*Tetrahedron* Vol. 36, pp. 183 to 188
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0040-4020/80/0115-0183/$02.00/0

# STEREOSELECTIVE SYNTHESIS OF (±)-SENEPOXYDE AND (±)-CROTEPOXIDE[1]

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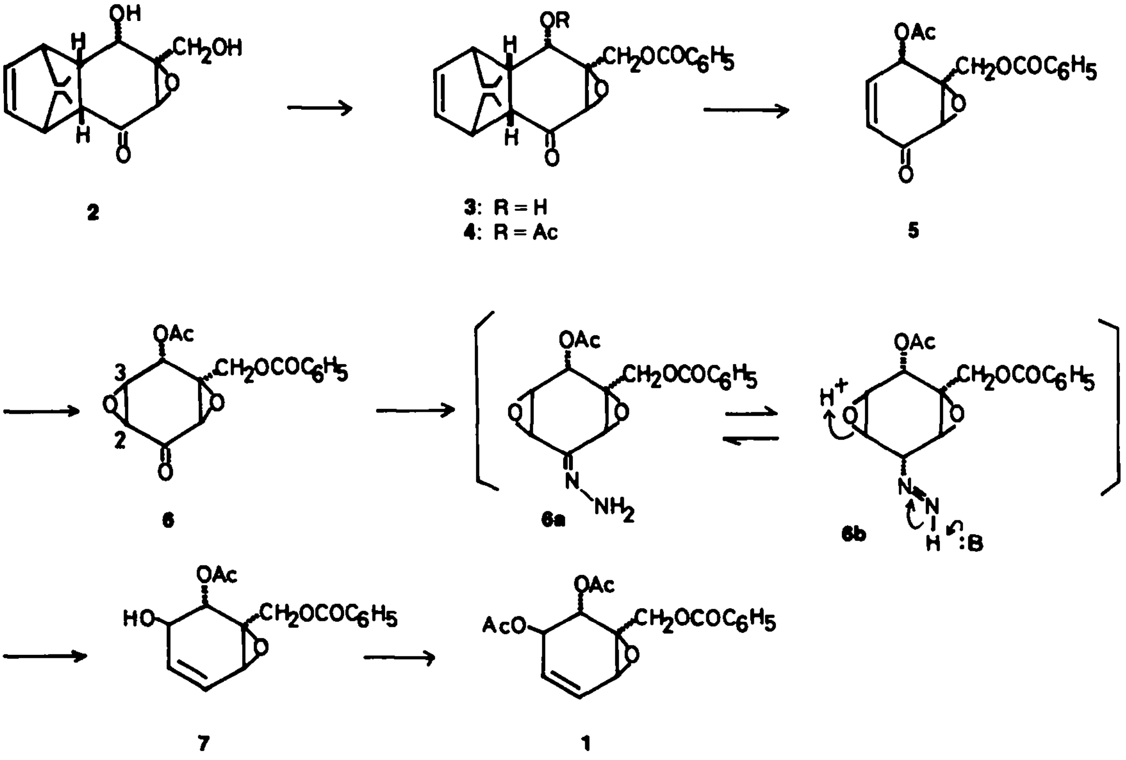
(*Received in Japan* 18 *June* 1979)

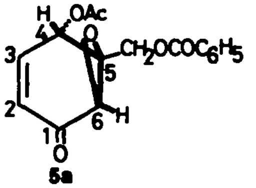
**Abstract**—Stereoselective synthesis of (±)-senepoxyde and (±)-crotepoxide is described starting from 2-hydroxymethyl-1,4-benzoquinone through the retro-Diels–Alder reaction.

Senepoxyde (1)[2] and crotepoxide (11)[3] are naturally occurring highly oxygenated cyclohexane derivatives, and noted for the strained structure having oxirane ring in the molecules. Polonsky *et al.*[2] isolated senepoxyde from fruits of *Uvaria catocarpa* which had been used for a folk medicine in France. Crotepoxide was isolated from the fruits of *Croton macrostachys* by Kupchan *et al.*[3] as a tumor inhibitor and subsequently from the leaves and stem of *Piper futokadzura* by Takahashi.[4] In the present paper, we describe the details of stereoselective synthesis of (±)-senepoxyde and (±)-crotepoxide starting from 2-hydroxymethyl-1,4-benzoquinone. In the synthesis, retrodiene reaction was effectively used for the preparation of the epoxycyclohexenones 5 and 13, key intermediates leading to senepoxyde and crotepoxide respectively.

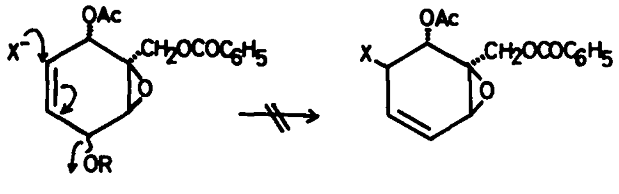
*Synthesis of* (±)-*senepoxyde.*[5] Senepoxyde (1) has one oxirane ring and two acetoxyl groups in the cyclohexene ring. One of the acetoxyl group (C-1) is *trans* and the other (C-2) is *cis* to the epoxide. Therefore, it was expected that, after stereoselective formation of the key intermediate 5, which has adequate stereochemistry with the epoxide and C-1 acetoxyl group, the second acetoxyl group at C-2 would be introduced from less hindered side, *trans* to C-1 acetoxy group in 5. For this purpose, the diol 2 was prepared according to previously reported procedure.[6] Treatment of the diol 2 with 1.2 equivalent of benzoyl chloride in pyridine afforded the benzoate 3, which was further acetylated with acetic anhydride-pyridine to the acetate 4. The retrodiene reaction of the acetate 4 in diglyme by heating at 160° for 1 hr under nitrogen gave an epoxycyclohexenone 5 in 78% yield. The stereochemistry of 5 was confirmed by the PMR spectrum, in which a long range coupling (J = 1.5 Hz)



between 4-H ($\delta$ 5.98) and 6-H ($\delta$ 3.57) in deformed W-configuration[7] (**5a**) was observed. Such a long range coupling is common for $\alpha$-epoxycyclohexenone, in which the epoxide occupies stable O-axial conformation, and in compound **5** the observation indicates that the acetoxyl group locates in *trans* position with the epoxide. Reduction of **5** with zinc borohydride afforded a product **8**, which was converted to the benzoate **9** with 2,4-dichlorobenzoyl chloride, and to the tosylate with tosyl chloride **10**. Attempts to convert each of these derivatives (**9** and **10**) to senepoxyde itself or its precursor through $S_N2'$ reaction in the presence of adequate nucleophiles such as $^-$OAc and $^-$OH under various conditions failed to recover only unchanged compound and/or give simply substituted product through $S_N2$ reaction. Therefore, another method involving reductive cleavage of $\alpha$-epoxyketone to an allyl alcohol using hydrazine[8] was attempted. In order to prepare a diepoxide which is used for the reductive cleavage the alcohol **8** was oxidized with *m*-chloroperbenzoic acid, but only starting material was recovered; the reason might be due to inductive effect induced by two electron attracting groups (OAc and OH), which decrease electron density of the double bond in **8**. Finally, direct epoxidation of the cyclohexenone **5** with hydrogen peroxide in aqueous potassium carbonate was attempted and obtained a diepoxide **6**, though during the reaction appreciable amount of product suffered hydrolysis, and we needed to acetylate the mixture of the products. The relative configuration of newly introduced epoxide was expected to be *trans* to the acetoxyl group, since hydroperoxide anion would attack to the double bond from more favorable side in regard to steric and electrostatic requirements. In fact the PMR spectrum showed that a signal at $\delta$ 6.00 due to $\alpha$-proton to acetoxyl group has rather small half width (3 Hz), which indicates that the proton occupies *trans* position to the vicinal hydrogen with a dihedral angle of nearly 90°. The findings are in accord with the stereochemistry retained stable O-axial conformation possessing two oxirane rings. Reductive cleavage of an epoxide ($C_2$–$C_3$) in the diepoxide **6** with hydrazine hydrate (*ca.* 2 equivs) in benzene-isopropyl alcohol-THF proceeded selectively to give the alcohol **7**. The reaction mechanism would be described as **6a** and **6b**. In the reaction, the regioselectivity might be explained by the favorable steric requirements of the transition state more flexibly induced from the disubstituted epoxide than that of the trisubstituted epoxide. Acetylation of **7** with acetic anhydride in pyridine afforded (±)-senepoxyde, m.p. 97–98°, which was identical with natural sample in IR, PMR, MS and behavior on tlc. Very recently another synthesis of (±)-senepoxyde has been reported.[9]



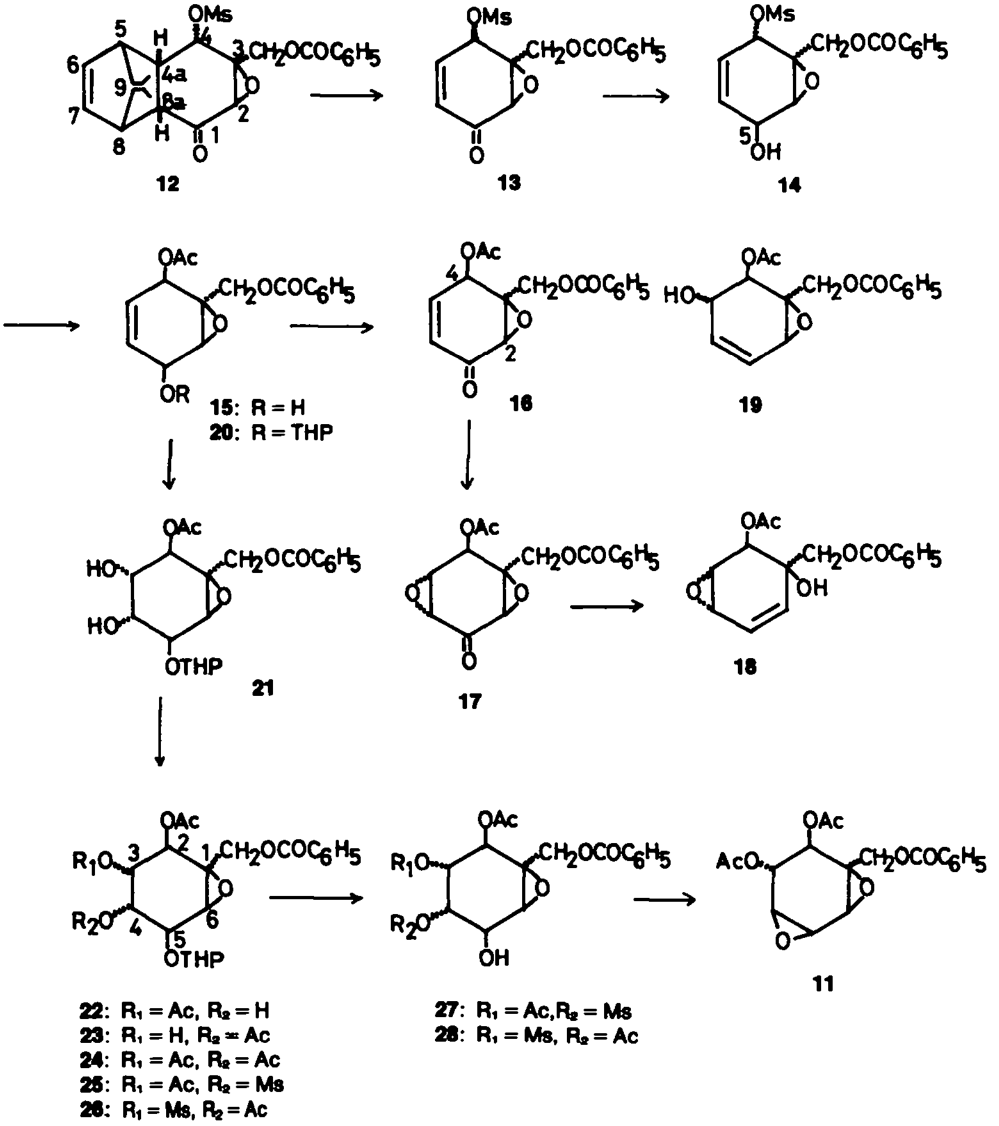
**5a**

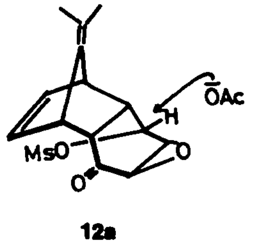


**8**: R = H
**9**: R = $COC_6H_5$ } X = $^-$OH, $^-$OAc
**10**: R = Ts

*Synthesis of (±)-crotepoxide.*[10,11] Crotepoxide (**11**) resembles to senepoxyde (**1**)[6] very closely in the substituents and the skeleton except the number of oxirane ring and the stereochemistry. Therefore, it was anticipated that crotepoxide would be synthesized via a similar method to the synthesis of (±)-senepoxyde.[5]

At first, our efforts were directed toward the synthesis of an $\alpha,\beta$-unsaturated ketone **16** from the common intermediate **2** for the synthesis of (±)-senepoxyde. Thus, direct epimerisation of acetoxyl group in **5** to **16** under basic or acidic conditions was attempted. However, because of instability of the $\alpha,\beta$-unsaturated ketone **5**, all attempts failed. Further attempts to epimerise by $S_N2$ inversion with the C-4 oxygen group in **2** were examined. Treatment of **3**, which was obtained from 2-hydroxymethyl-1,4-benzoquinone via three steps according to the same procedure used for the synthesis of (±)-senepoxyde, with MsCl-pyridine, gave a mesylate **12** in 91% yield. Acetolysis of the mesylate **12** under various conditions was unsuccessful. It was thought that the low reactivity of **12** would be attributed to the congested structure **12a** characteristic of such an *endo*-type Diels–Alder adduct. In order to remove the dimethylfulvene part responsible for this steric congestion, the retro-Diels–Alder reaction[1,6] of **12** was carried out at 120° in xylene under nitrogen to give an epoxycyclohexeneone **13** in 72% yield; above 120° the yield decreased because of the decomposition of **13**. All attempts obtaining a desired product **16** by acetolysis of **13** failed, since **13** was a vinylogue of unreactive $\alpha$-mesyloxy ketone. Therefore, **13** was reduced with zinc borohydride in THF-benzene to give an allyl alcohol **14** stereoselectively. The stereochemistry at C-5 in the alcohol **14** was confirmed by the fact that $\alpha$-proton to epoxy group showed a relatively small coupling (J = 2 Hz) with the vicinal proton in the PMR spectrum. This stereoselectivity was probably caused by the steric and/or electronic effect expected on the basis of the more stable "O-axial" conformation of the epoxy group. The results are compatible with the findings that reduction of terreic acid, an $\alpha$-epoxy




12a

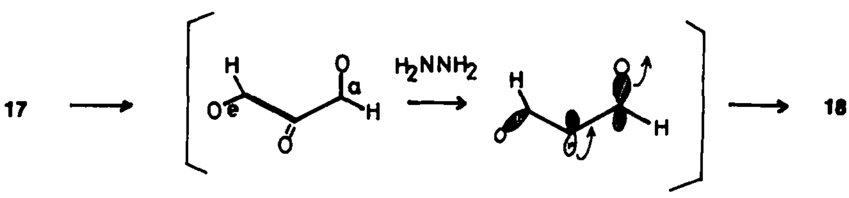
ketone, predominantly gave epiterremutin having *cis*-OH group to epoxy group.[7]

Treatment of 14 with anhydrous potassium acetate in acetone-acetic acid gave an acetate 15 in 54% yield from 13. Oxidation of 15 with manganese dioxide in chloroform gave a desired compound 16 in 75% yield. Inversion at C-2 in acetolysis was demonstrated by the fact that long range coupling of α-proton (δ 3.59) to epoxy group with the proton at C-2 through W-configuration[7] was no longer observed in the PMR spectrum of 16; in the epimer 5, long range coupling (J = 1.5 Hz) through W-configuration had been observed.

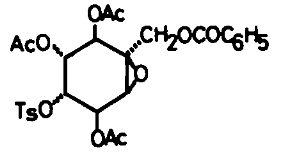
Epoxidation of 16 with potassium carbonate-hydrogen peroxide stereoselectively afforded the diepoxide 17 in 81% yield. It was expected that epoxidizing reagent would attack the double bond of 16 from the less hindered side to give a desired product 17.

Treatment of 17 with hydrazine[8] in the same manner as the synthesis of (±)-senepoxyde gave an unexpected-product 18 instead of a desired product 19. The structure of 18 was deduced by the fact that two protons were observed at δ 3.61 and δ 3.81 due to α-protons to epoxide in the PMR spectrum. This regioselectivity was explained by the fact that, in the predominant conformer 17a, the axial epoxy group was stereoelectronically subjected to reductive cleavage in preference to equatorial epoxy group as shown in 17b.

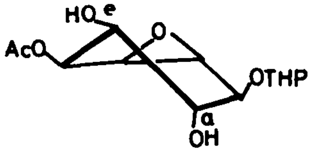
After all, the synthesis of (±)-crotepoxide has been achieved as follows. Protection of hydroxyl group of 15 with dihydropyran gave a tetrahydropyranyl ether 20 in a quantitative yield. Hydroxylation of 20 with osmium tetroxide gave a glycol 21 stereoselectively, since osmium tetroxide attacked preferentially from the less hindered side of the double bond of 20. The stereochemistry was



17a 17b



29



21a

confirmed by the analysis of the PMR spectrum of a product 22 in the next step.

Acetylation of 21 with acetic anhydride-pyridine (1.2 eq.) in anhydrous ether at 5° gave, accompanied by a small amount of a triacetate 24, a chromatographically inseperable mixture of diacetates 22 and 23 in a ratio of 3:1 as determined by the PMR signals ($\delta$ 2.15 and $\delta$ 2.12) due to C-2 acetate Me. The regioselective acetylation of the glycol 21 was expected from the favorable conformation 21a, in which OH group at C-3 occupies easily acylable equatorial position. In the PMR spectrum of 22, C-2 proton at $\delta$ 5.49 showed a coupling constant, 6 Hz. This value was somewhat small compared with *trans* diaxial coupling constant of a normal strain-free cyclohexane, but it would be acceptable by assuming that the oxirane ring distorts considerably the cyclohexane ring in 22. Indeed the abnormality is supported by the fact that, in 29 derived from natural crotepoxide,[4] C-2 proton showed a coupling constant, 5.5 Hz, which was moderately small as a *trans* diaxial coupling constant. The mixture of the acetates, 22 and 23 was used for further reaction since it is expected that in the final stage, the derivative 28 of undesired product 23 would be removed from synthetic crotepoxide. Mesylation of 22 with mesyl chloride-pyridine, followed by removal of tetrahydropyranyl group with *p*-toluenesulfonic acid in ethanol gave an alcohol 27. Treatment of 27 with basic alumina gave (±)-crotepoxide 11, m.p. 128–129°, identical with natural crotepoxide by tlc, PMR, IR and mass spectral comparison.

## EXPERIMENTAL

All m.ps are uncorrected and were determined on a Yanaco Micromelting Point Apparatus MP-30. IR spectra recorded on a Hitachi IR Spectrophotometer, Model 285 and PMR spectra on a Hitachi 90 MHz High Resolution Spectrometer Model R-22 and Japan Electrics JNM PS-100 High Resolution Spectrometers; the abbreviations s, d, t, q and m signify singlet, doublet, triplet, quartet and multiplet. Mass spectra were determined on Hitachi RMU-4 spectrometer.

The starting material the diol 2 was prepared by the same procedure described in the preceeding paper.[1]

*Benzoylation of* 2. To the ice cooled soln of 938 mg of 2 in 5 ml THF and 5 ml anhydrous pyridine was added 0.6 ml benzoyl chloride under stirring. After adding benzoyl chloride, stirring continued additional 2 hr at room temp. The mixture was poured onto ice-water and resulting crystals were collected and washed with $NaHCO_3$aq and then water. The crystals were dissolved in $CHCl_3$ and the soln was dried over $Na_2SO_4$ and evaporated *in vacuo* to give 1.31 g of 3, which was recrystallised from benzene to yield pure sample, m.p. 149.5 ~ 150.5°, IR $\nu_{max}^{KBr}$; 3400 (OH), 1700 (C=O) cm$^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 1.50 (6H, s, $CH_3$), 2.95 (1H, ddd, J = 12 Hz, 5 Hz, 3 Hz, CH), 3.16 (1H, dd, J = 12 Hz, 3 Hz, CH), 3.35 (1H, s, $\overset{O}{\triangle}\!\diagup^{H}$), 3.44 (1H, m, CH), 3.54 (1H, m, CH), 4.18, 5.02 (2H, ABq, J = 13 Hz, $-CH_2O$), 4.61 (1H, d, J = 5 Hz, –CH–O), 6.33 (2H, m, $=\!\diagup^{H}$), 7.50 (3H, m, ArH), 8.05 (2H, dd, J = 8 Hz, aHz, ArH). (Found: C, 72.10; H, 6.07. Calc. for $C_{22}H_{22}O_5$; C, 72.11; H, 6.05%).

*Acetylation of* 3. A soln of 1.31 g of 3 in a mixture of 5 ml $Ac_2O$ and 10 ml anhydrous pyridine was allowed to stand for 12 hr at room temp. The mixture was poured onto ice-water and the resulting crystals were collected asd washed with water and then dissolved in $CHCl_3$. The soln was dried over $Na_2SO_4$ and evaporated *in vacuo* to yield 1.41 g of 4. Recrystallisation of the acetate from EtOH gave pure 4, m.p. 151–152°, IR $\nu_{max}^{KBr}$; 1715 (COAr), 1730 ($OCOCH_3$), 1600 (Ar) cm$^{-1}$; PMR $\delta_{TMS}^{CDCl_3}$ 1.47 (6H, s, $CH_3$), 2.00 (3H, s, $OCOCH_3$), 2.97 (1H, ddd, J = 11 Hz, 5 Hz, 3 Hz, CH), 3.15 (1H, dd, J = 11 Hz, 3 Hz, –CH–), 4.06, 4.73 (2H, ABq, J = 12 Hz, $-CH_2O$), 5.89 (1H, dd, J = 5 Hz, 3 Hz, $=\!\diagup^{H}$), 5.99 (1H, d, J = 5 Hz, –CHOAc), 6.43 (1H, dd, J = 5 Hz, 3 Hz, $=\!\diagup^{H}$), 3.34 (1H, m, CH), 3.36 (1H, s, $\overset{O}{\triangle}\!\diagup^{H}$), 4.01 (1H, m, CH), 7.50 (3H, ArH), 8.04 (2H, ArH). MS *m/e* 408 ($M^+$). (Found: C, 70.29; H, 5.94. Calc. for $C_{24}H_{24}O_6$; C, 70.57; H, 5.92%).

*Retro-Diels–Alder reaction of* 4. A soln of 1.057 g of 4 in 10 ml diglyme was heated at 160° for 1 hr under $N_2$. The mixture was evaporated *in vacuo* and the residue was chromatographed on silicic acid eluting with benzene-EtOAc (95:5, v/v) to give 608 mg (78%) of oily 5, IR $\nu_{max}^{neat}$; 1750 ($OCOCH_3$), 1720 (COAr), 1690 (C=O) cm$^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$; 2.05 (3H, s, $OCOCH_3$), 3.57 (1H, dd, J = 1.5 Hz, 1.5 Hz, $\overset{O}{\triangle}\!\diagup^{H}$), 5.25, 5.00 (2H, ABq, J = 12 Hz, $-CH_2O$), 5.98 (1H, m, –CHOAc), 6.11 (1H, m, $=\!\diagup^{H}$), 6.67 (1H, dd, J = 10 Hz, 5 Hz, $=\!\diagup^{H}$), 7.50 (3H, ArH), 8.04 (2H, ArH). MS *m/e*; 302 ($M^+$), 242 ($M^+ - CH_3CO_2H$).

*Epoxidation of* 5. To a soln of 183 mg 5 in 3 ml THF was added peroxide soln prepared from 100 mg $K_2CO_3$ and 0.5 ml 30% $H_2O_2$ in 2.5 ml water under stirring. After 2 hr, salt water was added to the mixture, and this was extracted with $CHCl_3$. The combined extracts were dried over $Na_2SO_4$ and evaporated *in vacuo* to give a residue. The soln of the residue in 1 ml pyridine and 0.5 ml $Ac_2O$ was allowed to stand for 12 hr at room temp. The mixture was poured onto ice-water and extracted with $CHCl_3$. The extracts were dried over $Na_2SO_4$ and evaporated *in vacuo*. The resulting residue was chromatographed on silicic acid column, and the column was eluted with benzene–EtOAc (9:1, v/v) to yield 112 mg (60%) of 6, IR $\nu_{max}^{neat}$; 1720, 1740 (C=O) cm$^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$ 2.10 (3H, s, $OCOCH_3$), 3.47 (2H, m, $\overset{O}{\triangle}\!\diagup^{H}$), 3.59

(1H, dd, J = 4 Hz, 2 Hz,  ). 4.00, 4.89 (3H, ABq, J = 13 Hz, $CH_2O$), 6.00 (1H, s, –CHOAc), 7.50 (3H, ArH), 8.05 (2H, ArH). MS *m/e*: 318 ($M^+$), 259 ($M^+$ $-CH_3CO_2$).

(±)-*Senepoxyde* 1. To a soln of 43 mg of 6 in 1 ml benzene and 0.3 ml THF was added 0.5 ml (2eq) hydrazine soln which was prepared from 70 mg hydrazine hydrate, 0.7 ml i-PrOH and 1.3 ml THF. The mixture was allowed to stand for 12 hr at 5°. To the mixture was added small amount of water, and the mixture was extracted with $CHCl_3$. The extracts were dried over $Na_2SO_4$ and evaporated *in vacuo*. The residue was chromatographed on silicic acid column, which was eluted with benzene–EtOAc. The eluate was concentrated *in vacuo* to yield a residue which was treated with 0.05 ml $Ac_2O$ in pyridine and left overnight. To the mixture was added ice-water and this extracted with $CHCl_3$. The extracts were dried over $Na_2SO_4$ and evaporated *in vacuo*. The residue was chromatographed on silicic acid and the column was eluted with benzene–EtOAc (9:1, v/v) to give crystals, which was recrystallised with EtOH to give pure (±)-senepoxyde, m.p. 97–98° (natural sample[2], m.p. 84–85°). IR $\nu_{max}^{CCl_4}$ 1730 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$ 2.04 (3H, s, $OCOCH_3$), 2.06 (3H, s, $OCOCH_3$), 3.44 (1H, d, J = 4 Hz,  ), 4.25, 4.83 (2H, ABq, J = 12 Hz, $CH_2O$), 5.18 (1H, dd, J = 5.5 Hz, 2.5 Hz, CH), 5.59 (1H, d, J = 2.5 Hz, CH), 6.07 (1H, m, CH), 6.37 (1H, dd, J = 10 Hz, 4 Hz, CH), 7.50 (3H, m, ArH), 8.05 (2H, dd, J = 8 Hz, 2 Hz, ArH), MS *m/e*; 346 ($M^+$). (Found; C, 62.54; H, 5.38. Calc. for $C_{18}H_{18}O_7$; C, 62.42; H, 5.24%).

*Mesylate* 12. To a soln of 2.50 g 3 in 15 ml anhydrous pyridine was added 1 ml mesyl chloride and the mixture was allowed to stand for 3 hr at room temp. The mixture was poured into ice water the resulting ppt was collected, washed by water, dissolved in $CHCl_3$ and concentrated *in vacuo* to give 2.87 g of 12 as crystals in 91% yield. The crude sample was recrystallized from $CHCl_3$-EtOH to give a pure sample, m.p. 142–143°; IR $\nu_{max}^{KBr}$; 1720 (C=O), 1350, 1180 ($-SO_2O-$) $cm^{-1}$; PMR $\delta_{TMS}^{CDCl_3}$; 1.53 (3H, s, $=/^{CH_3}$), 3.20 (2H, m, –CH–), 3.43 (1H, s, –OCH–), 3.62 (2H, m, –CH–), 4.36, 4.88 (2H, ABq, $J_{AB}$ = 13 Hz, $-CH_2O-$), 5.86 (1H, d, J = 5 Hz, –CH–OMs), 6.38 (2H, m, $=/^{H}$), 7.60 (3H, m, ArH), 8.15 (2H, dd, J = 8.2 Hz, ArH), MS *m/e*: 338 ($M^+$ $-C_8H_{10}$), 243 (338–$CH_3SO_3$). (Found: C, 62.27; H, 5.75; S, 7.22. Calc. for $C_{23}H_{24}O_7S$: C, 62.16; H, 5.44; S, 7.20%).

*Retro-Diels–Alder reaction of* 12. A soln of 2.17 g in 12 in 50 ml xylene was heated at 120° under $N_2$ for 3 hr. The mixture was cooled, concentrated *in vacuo*, chromatographed on silicic acid using benzene-EtOAc (4:1, v/v) as solvent to give 1.14 g of 13 as an oil in 72% yield, IR $\nu_{max}^{neat}$: 1720, 1710, 1690 (C=O), 1360, 1180 ($-SO_2OCH_3$) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 3.10 (3H, s, $CH_3SO_2O-$), 3.64 (1H, dd, J = 1.5 Hz, J = 1.5 Hz, –OCH–), 4.36, 5.13 (2H, ABq, J = 12 Hz, $-CH_2O-$), 5.86 (1H, m, –CHOMs), MS *m/e*: 338 ($M^+$), 243 ($M^+$ $-CH_3SO_3$).

*Reduction of* 13 *with zinc borohydride.* To a soln of 470 mg of 13 in anhydrous THF (5 ml) and benzene (5 ml) was added dropwise 3 ml ethereal zinc borohydride at 0° and the mixture was stirred for 2 hr at 0°. EtOAc was added to the mixture and this was washed with dil AcOH. The aqueous layer was extracted with EtOAc. The combined extracts were dried over $Na_2SO_4$ and evaporated *in vacuo*. The residue was crystallised and recrystallised from EtOAc to give 14, m.p. 108–111°, IR $\nu_{max}^{KBr}$: 3500 (OH), 1715 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 3.04 (3H, s, $CH_3SO_2O-$), 3.67 (1H, m, –OCH–), 4.62 (1H, m, –CHO–), 4.26, 5.00 (2H, ABq, $J_{AB}$ = 12 Hz, $-CH_2O-$), 5.54 (1H, m, –CHOMs), 5.90 (2H, m, $=/^{H}$), MS *m/s*: 122 ($C_6H_5COOH$), 105, 77. (Found: C, 51.93; H, 4.83; S, 9.11. Calc. for $C_{15}H_{16}O_7S$: C, 52.94; H, 4.74; S, 9.40%).

*Acetolysis of* 14. The residue was dissolved in 10 ml acetone and 3 ml AcOH. To the soln was added anhydrous KOAc and the mixture was stirred for 3 hr at 50–60°. To the mix was added EtOAc and this was washed with brine. The aqueous phase was extracted twice with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$, concentrated *in vacuo*. The residue was purified on column chromatography eluting with $CHCl_3$-MeOH (98:2, v/v) to give 235 mg of crystalline material in 54% yield from 13. This was recrystallised from benzene-hexane to give a pure sample of 15, m.p. 97–98°, IR $\nu_{max}^{KBr}$: 3500 (OH), 1735 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 2.15 (3H, s, $-OCOCH_3$), 3.72 (1H, dd, J = 2 Hz, J = 2 Hz, –OCH–), 4.50 (1H, m, –CHO–), 4.40, 4.63 (2H, ABq, $J_{AB}$ = 12 Hz, $-CH_2O-$), 5.53, 5.72 (2H, m of ABq, $J_{AB}$ = 10 Hz, $=/^{H}$), 5.83 (1H, m, –CHOAc), MS *m/e*: 304 ($M^+$), 261 ($M^+$ $-COCH_3$), 245 ($M^+$ $-CH_3COO$). (Found: C, 63.05; H, 5.27. Calc. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30%).

*α,β-Unsaturated ketone* 16. A mixture of 118 mg 15 and 1 g $MnO_2$ in 4 ml $CHCl_3$ was stirred for 30 min at room temp. To the mixture was added $CHCl_3$ and filtered through Highflosupercel. The Highflosupercel was washed well with $CHCl_3$. The filtrates and washings were combined and concentrated *in vacuo* to give 85 mg of 16 as a crystalline material in 75% yield. This was recrystallised from EtOH to give a pure sample, m.p. 142–143°, IR $\nu_{max}^{KBr}$; 1745 ($OCOCH_3$), 1720 (COAr), 1685 (C=C–C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 2.18 (3H, s, $CH_3COO-$), 3.59 (1H, d, J = 2 Hz, –OCH–), 4.43, 4.72 (2H, ABq, $J_{AB}$ = 12 Hz, $-CH_2O-$), 6.01 (1H, m, $=/^{H}$), 6.47 (1H, m, $=/^{H}$), MS *m/e*: 302 ($M^+$). 243 ($M^+$ $-CH_2COO$). (Found: C, 63.53; H, 4.85. Calc. for $C_{16}H_{14}O_6$; C, 63.57; H, 4.67%).

*Epoxidation of* 16. To a soln of 220 mg of 16 in 3 ml THF were added a few pieces of ice and subsequently 2 ml of a peroxide soln made from 100 mg $K_2CO_3$, 2.5 ml water and 0.5 ml 30% $H_2O_2$. The mixture was stirred for 2 hr, and extracted with $CHCl_3$, washed with water, dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was dissolved in 1 ml anhydrous pyridine and 0.5 ml $Ac_2O$. The soln was allowed to stand for 12 hr at room temp., poured into ice water and extracted with $CHCl_3$. The extracts were dried over $Na_2SO_4$ and evaporated *in vacuo* to give an oily residue. The residue was chromatographed on silicic acid with benzene-EtOAc (9:1, v/v) to give 190 mg of 17 as a crystalline material in 81% yield. This was recrystallised from benzene-hexane to afford a pure sample, m.p. 123–124°, IR $\nu_{max}^{KBr}$: 1730, 1745 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 2.24 (3H, s, $CH_3COO-$), 3.50 (1H, dd, J = 4 Hz, J = 2.5 Hz, –OCH–), 3.59 (1H, d, J = 2.5 Hz, –OCH), 3.80 (1H, dd, J = 4 Hz, J = 2 Hz, –OCH–), 4.14, 4.63 (2H, ABq, $J_{AB}$ = 13 Hz, $-CH_2O-$ 5.79 (1H, d, J = 2 Hz, –CH–OAc), MS *m/e*: 318 ($M^+$), 259 ($M^+$ $-CH_3COO$), (Found: C, 60.27; H, 4.51. Calc. for $C_{16}H_{14}O_7$: C, 60.38; H, 4.43%).

*Reductive cleavage of* 17. To a soln of 103 mg 17 in 2 ml benzene and 1 ml THF was added 1.2 ml of a hydrazine soln (a mixture of 70 mg hydrazine hydrated, 1 ml THF and 1 ml i-PrOH). The soln was allowed to stand for 12 hr at room temp. The mixture was diluted with water, extracted with $CHCl_3$ and the combined extracts were evaporated *in vacuo*. The residue was chromatographed on silicic acid using benzene–EtOAc (4:1), v/v) as eluents to give 18. PMR $\delta_{TMS}^{CDCl_3}$: 2.24 (3H, s, $-OCOCH_3$), 3.62 (1H, m, –OCH–), 3.85 (1H, d, J = 4.5 Hz, –OCH–), 4.34 (2H, d, J = 1.5 Hz, $-CH_2O-$), 5.32 (1H, s, –CHOAc), 6.26 (2H, d, J = 3 Hz, $=/^{H}$).

*Tetrahydropyranyl ether* 20. A soln of 186 mg 15, 60 mg dihydropyran and 2 mg *p*-toluenesulfonic acid in 2 ml anhydrous THF was allowed to stand for 12 hr at room temp. To the mixture was added benzene, and this was washed with $NaHCO_3$aq. The aqueous layer was extracted with benzene. The combined extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give 240 mg of 20 as an oil in quantitative yield. IR $\nu_{max}^{neat}$: 1740, 1720 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 1.65 (6H, m, $CH_2$), 2.14 (3H, s, $-OCOCH_3$), 3.55 (1H, m, –OCH–), 3.82 (1H, dd, J = 2 Hz, J = 2 Hz, –OCH–), 4.00 (1H, m, –OCH–), 4.35, 4.65 (2H, ABq, $J_{AB}$ = 11 Hz, $=/^{H}$), 5.80 (1H, m, –CHOAc), MS *m/e*: 303 ($M^+$ –THP), 285 (303 $-H_2O$), 244 (303 $-CH_3COO$).

*Dihydroxylation of* 20. A soln of 104 mg 20 in 1 ml anhydrous ether and 0.05 ml anhydrous pyridine was stirred at 0°. To the soln was added a soln of 96 mg osmium tetroxide in 2 ml anhydrous ether in three portions, and the resulting mixture was stirred for 90 hr at room temp. After disappearance of 20 on tlc, to the mixture was added 300 mg $NaHSO_3$ in 1 ml water and 0.5 ml pyridine. The resultant mixture was stirred for 30 min, extracted with EtOAc, washed with brine, dried over $Na_2SO_4$, evaporated *in vacuo* and chromatographed on silicic acid using $CHCl_3$–MeOH (97:3, v/v) to give 47 mg of 21 in 40% yield. IR $\nu_{max}^{neat}$: 3500, 3400 (–OH), 1730 (C=O) $cm^{-1}$; PMR $\delta_{TMS}^{CDCl_3}$: 1.65 (6H, m, $CH_2$), 2.08 (3H, s, $-OCOCH_3$), 3.55 (1H, m, –OCH–), 3.68 (1H, d, J = 2.5 Hz, –OCH–), 3.80 4.05 (3H, m, –CH–O–), 4.15 (1H, m, –OCH–), 4.44 (2H, S, $-CH_2O$), 4.90 (1H, m, –OCHO–), 5.43 (1H, d, J = 4 Hz, –CHOAc), MS *m/e*: 422 ($M^+$).

*Selective acetylation of the diol* 21 *to* 22, 23 *and* 24. To an ice-cold soln of 56 mg of 21 in 0.1 ml anhydrous ether was added in ice-cold soln of 16 mg (1.24 eq) $Ac_2O$, 15 mg of anhydrous pyridine and 0.1 ml anhydrous ether. The resultant soln was allowed to stand for 24 hr at 5°. To the mixture was added water and this was extracted with EtOAc. The extracts were dried over $Na_2SO_4$, evaporated *in vacuo* and the residue was chromatographed on silicic acid using $CHCl_3$–MeOH (98:2, v/v) as eluents to give 24, IR $\nu_{max}^{neat}$ 1750, 1730 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$ 1.60 (6H, m, $-CH_2-$), 1.94 (3H, s, C-4 OAc), 1.97 (3H, s, C-3 OAc), 2.14 (3H, s, C-2 OAc), 3.60 (1H, m, –OCH–), 3.73 (1H, d, J = 2 Hz, –OCH–), 4.03 (1H, m, –OCH–), 4.22 (1H, dd, J = 6 Hz, 3 Hz, –CHO), 4.36, 4.58 (2H, ABq, $J_{AB}$ = 12 Hz, $-CH_2OCO$), 4.89 (1H, m, –OCHO–), 5.21 (1H, dd, J = 6 Hz, J = 2 Hz, C-4H), 5.28 (1H, dd, J = 6 Hz, J = 2 Hz, C-3H), 5.62 (1H, d, J = 6 Hz, C-2H), 7.55 (3H), 8.13 (2H) and a mixture of 22 and 23. IR $\nu_{max}^{neat}$; 3500 (OH), 1750, 1735 (C=O) $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$; from 22, 2.01 (3H, s, C-3 OAc), 2.15 (3H, s, C-2 OAc), 3.66 (1H, d, J = 3 Hz, –OCH–), 4.35, 4.55 (2H, ABq, J = 12 Hz, $-CH_2O-$), 5.05 (1H, dd, J = 6 Hz, J = 2 Hz, C-3H), 5.49 (1H, d, J = 6 Hz, C-2H), from 23, 1.97 (3H, s, C-4 OAc), 2.12 (3H, s, C-2 OAc), 3.73 (1H, d, J = 3 Hz, –OCH–), 4.34, 4.55 (2H, ABq, J = 12 Hz, $-CH_2O-$), 5.10 (1H, dd, J = 4 Hz, J = 2 Hz, C-4H), 5.52 (1H, d, J = 4 Hz, C-2H).

*Mesylation of* 22 *and* 23. To a soln of 30 mg 22 and 23 in 0.2 ml anhydrous pyridine was added 10 mg methanesulfonyl chloride and the mixture was allowed to stand for 2 hr at room temp. After addition of water, the mixture was extracted with $CHCl_3$. The combined extracts were dried over $Na_2SO_4$, and evaporated *in vacuo* to give a mixture of 25 and 26 in a ratio of 3:1. IR $\nu_{max}^{neat}$; 1750, 1730 (C=O) $cm^{-1}$; PMR $\delta_{TMS}^{CDCl_3}$ from 25, 3.03 (3H, s, $SO_3CH_3$), 4.94 (1H, dd, J = 5 Hz, J = 3 Hz, C-4H), from 26, 2.91 (3H, s, $SO_3CH_3$), 4.94 (1H, dd, J = 5 Hz, J = 2 Hz, C-3H).

*Treatment of* 25, 26 *with p-toluenesulfonic acid.* A soln of 40 mg of 25 and 26 and 3 mg *p*-toluenesulfonic acid in 0.5 ml EtOH was allowed to stand for 24 hr at room temp. To the mixture was added $NaHCO_3$aq, and the mixture was extracted with $CHCl_3$. The extracts were dried over $Na_2SO_4$, concentrated *in vacuo* and chromatographed on silicic acid using $CHCl_3$–MeOH (97:3, v/v) to give 25 mg of 27 and 28 in ratio of 3:1. IR $\nu_{max}^{neat}$; 3500, 1750, 1730 $cm^{-1}$.

(±)-*Croteposide* 11. A soln of 25 mg of 27 and 28 in a small volume of EtOAc was placed on a dry column of 2 g basic alumina. After 5 min the column was eluted with EtOAc. The eluates were evpaorated *in vacuo* and chromatographed on silicic acid using benzene EtOAc (4:1, v/v) to give (±)-11, m.p. 128–129° (natural (+)-crotepoxide[3], m.p. 150–151°). IR $\nu_{max}^{KBr}$: 1760, 1730, 1600, 710 $CM^{-1}$, $\nu_{max}^{CHCl_3}$: 1750, 1730, 1720, 1600 $cm^{-1}$, PMR $\delta_{TMS}^{CDCl_3}$: 2.02 (3H, s, $-OCOCH_3$), 2.11 (3H, s, $-OCOCH_3$), 3.11 (1H, dd, J = 1.5 Hz, 4 Hz, C-4H), 3.45 (1H, dd, J = 4 Hz, 2.5 Hz, C-5H), 3.67 (1H, d, J = 2.5 Hz, C-6H), 4.26, 4.59 (2H, ABq, $J_{AB}$ = 12 Hz, $-CH_2O-$), 5.01 (1H, dd, J = 1.5 Hz, 9 Hz, C-3 –CHOAc), 5.73 (1H, d, J = 9 Hz, C-2 CHOAc). (Found: C, 59.30; H, 5.00. Calc. for $C_{15}H_{18}O_8$: C, 59.66; H, 5.01%).

*Acknowledgements*—We wish to thank Mme J. Polonsky, Institut de chemie des substances Naturelles, CNRS, Gif-sur-Yvette, France, for providing valuable sample of natural senepoxyde. We also thank Dr. A. Ogiso, Central Research Laboratory, Sankyo Co., Ltd. for providing a sample of natural crotepoxide.

## REFERENCES

[1] This paper constitutes Part XIII of *Synthetic Studies of Highly Oxygenated Cyclohexane Derivatives*. For Part XII, see A. Ichihara, M. Kobayashi, K. Oda and S. Sakamura and R. Sakai, submitted for publication.

[2] F. Hollands, D. Becher, J. Gaudemer and J. Polonsky, *Tetrahedron* 24, 1633 (1968). Recently bioorganic chemistry of senepoxyde and crotepoxide was reviewed: B. Ganem, *Ibid.* 34, 3353 (1978).

[3] S. M. Kupchan, R. J. Hemingway and R. M. Smith, *J. Org. Chem.* 34, 3898 (1969). Recently crotepoxide was isolated as an insect antifeedant: Prof. K. Nakanishi's lecture in Hokkaido University, (1977).

[4] S. Takahashi, *Phytochem.* 8, 321 (1969).

[5] Preliminary communication, A. Ichihara, K. Oda, M. Kobayashi and S. Sakamura, *Tetrahedron Letters* 4235 (1974).

[6] A. Ichihara, M. Kobayashi, K. Oda and S. Sakamura, *Ibid.* 4231 (1974), *Tetrahedron* 35, 2861 (1979).

[7] G. Read and V. M. Ruiz, *J. Chem. Soc.* (C), 1945 (1970).

[8] P. S. Wharton and D. H. Bohlen, *J. Org. Chem.* 26, 3615 (1961).

[9] G. W. Holbert and B. Ganem, *J. Am. Chem. Soc.* 110, 352 (1978).

[10] For a preliminary communication of this work, see K. Oda, A. Ichihara and S. Sakamura, *Tetrahedron Letters* 3187 (1975).

[11] Recently other syntheses of (±)-crotepoxide were reported: M. R. Demuth, P. E. Garrett and J. D. White, *J. Am. Chem. Soc.* 98, 634 (1976): M. Matsumoto, S. Kobashi and K. Kuroda, *Tetrahedron Letters* 3361 (1977).