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Conversion of β-Senepoxide to Crotepoxide: Total Synthesis of (+)-Crotepoxide

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Synopsis. Total synthesis of (+)-crotepoxide has been accomplished by chemical conversion of (+)-β-senepoxide which was prepared from (−)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid.

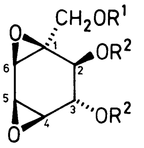
Crotepoxide (**1**) was isolated from *Croton macrostachys*[1,2] and *Piper futokadzura*,[3] and has been found to possess significant activity against Lewis lung carcinoma and Walker intramuscular carcinoma. The structure was established by an X-ray crystallographic analysis of the iodohydrin[4] of **1**. Although three total[5–7] and one formal[8] syntheses of the racemic modification of **1** have so far been reported, the optically active natural form (+)-**1** has never been synthesized.

In continuation of our study[9] of highly oxygenated cyclohexane compounds,[10,11] we now describe a total synthesis of (+)-**1** by the chemical conversion of (+)-β-senepoxide[12] [(+)-**6**], the absolute configuration of which has previously been confirmed by a total synthesis.[12,13]

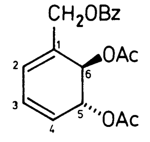
Several attempts to prepare **1** by direct introduction of the *cis*-1,2:3,4-diepoxy functions into *trans*-5,6-diacetoxy-1-benzoyloxymethyl-1,3-cyclohexadiene[14] (**4**) or its *O*-deacetylated derivative[15] using peroxy acid were unsuccessful, and the 4,5-epimer (**5**,[7] epicrotepoxide) of **1** was obtained as a sole diepoxide out of the four possible stereoisomers. Epoxidation of **6**, one of the monoepoxides derived from **4**, also produced **5** exclusively.[14] In this study, epoxidation of **6** to **1** was successfully undertaken through the intermediate bromohydrin **11** prepared from **6**.

Treatment of (±)-**6**[14] with 2 mol equiv *N*-bromoacetamide (NBA) or *N*-bromosuccinimide (NBS) in aqueous dimethyl sulfoxide[16] resulted in the cleavage of the epoxide group to afford the bromohydrin (±)-**7** (49%) and the dihydroxy compound (±)-**8** (21%). The structure of (±)-**7** was confirmed by its conversion to (±)-**6** (63%) with sodium hydrogencarbonate in methanol. A similar treatment of (±)-**6** with NBS in aqueous acetone, ethanol, or dioxane afforded (±)-**7** as the major product. In contrast, when aqueous *N*,*N*-dimethylformamide (DMF) was used as the solvent,[17] (±)-**6** produced two bromo formates [(±)-**9**, 26% and (±)-**10**, 38%], which were obtained by the prefered diaxial opening of the intermediate bromonium ions by an iminium ion. Considering from the product ratio, the formation of the bromonium ion seemed not to be affected by the orientation of the epoxide ring. The structures of (±)-**9** and (±)-**10** were confirmed on the basis of their ^{1}H NMR spectra, which showed the signals due to the ring protons on carbon atoms bearing the bromo atoms as doublets of doublets at δ 4.28 (J=2 and 7.5 Hz) and 4.43 (J=3 and 7.5 Hz), respectively. The former signal did not couple with the epoxide proton, supporting the structure proposed. A treatment of (±)-**9** with methanol at reflux temperature gave the bromohydrin (±)-**11** in good yield. The hydroxy tosylate **12**, prepared by treatment of **1** with *p*-toluenesulfonic acid, was shown to regenerate **1** under the influence of basic alumina.[3] When (±)-**11**, with the same configuration as **12**, was treated in a similar manner, (±)-**11** was recovered unchanged. Finally, it was found that (±)-**11** could be epoxidized only by use of a base strong enough to result in the undesired, partial *O*-deacylation. Thus, (±)-**9** was treated with potassium carbonate in methanol at room temperature for 3 h and the resulting diepoxide (±)-**2** was without isolation acetylated with acetic anhydride in pyridine to give the triacetate (±)-**3** in 60% yield. The ^{1}H NMR spectrum of (±)-**3** was very similar to that of **1**. This is consistent with the proposed structure and excludes a possible migration of the initially formed epoxide group via attack of the vicinal trans hydroxy group. Therefore, the crude (±)-**2** was first selectively benzoylated with benzoyl chloride in pyridine and then acetylated to give rise to a 20% yield[18] of racemic crotepoxide (±)-**1**, which was identified with an authentic sample by comparison of the ^{1}H NMR spectral data.[1]

Likewise, starting from optically active (+)-**6**,[13] (+)-**1** was synthesized. Thus, treatment of (+)-**6** with NBS in aqueous DMF afforded two bromo formates (+)-**9** (22%) and (+)-**10** (30%). The former was converted into (+)-**1** (23%), $[\alpha]_D$ +73° ($CHCl_3$), as described for the preparation of the racemate. The ^{1}H NMR spectrum and the optical rotation were similar with those of an authentic sample.[1]



	R^1	R^2
1	Bz	Ac
2	H	H
3	Ac	Ac



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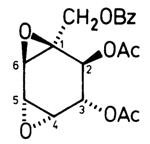

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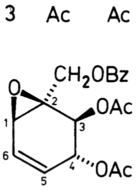

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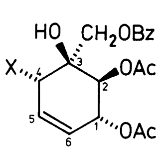
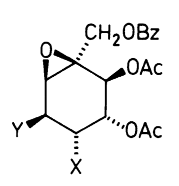


	X
7	Br
8	OH



	X	Y
9	Br	OCHO
10	OCHO	Br
11	Br	OH
12	OTs	OH

The absolute structure[4] of (+)-**1** was also supported by the present synthesis and could be correlated to that of (+)-**6**.

Experimental

Melting points were determined in an open capillary tube in a MEL-TEMP melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in chloroform-*d* solution[19] with tetramethylsilane as an internal standard. The peak positions are given in δ values. TLC was performed on precoated silica gel 60 F-254 (E. Merck, Darmstadt; 0.2-mm thickness). The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka; 300 mesh). Organic solutions were concentrated below 30 °C under reduced pressure.

(±)-1,2-Di-*O*-acetyl-(1,4/2,3)-3-*C*-benzoyloxymethyl-4-bromo-5-cyclohexene-1,2,3-triol [(±)-7] and (±)-1,2-di-*O*-acetyl-(1,4/2,3)-3-*C*-benzoyloxymethyl-5-cyclohexene-1,2,3,4-tetrol [(±)-8]. A mixture of (±)-*β*-senepoxide[14] (±)-**6** (200 mg, 0.58 mmol), NBA (160 mg, 1.16 mmol), dimethyl sulfoxide (2 ml), and water (21 μl, 1.17 mmol) was stirred at room temperature for 1 h. TLC (2-butanone-toluene 1 : 5) showed disappearance of (±)-**6** (R_f 0.57) and appearance of two major spots (R_f 0.32 and 0.12). The mixture was diluted with water (5 ml) and extracted with ether (20 ml). The extract was successively washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. The residue (260 mg) was chromatographed on silica gel (13 g) with 2-butanone-toluene 1 : 4 to give, as the first fraction, (±)-**7** (121 mg, 49%) as needles (from ethanol): Mp 106—107.5 °C. ^{1}H NMR (CDCl$_3$) δ=2.08 (3H, s, OAc), 3.80 (1H, br s, OH), 4.65 (1H, d, *J*=4.5 Hz, H-6), 4.52 (1H, d) and 4.73 (1H, d) (*J*=12 Hz, $C\underline{H}_2$OBz), 5.57—5.87 (3H, m, H-2, H-3, H-4), 6.01 (1H, ddd, *J*=1.5, 4.5, and 10.5 Hz, H-5), 7.30—7.67 (3H, m) and 7.98—8.09 (2H, m) (benzoyl).

Found: C, 50.64; H, 4.39%. Calcd for $C_{18}H_{19}BrO_7$: C, 50.60; H, 4.48%.

The second fraction gave (±)-**8** (45 mg, 21%) as a syrup. ^{1}H NMR (CDCl$_3$) δ=1.99 (3H, s) and 2.10 (3H, s) (OAc), 3.26 (2H, br s, OH), 5.42—5.60 (1H, br s, H-4), 5.69 (1H, dd, *J*=1.5 and 10.5 Hz, H-6), 5.94 (1H, dd, *J*=3.8 and 10.5 Hz, H-5), 7.30—7.66 (3H, m) and 7.99—8.09 (2H, m) (benzoyl).

Found: C, 56.83; H, 5.40%. Calcd for $C_{18}H_{20}O_8 \cdot H_2O$: C, 56.54; H, 5.76%.

The similar results were obtained when NBS was used instead of NBA.

Conversion of (±)-7 to (±)-6. A solution of (±)-**7** (20 mg, 0.05 mmol) in methanol (20 ml) was slowly evaporated in the presence of large excess of sodium hydrogencarbonate at 40 °C. The residue was extracted with chloroform and the product was purified by chromatography to give (±)-**6** (10 mg, 63%), identical with an authentic sample.[14]

(±)-4,5-Di-*O*-acetyl-2,3-anhydro-1-*O*-formyl-(1,2,3,4/5,6)-3-*C*-benzoyloxymethyl-6-bromocyclohexane-1,2,3,4,5-pentol [(±)-9] and (±)-3,4-Di-*O*-acetyl-1,2-anhydro-5-*O*-formyl-(1,2,3,6/4,5)-2-*C*-benzoyloxymethyl-6-bromocyclohexane-1,2,3,4,5-pentol [(±)-10]. A mixture of (±)-**6** (834 mg, 2.41 mmol), NBS (858 mg, 4.82 mmol), DMF (8.2 ml), and water (87 μl, 4.83 mmmol) was stirred at 30 °C for 4 d. TLC (2-butanone-toluene 1 : 5) showed disappearance of (±)-**6** (R_f 0.57) and appearance of two major spots (R_f 0.62 and 0.54). The mixture was processed as described for preparation of (±)-**7** and (±)-**8**. The products (1.35 g) were chromatographed on a silica-gel column (70 g) with 2-butanone-toluene 1 : 2. The first fraction gave (±)-**9** (292 mg, 26%) as prisms (from ether): Mp 113—114 °C. ^{1}H NMR (CDCl$_3$) δ=1.97 (3H, s) and 2.17 (3H, s) (OAc), 3.69 (1H, d, *J*=3 Hz, H-2), 4.58 (1H, dd, *J*=2 and 7.5 Hz, H-6), 5.15 (1H, dd, *J*=2 and 4.5 Hz, H-5), 5.52 (1H, d, *J*=4.5 Hz, H-4), 5.60 (1H, dd, *J*=3 and 4.5 Hz, H-1), 7.33—7.67 (3H, m) and 8.00—8.11 (2H, m) (benzoyl), 8.19 (1H, s, formyl).

Found: C, 48.68; H, 4.00%. Calcd for $C_{19}H_{19}BrO_9$: C, 48.43; H, 4.06%.

The second fraction gave (±)-**10** (431 mg, 38%) as prisms (from ethanol): Mp 85—87 °C. ^{1}H NMR (CDCl$_3$) δ=1.87 (3H, s) and 2.17 (3H, s) (OAc), 3.77 (1H, d, *J*=3 Hz, H-1), 4.43 (1H, dd, *J*=3 and 7.5 Hz, H-6), 4.30 (1H, d) and 4.57 (1H, d) (*J*=11.5 Hz, $C\underline{H}_2$OBz), 5.17 (1H, dd, *J*=2 and 4.5 Hz, H-4), 5.41 (1H, dd, *J*=2 and 7.5 Hz, H-5), 5.53 (1H, d, *J*=4.5 Hz, H-3), 7.33—7.67 (3H, m) and 8.00—8.11 (2H, m) (benzoyl), 8.03 (1H, s, formyl).

Found: C, 48.23; H, 3.98%. Calcd for $C_{19}H_{19}BrO_9$: C, 48.43; H, 4.06%.

Similarly, (+)-*β*-senepoxide[13] (+)-**6** (795 mg, 2.3 mmol) was treated with NBS in aqueous DMF to give, after chromatography, the (1*S*)-enantiomer (+)-**9** (241 mg, 22%), $[\alpha]_D^{21}$ +2.1° (*c* 2.4, CHCl$_3$), and the (3*S*)-enantiomer (+)-**10** (320 mg, 30%), $[\alpha]_D^{21}$ +40° (*c* 1.8, CHCl$_3$). Both compounds were characterized by comparison of their ^{1}H NMR spectral data with those of racemic modification. Mass spectrum, *m*/*z* (relative intensity); for (+)-**9**, 425.0203 ($M^+ - HCO_2$, 17.7), for (+)-**10**, 425.0215 ($M^+ - HCO_2$, 90.6).

(±)-4,5-Di-*O*-acetyl-2,3-anhydro-(1,2,3,4/5,6)-3-*C*-benzoyloxymethyl-6-bromocyclohexane-1,2,3,4,5-pentol [(±)-11]. A solution of (±)-**9** (110 mg, 0.23 mmol) in methanol (3 ml) was refluxed for 10 min. TLC (2-butanone-toluene 1 : 5) showed disappearance of (±)-**9** (R_f 0.62) and appearance of one major (R_f 0.28) and one minor spots (R_f 0.34). The mixture was concentrated and the residue was eluted from a silica-gel column (5 g) with 2-butanone-toluene 1 : 6 to give (±)-**11** (82 mg, 80%) as a syrup; ^{1}H NMR (CDCl$_3$) δ=1.95 (3H, s) and 2.14 (3H, s) (OAc), 3.00 (1H, br s, OH), 3.69 (1H, d, *J*=4.1 Hz, H-2), 4.41 (1H, m, H-1), 4.28 (1H, d) and 4.55 (1H, d) (*J*=11.5 Hz, $C\underline{H}_2$OBz), 5.14 (1H, dd, *J*=2.2 and 5.7 Hz, H-5), 5.62 (1H, d, *J*=5.7 Hz, H-4), 7.31—7.68 (3H, m) and 8.00—8.10 (2H, m) (benzoyl).

Found: C, 47.78; H, 4.22%. Calcd for $C_{18}H_{19}BrO_8 \cdot 0.5H_2O$: C, 47.84; H, 4.42%.

(±)-2,3-Di-*O*-acetyl-1,6 : 4,5-dianhydro-(1,2,4,5,6/3)-1-*C*-(acetoxymethyl)cyclohexane-1,2,3,4,5,6-hexol [(±)-3]. A mixture of (±)-**9** (30 mg, 0.06 mmol), anhydrous potassium carbonate (12 mg), and methanol (5 ml) was stirred at room temperature overnight. TLC (chloroform-methanol 8 : 1) showed a formation of one major (R_f 0.19) and one minor components (R_f 0.23). The mixture was neutralized with M hydrochloric acid and concentrated, and the residue was acetylated with acetic anhydride and pyridine in the usual way. The product was purified by chromatography on silica gel and crystallized from ethanol to give, as the main product, (±)-**3** (11 mg, 60%) as needles: Mp 70—70.5 °C; ^{1}H NMR (CDCl$_3$) δ=2.06 (6H, s) and 2.09 (3H, s) (OAc), 3.05 (1H, dd, *J*=1.5 and 3 Hz, H-4), 3.50 (1H, dd, *J*=2 and 3 Hz, H-5), 3.50 (1H, d, *J*=2 Hz, H-6), 3.79 (1H, d) and 4.42 (1H, d) (*J*=11 Hz, $C\underline{H}_2$OAc), 4.87 (1H, dd, *J*=1.5 and 9 Hz, H-3), 5.58 (1H, d, *J*=9 Hz, H-2).

Found: C, 52.19; H, 5.16%. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37%.

Synthesis of Crotepoxide. Compound (±)-**9** (169 mg, 0.36 mmol) was treated with potassium carbonate (75 mg, 0.54 mmol) in methanol (25 ml) as described for the preparation of (±)-**3**. The resulting trihydroxy compound was selectively benzoylated with benzoyl chloride (84 μl, 0.72 mmol) in pyridine (3 ml) at −15 °C for 10 min, and then for 5 h at room temperature. TLC (chloroform-methanol 8 : 1) showed one major spot (R_f 0.54), together with several minor spots. Acetic anhydride (1 ml) was then added to the mixture, and, after 2 h at room temperature, the mixture was processed in the usual way. The mixture of products was fractionated by a silica-gel column (10 g) with 2-butanone–toluene 1 : 10 to give, as a major product, (±)-**1** (26 mg, 20% based on **9** used) as needles (from ethanol): Mp 109—111 °C (lit,[4] Mp 110—111, 128—129 °C). Crystals show a double melting point (melted at 109—111 °C, resolidified, and then melted again at ca. 128 °C). The ^{1}H NMR ($CDCl_3$) spectral data were shown to be identical with those of an authentic sample.[4,5] (Found: C, 59.67; H, 4.89%).

Likewise, (+)-crotepoxide (+)-**1** was obtained, in 23% yield, by epoxidation of (+)-**9** followed by selective acylation; needles (from methanol): Mp 145—147 °C, $[\alpha]_D^{25}$ +73° (c 0.43, $CHCl_3$). lit,[1] Mp 150—151 °C, $[\alpha]_D^{25}$ +74° (c 1.7, $CHCl_3$). The ^{1}H NMR spectrum was superimposable on that of a racemic modification. (Found: C, 59.72; H, 4.88%).

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