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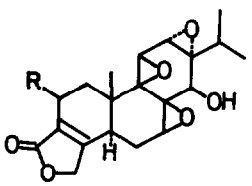
SYNTHESIS OF DITERPENOID EPOXIDES RELATED TO TRIPTOLIDE FROM RESIN ACIDS. SYNTHESIS OF METHYL 14β-HYDROXY-7β:8β,9β:11β,12α:13α-TRIEPOXYABIETAN-18-OATE

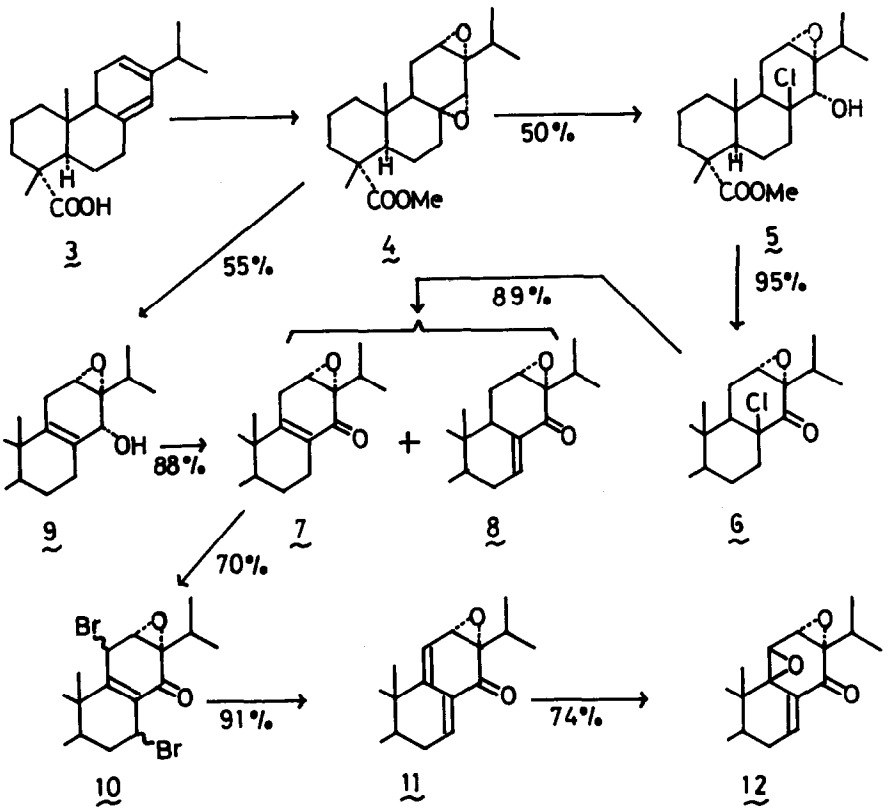
H. Koike and T. Tokoroyama*
Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

Triptolide 1 and tripdiolide 2 are highly active antileukemic principles isolated from Tripterygium wilfordii Hook by Kupchan and co-workers, which structurally represent novel diterpenoid triepoxides with 18(4→3)-abeo-abietane skeleton.[1] Related diterpenoid epoxides have also been characterized from the same or the other plants.[1,2] It is of particular interest that the characteristically hydrgen-bonded 9,11-epoxy-14-hydroxy systems of 1 and 2 are claimed to be responsible for their activity. The stereospecific elaboration of the highly complex oxygen functionality present in 1 and 2 are thus intriguing both from synthetic and biological point of view. We wish to report here the first successful synthesis of a 14β-hydroxy-7β:8β,9β:11β,12α:13α-triepoxide, which has the complete B/C ring moiety of 1 and 2, from a readily available resin acid.

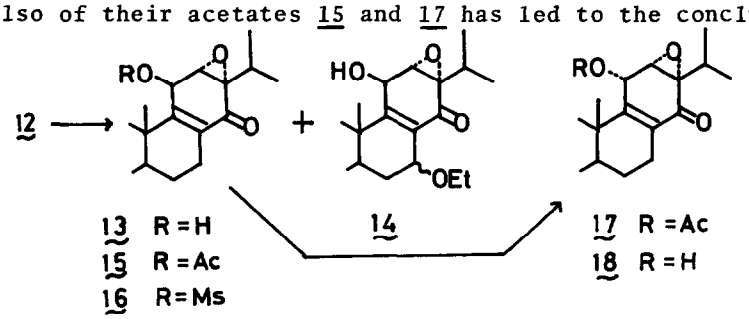


1 R=H
2 R=OH

Our starting material was levopimaric acid 3 which was transformed by known procedure[4] to the chlorohydrin 5 via the bisepoxide 4. Oxidation of 5 with Jones' reagent followed by treatment with Li_2CO_3, LiCl and DMF at 100° afforded the isomeric conjugated enones 7[IR(CCl_4): 1660, 1620 cm^{-1}] and 8 [IR(CCl_4): 1690, 1620 cm^{-1}] in ratio of 5:1 (89% yield). More conveniently 7 was obtained by Jones' oxidation of the allylic alcohol 9 which in turn was prepared in 55% yield through the treatment of 4 with catalytic amount of dry HCl in ether at -20°. Upon treatment with NBS in CCl_4 under refluxing 7 produced the 7,11-dibromide 10 [m.p.180-182°; PMR: 3.88(1H, d, J=3 Hz), 5.08(1H, d, J=3 Hz), 5.30 (1H, dd, J=2,5 Hz)] and then 10 was debrominated by the agency of zinc dust in refluxing THF to yield the diene 11 [IR(CCl_4): 1695, 1635, 1600 cm^{-1}; PMR: 3.42(1H, d, J=4 Hz), 5.70(1H, d, J=4 Hz), 6.94(1H, m)]. Exposure of 11 to MCPBA in CH_2Cl_2 at the presence of Na_2HPO_4 led to the formation of the bisepoxide 12 [IR(CCl_4): 1710, 1640 cm^{-1}; PMR: 3.82(1H, d, J=3 Hz), 4.08(1H, d, J=3 Hz), 6.70(1H, m)]. Other extensive attempts to introduce 7,8 or 9,11-epoxy group starting from 10, 11 or their reduction products[5] met with uniform failure. Here the configuration of the newly introduced epoxide ring in 12 was a question of the utmost concern. A priori the formation of both α and β-epoxides was equally presumed since the

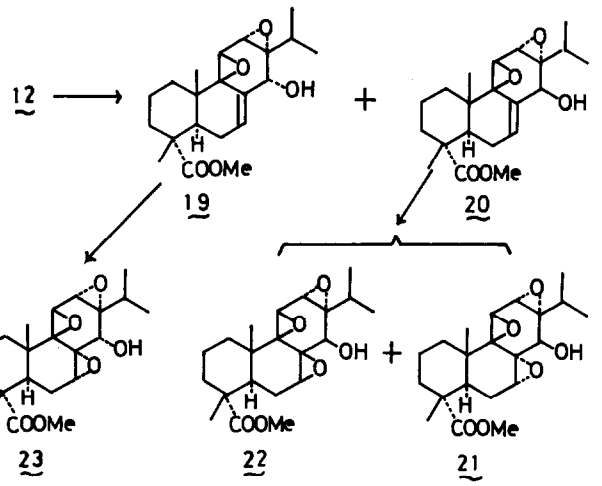


two major factors — namely the steric effects due to 10β-methyl and 12α:13α-epoxy groups would exert opposite influence to the approach of the reagent. Catalytic hydrogenation of 12 at the presence of Pd-C in ethanol furnished a hydrogenolysis product 13 (37% yield; PMR: 4.89(br d, J=8 Hz)] and the ethyl ether 14 (31% yield) which formed through Pd-assisted solvolytic opening of the vinyl epoxide ring. On acetylation 13 afforded the acetate 15 [IR: 1740, 1640, 1620 cm^{-1}; PMR: 3.53(1H, d, J=2 Hz), 6.26(1H, br s)]. The acetate 17 [IR: 1730, 1675, 1620 cm^{-1}; PMR: 3.74(1H, d, J=4 Hz), 5.76(1H, m)] and the alcohol 18 [PMR: 3.76(1H, d, J=5 Hz), 4.56(1H, dd, J=5,10 Hz)] with inverted configuration were obtained by a sequence of reactions (13→16→17→18): 1.mesylation(MsCl, Et_3N, CH_2Cl_2, 0°), 2.substitution($Et_4N^+OAc^-$, acetone, reflux) and 3.hydrolysis(10% Na_2CO_3, EtOH, room temp.). The spectroscopic scrutiny of the epimeric alcohol 13 and 18, and also of their acetates 15 and 17 has led to the conclusion that 13



has β-configuration and hence the newly introduced 9,11-epoxide ring in 12 is β. Firstly the chemical shift (δ 1.30) of 10-methyl proton signal in the PMR spectrum of 13 is decidedly deshielded as compared with those of the epimer 18 (δ 1.16) and the 11-deoxy-compound 7 (δ 1.10). Secondly in the PMR spectra added with $Eu(dpm)_3$, the 10-methyl protons of 13 show markedly larger shifts than those of 18, which exhibit LIS values comparative to those of C-4 methyl protons of 13 or 18. Thirdly the C-11 proton signil of the acetate 17 appears as double doublets, whereas that of the epimeric acetate 15 splits only to a doublet. The presence of the additional splitting (J=2 Hz) in 17 is reasonably ascribed to a homoallylic coupling with $C_{7\alpha}$-axial proton.[6] Finally in the CMR spectra the angular methyl carbon atoms at C-10 in 7, 13 and 18 appear at 20.7, 27.1 and 22.1 respectively, showing that the signal in 13 is appreciably deshielded by the δ effect due to the presence of the C-11 hydroxyl group in syn-diaxial like position.[7] Thus in the peracid oxidation of the dienone 11, the steric effect due to 12α, 13α-epoxide ring was proved to outweigh that of C-10 methyl group and the construction of 9β, 11β-epoxy group desired for the synthesis of triptolide 1 has been secured stereospecifically.

Subsequently we proceeded to the introduction of the 7,8-epoxide. Reduction of 12 with $NaBH_4$ produced an equal amount of the epimeric alcohols 19 [low melting point crystals; IR(CCl_4): 3560 cm^{-1}; PMR: 3.45(1H, d, J=3 Hz), 3.75(1H, d, J=3 Hz), 4.67(1H, dd, J=3,8 Hz), 6.11(1H, m)] and 20 [m.p.162-165°; IR(CCl_4): 3540 cm^{-1}; PMR: 2.92(1H, d, J=12 Hz), 3.51(1H, d, J=3 Hz), 3.95(1H, d, J=3 Hz), 4.36(1H, d, J=12 Hz)], readily separable by silica-gel chromatography. The alcohol 20 was assigned β-configuration from the presence of highly distinctive coupling (12 Hz) between C_{14}-H and hydroxyl proton, conformationally fixed by hydrogen bonding,[3] as reported also in the case of triptolide 1,[1] and hence 19 is α-alcohol. This assignment conforms with the fact that a considerable allylic coupling (J=3 Hz) is observed in the PMR spectrum of 19 but not in that of 20, since the inspection of model shows that C_{14}-proton of 19 is nearly perpendicular to the plane of the double bond, whereas that of 20 is almost in the plane. With the β-alcohol 20 in hand, we expected the syn-directing effect of the hydroxyl group would lead largely to the introduction of 7,8-epoxide ring from β-side.[8] However the epoxidation of 20 in Sharpless condition[9] was not effective, since the reaction was too sluggish. The oxidation of 20 with MCPBA-Na_2HPO_4 in CH_2Cl_2 solution proceeded only very slowly and the reaction for two weeks at ambient temperature afforded the 7α,8α-epoxide 21 [m.p.185.5-187.5°, 22% yield), as major product with small amount of the desired 7β,8β-epoxide 22 (m.p.179.5-181.5°, 3% yield). The isolated yield of 22 was considerably increased by the use of benzene (21, 54%; 22, 16%; 20, 23%) or acetonitrile (21, 19%; 22, 11%; 20, 43%) as the solvent. Moreover the photo-oxygenation of 20 in benzene solution at the presence of large excess of biacetyl (quarz vessel, high pressure Hg lamp)[10,11] yielded 13% of 21 and 19% of 22. The configuration of new epoxy groups in 21 and 22 was assigned by the comparison of the coupling pattern of C_7-proton resonances



in the PMR spectra of 20 and 21 with that of triptolide 1. As seen from the table, the other signals due to the protons of the hydroxy-triepoxide system in 21 also show an excellent correspondance to those of triptolide 1. Thus the

	C_7-H	C_{11}-H	C_{12}-H	C_{14}-H	C_{14}-OH
triptolide 1	3.46 (d, J=5 Hz)	4.00 (d, J=3 Hz)	3.60 (dd, J=1,3 Hz)	3.52 (dd, J=1,11 Hz)	2.83 (d, J=11 Hz)
21	3.32 (m)	3.89 (d, J=3 Hz)	3.56 (d, J=3 Hz)	3.72 (d, J=12 Hz)	2.95 (d, J=12 Hz)
22	3.23 (d, J=5 Hz)	4.04 (d, J=4 Hz)	3.50 (dd, J=1,4 Hz)	3.36 (dd, J=1,11 Hz)	2.77 (d, J=11 Hz)

construction of the B/C ring moiety of 1 has been accompolished. In contrast to 20, the reaction of 19 with MCPBA proceeded in normal rate and in the direction as expected from syn-directing effect of the C_{14}hydroxyl group. Thus the exposure of 19 to the same condition as the case of 20 led to the stereoselective formation of 23 [m.p.207-210°; PMR: 3.43(1H, m), 3.50(1H, d, J=3 Hz), 4.27(1H, m)]. The relatively free C_{14}-hydroxyl group in 19 would contribute normally to the stabilization of the transition state leading to syn-epoxidation, whereas the strongly hydrogen-bonded hydroxyl group in 20 is no longer capable of such effect and rather would hinder the approach of the reagent from β-side.

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