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SYNTHESIS OF RACEMIC FECAPENTAENE-12, A POTENT MUTAGEN FROM HUMAN FECES, AND ITS REGIOISOMER

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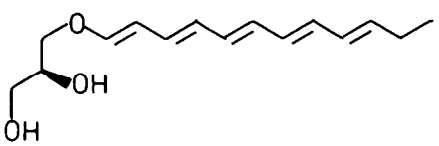
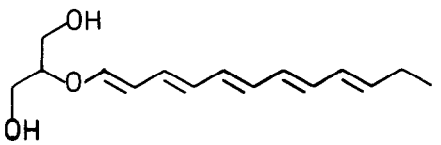
Summary: Racemic fecapentaene-12 [3-(1,3,5,7,9-dodecapentaenyloxy)-1,2-propanediol (1)] and its regioisomer 2-(1,3,5,7,9-dodecapentaenyloxy)-1,3-propanediol (2) have been synthesized. The latter compound is comparably mutagenic to 1.

Recently we elucidated the structure of a potent mutagen produced by colonic bacteria in persons at high risk for colon cancer as the unusual glycerol enol ether 1.[1] Similar conclusions were reached independently by Bruce, who suggested the name fecapentaene for this class of compounds,[2] and we have adopted his nomenclature. In this communication we report the first synthesis of racemic fecapentaene-12 (1) and its regioisomer 2.



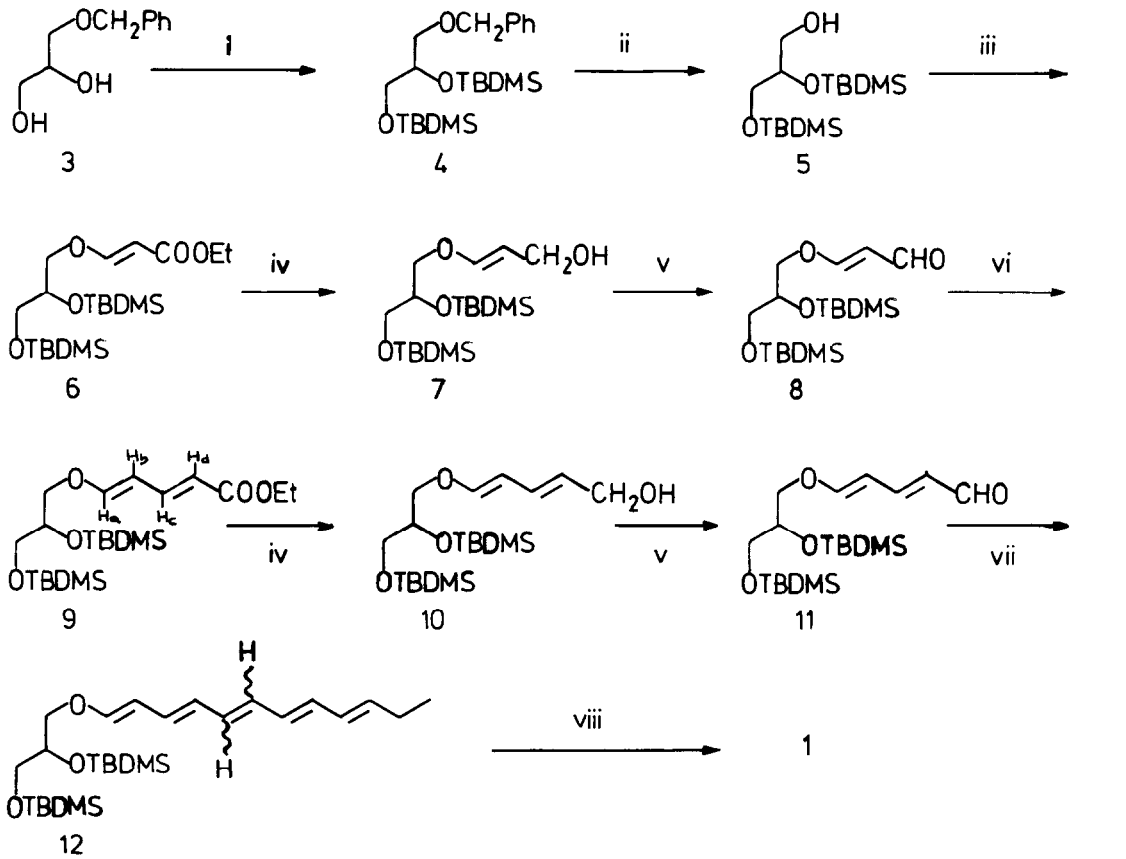
1



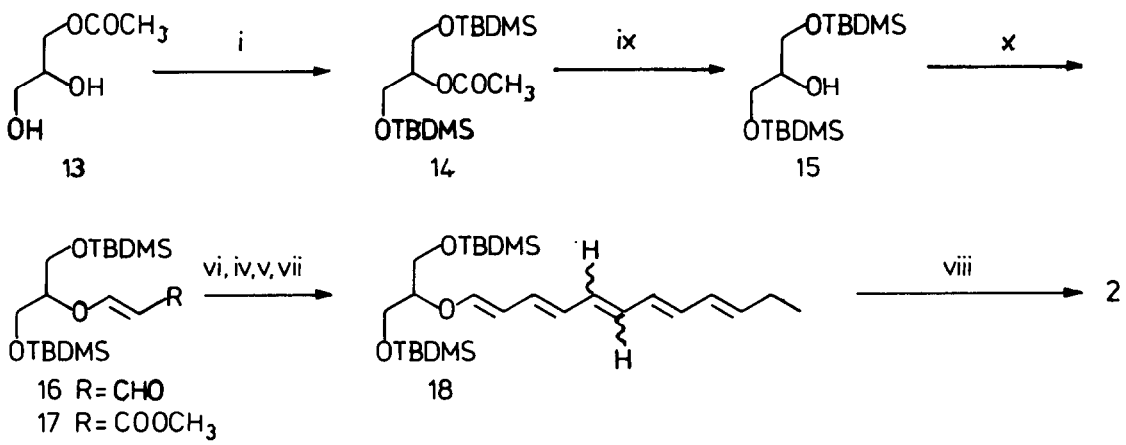
2

Treatment of glycerol monobenzyl ether 3[3] with t-butyldimethylsilyl chloride (TBDMS-Cl) under standard conditions[4] gave a quantitative yield of the corresponding TBDMS ether 4 [b.p. 148-150° (3 mm)].[5] Debenzylation of 4 was effected by hydrogenolysis under mild conditions (Scheme 1) giving the alcohol 5[6] in 98% yield. This reaction was sluggish in the absence of TBDMS-Cl, which presumably is reduced to TBDMS-H and activates the catalyst.[7] This debenzylation procedure is superior to that employing high pressure, which is known to cause silyl migration and desilylation.[8]

The alcohol 5 served as the key intermediate for the construction of the C-12 side-chain (Scheme 1) ; a stepwise approach was selected because of its versatility in the synthesis of less unsaturated analogs of 1. To this end, Michael addition of the alcohol 5 to ethyl propiolate gave the unsaturated ester 6 in 74% yield. The E stereochemistry of the double bond in 6 was apparent from the 12 Hz coupling constants of its olefinic protons. Reduction of the ester 6 with DIBAL-H afforded the corresponding alcohol 7 in quantitative yield. Oxidation of 7 with manganese dioxide gave the unsaturated aldehyde 8 [δ 9.27 (1H, d, J = 9Hz, CHO), 7.23 (1H, d, J = 12 Hz, O-CH=C), 5.53 (1H, dd, J = 12 and 9 Hz, C=CH-CHO), 4.00-3.33 (5H, m, glycerol



SCHEME 1



SCHEME 2

REAGENTS: i) t-Butyldimethylsilyl chloride, imidazole, dry DMF, 30°, 24h; ii) H_2, 5% Pd-carbon, t-butyldimethylsilyl chloride, hexane, 30°, 2h; iii) ethyl propiolate, dry toluene, N-methyl morpholine, 0°C, 1h; iv) DIBAL-H, dry toluene, -78°, 1 h; v) MnO_2, hexane-ether, 80°, 3 h; vi) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, NaH, dry THF, 0°C, 1h; vii) $Br^-Ph_3P^+CH_2(CH=CH)_2CH_2CH_3$, n-BuLi, THF, -78° (30 min) → 30° (30 min); viii) $(n\text{-}Bu)_4NF$, THF, Et_3N, 30°C, 1h; ix) 0.1N NaOH, CH_3OH, 30°, 1h; x) propiolaldehyde, ether, Et_3N, 0° (2h) → 27° (1h).

CH), 0.80 (18 H, s, 2x $SiC(CH_3)_3$), 0.03 and 0.00 (6H each, s, 2x $Si(CH_3)_2$)] in 50% yield. The remainder of the product consisted chiefly of 5, probably arising from 8 due to a Michael attack of hydroxide ion present on the surface of MnO_2. Use of MnO_2 (pH = 8) prepared according to the method of Stork and Tomasz[9] did not circumvent this decomposition which also occurred during the oxidation of 10 to 11.

Wittig-Horner reaction[10] of the aldehyde 8 with the ylide prepared from diethyl carbethoxymethylphosphonate gave the diene ester 9 (44%) with E,E stereochemistry as deduced from its ^1H nmr spectrum [δ 7.20 (1H, dd, J = 15 and 12 Hz, Hc), 6.82 (1H, d, J = 12 Hz, Ha), 5.62 (1H, d, J = 15 Hz, Hd), 5.58 (1H, overlapping dd, J = 12 Hz, Hb), 4.10 (2H, q, J = 7.5 Hz, $CO_2CH_2CH_3$), 4.00-3.33 (5H, m, glycerol CH), 1.10 (3H, t, J = 7.5 Hz, $CO_2CH_2CH_3$), 0.83 (18H, 2x $SiC(CH_3)_3$) and 0.00 (12H, br s, 2x $Si(CH_3)_2$)]. DIBAL-H reduction of the ester 9 afforded the diene alcohol 10 (90%) which on oxidation with MnO_2 gave the diene aldehyde 11 (50% as estimated by ^1H nmr), contaminated with the decomposition product 5. The aldehyde 11 without further purification was subjected to a Wittig reaction with the phosphorane derived from (E,E)-2,4-heptadienyltriphenylphosphonium bromide[11] to yield a mixture of E and Z pentaenes 12. Deprotection of this mixture yielded a mixture of E and Z isomers of racemic fecapentaene-12 (1) which, like the natural product,[1] isomerized on standing to a mixture identical with an authentic sample as judged by TLC, co-HPLC, and UV.[12] Hydrogenation of 12 yielded a saturated derivative identical (TLC) with authentic material.

In connection with other studies we observed that treatment of the readily available monoacetin 13 with TBDMS-Cl under standard conditions yielded the 1,3-derivative 14, after acetyl migration.[13] Hydrolysis of 14 followed by Michael addition of the resulting alcohol 15 to propiolaldehyde afforded 16 with E stereochemistry as indicated by its ^1H nmr spectrum. Conversion of 16 to the pentaene 2 proceeded by the methods previously described (Scheme 2) and yielded a product isomeric with fecapentaene-12. The structure of 2 was confirmed by its ^1H nmr spectrum [$\delta(C_6D_6)$ 6.72 (1H, d, J = 12, -OCH=), 6.25-6.4 and 6.1-6.25 (8H, m, CH=CH), 5.75 (1H, m, OCH=CH), 3.4-3.9 (5H, m, glyceryl CH) 2.08 (2H, dq, J ~ 8Hz, $=CHCH_2CH_3$), 1.00 (3H, t, $-CH_2CH_3$)], and by hydrogenation of its protected derivative 18 to the saturated analog and comparison with an authentic sample (TLC). Compound 2 was found to be as mutagenic in the Ames test as fecapentaene-12.[12]

An interesting observation was made whilst attempting to find optimum conditions for the Michael reaction of alcohol 5 with methyl propiolate. Use of triethylamine in THF at 0°C for 1 hr yielded a mixture of the expected adduct 6 and its isomer 17. Apparently, silyl migration of 5 to give the isomer 15 occurred at a rate faster than Michael addition; presumably relief of steric crowding provides the driving force for this unusual reaction.

The availability of fecapentacene-12 by this route will make it possible for us to explore further its role in the etiology of human colon cancer.

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5. Structural assignments of all new compounds are based on i.r., ^{1}H n.m.r. in $CDCl_3$, and, in most cases, mass spectroscopic evidence.
6. Compounds 5-12 (scheme 1) and 14-17 (scheme 2) are all obtained as nondistillable oils.
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