Efficient, Low-Cost Synthesis of Retinal (Vitamin A Aldehyde)

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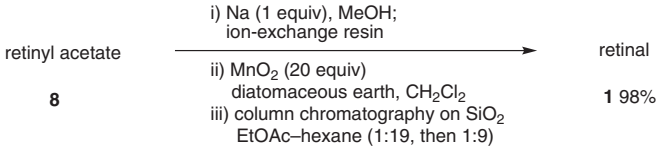
Abstract: Inexpensive retinyl acetate has been subjected to transesterification followed by allylic oxidation to give retinal in 98% yield as a 92:8 mixture of all-*trans*/13-*cis* isomers after chromatographic separation. More convenient methods of isolating the all-*trans* isomer have also been employed.

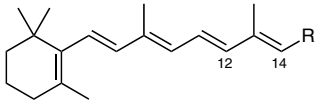
Key words: retinyl acetate, retinal, transesterification, allylic oxidation, isomerization



Scheme 1

Retinal (vitamin A aldehyde; **1**, Figure 1) is an important metabolite of retinol (vitamin A; **2**) and is essential as the mammalian visual pigment chromophore.[1] It may also play a role in adipogenesis in mammals.[2] Furthermore, **1** is the immediate metabolic precursor of retinoic acid (**3**), the principal active form of the vitamin in controlling epithelial cell differentiation.[3] As a result of its important role in retinoid homeostasis and the importance of these molecules in a variety of physiological processes, many studies are performed using this material. Our current interest in this polyene stems from our use of **1** as a reactant for the synthesis of retinoids **4** and **5**, analogues of *N*-(4-hydroxyphenyl)retinamide (4-HPR; **6**) (Figure 2), a long-known analogue of **3** with cancer chemopreventive and chemotherapeutic activity, and reduced toxicity.[4] The unhydrolyzable analogues **4** and **5** are at least as effective as **6**, but clearly show reduced toxicity relative to the parent retinamide.[5,6] Our synthesis of these two analogues makes use of **1**, activated as the umpoled synthon **7**, for reaction with a suitable electrophile. The promise of these two analogues necessitates the preparation of multigram quantities for detailed studies of their biological activity.

As a starting material, retinal (**1**) is an expensive reactant, costing from about $8000–$20000/100 g depending on source and purity required. While it is possible to oxidize retinol (**2**) to **1** with relative ease, **2** is virtually as expensive as **1**, probably due to its relative instability. The ester retinyl acetate (**8**) is prepared on industrial scale to provide a relatively stable source of **2** for vitamin supplementation. This material can be obtained for about $100–$200/100 g and has been employed as a source to provide **1** via hydrolysis and oxidation.[7]



1 R = CHO

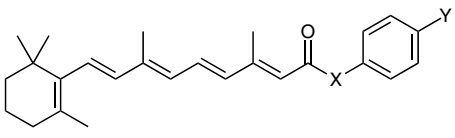
2 R = CH_2OH

3 R = COOH

7 R = CH(OTBS)CN

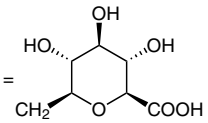
8 R = CH_2OAc

Figure 1 Retinal (**1**) and related compounds



4 X = CH_2, Y = OH

5 X = CH_2, Y =



6 X = NH, Y = OH

Figure 2 Retinoids **4** and **5** and retinamide **6**

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In our experience, alkaline hydrolysis of **8** on larger scales leads to significant decomposition of the base labile **2**. This is a sufficiently general problem that Sigma-Aldrich has introduced a flow process microreactor useful for this situation and has applied the device (costing ca. $25000) to the industrial-scale saponification of **8** to **2** in 70% yield.[8] Alternatively, reductive cleavage of **8** to **2** has been used with little detail provided.[9] In our hands, this approach also results in significant decomposition of **2**. Once **2** is obtained, oxidation to **1** is most frequently accomplished using activated MnO_2.[10] We and others find that reacting **2** with activated MnO_2 does produce **1**, but typically requires many days of stirring. Also, variable and sometimes poor recoveries with overoxidation product contaminants are observed. Many years ago, Wald passed **2** over a MnO_2 column to produce **1** smoothly, although the extent of side-product formation increased with column length.[11] Thus, an improved, low-cost process for generating **1** would be useful.

We hypothesized that transesterification of **8** in anhydrous methanol with catalytic sodium would generate **2** with minimal exposure to base. We were disappointed to learn that this process has been tried and requires many hours for completion (20–24 h) and gives only modest yields of **2** (40–50%).[12] However, when one equivalent of sodium metal and a dilute methanolic solution of **8** (Scheme 1) were employed, the transesterification was complete in 30–60 minutes and the resulting **2** could be separated from the basic medium quickly by volume reduction and passage through an ion-exchange resin (Amberlite IRA-400, chloride form). After extensive experimentation on the ratio of MnO_2 to **2** and the ratio of inert matrix to MnO_2, it was determined that a column packed with a 5–10:1 (w/w) mixture of diatomaceous earth to MnO_2 containing 20 equivalents of MnO_2 relative to **8**, and eluted with CH_2Cl_2, readily oxidizes **2** to **1**. Depending on reaction scale, the retinoid-containing column needs to sit for 2–12 hours prior to elution with CH_2Cl_2 to effect complete oxidation, although 3.5 hours is usually a sufficient delay before elution. Careful column chromatography can then separate the resulting isomers of **1**. Yields of the retinal (**1**) over the two steps on a one-gram scale have been as good as 98% with a 92:8 ratio of the separated all-*trans*/13-*cis* isomers being formed. If it proves desirable to avoid the final lengthy column chromatography, formation of the reversible crystalline retinal complex with hydroquinone[13] allows for easy isolation of at least 55% of the all-*trans* retinal. The remaining sample enriched in the 13-*cis* isomer can then be subjected to iodine-catalyzed photoisomerization.[14] In our hands, this produced a 3:1 equilibrium mixture of all-*trans*/13-*cis* isomer in 1.5 hours from which more all-*trans* isomer could be isolated.

All reagents were purchased as reagent grade from Sigma-Aldrich and were used as obtained. Reactions were performed in oven-dried glassware under an argon atmosphere and gold fluorescent lights. Column chromatography was performed on silica gel 60 (70–230 mesh) from Merck. Analytical TLC was performed on silica gel 60 F245 aluminum plates from Merck. Analytical HPLC was done on a Beckman Instruments unit (model 127 pump, model 166 detector) using 1 mL/min of 90% MeOH–H_2O through a Polaris C18, 4.6 × 250 mm column with monitoring at 360 nm. ^1H and ^{13}C NMR spectra were recorded in acetone-d_6 on a Bruker DRX400 instrument (400 MHz for ^1H). Electrospray mass spectra were measured on a Micromass QTOF mass spectrometer in the Ohio State University Campus Chemical Instrument Center.

Retinal (1)

To a stirred solution of **8** (1.08 g, 3.28 mmol) in anhyd MeOH was added Na pieces (0.078 g, 3.38 mmol) and the mixture was allowed to stir for 45–60 min at which time TLC indicated the complete consumption of **8**. The solution was concentrated by one half and passed through a column containing Amberlite IRA-400 (chloride form, 0.8 g, 1.4 meq/mL exchange capacity) and the eluent was concentrated. The residue containing **2** was suspended in CH_2Cl_2 (5 mL) and the soluble portion eluted into a column composed of a slurry of oven-dried MnO_2 (5.4 g, 61.87 mmol) and of diatomaceous earth (53.8 g) in CH_2Cl_2 (200 mL). Once the crude **2** was eluted well into the column bed, flow was stopped for 12 h and the column was protected from light and air. The column was then eluted with CH_2Cl_2, the solvent was evaporated, and the residue was column chromatographed (silica gel; 19:1 hexanes–EtOAc, then 9:1 hexanes–EtOAc) to give 0.85 g (90%) of solid **1** and 0.08 g (8%) of liquid 13-*cis* isomer[15] of retinal.

Alternatively, to a solution of retinal isomer mixture in Et_2O (ca. 500 mg/mL) was added 3 volumes of a warm ethereal solution of hydroquinone (1.5 equiv). The Et_2O was then evaporated with argon and the resulting pink solid triturated with petroleum ether (bp 35–60 °C) and allowed to stand on ice for 1 h. The solid was then vacuum-filtered with cold petroleum ether rinsing, dissolved in Et_2O, washed 3 times with aq 5 N KOH (until all purple color was extracted into the H_2O), then with brine. Evaporation of the Et_2O provided the *trans*-**1** in 55% yield. To a ~2 mg/mL methanolic solution of the residue from the petroleum ether trituration (~5:1 13-*cis*/*trans* retinal) was added 3 drops of a 3.2 mg/mL methanolic solution of I_2 and the solution was irradiated at 520 nm for 75 min. After this time, HPLC analysis showed no further change to the then 3:1 mixture of *trans*/13-*cis* retinal from which more *trans*-**1** could be isolated by the hydroquinone complexation method.

Mp 58–59.5 °C; R_f = 0.37 (hexanes–EtOAc, 4:1); HPLC: t_R = 9.8 min (>98%).^1H NMR: δ = 1.04 [s, 6 H, $C(CH_3)_2$], 1.48 (m, 2 H, CH_2), 1.62 (m, 2 H, CH_2), 1.72 (s, 3 H, CH_3) 2.04 (m, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 5.91 (d, *J* = 8 Hz, 1 H, 14-CH), 6.2–6.5 (m, 4 H, vinyls), 7.29 (dd, *J* = 11.5, 14.1 Hz, 1 H, 12-CH), 10.13 (d, *J* = 8 Hz, 1 H, CHO).

^{13}C NMR (100 MHz): δ = 12.95, 19.8, 21.9, 29.2, 33.6, 34.8, 40.2, 129.7, 129.8, 130.5, 130.7, 133.1, 135.8, 138.2, 138.4, 141.3, 155.1, 191.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{28}O$ + Na: 307.2038; found: 307.2025.

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