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.

Acknowledgement. This research was supported by a grant (1985) from Korea Research Foundation.

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

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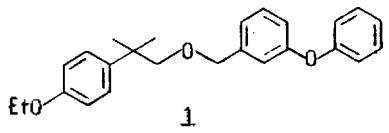
Received December 3, 1986

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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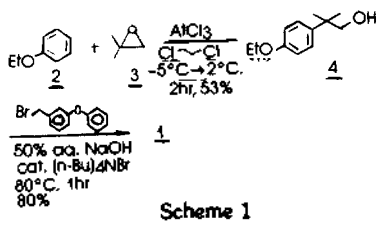
Ethoproxyfen (MTI-500)

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).



Scheme 1

The key intermediate, 2-(4-ethoxyphenyl)-2-methylpropyl alcohol(**4**) was prepared from $AlCl_3$ catalyzed Friedel-Crafts reaction of phenetole with 2,2-dimethyloxirane. In the literature, the alkylation reactions of aromatic rings by epoxides in the presence of Lewis acids to give arylalcohols are known. Thus the reaction of benzene with ethylene oxide is industrially exploited for the preparation of β-phenylethyl alcohol[8]. With the more substituted carbon atom of propylene oxide, benzene attacks the more substituted carbon atom to give 2-phenylpropanol[9,10].

Aluminum chloride catalyzed Friedel-Crafts reaction of phenetole(**2**) with 2,2-dimethyloxirane[11,12] in the presence of 1,2-dichloroethane afforded 2-(4-ethoxyphenyl)-2-methylpropyl alcohol(**4**)[12] (TLC:SiO_2, CH_2Cl_2, Rf~0.20), p-isomer as the only product[13] in 53% yield. The alchol **4** was alkylated with 3-phenoxybenzyl bromide[14] by the known method[15] to give the final product, 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether(**1**)[12] (TLC:SiO_2, $CHCl_3$/benzene = 6:4, Rf~0.63).

Acknowledgement. This research was supported by a generous grant (1984) from the Korea Research Foundation.

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12. Satisfactory physical properties and spectroscopic data (^{1}H-NMR, IR) were obtained for the compound; 2,2-dimethyloxirane(**3**); bp 45-52°C; ^{1}H-NMR(80 MHz, $CDCl_3$) δ 1.30(s, 6H), 2.62(s, 2H). 2-(4-ethoxypheny)-2-methylpropanol(**4**); mp 45-51°C; IR(NaCl, neat) 3500, 3000, 1600, 1050, 800 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.32(s, 6H), 1.41(t, 3H, J = 7Hz), 3.58(d, 2H, J = 4Hz), 4.03(q, 2H, J = 7Hz), 6.89(d, 2H, J = 10Hz), 7.30(d, 2H, J = 10Hz); ^{13}C-NMR($CDCl_3$) δ 14.86, 24.45, 39.46, 63.40, 73.18, 114.41,

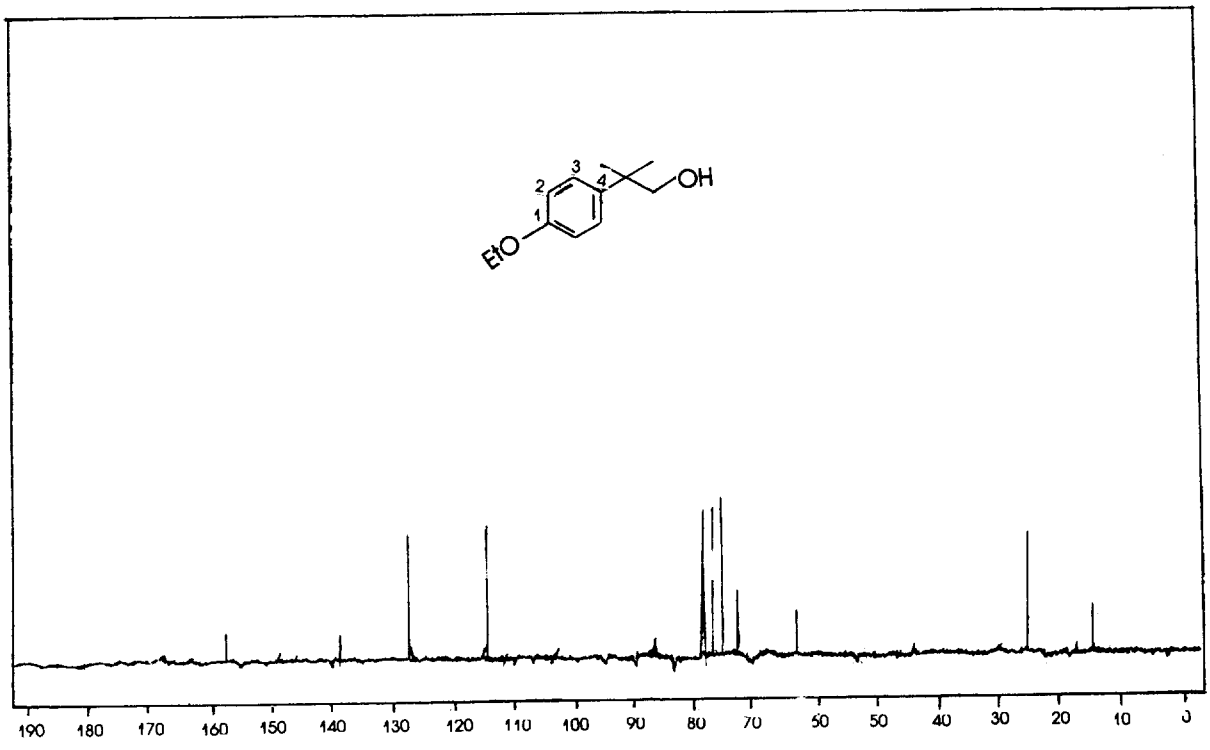

Fig. 2

127.25, 138.14, 157.31. 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether(**1**); mp 36-39°C; IR(NaCl, neat) 3000, 1600, 1100, 850, 700 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.32(s, 6H), 1.42(t, 3H, J=7Hz), 3.42(s, 2H), 4.00(q, 2H, J=7Hz), 4.44(s, 2H), 6.75-7.42(m, 13H).

13. The p-isomer **4** was identified on the basis of the proton decoupled ^{13}C-NMR spectrum. For the p-isomer **4**, there are four different kinds of aromatic carbon present(Fig. 2). The shifts for C-1 and C-4 are nearly identical with lower intesity, whereas C-3 has a chemical shift near that of benzene, and C-2 is shielded, as expected for carbon ortho to an oxygen function (Figure 2).
14. 3-Phenoxybenzyl bromide was easily prepared from 3-phenoxybenzyl alcohol by treatment with aqeous HBr and a catalytic amount of H_2SO_4.
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Synthetic Studies on Penems and Carbapenems (V)[1]. Preparation of 6-Acetylpenicillanate Derivatives

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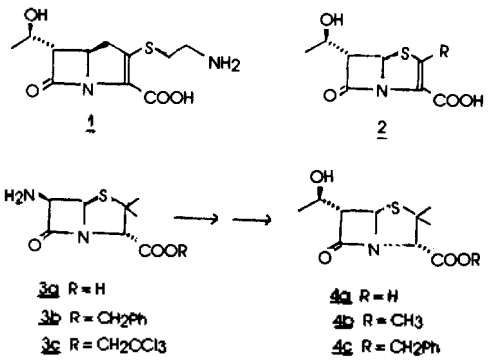
6-Aminopenicillanic acid (6-APA, **3a**) is regarded as one of the best starting materials for preparation of thienamycin (**1**)[2,3] and penems (**2**)[4], since it provides their necessary stereochemistry at C-5 and C-6 positions. Synthesis of thienamycin or penems from 6-APA requires stereospecific transformation of the amino group to a hydroxyethyl group[2] (Scheme 1). During these processes, it is necessary to retain the stereochemistry at C-5[5] and to invert that at C-6[4]. *Trans* configuration of the hydroxyethyl group at C-6 position relative to the sulfur atom at C-5 in the penicillin ring is easily achieved during alkylation since the *trans* analog is energetically preferred to the *cis*. After fixing the configuration at the C-6 position with a hydroxyethyl group, stereospecific formation of a new carbon-carbon or carbon-sulfur bond at the C-5 position can be achieved[6].

The hydroxyethyl chain of thienamycin was found to have *R*-configuration[7]. Stereospecific formation of the hydroxyethyl chain was primarily achieved by two methods. 6-APA is diazotized in the presence of bromine[1,8] or iodine[9] to give 6,6-dibromo- or 6,6-diiodopenicillanic acid, which is methylated with diazomethane. Methyl 6,6-dibromo- or 6,6-diiodopenicillanate is then converted to methyl 6-bromo- or 6-iodo-6-(1-hydroxyethyl)penicillanate by treating with methylmagnesium bromide or iodide and condensing with acetaldehyde. They are then reduced with Zn-AcOH or Zn-NH_4Cl-NH_4OH[1] to give methyl 6-(1-hydroxyethyl)penicillanate. The best crystallized yield for methyl (6*S*)-6-[(1*R*)-1-(β,β,β-trichloroethoxycarbonyloxy)ethyl] penicillanate from 6-APA was 47%[1]. Also, derivatives of optically enriched benzyl 6-(1-hydroxyethyl)penicillanate (**4c**) was obtained by stereospecific reduction of benzyl 6-acetylpenicillanate (**5c**) with diisopropylamineborane in the presence of magnesium trifluoroacetate[3]. Benzyl 6-acetylpenicillanate was prepared by reaction of benzyl 6-diazopenicillanate with acetaldehyde.

In order to develop the stereospecific reduction of 6-acetylpenicillanates, we examined various methods for preparation of 6-acetylpenicillanates (**5**, **6**) from 6-APA. In the course of synthesis of thienamycin or its analogs, several workers examined oxidation of 3-(1-hydroxyethyl)azetidin-2-one derivatives to 3-acetyl analogs and their stereospecific reduction[10], but extensive studies on the preparation of 6-acetylpenicillanates were not carried out at all.

Benzyl and β,β,β-trichloroethyl 6-acetylpenicillanates (**5c**, **6c** and **5d**, **6d**) were found to be very unstable[2,3]. The only



Scheme 1