Pergamon

Tetrahedron Letters, Vol. 38, No. 2, pp. 249-250, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02273-3

A Simple Preparation of 17(*R*)-Hydroxyeicosatetraenoic and Eicosapentaenoic Acids from the Eicosanoylphloroglucinols, Components of the Brown Alga, *Zonaria diesingiana*

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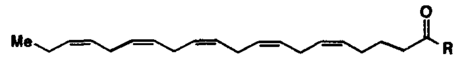
Abstract: The alkaline treatment of 17(*R*)-hydroxyeicosatetraenoylphloroglucinol and eicosapentaenoylphloroglucinol, which are the major components of the methanol extract of the brown alga, *Zonaria diesingiana* (Dictyota) afforded 17(*R*)-hydroxyeicosatetraenoic and eicosapentaenoic acids, respectively, in good yields. The conformation of methyl ester of the 17(*R*)-hydroxy acid in a solution was studied by using 2NMA, a chiral anisotropic reagent.

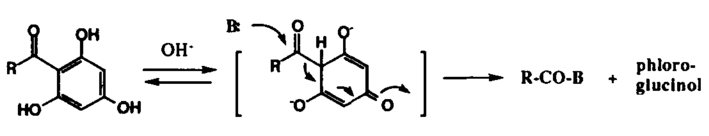
The importance of hydroxyeicosanoids, the early stage-products of the arachidonic cascade, is well recognized and prompt study of their physiological significance has been undertaken.[1] In 1982, Gerwick *et al.* obtained a series of phloroglucinols connected with eicosanoids, such as **1** and **5**, from a brown alga.[2] We have also isolated the same compounds from *Zonaria diesingiana* (Dictyota), and reported the round-shaped conformation of the MTPA ester of dimethyl-**1**.[3] We further needed to know the conformation of 17(*R*)-hydroxyeicosatetraenoic acid (**2**) itself, and planned next to cut the eicosatetraenoyl fragment out of **1**.

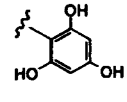
At first, Beckmann rearrangement of the oxime of **1** was attempted: **1** was treated with hydroxylamine with an excess of sodium hydroxide in refluxing aqueous ethanol. The crude product was heated with silica gel to bring about the rearrangement, which gave two separable compounds in a very poor yield. Neither of the substances, however, was found to be the expected rearrangement product, because the ^{1}H NMR spectra of both revealed no aromatic protons. We, therefore, repeated the reaction by using the more abundant component **5**, obtaining compounds A and B in 50 % and 25 % yields, respectively. The ^{1}H and ^{13}C NMR spectra of both compounds indicated the presence of the eicosapentaenoyl group and absence of the aromatic group. The IR spectrum of A showed a strong band at 1646 cm^{-1} and that of B, a strong band at 1709 cm^{-1}. B was methylated with diazomethane to give methyl eicosapetaenoate (**7**), which was identified by NMR[4] and mass spectra, while A was not methylated. The mass spectrum of A showed the M$^+$ at *m/z* 317, suggesting the structure **8**[5] of A. So the products obtained from **1** must be **2** and **4**. The probable mechanism[6] to

1 : R = THXP **2**: R = OH **3**: R = OMe **4**: R = NHOH



5 : R = THXP **6**: R = OH **7**: R = OMe **8**: R = NHOH





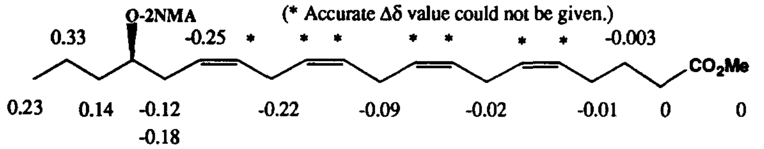
THXP (trihydroxyphenyl)

produce **6** and **8** is shown above. Actually, the reaction proceeded even under argon (Oxygen is not involved in this reaction.) and phloroglucinol was isolated from the reaction mixture in a good yield.

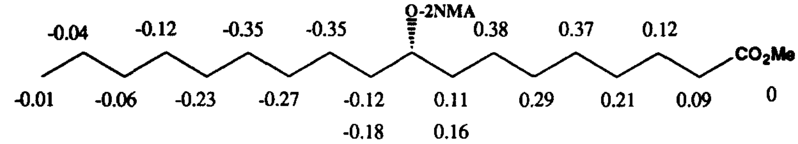
Refluxing a mixture of **5** (10 mg) and sodium hydroxide (14.7 mg) in ethanol (1 mL)-water (0.2 mL) for 3 h gave **6** in 75% isolation yield. Also, 17(*R*)-hydroxyeicosatetraenoic acid (**2**),[7] $[\alpha]_D$ +5° (c 0.38, $CHCl_3$), was obtained in 60% isolation yield from **1** under these reaction conditions. The optical rotation of the methyl ester (**3**), $[\alpha]_D$ +3.6° (c 0.5, acetone), was identical with the reported value.[8]

It is particularly noted that the content of **1** and **5** in the brown alga is quite high; 5% and 30%, respectively, of the methanol extract of *Z. diesingiana*, which is very commonly seen in the temperate and subtropical zones. Both compounds are extremely stable even at room temperature, possibly because the labile polyolefin part coexists with the phloroglucinol, an efficient antioxidant.

17(*R*)-Hydroxyeicosatetraenoic acid (**2**) was converted into diastereomeric 2NMA[9] (2-naphthylmethoxyacetic acid) esters, and the $\Delta\delta$ values $[\delta_{(R)} - \delta_{(S)}]$ of the protons were calculated. These values, supporting the 17(*R*)-configuration, are shown in structure **2'**. For comparison, the $\Delta\delta$ values obtained for the 2NMA ester of 9(*S*)-hydroxystearate (**9**) are also given. The significant $\Delta\delta$ values are observed for H-3 and 4, 14 and 13 bonds apart from the 2NMA-oxy group, respectively, in **2'**.



2'



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References and Notes

1. See, for example, Macica, C.; Balazy, M.; Falck, J. R.; Mioskowski, C.; Carroll, M. A. *Am. J. Physiol.*, **1993**, *265*, G735-G741.
2. Gerwick, W.; Fenical, W. *Phytochem.*, **1982**, *21*, 633-637.
3. Kusumi, T.; Ooi, T.; Uchimura, H. *Tetrahedron Lett.*, **1994**, *35*, 3127-3128.
4. Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*, Vol. 1, Aldrich Chemical Company, Milwaukee, **1993**, 758A.
5. ^{13}C NMR of **8**: δ ($CDCl_3$): q; 14.09: t; 20.39, 25.11, 25.38, 25.46 (x3), 26.36, 32.23: d; 126.85, 127.70, 127.90, 127.97, 128.11, 128.16, 128.44, 128.58, 128.86, 131.89: s; 171.62.
6. The dianion of phloroglucinol is known to exist in the dioxo form: Coffey, S. ed., *Rodd's Chemistry of Carbon Compounds*, 2nd edition, Elsevier, Amsterdam, **1971**, 415.
7. ^{13}C NMR of **2**: δ ($CDCl_3$): q; 13.93: t; 18.81, 24.39, 25.59, 25.64, 25.72, 26.32, 32.81, 35.13, 38.66: d; 71.39, 125.39, 127.77, 127.82, 128.15, 128.25, 128.73, 128.93, 131.41: s; 176.97.
8. a) Falck, J. R.; Lumin, S.; Lee, S. -G.; Heckmann, B.; Mioskowski, C.; Karara, A.; Capdevila, J. *Tetrahedron Lett.*, **1992**, *33*, 4893-4896. b) Heckmann, B.; Mioskowski, C.; Lumin, S.; Falck, J. R.; Wei, S.; Capdevila, J. H. *Tetrahedron Lett.*, **1996**, *37*, 1425-1428.
9. Kusumi, T.; Takahashi. H.; Hashimoto, T.; Kan, Y.; Asakawa, Y. *Chem. Lett.*, **1994**, 1093-1094.

(*Received in Japan* 19 *September* 1996; *revised* 13 *November* 1996; *accepted* 15 *November* 1996)