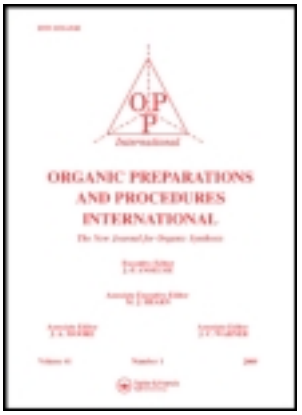

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An Improved Synthesis of Retinal (Vitamin A Aldehyde)

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OPPI BRIEF

An Improved Synthesis of Retinal (Vitamin A Aldehyde)

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In recent years, we have been engaged in the synthesis and study of vitamin A analogs (retinoids) as breast cancer chemotherapeutic and chemopreventive agents.[1,2] For these syntheses, a substantial amount of retinal (**2**, vitamin A aldehyde) is needed. This relatively unstable polyene is expensive, costing about $200/g. Recently, we published an efficient synthesis of **1** starting from retinyl acetate (**1**)[3] which is available at low cost (<$5/g) because of its production as a vitamin supplement. This synthesis proceeded with transesterification of **1** with methanol followed by oxidation of the obtained retinol upon passage through a column of MnO_2/diatomaceous earth. Although the yields of **2** were good, about 8% of the retinal obtained was the 13-*cis* isomer which required careful chromatographic removal to give a solid product. We now find, however, that scaling of this oxidation column to handle greater than about one gram g of **1** results in a column of unwieldy proportions and slows elution of **1** sufficiently to result in a significant increase in the formation of side-products and in a reduction in yields. We now report a modification of this synthesis which is much faster, is easily scaled to use at least 5 g of **2** as starting material, and produces no more than 2–4% of the 13-*cis* isomer of **1**. As we previously reported,[3] stirring **2** in a dilute anhydrous methanolic solution with one equivalent of sodium metal completes transesterification to retinol in forty minutes. We now recommend no volume reduction of the resulting solution before passage through an ion-exchange resin (Amberlite IRA-400, chloride form) to give a quantitative yield of the base labile retinol, which is used as obtained. Removal of methanol gives a red oil which is dissolved in a minimum amount of dry dichloromethane followed by addition of activated MnO_2 (25 equiv.) and dry ethyl acetate.[4] The thick suspension was stirred for 4.5–5.0 h to complete the oxidation to **2**. After filtration of the suspension through a pad of diatomaceous earth to remove insoluble inorganic materials, the filtrate was evaporated *in vacuo* to provide product **2** as a yellow-orange solid in 85% yield. If desired, further purification may be accomplished using flash

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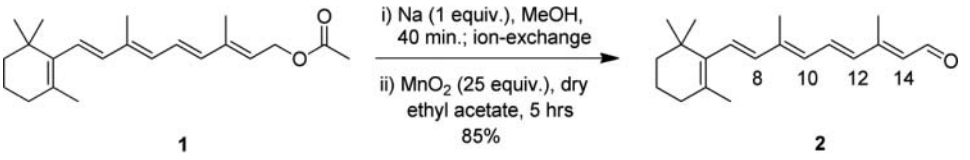
column chromatography[5] on silica gel (5% ethyl acetate/hexane, followed by 10% ethyl acetate/hexane) .



Scheme 1

Experimental Section

All solvents and reagents were purchased as reagent grade from Sigma-Aldrich (Milwaukee, WI) and were used as obtained. Reactions were performed in oven-dried glassware under an argon atmosphere and gold fluorescent lights. Analytical TLC was acquired on silica gel 60 F254 aluminum-backed plates from Merck (Darmstadt, Germany). Flash column chromatography was carried out on silica gel 60 (230–400 mesh) from Merck. Analysis by HPLC was performed on a Beckman Instruments unit (model 127 pump, model 166 detector) using 1 mL/min of 90% MeOH-H_2O through a Polaris C18 column with monitoring at 360 nm.^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Instruments DRX400 spectrometer (Billerica, MA) operating at 400 MHz for ^{1}H measurements. Electrospray mass spectra were measured on a Micromass QTOF mass spectrometer in the Ohio State University Campus Chemical Instrument Center.

Procedure

To a stirred solution of **1** (5.10 g; 15.5 mmol) in 500 mL of anhydrous methanol was added sodium pieces (0.39 g; 1.1 equiv.) and the mixture stirred for 40 minutes at which time TLC (20% ethyl acetate/hexane) indicated complete consumption of **2**. The solution was passed through Amberlite IRA-400 ion-exchange resin (6.5 g; chloride form) and the column was rinsed with methanol. The eluent was concentrated under reduced pressure to a red oil which was dissolved in the minimum amount of dry dichloromethane (2–3 mL). After addition of activated MnO_2 (33.0 g; 24.4 equiv.) and dry ethyl acetate (40 ml dried over 4 Å molecular sieves), the thick suspension was stirred for 5 hrs at which time TLC indicated complete oxidation to **1**. After filtration of the solution through a pad of diatomaceous earth and rinsing with dichloromethane, the filtrate was evaporated *in vacuo* to give **2** (3.75 g, 85%) as a yellow-orange solid, mp. 57.5–60°C (*lit.*[6] mp. 57°C); HPLC: t_R = 10.3 min (∼96%).^{1}H NMR ($CDCl_3$): δ 0.93 (s, 6H, CMe_2), 1.36 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.90 (m, 2H, CH_2), 1.91 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 5.83 (d, 1H, J = 8 Hz, 14-CH), 6.03–6.25 (m, 4H, vinyls), 7.03 (dd, 1H, J = 11.6 and 14.9 Hz, 12-CH), 9.97 (d, 1H, J = 8 Hz, CHO). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.7, 19.9, 22.4, 29.7, 33.8, 34.9, 40.3, 129.7, 130.19, 130.21, 130.96, 133.1, 135.3, 137.8, 138.3, 141.7, 155.1, 191.3. HRMS (ESI): *m/z* $[M + Na]^+$: Calcd for $C_{20}H_{28}O$ + Na: 307.2038. Found: 307.2040.

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