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SYNTHETIC STUDIES ON OPTICALLY ACTIVE EPOXYTERPENES FROM L-GLUTAMIC ACID—II SYNTHESES OF R-(+)-10,11-EPOXYFARNESOL AND R-(+), S-(-)-SQUALENE-2,3-OXIDE

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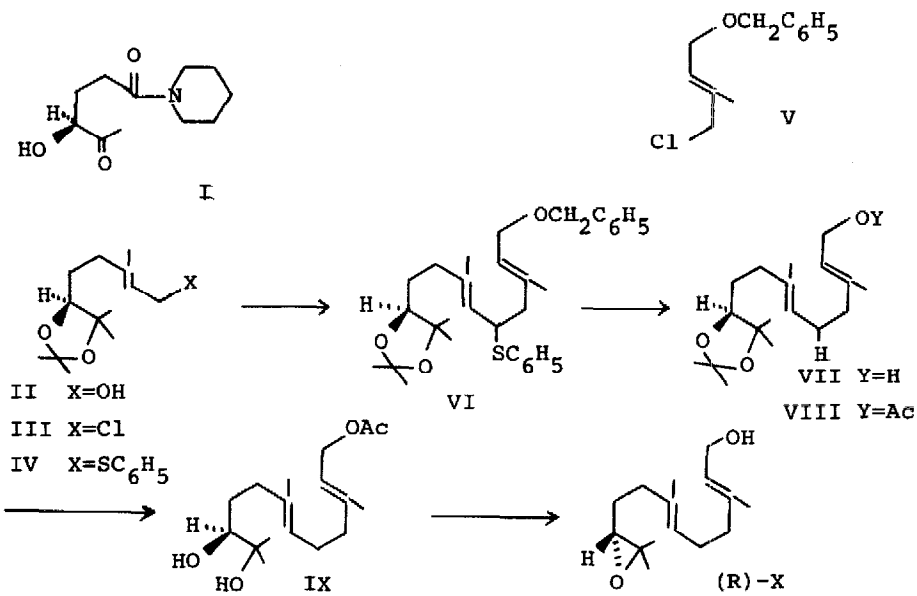
In the preceding paper[1], we demonstrated the use of an optically active α-amino acid, L-glutamic acid, for the syntheses of optically active epoxygeraniol and its derivatives which are generally very difficult to obtain in optically active forms. The subject of this communication is the first total synthesis of their higher homologues, optically pure (R)-(+)-10,11-epoxyfarnesol ((R)-X) and R-(+)-, S-(-)-squalene-2,3-oxide((R)- and (S)-XVI) which are considered to be the key biological intermediates of cyclic terpenes and steroids.[2] The reaction sequence is shown in Schemes 1 and 2.

The (S)-alcohol[1] (II) prepared from the optically pure (S)-amide[3] (I), m.p. 62-64°, $[\alpha]_D^{25}$+15.1°(c=1.05, MeOH), was converted by treatment with methanesulfonyl chloride in the presence of lithium chloride and s-collidine[5] at 0° for 3 hr to the chloride(III) which afforded the (S)-thioether[4] (IV), oil, $[\alpha]_D^{22}$-2.9°(c=1.57, MeOH), by reaction of III with the sodium salt (from NaH) of thiophenol at -20° for 40 min.

Reaction of IV with n-BuLi in the presence of DABCO at -20°C for 1 hr followed by addition of the chloro-ether[6] (V) at -70° afforded the thioether[4a] (VI) (83%). Reduction of VI with lithium in ethylamine[6a,7] at -70° for 15 min produced the (S)-alcohol[4] (VII), oil, $[\alpha]_D^{20}$+2.8°(c=2.17, Benzene) (78%). VII was treated with acetic anhydride-pyridine in ether to afford the (S)-acetate[4a]

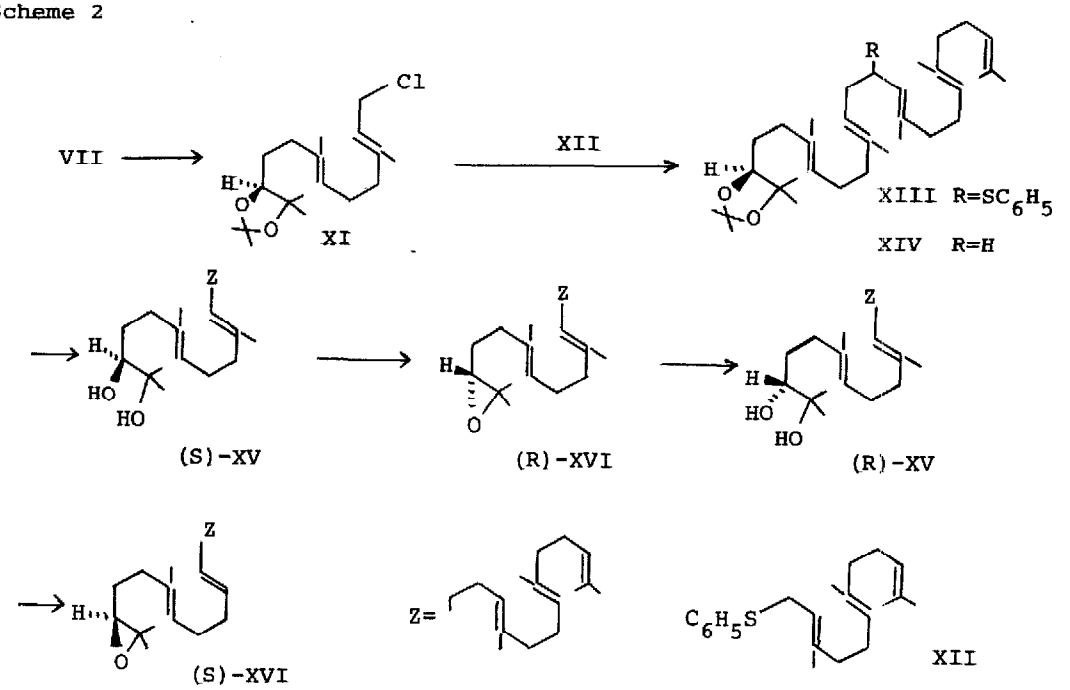
Scheme 1



(VIII), oil, $[\alpha]_D^{26}$-1.3°(c=2.04, MeOH), which was quantitatively transformed by hydrolysis with 90% acetic acid at 50-55° for 6 hr into the (S)-diol[4a] (IX). Epoxydation of IX by successive treatment with methanesulfonyl chloride in pyridine at -20° for 1.5 hr and with sodium methoxide in methanol at -20° for 1 hr gave (R)-(+)-10,11-epoxyfarnesol[4] ((R)-X), oil, $[\alpha]_D^{25}$ + 6.7°(c=1.24, MeOH) (46% from VIII).

The synthesis of (R)- and (S)-squalene-2,3-oxide is shown in Scheme 2. Reaction of the (S)-alcohol (VII) with methanesulfonyl chloride, lithium chloride and s-collidine[5] at 0° for 2.5 hr afforded the chloride (XI) which was condensed with the lithium salt (from n-BuLi) of the thioether[8] (XII) at -70° for 1.5 hr to give the acetonide thioether[4a] (XIII) in high yield. Reduction of XIII using lithium in ethylamine[8] at -70° for 15 min afforded the (S)-acetonide[4a] (XIV), oil, $[\alpha]_D^{20}$+1.86°(c=1.36, Benzene)(79%). Hydrolysis of XIV with 4N-HCl-THF-dioxane (1:3:8) at 35-40° for 18 hr produced the (S)-diol[4,9] ((S)-XV), oil, $[\alpha]_D^{25}$-13.0°(c=1.64, MeOH)(60%). Epoxydation of XV with methanesulfonyl chloride in pyridine(3.5 hr at -20°) and subsequent treatment with sodium methoxide in methanol at room temperature for 45 min gave (R)-(+)-

Scheme 2



squalene-2,3-oxide[4,10] ((R)-XVI), oil, $[\alpha]_D^{25}$+2.3°(c=1.49, MeOH)(74% from XV). Enantiomeric conversion[1] of (R)-XVI into (S)-squalene-2,3-oxide[4,10] ((S)-XVI), oil, $[\alpha]_D^{25}$-2.0°(c=1.01, MeOH), was carried out by the sequence: (1) hydrolysis of (R)-XVI with 3% $HClO_4$-DME (1:10)(5 hr, room temperature) affording the (R)-diol ((R)-XV), (2) treatment of (R)-XV with methanesulfonyl chloride in pyridine (2 hr, -20°), and (3) epoxidation with sodium methoxide in methanol (30 min, 0°) (70% overall yield).

Both (R)-epoxyfarnesol and (R)- and (S)-squalene-2,3-oxide produced by the above process were shown to be identical with dl-authentic samples[11,12] by comparison of their spectral data (nmr, ir). It should also be noted that synthetic (R)-epoxyfarnesol ((R)-X), $[\alpha]_D^{25}$+6.7°(c=1.24, MeOH), showed a higher optical value than the reported one[13], and that the optical values of (R)- and (S)-squalene-2,3-oxide were quite close to those reported in a recent paper.[10]

Enzymatic works[14] on optically active epoxyfarnesol and squalene-2,3-oxide should clarify the initial steps in their cyclization leading to cyclic terpenes and steroids.

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