Tetrahedron Letters No. 29, pp 2557 - 2560, 1976. Pergamon Press. Printed in Great Britain.

SYNTHETIC STUDIES ON OPTICALLY ACTIVE EPOXYTERPENES FROM L-GLUTAMIC ACID — I
SYNTHESES OF R-(+)-EPOXYGERANIOL, R-(+)-MARMIN AND R-(+)-EPOXYAURAPTEN

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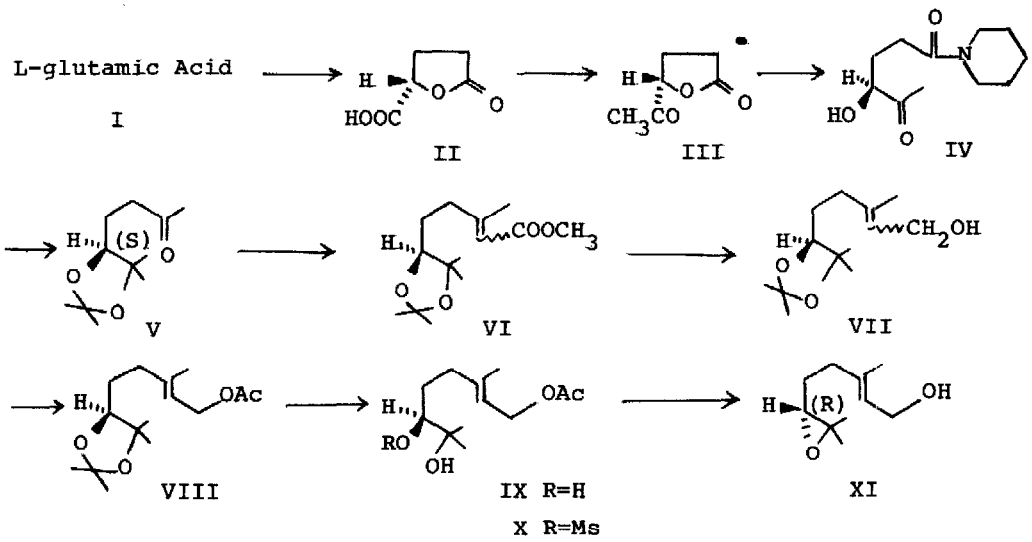
(Received in Japan 15 May 1976; received in UK for publication 3 June 1976)

Some optically active epoxyterpenes[1] (e.g. juvenile hormones, epoxyfarnesol, epoxysqualene) have aroused much interest in recent years because of their biological activity or biosynthetic intermediacy for cyclic terpenes and steroids. Although many synthetic works have appeared on the racemic compounds, the optically active compounds, except few recent papers[2], have received little attention.

Our studies into new general synthetic routes for optically active epoxyterpenes have developed a stereoselective synthesis of the most simple epoxyterpene, R-(+)-epoxygeraniol[3] (XI), and its naturally occurring derivatives, R-(+)-epoxyaurapten[4] (XV) and (+)-marmin[5] ((R)-XIV), from L-glutamic acid (I) with retention of optical activity, resulting in determination of the absolute configuration of the chiral epoxy groups as shown in Schemes 1 and 2.

The (S)-lactone-acid (II)[6,7] obtained from L-glutamic acid (I) by nitrous acid deamination was converted with thionyl chloride into the acid chloride which was then treated with an excess of diazomethane followed by treatment with 57% aqueous hydrogen iodide to give the keto-lactone[7] (III), b.p. 83° (0.2 mm), $[\alpha]_D^{25}$ +13.4° (c=0.25, CH_3OH), a key intermediate for epoxyterpene synthesis, in a yield of 32% from I. Amidation of III with piperidine gave quantitatively the amide[7] (IV), m.p. 44-47°, $[\alpha]_D^{25}$ +4.8° (c=0.45, CH_3OH) which was found to be partially racemized as described in the following paper. Treatment of IV with an excess of methylmagnesium iodide in ether followed by acetonization

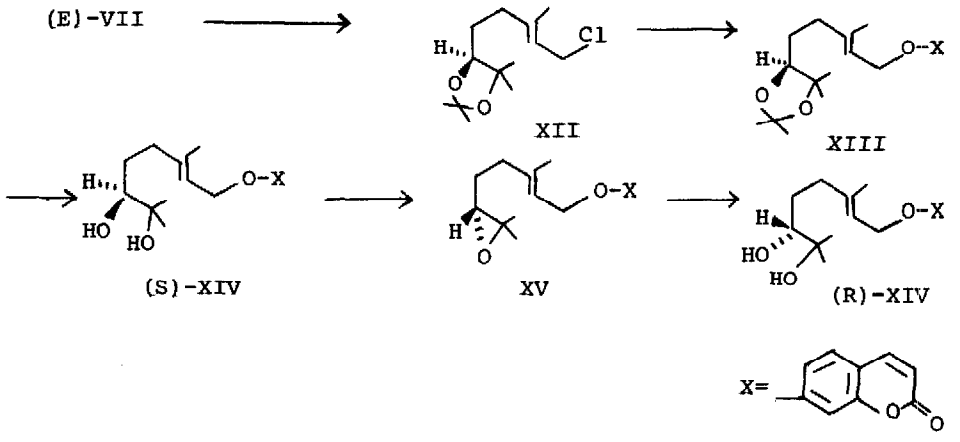
Scheme 1



with acetone and p-toluenesulfonic acid yielded the (S)-acetonide[7] (V), b.p. 80° (9 mm), $[\alpha]_D^{28}$ -8.7° (c=0.40, CH_3OH) (86% from IV). The Wittig reaction of V with trimethyl phosphonoacetate and sodium hydride in tetrahydrofuran at 60-65° for 3 hr gave the ester[7a] (VI) (75%) as a mixture of isomers (the ratio (Z)/(E)= 26/74). Subsequent reduction of this isomeric mixture with $LiAlH_4$ followed by chromatographic separation over silica gel containing 10% silver nitrate with ether-n-hexane as eluting solvent yielded the (Z)-alcohol[7a,8] ((Z)-VII) (20%) and the (E)-alcohol[7a,8] ((E)-VII) (61%). The latter was acetylated with Ac_2O-pyridine to give the (E)-acetate[7] (VIII), b.p. 108° (2 mm), $[\alpha]_D^{23}$ -1.2° (c=3.18, CH_3OH) (96%). Selective hydrolysis of the acetonide group in VIII was carried out by reaction of VIII with 90% acetic acid at 50° for 7 hr to give the diol-acetate (IX) (83%) which was further converted to the corresponding monomesylate (X) by treatment of IX with methanesulfonyl chloride in pyridine at -20° for 1 hr. Reaction of X with sodium methoxide in methanol at 0°C for 1.5 hr afforded (R)-(+)-epoxygeraniol (XI)[7], oil, $[\alpha]_D^{31}$ +4.5° (c=0.56, CH_3OH), with the inversion of configuration at the chiral center of X (78% from IX).

As shown in Scheme 2, for the synthesis of naturally occurring (+)-epoxy-aurapten[4] (XV) and (+)-marmin[5] ((R)-XIV), (E)-VII was converted to the chloride (XII)[7a] by successive treatment[9] with BuLi and TsCl in the presence

Scheme 2



of LiCl. Condensation of XII with the sodium salt of 7-hydroxycoumarin in DMF at room temperature for 16 hr yielded the acetonide ether[7] (XIII), m.p. 84-86°, $[\alpha]_D^{25}$-5.4°(c=0.46, EtOH). Subsequent deacetonization of XIII with dilute aq. HCl gave (S)-(-)-marmin[7] ((S)-XIV), m.p. 108-121°, $[\alpha]_D^{25}$-14°(c=0.32, EtOH), having an optical purity of about 56% compared with the compound obtained from a natural source,[5] and with opposite absolute configuration.

Sulfonylation of (S)-XIV with methanesulfonyl chloride in pyridine at -20° for 35 min followed by epoxydation with sodium methoxide in methanol at -20° for 2.5 hr afforded (R)-(+)-epoxyaurapten[4,7] (XV), m.p. 49-56°, $[\alpha]_{578}^{23}$+5.1° (c=0.37, $CHCl_3$)(70%) with optical purity of about 24%, and the same absolute configuration as the natural compound. Spectral data of XV are in good agreement with reported data.[4]

Regiospecific addition[10] of H_2O to XV with 0.1 N-H_2SO_4-THF(1:1) at room temperature for 1.5 hr gave natural (R)-(+)-marmin((R)-XIV),[5,7] m.p. 104-119°, $[\alpha]_D^{25}$ + 11°(c=0.16, EtOH) (88%).

Although some improvement of the optical retention is needed for further application of these reaction sequences[11], they seem to be adequate for the synthesis of optically active epoxides and glycol diols from III. This work also disclosed that (+)-epoxygeraniol, naturally occurring (+)-marmin and (+)-epoxyaurapten all have epoxy-groups of (R)-configuration.

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