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An Efficient Synthetic Route to Vitamin-A and its Derivatives

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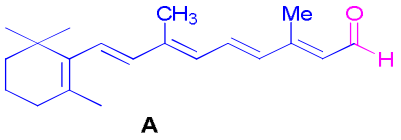
ABSTRACT

Novel and efficient method for the preparation of Retinal (vitamin A) and its derivatives from the readily available starting materials. All the newly synthesized molecules are characterized by their spectral and analytical data.

Graphical Abstract

AN EFFICIENT SYNTHETIC ROUTE TO VITAMIN-A AND ITS DERIVATIVES Sushanta Maiti, D.Rambabu, ASG Prasad, G.Venkata Rao and M V.Basaveswara Rao *	 **A** Retinal (Vitamin-A aldehyde) Efficient synthesis of Retinal (Vitamin A) and its derivatives

Keywords: Retinoids, Retinal (Vitamin A).

INTRODUCTION

Retinoids are involved in many biological processes - photoreception; human and animal reproduction; development of tissues and organs during embryogenesis; regulation of cellular proliferation and differentiation. The key for this great diversity of biological functions is the existence of multiple specific binding proteins and nuclear receptors for Vitamin A metabolites[1]. Retinal (vitamin A aldehyde; **A**, Figure**1**) is an important metabolite of retinol (vitamin A; **B**) and is essential as the mammalian visual pigment chromophore[2]. It may also play a role in adipogenesis in mammals[3]. Furthermore, **A** is the immediate metabolic precursor of retinoic acid (**C**), the principal active form of the vitamin in controlling epithelial cell differentiation [4]. Retinal analogs

shows cancer chemo preventive, chemo-therapeutic activity, and reduced toxicity[5]. The role of vitamin A and its metabolites in the life processes starting with the historical background discussed in the recent review[6]. The important role in retinoid homeostasis and the importance of these molecules in a variety of physiological processes.

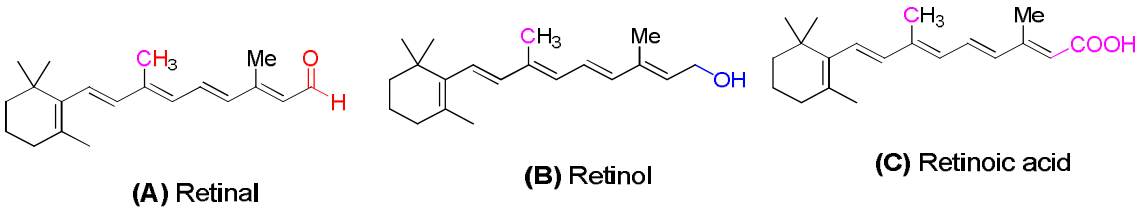
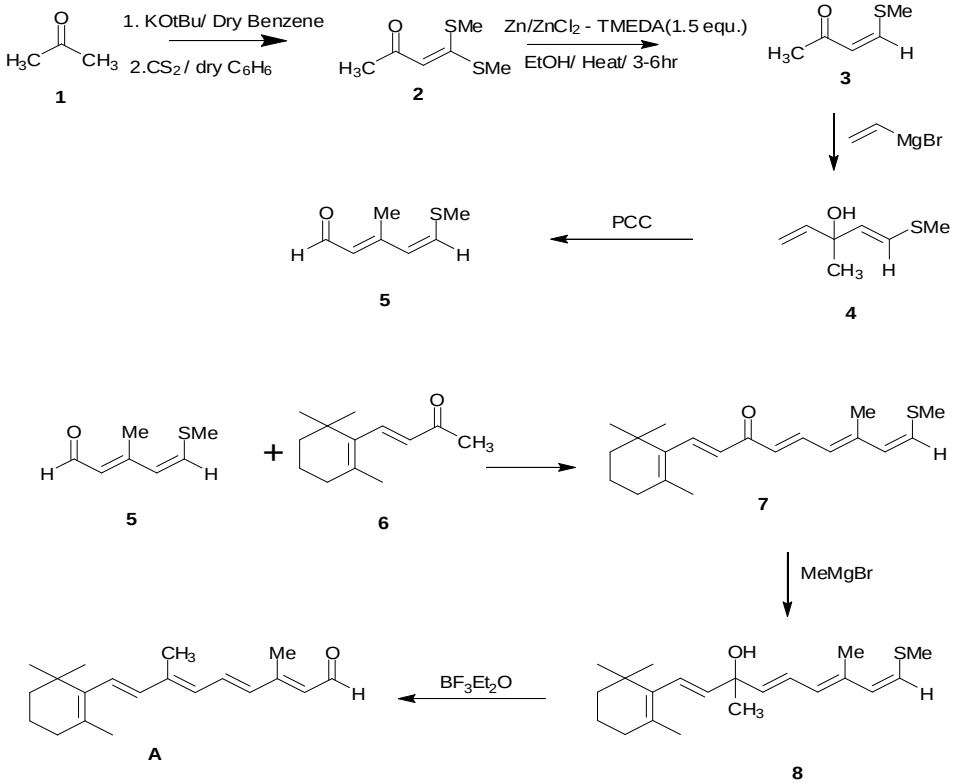


Figure 1. Retinal (A) and related compounds

Retinal analogues, containing coumarin or polycyclic aromatic fluorophores, were synthesized and their recombination with bacterioopsin was tested[7]. These compounds are members of the bacterial rhodopsins family[8] and may be applied in the search for molecular electronic devices[9]. Some of the retinoids and their analogues have been prepared by metal catalyzed cross coupling reactions[10]. Creemers et al., reported ^{13}C-Labeled retinal via a modular total organic synthetic Strategy[11]. In this present communication we reported synthesis of retinal (vitamin A aldehyde) and well characterized by spectral data.

MATERIALS AND METHODS

General. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 solution by using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. MS spectra were obtained on a mass spectrometer. All chemicals and reagents were purchased from commercial sources and purified before use.



Scheme 1. Synthesis of Retinal (Vitamin A)

RESULTS AND DISCUSSION

4,4-bis(methylthio)but-3-en-2-one (2).
^{1}HNMR (400 MHz, DMSO-d_6): δ 5.75 (s, 1H), 2.3 (s, 3H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.9, 169.7, 102.8, 28.3, 17.9. EI-MS: m/z 163.02 $(M+H)^+$.

4-(methylthio)but-3-en-2-one (3).
^{1}HNMR(400MHz, DMSO-d_6): δ 7.51 (d, *J* = 8.8 Hz, 1H), 6.02 (d, *J* = 8.8 Hz, 1H),2.3 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.9, 145.5, 120.3, 28.7, 21.2; EI-MS: m/z 117.03 $(M+H)^+$.

3-methyl-1-(methylthio)penta-1,4-dien-3-ol (4).
^{1}H NMR (400 MHz, DMSO-d_6): δ 6.33 (d, *J* = 13.5 Hz, 1H), 5.91 (dd, *J* = 11 Hz,14 Hz, 1H), 5.53 (d, *J* = 13.5 Hz, 1H), 5.25 (dd, *J* = 1.5 Hz, 14 Hz, 1H), 5.23(dd, *J* = 1.5 Hz, 11 Hz, 1H), 2.25 (s, 3H), 1.51 (s, 3H), 2.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.1, 129.1, 120.2, 116.6, 72, 30.9, 21.5; EI-MS: m/z 143.06 $(M-H)^+$.

3-methyl-5-(methylthio)penta-2,4-dienal (5)
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.8 (s, 1H), 6.38 (d, *J* = 11.5 Hz, 1H), 6.11 (d, *J* = 11.5 Hz, 1H), 6.02 (s, 1H), 2.26 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.3, 158.4, 133.8, 119.6, 21.7, 21.6; EI-MS: m/z 143.05 $(M+H)^+$.

7-methyl-9-(methylthio)-1-(2,6,6-trimethylcyclohex-1-enyl)nona-1,4,6,8-tetraen-3-one (7)
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 (m, 2H), 6.70 (d, *J* = 14.2 Hz, 2H), 6.37 (d, *J* = 11.4 Hz, 1H), 6.25 (d, *J* = 14.3 Hz, 1H), 6.08 (d, *J* = 11.4 Hz, 1H), 2.25 (s, 3H), 2.01 (t, *J* = 14.3 Hz, 2H), 1.72 (s, 6H), 1.65 (m, 2H), 1.55 (t, *J* = 14.3 Hz, 2H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.8, 156.9, 152.1, 138.1, 136.9, 133.8, 132.3, 128, 124.6, 119.6, 40.4, 34.2, 33.6, 28.2, 22.3, 21.6, 19.1, 17.8; EI-MS: m/z 317.2 $(M+H)^+$.

3,7-dimethyl-9-(methylthio)-1-(2,6,6-trimethylcyclohex-1-enyl)nona-1,4,6,8-tetraen-3-ol (8)
^{1}H NMR (400 MHz, DMSO-d_6): δ 6.51 (dd, *J* = 14.2 Hz, 14.6 Hz, 1H), 6.38 (d, *J* = 11.4 Hz, 1H), 6.25 (d, *J* = 14.4 Hz, 1H), 6.23 (d, *J* = 14.2 Hz, 1H), 6.08 (d, *J* = 11.4 Hz, 1H), 5.92 (d, *J* = 14.6 Hz, 1H), 5.8 (d, *J* = 14.4 Hz, 1H), 2.25 (s, 3H),2.1 (s, 1H), 2.01 (t, *J* = 14.3 Hz, 2H), 1.72 (s, 6H), 1.65 (m, 2H), 1.55 (t, *J* = 14.3 Hz, 2H), 1.5 (s, 3H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.1, 136.9, 135.5, 133.8. 133.6, 132.2, 129.7, 128, 40.4, 34.5, 33.6, 32.1, 28.2, 22.3, 21.6, 19.1, 17.8; EI-MS: m/z 331.2 $(M-H)^+$.

3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenal (A)
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.8 (s, 1H), 6.56-6.52 (m, 4H), 6.2 (d, *J* = 14.4Hz, 1H), 6.02 (s, 1H), 2.01 (t, *J* = 14.3 Hz, 2H), 1.72 (s, 9H), 1.65(m, 2H), 1.55 (t, *J* = 14.3 Hz, 2H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.2, 158.4, 138.1, 136.9, 135.4, 135.3, 135.2, 132.3, 130.6, 128.9, 128, 40.4, 34.6, 33.6, 28.2, 22.5, 19.1, 17.8, 16.8; EI-MS: m/z 285.2 $(M+H)^+$.

APPLICATIONS

This synthesis is useful in the synthesis of Retinal (Vitamin-A) and its derivatives.

CONCLUSIONS

In conclusion, we have described a novel and efficient synthetic method for the preparation of Retinal (vitamin A aldehyde).

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