Journal of Natural Products
Vol. 51, No. 1, pp. 176-179, Jan-Feb 1988

ON THE STEREOCHEMISTRY OF FECAPENTAENE-12

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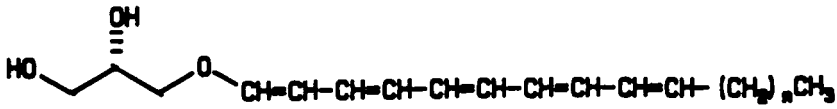
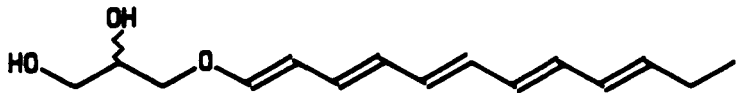
Fecapentaene-12 [**1**] is a potent mutagen that occurs in human feces. It was first detected by Bruce and his coworkers (1), and its structure was elucidated by ourselves (2,3) and Bruce (4,5). Fecapentaene-12 is the major Et_2O-extractable mutagenic component in the feces of some donors, but other donors also produce fecapentaene-14 [**2**] (6). The fecapentaenes as a class may well be implicated in the etiology of human colon cancer, inasmuch as their occurrence can be correlated with populations at risk for colon cancer (7). A knowledge of the stereochemistry of fecapentaene-12 is, thus, important in the synthesis of appropriate compounds for biological testing.

The absolute stereochemistry of fecapentaene-12 was determined as *S* during its initial structural studies (2,3), but the stereochemistry of the unsaturated system has not yet been clarified, although comparisons between synthetic samples and the natural product have shown that the all-*E* isomer is a significant component of the mixture (8–10). We now wish to report the results of a comparison of natural fecapentaene-12 with two different synthetic samples.

Synthetic fecapentaene-12 has been prepared by several methods. In addition to those already cited, which yield, respectively, mixtures of *E* and *Z* isomers at the 5-position [**3**, **4**] (8,9) and



1 n=1
2 n=3



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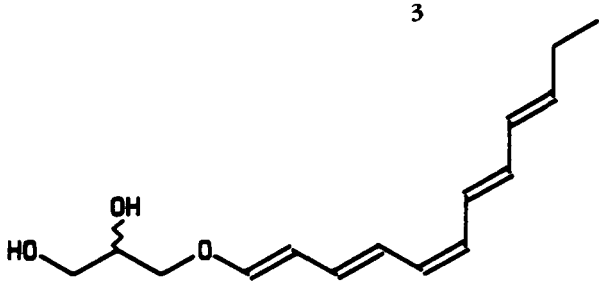

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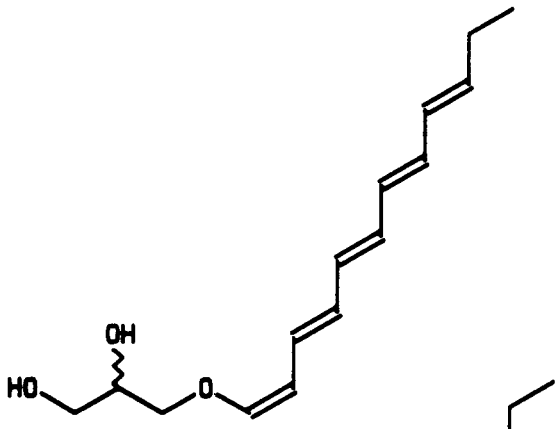
the 1-position [**3**, **5**] (10), it has been prepared as the 1-*Z* isomer [**5**] (11) and the all-*E* isomer [**3**] (11,12). The availability of the isomers **3**, **4**, and **5** enables us to draw the following conclusions about the stereochemistry of natural fecapentaene-12.

In the first place, the natural product consists largely of the *E* isomer at the C-1 position, as indicated by its ^{1}H-nmr spectrum (2,3); however, a careful comparison of the published spectrum (3)[1] with the spectra of the separate, synthetically derived 1-*E* and 1-*Z* isomers **3** and **5** (11) indicates that the natural product contains a small amount (approximately 10%) of a 1-*Z* isomer, probably **5**. Surprisingly, the 1-*Z* isomer **5** and the 1-*E* isomer **3** co-chromatographed in all the hplc systems we tested, and so it was not possible to obtain independent evidence for the presence of **5** in the natural product.

Fecapentaene-12 can be resolved into three peaks by hplc (6), and the mixture of all-*E*- and 5-*Z*-fecapentaene-12 [**3**, **4**] separates cleanly into two peaks. The retention volumes of these peaks are recorded in Table 1. From these data it can be seen that natural fecapentaene-12 consists of isomers that co-chromatograph with the all-*E* and 1-*Z* isomers [**3**, **5**] and the 5-*Z* isomer [**4**]. The mixture contains one more isomer with an intermediate retention volume. This new isomer may well be the 3-*Z* isomer [**6**], because its retention volume is intermediate between those of the 1-*Z* and 5-*Z* isomers.



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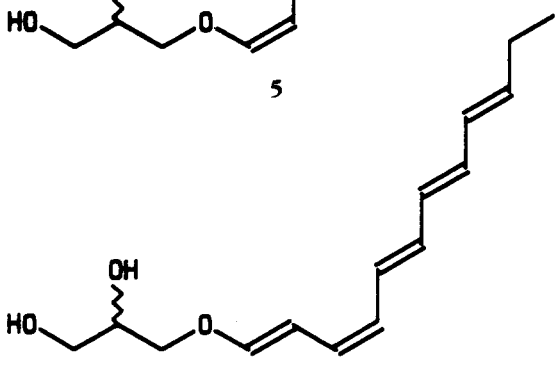

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We recognize that these results are not unambiguous, for many *E*/*Z* isomers of fecapentaene-12 are possible, and the observed coincidences of retention volumes may be accidental. Nevertheless, the most probable explanation of the ^{1}H-nmr and hplc observations is that natural fecapentaene-12 consists of a mixture of the 1-*Z* [**5**], 3-*Z* [**6**], and 5-*Z* [**4**] isomers, together with the all-*E*

[1]The spectrum was obtained in $CDCl_3$ and not in C_6D_6 as stated in Hirai *et al.* (3).

TABLE 1. Retention Volumes of Fecapentaene-12 Isomers.

Isomer		Retention Volume (ml)[a]		
Natural Fecapentaene-12		4.05,	4.22,	4.48
all-*E*	[**3**]			4.48
5-*Z*	[**4**]	4.05		
1-*Z*	[**5**]			4.48

[a]See Experimental section for conditions.

isomer [**3**]. The proportion of each isomer varies from batch to batch, but the one reproduced[2] appears to consist of about 10% 5-*Z* [**4**], 45% 3-*Z* [**6**], and 45% all-*E* and 1-*Z* [**3**+**5**], with compound **5** estimated from ^{1}H nmr to comprise some 20% of the latter mixture.[3]

It is worth noting, finally, that in the last analysis the biological activity of fecapentaene-12 may not be strongly dependent on its stereochemistry. At least in the Ames test, the activity of the natural product is very similar to that of the racemic synthetic mixture [**3**+**5**] (13), and also to that of the all-*E* compound **3** (14). Two synthetic model compounds, one in which a methyl group replaces the glyceryl moiety (15) and one in which the vicinal hydroxyl groups are protected as an acetonide,[4] were also shown to be strong mutagens, albeit at a somewhat reduced level. It, thus, appears that the significant structural feature for biological activity is the presence of a pentaenyl enol ether unit with stereochemical factors playing at most a minor role (13).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Synthetic methods and analytical techniques were as described previously (13). Pure 1-*E* and 1-*Z*-fecapentaene-12 [**3** and **5**] were prepared as previously described (11), and a mixture of 5-*E*- and 5-*Z*-fecapentaene-12 [**3**, **4**] was prepared by the method of Nicolaou *et al.* (9). Hplc analyses were carried out on a Waters' Associates Novapak® C-18 column, 5-μm particle size, in an RCM-100 radial compression module. The solvent system was MeCN-H_2O-MeOH-THF, 36.2:32.0:25.4:6.4 at a flow rate of 1.0 ml/min; detection was by uv absorption at 340 nm. Peak identification was by comparison of the retention volumes of the natural product with those of the synthetic samples described above.

ACKNOWLEDGMENTS

This work was supported by Grant CA 23857 from the National Cancer Institute. We thank Dr. J.J. Krepinsky for communicating the results of his related work to us.

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[2]Figure 1a in Baptista *et al.* (6).

[3]To arrive at these figures it has been assumed that all isomers have nearly identical extinction coefficients at 340 nm.

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Received 22 July 1987