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PREPARATION OF ENANTIOMERS OF 17-EPOXY EICOSAPENTAENOIC ACIDS AND THEIR 18-HYDROXY DERIVATIVES#

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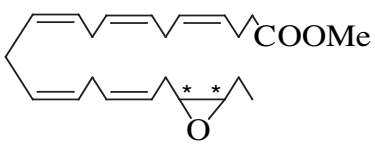
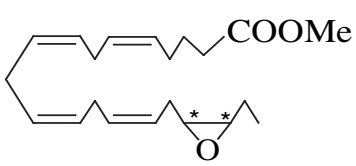
Abstract-By the action of NBS in aq DME, *dl*-17-bromo-18-hydroxy EPA methyl ester (**6**) was prepared, which was effectively resolved by lipase PS and vinyl acetate in the presence of a thiacrown ether to give the resolved bromoacetate (**7**) and bromohydrin (**8**), each being transformed into the corresponding epoxide (**3** and **4**). The absolute configuration of **8** was established by the Kusumi-Moscher method. Both epoxides were treated with LDA to provide allyl alcohols (**5a** and **b**), accompanied with the formation of cyclopropyl derivatives (**10a** and **b**).

In the course of our study concerning oxygenated fatty acids, we needed the preparation of both enantiomers of terminal epoxides of docosahexaenoic acid (DHA) (**1** and **2**) and eicosapentaenoic acid (EPA) (**3** and **4**) for biological evaluation of the oxygenated ω−3 polyunsaturated fatty acids. This communication deals with the preparation of both enantiomers of epoxy EPA (**3** and **4**) and their 18-hydroxy derivative (**5**) by the application of our previously developed procedure for the preparation of **1** and **2**.[1]

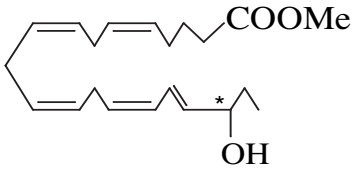
The preparation of both enantiomers (**3** and **4**) commenced from our recent findings, in which we revealed the terminal double bonds of ω-3 unsaturated fatty acids such as α-linolenic acid, DHA and EPA can be oxidized by the action of NBS in aqueous organic solvent with high regioselectivity.[2] When EPA methyl ester[3] was submitted to the reaction with NBS (1.3 eq) in aqueous dimethoxyethane (DME) followed by purification with preparative flash chromatography, racemic 17-bromo-18-hydroxy-EPA methyl ester (**6**) was obtained in 37 % conversion yield, accompanied with 18-bromo-17-hydroxy derivative as a major isomer.



1 (19S, 20R)-β-Epoxide
2 (19R, 20S)-α-Epoxide

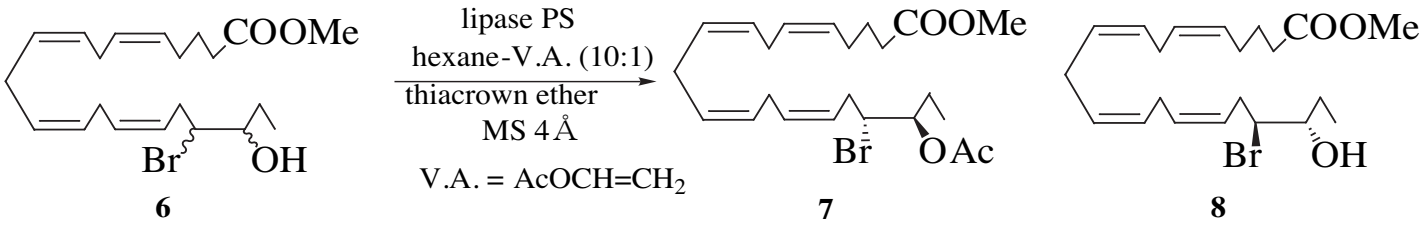


3 (17S, 18R)-β-Epoxide
4 (17R, 18S)-α-Epoxide



5 18-Hydroxy EPA

Dedicated to Professor James P. Kutney for the celebration of his 70th birthday.

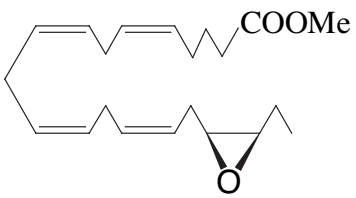


6 **7** **8**

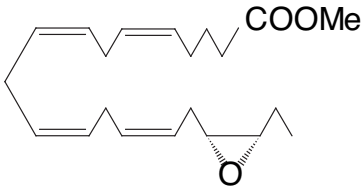
Table 1. The acylation reaction of *dl*-bromohydrin (**6**) by lipase PS[a)]

Thiacrown ether	Time (day)	Specific rotation $[\alpha]_D^{23}$ of **7** (yield)	Specific rotation $[\alpha]_D^{24}$ of **8** (yield)
(5 mol%)	1	+20.5° (*c* 1.0, MeOH) (43%)	-12.3° (*c* 1.0, MeOH) (49%)

a) The reaction was carried out using **6** (70 mg, 0.17 mmol), lipase PS (70 mg), vinyl acetate (0.3 mL) and 4Å molecular sieves (10 mg) in hexane (3 mL) in the presence of thiacrown ether (10 mg) at room temperature.



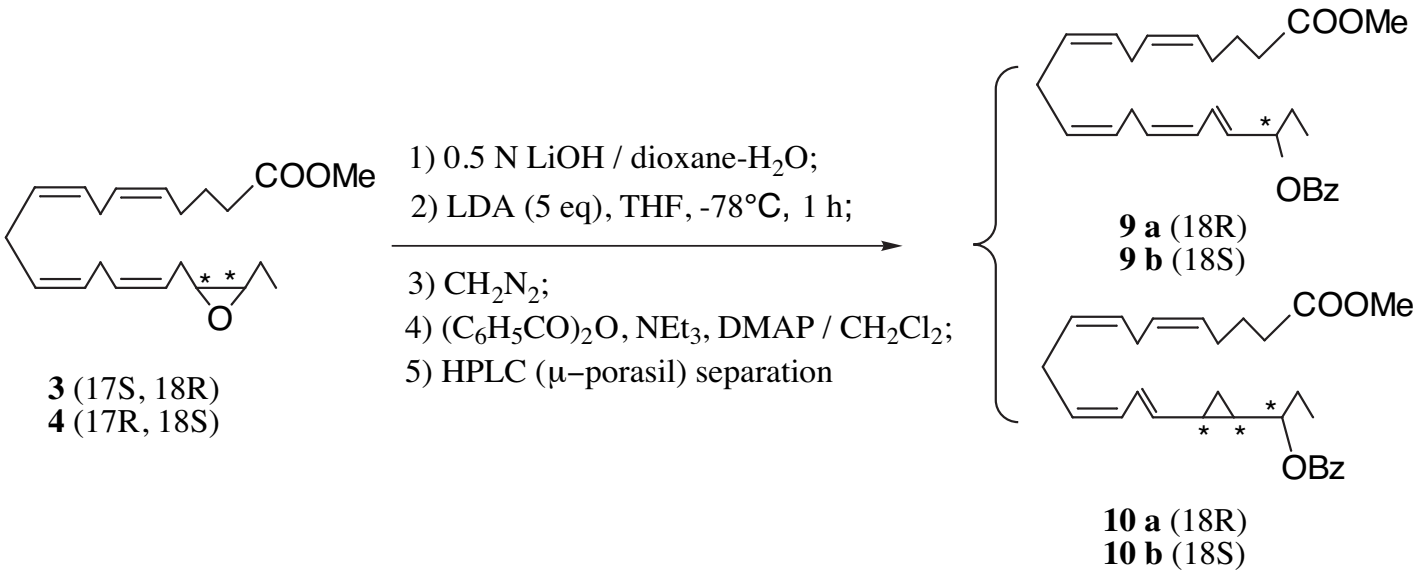
3 (17S, 18R)
$[\alpha]_D^{23}$ -4.4° (c 1.0 MeOH)

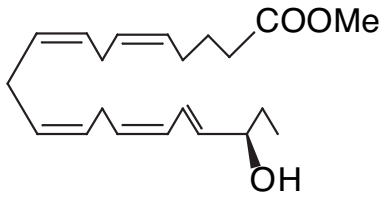


4 (17R, 18S)
$[\alpha]_D^{24}$ +4.5° (c 1.0 MeOH)

The optical resolution of *dl*-bromohydrin (**6**) was carried out by acylation with vinyl acetate in the presence of Lipase Amano PS.[4] Table 1 shows the results of the enantioselective acylation effected by the 1,4,8,11-tetrathiacyclotetradecane (thiacrown ether).[5] The absolute configuration of the resolved compounds[6] (**7** and **8**) was deduced from a comparison of the sign of optical rotation with those prepared from DHA and α–linolenic acid. In order to confirm the deduction, *dl*- and resolved bromohydrins were converted to the corresponding (*R*)-MTPA esters. The chemical shift of the terminal methyl group from *dl*-form (**6**) was measured at 0.84 and 0.96 ppm while the methyl signal from the resolved bromohydrin (**8**) appeared only at 0.96 ppm, demonstrating the terminal methyl group of the 18*S* configuration of **8** suffers no influence of the phenyl group of the (*R*)-MTPA moiety.[7] The methyl signals in the NMR spectra clearly shows the enantiomeric excess of the resolved bromohydrin (**8**) is more than 98%.

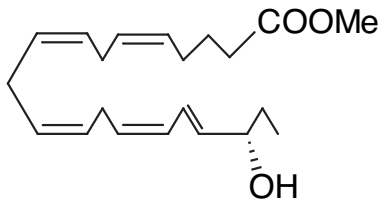
By treatment with methanolic KOH followed by esterification with CH_2N_2, the bromoacetate (**7**) and the resolved bromohydrin (**8**) were transformed into the corresponding epoxides (**3** and **4**) in high yields, possessing the optical rotations of -4.4 and +4.5, respectively. The free acids obtained from the epoxy methyl esters (**3** and **4**) were submitted to the epoxide ring-opening reaction with LDA in THF, providing a *ca*. 1:1 mixture of allyl alcohols (**9 a** and **b**) and cyclopropyl alcohols (**10 a** and **b**) in *ca*. 70% overall yields, which was separated by preparative HPLC after conversion to the corresponding benzoates.





5 a (18R)

$[\alpha]_D^{25}$ -18.4° (*c* 0.5, $CHCl_3$)



5 b (18S)

$[\alpha]_D^{25}$ +17.9° (*c* 0.5, $CHCl_3$)

The conjugated *Z, E* diene moieties of **9** and **10,** in particular of **10**, are fairly unstable and apt to isomerize to the stable *E, E* geometry in each compound. The conjugated diene moiety possessing *Z,E*-geometry in each alcohol was confirmed by comparison of the NMR spectra[8] with those of the related fatty acids.[9] The free alcohols (**5 a** and **b**) were obtained from the benzoates after hydrolysis (aq LiOH in dioxane-H_2O, rt) and then esterification with CH_2N_2. The allyl alcohols (**5a** and **b**) showed almost the same absolute value of optical rotation ($[\alpha]_D$) with opposite signs. The stereochemistry of the resulting cyclopropane ring of the benzoates was assigned as 15*S*, 17*S*, 18*R* for **10a** and 15*R*, 17*R*, 18*S* for **10b**, respectively on the basis of S_N2 type ring-opening of the starting epoxides.

The biological activities of the oxygenated EPA derivatives prepared so far are now under examination.

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1. a) T. Kato, T. Ishimatsu, A. Aikawa, K. Taniguchi, T. Kurahashi, and T. Nakai, *Tetrahedron: Asymmetry*, 2000, **11**, 851. b) T. Kato, T. Nakai, T. Ishimatsu, M. Hoshikawa, and T. Namai, *Heterocycles*, 2000, **52**, 1353.
2. T. Kato, T. Hirukawa, and K. Namiki, *Tetrahedron Lett*., 1992, **33**, 1475.
3. The starting material, EPA, was kindly provided by Nippon Suisan Kaisha (Nissui), Ltd., to whom the

authors express their appreciation.
4. The authors are grateful to Amano Pharmaceutical Co., Ltd. for providing lipase PS.
5. a) T. Itoh, K. Mitsukura, W. Kanphai, Y. Takagi, H. Kihara, and H. Tsukube, *J. Org. Chem.*, 1997, **62**, 9165. b) T. Itoh, Y. Takagi, T. Murakami, Y. Hiyama, and H. Tsukube, *J. Org. Chem.*, 1996, **61**, 2158. c) Y. Takagi, J. Teramoto, H. Kihara, T. Itoh, and H. Tsukube, *Tetrahedron Lett.*, 1996, **37**, 4991.
6. The structure and purity of all the new compounds were confirmed by HPLC analyses and physical evidence (^{1}H and ^{13}C NMR and HRMS).
7. I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092. The authors are grateful to Professor T. Kusumi for his discussion on the method.
8. **5** δ_H (270 MHz, $CDCl_3$) 0.94 (3H, t, *J*=7.6), 1.61 (4H, m), 2.10 (2H, m), 2.33 (2H, t, *J*=7.3), 2.83 (4H, m), 2.97 (2H, m), 3.67 (3H, s), 4.10 (1H, dd, *J*=6.8, 13.0), 5.39 (7H, m), 5.68 (1H, dd, *J*=6.8, 15.1), 6.05 (1H, t, *J*=11.1), and 6.53 (1H, dd, *J*=11.1, 15.1). δ_C (68 MHz, $CDCl_3$) 174.11 (s), 136.28 (d), 130.15 (d), 128.97 (d), 128.81 (d), 128.53 (d), 128.29 (d), 128.06 (d), 127.97 (d), 127.64 (d), 125.51 (d), 74.07 (d), 51.51 (q), 33.43 (t), 30.17 (t), 26.54 (t), 26.09 (t), 25.66 (t), 25.62 (t), 24.75 (t), and 9.72 (q).
10 δ_H (270 MHz, $CDCl_3$) 0.78 (2H, m), 1.00 (3H, t, *J*=7.3), 1.20 (1H, m), 1.68 (3H, m), 1.81 (2H, m), 2.10 (2H, m), 2.31 (2H, t, *J*=7.4), 2.78 (2H, m), 2.86 (2H, m), 3.66 (3H, s), 4.62 (1H, dd, *J*=7.0, 12.8), 5.34 (6H, m), 5.90 (1H, t, *J*=11.1), 6.37 (1H, dd, *J*=11.1, 15.1), 7.46 (3H, m), and 7.52 (2H, m).
9. T. Kato, Y. Yamaguchi, T. Namai, and T. Hirukawa, *Biosci. Biotech. Biochem.*, 1993, **57**, 283.