aldehyde **4** was obtained by oxidation of **14**($[\alpha]_D^{20} = +44°$, C = 0.1, $CHCl_3$) by pyridinium chlorochromate in dichloromethane in 61% yield. The chiral sample of the aldehyde **4**($[\alpha]_D^{20} = +113°$, C = 0.1, $CHCl_3$) afforded optically active hydroazulenic major alcohol ($[\alpha]_D^{20} = -92°$, C = 0.1, $CHCl_3$) in stannic chloride–benzene system.

Optically active alcohols **5** and **6** and ketone **8** will serve as important chiral intermediates in future synthesis of guaiazulenic sesquiterpenes.

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A Short Synthesis of Ethoproxyfen (MTI-500), A Non-ester Pyrethroid Insecticide

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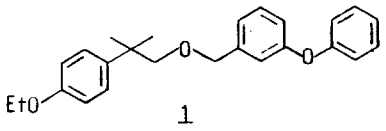
Insecticidal activity of agriculturally useful pyrethroids was believed to be linked to the ester function. Several highly active ester emerged by combination of a large number of acid containing cyclopropane ring and alcohol moieties[1]. Thereafter, 2-substituted isovaleric acid esters not containing cyclopropane ring such as fenvalerate, fluvalinate, and flucythrinate have become important pyrethroid insecticides[1].

The first non-ester pyrethroids showing promising insecticidal potential were oxime ethers[2,3], but their persistence under field conditions was too low to allow their agricultural exploitation.

Recently, an exciting new group of ether pyrethroids was disclosed[4] as a non-ester pyrethroid showing promising insecticidal activity. One of this group, 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether[5] (Ethoproxyfen, Ethofenprox, or MTI-500) (**1**) is presently being developed as an agricultural insecticide under the trade name Trebon® by Mitsui Toatsu Chemicals, Inc., Japan.

Ethofenprox (**1**) (Figure 1) is exceptionally effective as a contact and stomach poison against pest insects, including Lepidoptera, Hemiptera, Coleoptera, Diptera and Orthoptera



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Ethoproxyfen (MTI-500)

but has remarkably weak toxicity to mammals. In addition, it is less toxic to fish than the conventional synthetic pyrethroids[6]. It is suitable as a pesticide for rice, vegetables and fruits, as for medical, veterinary, urban, industrial and forest uses. Also it is stable under acidic or alkaline conditions and characterized by the advantage that it can be mixed with alkaline agricultural chemical[6].

Several syntheses of ethoproxyfen have been reported[7]. Here, we wish to report a short and convergent synthesis of ethoproxyfen by utilizing aluminum chloride catalyzed Friedel-Crafts reaction of phenetole with 2,2-dimethyloxirane, followed by alkylation with 3-phenoxybenzyl bromide (Scheme 1).