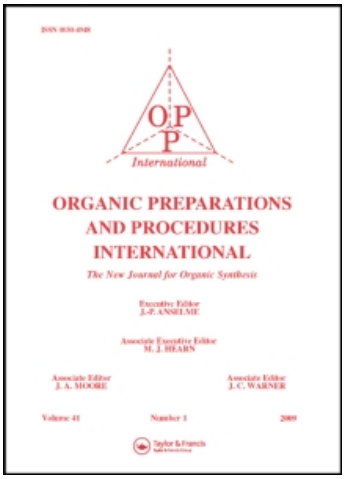

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A FACILE PREPARATION OF 2(Z), 5(Z), 8(Z)-TETRADECATRIEN-1-OL, A KEY INTERMEDIATE FOR EICOSANOID SYNTHESIS

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A FACILE PREPARATION OF 2(Z), 5(Z), 8(Z)-TETRADECATRIEN -1-OL, A KEY INTERMEDIATE FOR EICOSANOID SYNTHESIS

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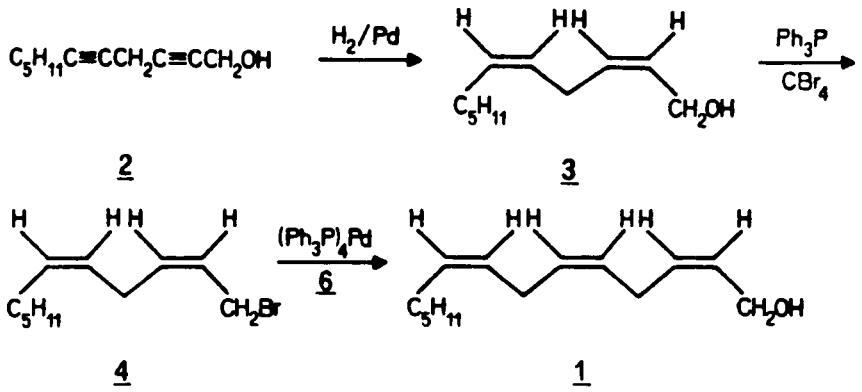
Eicosanoids are a class of arachidonic acid metabolites, some of which are involved in biological processes as mediators in inflammation and regulators of immune response.[1] Their wide-ranging biological activity and low availability from natural sources have stimulated many efforts to develop synthetic strategies for their construction.[2] This communication reports an efficient preparation of 2(Z), 5(Z), 8(Z)-tetradecatrien-1-ol 1, a key intermediate for eicosanoid synthesis.[3]

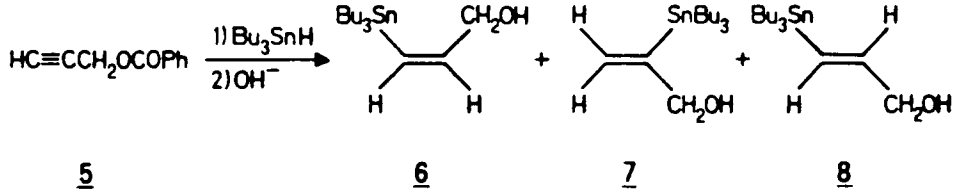
According to the strategy envisioned, compound 1 was obtained by a palladium-mediated coupling of 2(Z), 5(Z)-undecadienyl bromide (4) and 2(Z)-3-tributylstannyl-propen-1-ol (6), which proceeds with stereoretention both in the vinyltin partner and in the allyl halide.[4] To date, the reported syntheses of 1 have utilized the catalytic reduction of the corresponding triynes[3,5] which are known[5] to be very unstable towards oxidizing agents and quite difficult to purify and store. The stability of the intermediates in our method provides several advantages.



Mild hydrogenation of 2,5-undecadiyn-1-ol (2) [prepared in 90% yield[6] from 1-heptyne

and 4-chloro-2-butyn-1-ol] over Lindlar's catalyst gave 2(Z),5(Z)-undecadien-1-ol (3) in 85% yield[7] after purification by flash column chromatography. The all cis stereochemistry was assigned by the value of the coupling constant (10.8 Hz) of the vinyl protons in the ^{1}H NMR spectrum of 3; the spectrum was recorded in the presence of Eu(fod)$_3$ which permits a separation of the very complex vinyl resonances. The dienol 3 was converted to the bromide 4 with carbon tetrabromide and triphenylphosphine. Palladium mediated alkylation of 2(Z)-3-tributylstannyl-propenol 6 [contaminated by 12.5% of 2-tributylstannyl-2-propen-1-ol (7)][4,8] with 4 yielded compound 1 in 64% yield as a single isomer after purification by flash column chromatography as demonstrated by capillary gas-chromatographic analysis.

Attempts were made to improve the regio- and stereoselectivity of the hydrostannation of 2-propyn-1-ol: 2-propyn-1-ol benzoate 5, after reaction with tributyltin hydride followed by alkaline hydrolysis, afforded a mixture of 6, 7 and 8 in the ratio 7:1:3.5 (by ^{1}H NMR spectrum of the crude reaction mixture) thus improving the regioselectivity of the reaction with respect to already reported data (4:1:1.4);[8] the use of esters, such as acetate, failed to provide better results. While the (E)-isomer 8 could be isolated in pure form, preparative chromatographic systems did not allow the separation of compounds 6 and 7; therefore the mixture was used for the subsequent reaction.



5 6 7 8

EXPERIMENTAL SECTION

IR spectra were recorded on a Perkin Elmer 457 spectrophotometer. ^{1}H NMR spectra were measured in deuterochloroform with a Varian XL-200 (200MHz). Chemical shifts are reported in ppm (δ) from internal TMS. Microanalyses were carried out in the microanalytical laboratory of our Department using a Perkin Elmer 240 instrument. Boiling points refer to bulb-to-bulb distillation using a Buchi GKR-50 apparatus. Analytical gas-liquid chromatography was performed with an OV-1 capillary column by using a Dani 3900 instrument with flame ionization detector.

2(Z),5(Z)-Undecadien-1-ol (3).- Diyne 2 (10.0 g, 0.061 mol) was dissolved in n-hexane (100 ml) and quinoline (10 ml) and hydrogenated over Lindlar's catalyst (0.8 g) with 1 atm hydrogen at room temperature. After the uptake of the theoretical amount of hydrogen (1 hr), the mixture was diluted with diethyl ether (50 ml), filtered through florisil and the filtrate washed with a cold aqueous 3N HCl solution solution (3 x 50 ml) and then with a saturated aqueous $NaHCO_3$ solution (100 ml). The organic layer was dried over Na_2SO_4 and the solvents evaporated. Flash column chromatography (silica gel, light petroleum/ethyl acetate 8:2) provided 3 (8.7 g, 85%), bp. 95°/0.6 mmHg; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.68-5.12 (m, 4H), 4.22 (d, 2H, ^{3}J = 6.0 Hz), 2.80 (bt, 2H, ^{3}J = 6.0 Hz), 2.10-1.94 (m, 2H), 1.46-1.12 (m, 6H), 0.88 (t, 3H, ^{3}J = 7.0 Hz); IR ($CHCl_3$): 3320 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.57; H, 11.90. Found: C, 78.50; H, 11.86

2(Z),5(Z)-Undecadienyl Bromide (4).- To a solution of compound 3 (7.5 g, 0.045 mol) in anhydrous diethyl ether (120 ml), were added carbon tetrabromide (29.6 g, 0.089 mol) and triphenylphosphine (23.4 g, 0.089 mol) at 0°. The mixture was stirred 4 hrs at room temperature. The solvent was evaporated in vacuo, the residue taken up with n-pentane (100 ml) and filtered; the precipitate was exhaustively washed with n-pentane and the combined organic layers were concentrated in vacuo and applied to a silica gel column. By eluting with n-pentane, pure 4 (9.9 g, 95%) was obtained, bp. 80°/0.4 mmHg; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.80-5.30 (m, 4H), 4.03 (d, 2H, ^{3}J = 6.5 Hz), 2.90 (bt, 2H, ^{3}J = 6.0 Hz), 2.20-1.90 (m, 2H), 1.50-1.10 (m, 6H), 0.90 (t, 3H, ^{3}J = 7.0 Hz).

Anal. Calcd for $C_{11}H_{19}Br$: C, 57.14; H, 8.23, Found: C, 57.18; H, 8.20

2(Z),5(Z),8(Z)-Tetradecatrien-1-ol (1).- A mixture of compound 5 (20.0 g, 0.125 mol), tributyltin hydride (16.8 ml, 0.063 mol), azo-bis-isobutyronitrile (1.0 g, 0.006 mol) was stirred, under an argon atmosphere, for 2 hrs at 65°. After cooling to room temperature, methanol (100 ml) and a 10% methanolic KOH solution (100 ml) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo, the residue was taken up with water (100 ml) and extracted with diethyl ether (3 x 50 ml). After drying over Na_2SO_4 and evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, light petroleum/ethyl acetate 9:1). While compound 8 (5.8 g, 26.5%) was obtained in a pure form, the mixture of compounds 6 and 7 (14.2 g, 65%) could not be separated, the ratio of 6 to 7 was 7:1.

To a solution of 4 (9.0 g, 0.039 mol) and the mixture of 6 and 7 (13.5 g, 0.039 mol) in anhydrous chloroform (20 ml), was added tetrakis(triphenylphosphine)palladium(0) (0.45 g, 0.39 mmol). The reaction mixture was heated at 65° in a sealed vessel for 48 hrs. After cooling to room temperature, the solvent was evaporated and the residue purified by flash column chromatography on silica gel. By eluting with light petroleum/ethyl acetate (8:2), pure 1 (5.2 g, 64%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.70-5.27 (m, 6H), 4.18 (d, 2H, ^{3}J = 5.6 Hz), 2.85-2.65 (m, 4H), 2.08-1.92 (m, 2H), 1.42-1.19 (m, 6H), 0.88 (t, 3H, ^{3}J = 6.5 Hz); IR ($CHCl_3$): 3350 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.77; H, 11.54, Found: C, 80.72; H, 11.50

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