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SYNTHESIS OF 6-(R)-HYDROXY-7,9-OCTADECADIYNOIC ACID, A HMG-CoA REDUCTASE INHIBITOR

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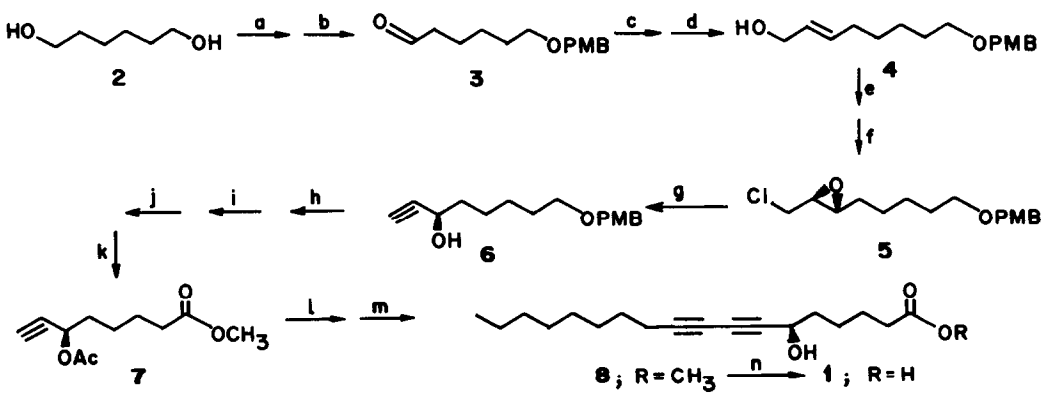
Abstract: We, herein, report the first enantiospecific synthesis of 6-(R)-hydroxy-7,9-octadecadiynoic acid, a HMG-CoA reductase inhibitor.

Considerable evidence exists for correlation between coronary heart disease and elevated levels of plasma cholesterol[1,2], which is largely produced by de novo synthesis[3] in the liver and intestine. The major rate-limiting step in cholesterol biosynthesis is the reduction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate which is catalysed by HMG-CoA reductase[4]. The activity of this enzyme has recently been shown to be inhibited by six novel acetylenic fatty acids isolated from root bark of Paramacrolobium caeruleum, one of which is 6-hydroxy-7,9-octadecadiynoic acid[5]. Its enantiomers have not been isolated. Neither the acid nor its enantiomers have been synthesized. The enantiospecific synthesis of the (R) isomer (1) is reported here for the first time using Sharpless epoxidation and acetylenic coupling as key reactions as shown in the Scheme.

SCHEME



Conditions:) NaH, THF, PMB-Br, 0°C; b) PCC, DCM; c) Ph_3P=CH-$COOC_2H_5$, C_6H_6, reflux, 5 h; d) DIBAL-H (2.2 eq.), DCM, -78°C; e) (-)DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, dry DCM; f) CCl_4, PPh_3, $NaHCO_3$, reflux; g) n-BuLi (3 eq.), THF, -78°C; h) Acetyl-Cl, TEA, dry DCM; i) DDQ, DCM, water; j) Jones oxidation; k) CH_2N_2, ether; l) 1-Bromodec-1-yne, Et_2NH, $(Ph_3P)_2PdCl_2$, CuI, C_6H_6, R.T.; m) K_2CO_3, methanol, R.T., 15 min; and n) KOH, EtOH, H_2O, 1 h.

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Accordingly, 1,6-hexanediol (2) was converted to 6-(p-methoxybenzyloxy)hexan-1-al (3) in two steps in overall 70% yield. 3 was further transformed into E-allylic alcohol (4) via two-carbon homologation using (carbethoxymethylene)triphenylphosphorane followed by DIBAL-H (2.2 eq.) reduction. Catalytic Sharpless asymmetric epoxidation[6] using (-)DIPT furnished the (R,R) epoxyalcohol, which by standard procedure gave epoxychloride (5). 5 on treatment with n-BuLi (3 eq.)[7] at -78° gave substituted (R) propargyl alcohol[8] (6). 6 was transformed to the chiral methyl ester (7) using standard chemical transformations, namely acetylation, PMB-deprotection, Jones oxidation and esterification, in overall 45% yield from 3. 7 on coupling with 1-bromodec-1-yne using Sonogashira's[9] protocol furnished a coupled product, which on deacetylation afforded (8) in overall 54% yield; $[\alpha]_D$ =-3.5° (c = 0.5, $CHCl_3$). 8 on saponification followed by acidification provided[10] 1 in 95% yield. Thus, this approach gives an access to synthesise the (S) isomer of 1 and other similar fatty acids.

References and Notes

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7) Authors are grateful to Dr J.S. Yadav for providing the experimental details for this reaction. See: J.S. Yadav, P.K. Deshpande, G.V.M. Sharma, Tetrahedron (in press) and also S. Takano, K. Samizu, T. Sugihara and K. Ogasawara, J. Chem. Soc., Chem. Commun., **No.18**, 1344 (1989).
8) Ee 93% determined by HPLC and NMR studies of mosher ester of 7.
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10) For 1, IR (in $CHCl_3$), 3500-3000, 2235 and 1709 cm^{-1}; (200 MHz), ^1H NMR 10.0 (br, 1H, $-CO_2\underline{H}$, D_2O exchangeable), 4.35 (t, 1H, C$\underline{H}$-O, J = 7 Hz), 2.2 (m, 4H, C-$\underline{CH_2}$, $\underline{CH_2}$-CO), 1.65-1.2 [m, 18H, -$(\underline{CH_2})_9$-], 0.9 (t, 3H, -$\underline{CH_3}$, J = 7.1 Hz); Mass (m/e) of 8 M^+, 306. These data agree with the reported data[5] of the natural acid. All the other compounds also gave satisfactory IR, NMR and Mass spectra.

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