Efficient Synthesis of 11-cis-Retinoids

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Abstract: The light sensitivity and unstable nature of 11-cis-retinoids makes them ideal visual chromophores in nature. The synthesis of 11-cis-retinal analogues is of paramount importance in bioorganic studies of rhodopsin, the photoreceptor of the visual transduction pathway, but the instability of 11-cis-retinoids complicates their synthesis and there is no general synthetic route. Common strategies to the cis geometry have failed in the case of 11-cis-retinoids, and most often low yields and complex isomeric mixtures are obtained. Herein we report an efficient, general, and mild preparation of 11-cis-retinoids by semi-hydrogenation of 11-yne-retinoid precursors with Cu/Ag-activated zinc dust.

Keywords: 11-cis-retinoids · chromophores · enynes · hydrogenations · retinal analogues · zinc reductions

Introduction

Visual transduction is initiated by photoisomerization of the 11-cis-retinal chromophore to all-trans-retinal, which in turn leads to a series of conformational changes in rhodopsin, and eventually results in the enzymatic cascade responsible for vision.[1–3] Although the initial and final states of the chromophore/opsin interactions have been clarified to a considerable degree,[4–8] the nature of the discrete intermediates along the transduction pathway remains uncertain on a molecular structural basis. One of our main objectives is to study this by tracing the changes in chromophore/opsin interactions with photoaffinity analogues such as the tritiated 1. We could thus elucidate the position of the β-ionone ring with relation to the protein by identification of the cross-linked sites. A general synthetic method yielding 11-cis-retinoids, as well as analogues with photolabile moieties such as 1, would greatly facilitate bioorganic studies of rhodopsin.

The synthesis of 11-cis-retinal analogues is complicated by their unusual instability to light and temperature, and by their facile isomerization under conditions which most Z double bonds survive. Most schemes geared towards the introduction of the 11-cis geometry (especially those close to the end of the synthetic scheme) have either failed or resulted in low yields with formation of complex isomeric mixtures.[9–15] In addition, the more common photoisomerization strategy of all-trans-retinoids and subsequent HPLC purification of the 11-cis isomer is not compatible with analogues that contain light-sensitive functional groups. Moreover, in some cases it has been difficult to separate by chromatography the isomeric mixture of retinals obtained from photoisomerization. The unusual difficulty encountered in generating the 11-cis geometry is probably associated with the steric hindrance between 10-H and 13-Me, which leads to a nonplanar conformation which could isomerize easily to relieve stress under most experimental conditions.[1, 16–18] Very recently, Uenishi et al. have developed an elegant synthesis of 11-cis-retinal itself based on the Suzuki coupling of the C12–C13 bond.[19] The preparation of 11-cis-retinal analogues with a photolabile group, such as 1, has also been accomplished by enzymatic isomerization of all-trans precursors by means of retinochrome isolated from the visual cells of cephalopods.[20] Although efficient, this method is unsuitable for securing relatively large quantities of compound. We have therefore focused on the chemical synthesis of the 11-cis-retinoids. Here we report an efficient, nonphotochemical preparation of 11-cis-retinoids by zinc-mediated semi-hydrogenation of 11-yne-retinoid precursors.

Results and Discussion

Although numerous synthetic routes (summarized in Scheme 1) were pursued to prepare 11-cis-retinoids, none of them gave satisfactory results.
Scheme 1(a): The Wittig and Horner–Wadsworth–Emmons (HWE) reactions illustrated in Scheme 1(a) were performed to generate the 11-cis geometry from unstabilized ylides and bis(trifluoroethyl) phosphonates; however, at best they gave a mixture of isomers with no more than 25% of 11-cis. Although it is possible that the initial product of the Wittig reaction is predominantly cis, it seems likely that the product would isomerize to the trans isomer under basic reaction conditions.

Scheme 1(b): Formation of the 9-ene via ylides which contain the 11-cis geometry was also fruitless, presumably because of similar isomerization to the trans isomer.

Scheme 1(c): Compound 3 was obtained from aldehyde 2 by Stork’s preparation of cis-vinyl iodides (Scheme 2). Stille-type couplings of the C12 –C13 bond with iodide 3 and the vinyl–tin 4 or vinyl–zinc 5 electrophiles were attempted, but none of the desired 11-cis-retinoid was isolated from these reactions (performed under various conditions with different sources of Pd2+ and Pd0). The products obtained were mostly mixtures of different trans isomers. In addition, evidence for dimerization of the starting vinyl iodide 3 was noted in mass-spectral studies.

Scheme 1(d): Reaction of mixed high-order cuprates (obtained from cis-vinyl iodide 3) with α,β-unsaturated acetylenic esters was also unsuccessful and led to complex mixtures of products.

In order to pursue the synthesis of 11-cis-retinoids by the semi-hydrogenation of 11-yne precursors, straightforward syntheses of 10a, 10b, 11a, and 11b were first performed (Scheme 3). 4-Hydroxy-β-ionone, readily prepared from β-ionone (6a), was protected with triethylsilyl chloride to afford 6b. Subsequent HWE coupling with dimethyl (3-trimethylsilyl-2-propynyl)phosphonate yielded the alkyne 7b (97%; 5:1 E:Z at C9). Deprotection of both silyl groups with tetrabutylammonium fluoride (TBAF) gave the terminal acetylene 8b. Palladium coupling of 8b with vinyl iodide 9 proceeded with complete stereochemical retention to yield the 11-yne precursor 10b (91%).

Semi-hydrogenation of 10b was attempted with different reducing systems [Scheme 1(e)]. Heterogeneous catalytic systems such as the Lindlar catalyst gave variable results which depended on the level of catalyst ‘poisoning’ with additives such as pyridine, quinoline, 2,2-diethanol, and also on the modified Lindlar catalyst (prepared with different co-metals such as Mn2+, Ba2+, and Ni2+). In these cases, the catalyst was either weakened to the extent that it did not reduce the triple bond or reduced the C5 and/or C13 double bonds at the same rate, or faster, than the triple bond of the 11-yne. Presumably, the electron density of the

Scheme 3. Synthesis of the 11-yne precursors 11a and 11b (TMS = trimethylsilyl, TBS = tert-butylimidethylsilyl, NaHMDS = sodium bis(trimethylsilyl)amide).
triple bond within the polyene system is not appreciably greater than that of the CS and C13 double bonds, and therefore we were not able to refine the hydrogenation power of the catalyst and thus selectively reduce the acetylene. Other systems such as nickel boride bound to borohydride exchange resin[29] and homogeneous catalytic systems[30] also failed to yield the desired 11-cis-ene.

In contrast to the attempted conversions outlined above, the following conditions finally gave satisfactory results. Zinc-mediated semi-hydrogenation of acetylenic compounds has been reported, but in most cases α-branched acetylenes are not reduced or are reduced at low yields with elevated temperatures (unsuitable for retinoid synthesis).[30, 31] However, reduction of 11-yne precursor 10b with Cu/Ag-activated Zn dust in methanol/water at room temperature proceeded surprisingly smoothly to form the desired 11-cis-retinoid 12 with 100% cis stereoselectivity in high yield (Scheme 4). Removal of the TBS group from 12 with TBAF gave 11-cis-4-hydroxyretinol (13b), accompanied by 5–15% isomerization of the polyene stereochemistry (presumably either by addition–elimination of fluoride anion or because of the basicity of the reagent). However, this was minimized when the reaction was performed at 0°C. As shown in Scheme 5, semi-

![Scheme 4. Semi-hydrogenation of the 11-yne precursor 10b over activated Zn.](image)

hydrogenation of 11b (obtained by deprotection of 10b) with activated Zn also occurred efficiently to produce 13b, mainly as the 11-cis isomer (>95%). Double oxidation of 11-cis-4-hydroxyretinol (13b) with manganese dioxide[32] provided 11-cis-4-oxo-retinal (14b).

Synthesis of 11-cis-retinal (14a), the natural chromophore, was accomplished similarly from the β-ionone (6a) via the 11-yne retinoid 11a (Scheme 3). Efficient reduction of the 11-yne gave Z:E selectivity of 13:1 at C11 (Scheme 5).[33] and was followed by oxidation of 11-cis-retinol with tetrabromoplatinum perruthenate (TPAP)/4-methylmorpholine N-oxide (NMO)[34] to form the 11-cis-retinal (14a) in quantitative yield. (The same reaction with manganese dioxide resulted in lower yield.) Attempts to reduce 10a were futile and the starting material was recovered. Since the low solubility of 10a could be the cause of its lack of reactivity, the reduction was carried out in various solvent systems such as THF/water, DMF/water, 2-propanol/THF/water, and tert-butyl alcohol/water, but none was successful. On the other hand, the 11-yne-

![Scheme 5. Synthesis of 11-cis-retinoids. Oxidation of 13a→14a was accomplished with TPAP/NMO, whereas oxidation of 13b→14b used MnO2.](image)

retinoids 10b, 11a, and 11b (with free hydroxyl(s) either at C4 or in the side-chain) were reduced successfully. It is possible that in these cases the free hydroxyl(s) coordinate to the activated zinc and thus facilitate the reduction. It is also interesting to note that for substrates with unprotected 15-hydroxyl groups (11a and 11b), reduction proceeds with lower stereoselectivity.

In conclusion, an efficient and general synthesis of 11-cis-retinoids has been achieved by the activated-zinc reduction of 11-yne-retinoid precursors. The mild and selective nature of this reduction system should allow the synthesis of a variety of 11-cis-retinoids. The production of 13H-15-11-cis-3-diazo-4-oxo-retinal (1) from the 4-oxo-analogue 14b, together with photoaffinity results, will be reported in due course.

**Experimental Section**

All purchased chemicals were obtained from Aldrich. The solvents used in the reactions were freshly distilled to dryness and used under an argon atmosphere. 1H NMR spectra were obtained on a Bruker DMX500 instrument and the residual protons solvent (CDCl3 or CD2OD) was used as internal reference. 13C NMR was recorded at 75 MHz on a Bruker DMX 300 instrument. Low-resolution and high-resolution FAB mass spectra were measured on a JEOL JMS-DX303 HF mass spectrometer with a glycerol matrix and Xe ionizing gas. Flash column chromatography was performed with ICN silica gel (32–63 mesh). The reactions of compounds with more than 3 conjugated double bonds were performed in the dark room with minimal red lighting (photographic safety lamps). 11-cis Retinoids are unstable compounds and must be stored in absolute darkness. They isomerize easily in the presence of trace acids. We have found that they can be stored very well as frozen solutions in benzene at −78°C.

**Compound 7b:** Dimethyl (3-trimethylsilyl-2-propynyl)phosphonate[25] (2.3 g, 10.5 mmol) in anhydrous THF (50 mL) at 0°C under argon was treated with nBuLi (10.5 mmol) to give a red solution. The ice-bath was removed and the reaction mixture was stirred at room temperature for 15 min, after which time 6b[26] (1.7 g, 5.28 mmol) in anhydrous THF (5 mL) was added. The mixture was stirred for an additional 3 h, and was then quenched with aqueous NH4Cl and extracted with Et2O (2×). The combined organic phases were washed with saturated NaCl and dried over anhydrous Na2SO4. The product was purified by column chromatography (hexanes/EtOAc, 4:1) to yield 7b (214.9 g, 97%; 5:1 E/Z at C9). 1H NMR (500 MHz, CDCl3): δ = 0.21 (s, 3H), 0.64 (dd, J = 9.7, 15.9 Hz), 0.98 (t, J = 9H), 1.00 (s, 3H). 1.02 (s, 3H), 1.38 (m, 1H); 1.40 (s, 3H); 1.43 (m, 1H); 1.64 (m, 2H), 1.72 (s, 3H), 1.82 (m, 1H), 2.05 (s, 3H), 4.04 (t, J = 5.5 Hz), 5.54 (s, 1H), 6.09 (d, 1H); 16.1 Hz), 6.21 (d, 1H); 16.1 Hz). Compound 7b was not characterized further and was used directly in the following reaction.

**Compound 8b:** Acetylene 7b (1.7 g, 4.1 mmol) in solution in THF (20 mL) was treated with nBuNF (6.4 mL, 1 M in THF, 16.35 mmol) and then stirred at room temperature for 2 h. The mixture was quenched with aqueous NH4Cl and extracted with Et2O (2×). The combined organic phases were washed with saturated NaCl and dried over anhydrous Na2SO4. The product was purified by column chromatography (hexanes/ EtOAc, 3:1) to yield 8b (929 mg, 98%). 1H NMR (500 MHz, CDCl3): δ = 1.00 (s, 3H); 1.03 (s, 3H); 1.43 (m, 1H); 1.63 (m, 1H); 1.70 (m, 1H); 1.74 (s, 3H); 1.90 (m, 1H); 2.07 (s, 3H); 3.30 (d, 1H); J = 2.00 Hz); 4.00 (t, 1H); J = 4.6 Hz); 5.43 (s, 1H); 6.11 (d, 1H); J = 16.1 Hz); 6.25 (d, 1H); J = 16.1 Hz);
Compound 10b: Vinyl iodide \( W^0 \) (268 mg, 0.86 mmol) was dissolved in \( \text{PrOH} \) (3 mL) and tetrakis(triphenylphosphine) palladium (8.2 mg, 0.007 mmol) was added. The mixture was then stirred at room temperature for 5 min, following which Cu (1 mg, 0.007 mmol) was added. After 5 min, acetylene \( 8b \) (165 mg, 0.70 mmol) was introduced, and the mixture was stirred at room temperature for 3.5 h. The reaction was then quenched by the removal of solvent under reduced pressure. The residue was dissolved in \( \text{Et}_2\text{O} \), extracted with aqueous \( \text{NH}_4\text{Cl} \), washed with saturated \( \text{NaCl} \), and dried over anhydrous \( \text{Na}_2\text{SO}_4 \). The crude product was purified by column chromatography (EtOH/acetone, 1:19) to yield \( 10b \) (170 mg, 0.41 mmol) was added to this mixture, which was then stirred at room temperature in the dark for 5 min, following which CuI (1.4 mg, 0.007 mmol) was added. After 5 min, Cu(OAc)\(_2\) (1 g) was added and the flask was sealed immediately. The mixture was stirred vigorously for 15 min. The mixture was then stirred at room temperature for 3.5 h. The reaction was then quenched by the removal of solvent under reduced pressure to yield \( 10b \) (180 mg, 0.41 mmol).

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[26] The vinyl iodide \( 9 \) was obtained by reduction of 2-butyne-1-ol mediated by titanocene dichloride (ref. [35]). Subsequent quenching with iodine was followed by protection of the primary alcohol with tributylmethylbenzyldicyclohexyl chloride.


[33] The reduction of \( 11a \) and \( 11b \) was much more sensitive to the quality of the catalyst. Slight contamination such as trace acid led to isolation of mostly trans-reduced product. To obtain good stereoselectivity, the solvents used for preparation and washing of the zinc catalyst were of highest purity. The catalyst was not allowed to dry in air during preparation, and oxygen was excluded during the reduction. Interestingly, the reduction of \( 10b \) is not as sensitive and is much more forgiving, as it occurs with very high stereoselectivity.