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NEW MASKED BUILDING BLOCK FOR ISOPRENOID POLYENE CHAIN SYNTHESIS

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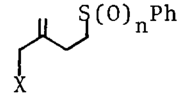
Summary: The new building blocks 2, 3, and 4 have been effectively synthesized starting from 2-hydroxymethyl-4-phenylthio-1-butene (1a). A convenient synthesis of retinoic acid methyl ester (9) using 2 is also described.

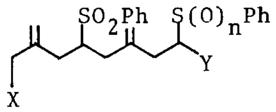
The isoprenoid conjugated polyenes are important key intermediates for the construction of the skeletons of natural carotenoids,1) and various synthetic methods have been developed against this system.1,2) Previously we have reported the convenient synthetic method for 2-hydroxymethyl-4-phenylthio-1-butene (1a) and its application to terpenoid synthesis.3) In this communication we wish to describe the synthesis of novel building blocks 2-4 leading to isoprenoid conjugated polyenes starting from 1a and synthetic application to retinoic acid

C_5 Unit



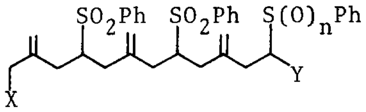
1a X=OH, n=0
b X=OH, n=2
c X=OTHP,n=2
d X=Cl, n=0

C_{10} Unit



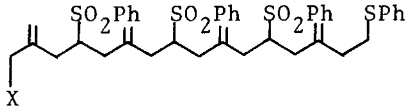
2a X=OTHP,n=0,Y=H
b X=OTHP,n=2,Y=H
c X=OH, n=0,Y=H
d X=OH, n=2,Y=H
e X=OAc, n=1,Y=H
f X=OAc, n=0,Y=OAc
g X=OBz, n=0,Y=H
h X=OBz, n=0,Y=OAc
i X=Cl, n=0,Y=H

C_{15} Unit



3a X=OTHP,n=0,Y=H
b X=OTHP,n=2,Y=H
c X=OH, n=0,Y=H
d X=OAc, n=1,Y=H
e X=OAc, n=0,Y=OAc

C_{20} Unit



4a X=OTHP
b X=OH

methyl ester (9) whose biological activity against human being (acne, untiulcer etc.) now receives much attention.[4)] It is noteworthy that these blocks 2-4 are tolerant under various reaction conditions, accordingly easy to manipulate, and that labile conjugated polyenes are completely protected until the final step of the synthesis.

The C_{10} building block 2a was smoothly constructed by alkylation of the sulfone 1c with the chloride 1d. A solution of the sulfone 1c (16.8 mmol) and HMPA (18.5 mmol) in THF (40 ml) was treated with n-BuLi (18.5 mmol) at -78 °C and the resulting wine red solution was stirred for 30 min at this temperature. Then the chloride 1d (18.5 mmol) in THF (5 ml) was added dropwise and stirring was continued for 1 h. After usual work-up, the product was isolated by column chromatography on silica gel to afford the C_{10} unit 2a (14.2 mmol, 84.5 % based on 1c): NMR (CCl_4) δ 1.20-1.80 (m, 6H, CH_2), 2.00-2.60 (m, 6H, $CH_2C{=}C$), 2.84 (t, 2H, CH_2S, J = 7 Hz), 3.10-4.00 (m, 5H, CH_2O and $CHSO_2$), 4.35 (m, 1H, OCHO), 4.76 (s, 3H, $C{=}CH_2$), 4.91 (s, 1H, $C{=}CH_2$), 7.11 (m, 5H, SPh), 7.30-7.85 (m, 5H, SO_2Ph).

The C_{15} building block 3a was synthesized by alkylation of the dianion of 2b with 1d. The diglyme solution of 2b containing HMPA (2 eq) was treated with n-BuLi (3 eq) at -78 °C for 1 h and with 1d for 3 h at -50∼-30 °C to furnish 3a (49 % based on 2b): NMR (CCl_4) δ 1.20-1.90 (m, 6H, CH_2), 1.90-2.55 (m, 10H, $CH_2C{=}C$), 2.75 (t, 2H, CH_2S, J = 7 Hz), 3.26-4.00 (m, 6H, CH_2O and $CHSO_2$), 4.40 (m, 1H, OCHO), 4.70-5.00 (m, 6H, $C{=}CH_2$), 7.20 (m, 5H, SPh), 7.35-8.00 (m, 10H, SO_2Ph).

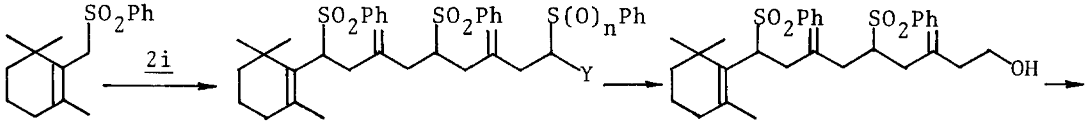
The C_{20} building block 4a was provided by alkylation of the trianion of 3b with 1d in the same manner (30 % yield based on 3b): NMR (CCl_4) δ 1.20-1.85 (m, 6H, CH_2), 1.85-2.60 (m, 14H, $CH_2C{=}C$), 2.78 (t, 2H, CH_2S, J = 7 Hz), 3.20-4.00 (m, 7H, CH_2O and $CHSO_2$), 4.40 (m, 1H, OCHO), 4.70-5.00 (m, 8H, $C{=}CH_2$), 7.20 (m, 5H, SPh), 7.30-8.00 (m, 15H, SO_2Ph).

The sulfone 2d was obtained from the alcohol 2c by SeO_2-H_2O_2-MeOH oxidation.[5)] To a solution of 2c (12 mmol) in MeOH (20 ml) was added a mixture of SeO_2 (24 mmol) and H_2O_2 (30 mmol) dropwise at 0 °C and the mixture was stirred for 1 h at room temperature, then poured into cold Na_2SO_3 solution. Extraction with ethylacetate and concentration of the solvent gave the crude oil of 2d which was chromatographed on silica gel (10.7 mmol, 89 %). Diacetate 2f was conveniently prepared from 2c according to the following sequence of reactions. Acetylation (Ac_2O-Py), oxidation (H_2O_2-MeOH), and the Pummerer reaction of the resulting sulfoxide (Ac_2O-cat. $(CF_3CO)_2O$, r. t., 40 h)[6)] gave 2f in 70 % yield based on 2c. The chloride 2i was obtained by treatment of 2c with LiCl-CH_3SO_2Cl-γ-collidine in DMF.[3)]

The derivatives of 3a were provided in the same manner as described above.

Utilization of the block 2i was demonstrated by the synthesis of retinoic acid methyl ester. Our synthetic route is shown in the following scheme. Alkylation of the sulfone 5[7)] (containing 20 % of homoallyl isomer) (30 mmol) with the C_{10} block 2i (24 mmol) (diglyme, HMPA, n-BuLi, -78 °C, 2 h) gave the C_{20}

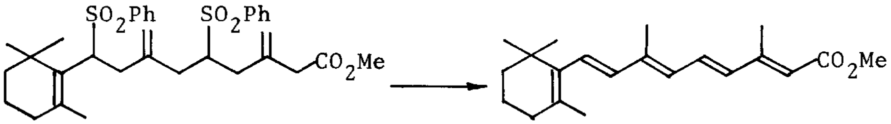
skeleton 6a in 80 % yield (homoallyl sulfone was recovered intact). Oxidation of the sulfide 6a to the sulfoxide 6b was carried out using H_2O_2 (5 eq)-MeOH at room temperature. Pure 6b was isolated by column chromatography (silica gel, hexane-EtOAc 1:1). The Pummerer reaction of 6b (4.7 mmol) was carried out employing Ac_2O-cat.$(CF_3CO)_2O$[6] (40 ml:0.4 ml) at room temperature for 48 h to give the acetate 6c[8] which was reduced by excess amount of $NaBH_4$(EtOH) at room temperature for 12 h to provide the alcohol 7 in 71 % yield based on 6b (silica gel, hexane-EtOAc 1:1). Oxidation of 7 with the Jones reagent (CrO_3-H_2SO_4) in acetone at 0 °C for 30 min followed by esterification (CH_2N_2) gave the ester 8 in 68 % yield (silica gel, hexane-EtOAc 5:1). Desulfonylation of 8 by NaOMe-MeOH (reflux 7 h) occurred smoothly to give the crude retinoic acid methyl ester. The methyl ester thus obtained was passed through a short column chromatogrphy (silica gel, hexane-ether 100:1) to give 9[9] as a mixture of 13-E and 13-Z isomers (ca. 6:4) in 78 % yield, which was confirmed by careful comparison of the NMR spectrum with those reported.[10] In addition, two spots were observed on TLC (silica gel, hexane-EtOAc 25:1, R_f = 0.45 and 0.40). To sustain the above observation, we alternatively synthesized a mixture of 13-E and 13-Z isomers (6:4) from all trans retinoic acid methyl ester (NaOMe-MeOH, reflux, 8.5 h). Identity of the NMR spectrum and homogeneity on TLC of 9 with that of an authentic specimen were fully confirmed.



5

6a n=0, Y=H
b n=1, Y=H
c n=0, Y=OAc

7



8

9

R specrta δ (CCl_4)

a 0.79 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.34-1.70 (m, 4H, CH_2), 2.00 (s, 3H, CH_3), 1.90-2.50 (m, 10H, $CH_2C{=}C$), 2.86 (t, 2H, CH_2S, J = 7 Hz), 3.25 (m, 1H, $CHSO_2$), 3.90 (t, 1H, $CHSO_2$, J = 7 Hz), 4.65-4.80 (bs, 4H, $C{=}CH_2$), 7.20 (m, 5H, SPh), 7.40-8.00 (m, 5H, SO_2Ph).

c 0.75 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.25-1.70 (m, 4H, CH_2), 2.00 (s, 6H, $COCH_3$ and CH_3), 1.90-2.95 (m, 10H, $CH_2C{=}C$), 3.25 (m, 1H, $CHSO_2$), 3.85 (t, 1H, $CHSO_2$, J = 7 Hz), 4.60-4.95 (m, 4H, $C{=}CH_2$), 6.00 (t, 1H, CHO, J = 7 Hz), 7.35 (m, 5H, SPh), 7.45-8.00 (m, 5H, SO_2Ph).

7 0.71 (s, 3H, CH_3), 0.78 (s, 6H, CH_3), 0.83 (s, 3H, CH_3), 1.20-1.60 (m, 4H, CH_2), 1.92 (s, 3H, CH_3), 1.85-2.70 (m, 10H, $CH_2C{=}C$), 3.10-4.00 (m, 4H, $CHSO_2$ and CH_2O), 4.60-4.90 (m, 4H, $C{=}CH_2$), 7.30-7.90 (m, 10H, SO_2Ph).

3 0.70 (s, 3H, CH_3), 0.78 (s, 6H, CH_3), 0.90 (s, 3H, CH_3), 1.25-1.70 (m, 4H, CH_2), 1.92 (s, 3H, CH_3), 1.85-2.50 (m, 8H, $CH_2C{=}C$), 2.87 (s, 2H, CH_2CO), 3.20 (m, 1H, $CHSO_2$), 3.52 (s, 3H, OCH_3), 3.72 (t, 1H, $CHSO_2$, J = 7 Hz), 4.60-4.94 (m, 4H, $C{=}CH_2$), 7.35-7.94 (m, 10H, SO_2Ph).

ferences and Notes

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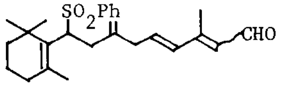
Hydrolysis of the acetate 6c under various conditions (1N NaOH-dioxane, 1N Na_2CO_3-MeOH, 1N K_2CO_3-MeOH) gave the following aldehyde in poor yield.



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