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SYNTHESIS OF (8Z,14Z)-13,13-DIMETHYLEICOSA-8,14-DIEN-11-YNOIC ACID AS AN INHIBITOR OF PROSTAGLANDIN CYCLOOXYGENASE

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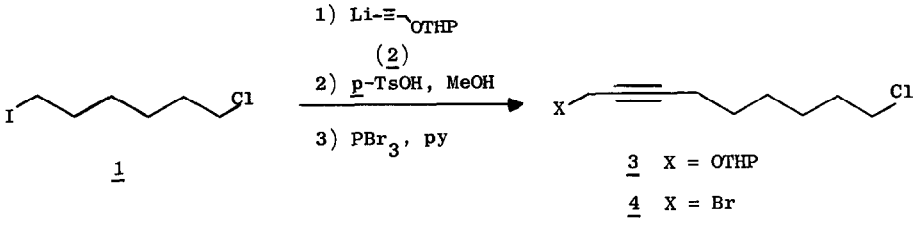
As a continuation of our program to prepare (8Z,11Z,14Z)-8,11,14-eicosatrienoic acid analogs[1] with potential prostaglandin synthetase inhibitory activity, (8Z,14Z)-13,13-dimethyleicosa-8,14-dien-11-ynoic acid (11) was synthesized. This analog, which was envisioned as an inhibitor of prostaglandin cyclooxygenase, was readily prepared in a 3 + 10 step convergent synthesis using the two intermediates 1-bromo-9-chloro-2-nonyne (4) and (4Z)-3,3-dimethyldec-4-en-1-yne (9).

Displacement[2] of iodide from 1-chloro-6-iodohexane[3] by the lithium salt of tetrahydro-2-(prop-2'-ynyloxy)pyran[4] (2) (THF/NH_3, 8 hr) afforded 3 (77% yield).[5] Acid-catalyzed removal of the tetrahydropyranyl protecting group (p-TsOH, MeOH, 5 hr reflux, 88% yield) and PBr_3 treatment[6] (Et_2O, pyridine, 0°, 30 min PBr_3 addition, 3-hr reflux, 65% yield) gave the intermediate 1-bromo-9-chloro-2-nonyne (4).

2,2-Dimethyl-1,3-propanediol was converted to the hydroxy monobenzyl ether 6 (NaH, DMF, ϕCH_2Cl, amb temp, 14 hr,[7] 52% yield), which was oxidized with Collins reagent[8] to the aldehyde (bp 76-78°/0.5 mm, 50% yield). Immediate treatment with hexyltriphenyl phosphorane ($C_6H_{13}\phi_3Br$,[9] NaH, DMSO, 24 hr, room



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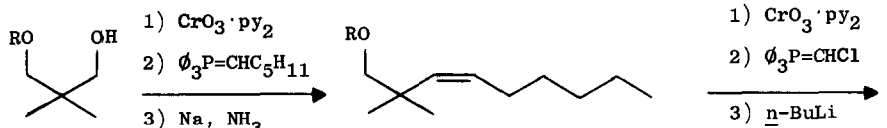
3 X = OTHP

4 X = Br

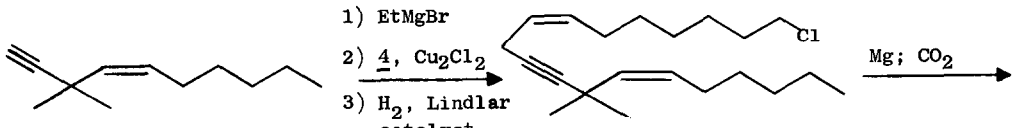


5 R = H

6 R = $CH_2\phi$

7 R = $CH_2\phi$

8 R = H



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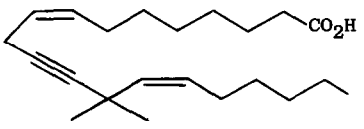

11

temp, 70% yield) afforded the Z-olefin 7, as the major product: bp 141-142°/ 0.9 mm; ir (film) 2930, 2860, 1450, 1100, 760, 740, 700 cm^{-1}; nmr ($CDCl_3$) δ 2.0 (m, $J_{1,3}$ = -1.7, $J_{1,4}$ = -1.7, $J_{2,3}$ = 7.5, $J_{2,4}$ = 7.5, $J_{3,4}$ = 14, 2, H(1)C=CH(2)-CH(3)H(4)), 3.26 (s, 2, $CH_2OCH_2C_6H_5$), 4.54 (s, 2, $CH_2C_6H_5$), 5.47 (m, $J_{1,2}$ = 12, $J_{2,3}$ = 7.5, $J_{2,4}$ = 7.5, 1, H(1)C=CH(2)-CH(3)H(4)), 5.52 (m, $J_{1,2}$ = 12, $J_{1,3}$ = -1.7, $J_{1,4}$ = -1.7, 1, H(1)C=CH(2)-CH(3)H(4)), 7.30 (s, 5, C_6H_5). Debenzylation (Na, Et_2O/NH_3, 40 min) afforded the alcohol 8, (80% yield) which was oxidized with Collins reagent[8] to the aldehyde. Wittig reaction[10] [(chloromethyl)-triphenylphosphonium chloride, (n-BuLi, THF-Et_2O, -78° 3 hr, 65% yield] followed by dehydrochlorination (n-BuLi, Et_2O-hexane, 0° addition, amb. temp. 2.5 hr, 80% yield) afforded the enyne 9: ir (film) 3340 (HC≡C), 2100 (C≡C), 1650 (C=C), 1460, 1240, 730 cm^{-1}; nmr ($CDCl_3$) δ 1.40 (s, 6, $C(CH_3)_2$), 2.17 (s, 1, HC≡C), 5.36 (m, 2, HC=CH). Freshly distilled (100°/15 mm) enyne 9, after conversion to the Grignard reagent (EtMgBr, Et_2O)[11] was coupled to the freshly distilled propargylic bromide 4 (Cu_2Cl_2, Et_2O-THF, 2.5 hr) to afford a 51% yield of (13Z)-1-chloro-12,12-dimethylnonadeca-7,10-diyn-13-ene: ir ($CHCl_3$) 2200 (C≡C), 1310 (C≡CCH_2C≡C); nmr ($CDCl_3$) δ 1.30 (s, 6, $C(CH_3)_2$), 3.10 (t, J - 2, 2, C≡CCH_2C≡C), 3.52 (t, J - 6, 2, CH_2Cl), 5.28 (m, 2, HC=CH).

Selective hydrogenation[11] of the Grignard coupling product (Lindlar catalyst,[12] 80 min; silica gel chromatography with hexane) reduced the less hindered acetylenic bond to give (7Z,13Z)-1-chloro-12,12-dimethylnonadeca-7,13-dien-10-yne (10): 78% yield; ir (film) 1650 (C=C), 1460, 1290, 730 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (s, 6, $C(CH_3)_2$), 2.90 (d, J = 4.5, 2, C=CCH_2C≡C), 3.50 (t, J = 6, 2, CH_2Cl), 5.05-5.6 (2 m, 4, HC=CH). Grignard formation[11] of the chlorodienyne 10, followed by carbonation, produced after chromatography (silica gel, 10% EtOAc in hexane) a 34% yield of the target compound 11. ir (film) 2670, 1710, 1650, 1430, 1370, 930 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (s, 6, $(CH_3)_2$), 2.34 (m, 2, CH_2CO_2), 2.90 (d, J = 6, 2, C=CCH_2C=C), 5.2-5.8 (m, 4, HC=CH), 10.0 (s, 1, CO_2H); $n_D^{27°}$ 1.4772; VPC (3% OV-1, 1/8" x 6' column, 270°) of methyl ester, one peak (rt = 4.3 min).

Biochemical studies with this 13,13-dimethyl analog showed that the absence of the L-hydrogen at C-13, which is normally lost during bioconversion of eicosatrienoic acid by either purified prostaglandin cyclooxygenase or soybean lipoxygenase, prevented oxidation by either enzyme but still allowed normal competitive binding (K_I ~8 μM) to the active site. This K_I value is comparable to those reported for other long-chain poly-unsaturated acids (2-15 μM).[13] The reversible, competitive nature of the inhibition by this analog appears to be due to simple acyl chain adsorption to the active site; no irreversible inactivation occurred as seen for some other substrate analogs.[14]

Acknowledgements

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