The Synthesis of Methyl Vitamin A

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Synthesis of methyl vitamin A from β -irone is described.

In a previous paper¹⁾ we described a novel synthetic procedure of dienones and the synthesis of irone and ionone by this procedure. If β -irone is used as a starting material, methyl vitamin A will be obtained by the same procedure as vitamin A synthesis,²⁾ and the synthesis of dimethyl β -carotene can also be achieved. We are much interested in the biological properties of these two compounds as homologues of vitamin A and β -carotene.

In this paper we wish to report the synthesis of methyl vitamin A by the route shown in Fig. 1.

by crystallization from the reaction mixture could not be achieved in spite of several trials, probably because of the difficulty to remove minor products. So the synthesis was carried out by employing the procedure described by Pommer *et al.*,³⁾ which is the shortest way to reach the final product though the stereoselectivity is sacrificed. The grignard reaction of β -irone (I) with vinyl magnesium chloride afforded an allyl alcohol (II) which was converted to a triphenyl phosphonium salt (III) by treating with triphenyl-phosphine hydrochloride. Without isolation of the salt (III),

FIG. 1.

The stereoselective method, *i.e.* Matsui's procedure^{2a)} seemed to be applicable to this synthesis of methyl vitamin A. However, in this case purification of ironylideneacetic acid

the Wittig reaction with *n*-butyl β -formyl-*trans*-crotonate in the presence of sodium ethoxide afforded a crude ester (IVa), which was immediately saponified with methanolic potassium hydroxide to give methyl vitamin A acid. Pure all-*trans*-methyl vitamin A acid (IVb) was obtained as yellow crystals in 19%

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yield from β -irone by silica gel chromatography, which was then converted to its methyl ester (IVc) with diazomethane. The ester (IVc) was reduced with lithium aluminum hydride in anhydrous ether at -30°C to give methyl vitamin A (V). The structures of these novel compounds were supported by their physical properties. The physiological activity of methyl vitamin A, *i.e.*, vitamin A effect on rat *etc.*, is now under investigation and the result will be reported elsewhere.

EXPERIMENTAL

Mps were uncorrected. The NMR spectra were recorded with spectrometers JNM-XL-60 and Varian HA-100. The IR spectra were taken with spectrometers, Hitachi EPI-G-22 and JASCO IR-A1. The UV spectrum was recorded with a spectrometer Cary-14.

Vinyl ironol (II). To a solution of vinyl magnesium chloride, prepared from Mg (0.95g, 0.04 g atom) and vinyl chloride in THF (100 ml) by the procedure of Suga *et al.*,⁴⁾ β -irone (3.8 g, 0.018 mole) in THF (10 ml) was added dropwise at 40°C in a period of 20 min. After the addition was complete, the mixture was stirred for additional 3 hr at room temperature, poured into aqueous NH_4Cl solution and extracted with ether. The extract was washed with water and dried over Na_2SO_4 . The solvent was removed *in vacuo* and the resulting oil was distilled under reduced pressure to give vinyl ironol (II, 3.9 g, 90.4%). Bp $99\sim 100^{\circ}\text{C}$ (0.25 mmHg), $n_D^{26}=1.5057$, IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3380 ($-\text{OH}$), 980 and 920 ($\text{CH}_2=\text{CH}-$), NMR $\delta_{\text{TMS}}^{\text{CCl}_4}$ ppm: 0.84 and 1.00 ($2\times 3\text{H}$, each singlet, *gem*-dimethyl), 0.80~0.90 (3H , doublet, $\text{CH}_3-\text{CH}-$), 1.38 (3H , singlet, $\text{CH}_3-\text{C}-$), OH 1.64 (3H , singlet, $\text{CH}_3-\text{C}=\text{C}-$), 1.00~2.00 (5H, broad, methylene and methine protons), 4.80~6.20 (5H, multiplet, vinyl protons). *Anal.* Found: C, 81.80; H, 11.20. *Calcd.* for $\text{C}_{16}\text{H}_{26}\text{O}$; C, 81.99; H, 11.18.

Methyl vitamin A acid (IVb). A mixture of vinyl ironol (2.3 g, 0.01 mole) and triphenylphosphine hydrochloride (3.5 g, 0.012 mole) in absolute ethanol (25 ml) was stirred at $20\sim 25^{\circ}\text{C}$ under a nitrogen atmosphere for 3 hr to prepare ironylidene-ethyl triphenyl phosphonium chloride. To this stirred solution, sodium ethoxide prepared from Na (0.45 g, 0.020 g atom) and absolute ethanol (5 ml), and *n*-butyl β -formylcrotonate (1.7 g, 0.010 mole) in ethanol (10 ml) were added dropwise simultaneously at $-30\sim -40^{\circ}\text{C}$ in a period of 15 min. After the addition was complete,

the mixture was stirred at -10°C for 30 min and at 20°C for additional 2 hr, poured into dilute HCl solution and then extracted with hexane. The solvent was removed *in vacuo* and the residual oil (4.8 g) was immediately saponified by refluxing with potassium hydroxide (1 g) in methanol (16 ml) and water (4 ml) for 2 hr. Water was added to the reaction mixture and the neutral fraction was removed by extraction with hexane. The aqueous layer was acidified with dilute HCl solution and extracted with ether repeatedly. The extract was washed with water and dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residual oil (4.3 g) was separated by silica gel chromatography to give a mixture of vitamin A acid (0.9 g, 29.0%), from which all-*trans* vitamin A acid was obtained as a yellow crystalline product (600 mg, 19.4%) by repeated recrystallization from hexane-ethanol.

mp 144°C IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3200~2300 ($-\text{C}-\text{OH}$), 1680 $\text{C}=\text{O}$ ($-\text{C}-$), 1595, 1560 (conjugated polyene), UV $\epsilon_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 341 (39600). NMR $\delta_{\text{TMS}}^{\text{CHCl}_3}$ ppm: 0.88 and 1.03 ($3\text{H}\times 2$, singlet, *gem*-dimethyl), 0.91 (3H , doublet, $J=7\text{Hz}$, CH_3CH) 1.30~1.70 (5H, broad, methylene and methine protons), 1.71 (3H , singlet, allylic methyl in cyclohexene ring), 2.02 (3H , singlet, C_7 -methyl) 2.37 (3H , singlet, C_3 -methyl) 5.77 (1H, singlet, C_2 -vinyl proton) 5.40~5.90 (4H, multiplet, C_4 , C_6 , C_8 , C_9 -H) 6.96 (1H, doublet, C_4 -H, $J_{\text{C}_4-\text{C}_3}=15\text{Hz}$, $J_{\text{C}_4-\text{C}_6}=11\text{Hz}$) 11.6 (1H, broad, $-\text{OH}$). *Anal.* Found: C, 79.95; H, 9.39. *Calcd.* for $\text{C}_{21}\text{H}_{30}\text{O}_2$; C, 80.21; H, 9.62.

Methyl vitamin A (V). To an ethereal solution (100 ml) of methyl vitamin A acid (2.1 g, 0.007 mole), diazomethane (1.0 g, 0.024 mole) in absolute ether (55 ml) was added dropwise at 0°C . After the addition was complete, the mixture was stirred for additional 1 hr under nitrogen at 0°C . Unreacted diazomethane was decomposed by excess 50% acetic acid. The ether solution was washed with aqueous sodium bicarbonate solution and water and dried over Na_2SO_4 . The solvent was removed *in vacuo*. To the resulting oil (2.1 g) in absolute ether (80 ml), LiAlH_4 (270 mg, 0.007 mole) in ether (11 ml) was added dropwise at -50°C . After the reaction mixture was stirred for 2 hr at -50°C , methyl acetate was added. The mixture was poured into aqueous 0.5 N H_2SO_4 solution and crushed ice, and extracted with ether. The extract was washed with aqueous sodium bicarbonate solution and water and dried over Na_2SO_4 . Solvent was removed *in vacuo* and the resulting oil was separated by silica gel chromatography. All-*trans* methyl vitamin A was obtained as a yellowish oily product (570 mg, 28.3%). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3340 ($-\text{OH}$), NMR $\delta_{\text{TMS}}^{\text{CCl}_4}$ ppm: 0.88 and 1.02 ($2\times 3\text{H}$, each singlet, *gem*-dimethyl), 0.90 (3H , doublet, $J=8\text{Hz}$, $\text{CH}_3-\text{CH}-\text{C}-$), 1.68, 1.84 and 1.95 ($3\times 3\text{H}$,

each singlet, $\text{CH}_3-\overset{\text{I}}{\text{C}}=\text{C}\langle$, 5.80~6.60 (6H, multiplet, C₂, C₄, C₅, C₆, C₈, C₉, -H).

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