Efficient Synthesis of 11-*cis*-Retinoids

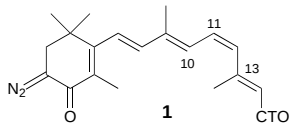
Babak Borhan, María L. Souto, Joann M. Um, Bishan Zhou, and Koji Nakanishi*[a]

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/receptor 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.



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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.

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Results and Discussion

Although numerous synthetic routes (summarized in Scheme 1) were pursued to prepare 11-*cis*-retinoids, none of them gave satisfactory results.

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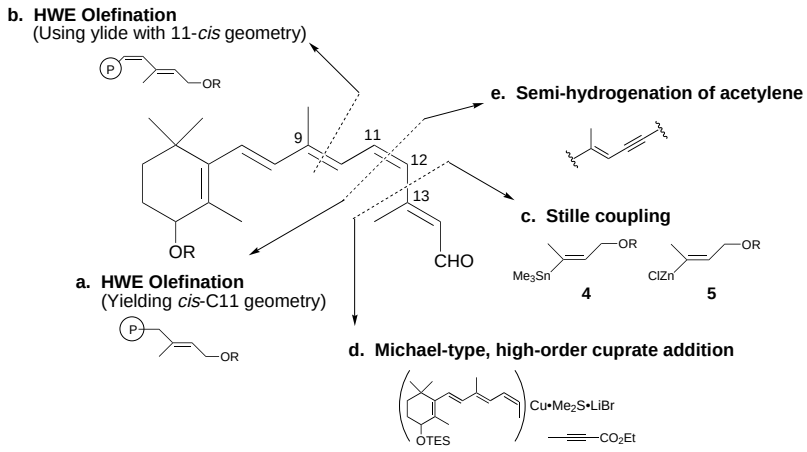
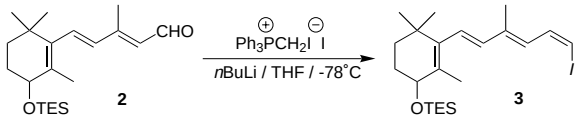


Scheme 1. Synthetic schemes used in the preparation of 11-*cis*-retinoids (TES = triethylsilyl).

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*.[21, 22] 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.



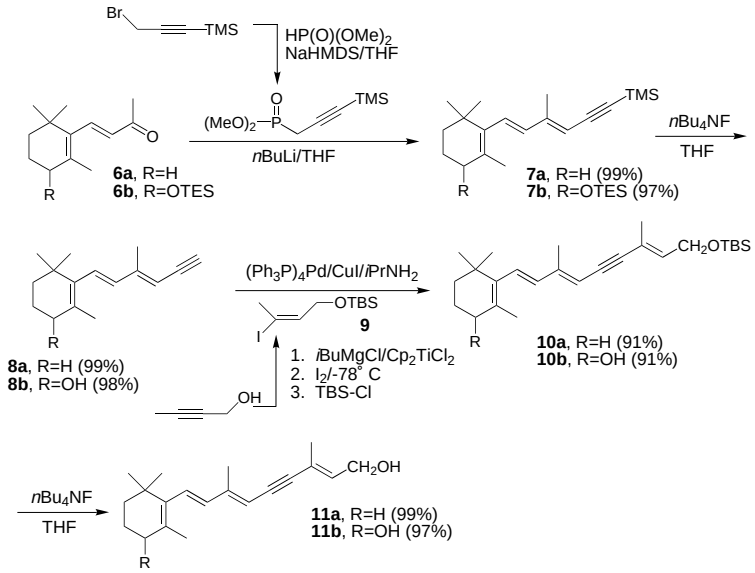
Scheme 2. Synthesis of the *cis*-vinyl iodide **3**.

Scheme 1(c): Compound **3** was obtained from aldehyde **2** by Stork's preparation of *cis*-vinyl iodides (Scheme 2).[23] 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 Pd^{2+} and Pd^{0}). 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, straightfoward syntheses of **10a**, **10b**, **11a**, and **11b** were first performed (Scheme 3). 4-Hydroxy-β-ionone, readily prepared from β-ionone (**6a**),[24] was protected with triethylsilyl chloride to afford **6b**. Subsequent HWE coupling with dimethyl (3-trimethylsilyl-2-propynyl)phosphonate[25] 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**[26] proceeded with complete stereochemical retention to yield the 11-yne precursor **10b** (91%).

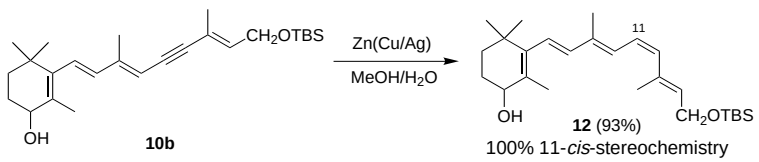
Semi-hydrogenation of **10b** was attempted with different reducing systems [Scheme 1(e)]. Heterogeneous catalytic systems such as the Lindlar catalyst gave variable results which depended on the level of catalyst 'poisoning' with additives such as pyridine, quinoline, 2,2′-(ethylenedithio)-diethanol, and also on the modified Lindlar catalyst (prepared with different co-metals such as Mn^{2+}, Ba^{2+}, and Ni^{2+}).[27] 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*-butyldimethylsilyl, NaHMDS = sodium bis(trimethylsilyl)amide).

triple bond within the polyene system is not appreciably greater than that of the C5 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[28] and homogeneous catalytic systems[29] also failed to yield the desired 11-*cis*-ene.

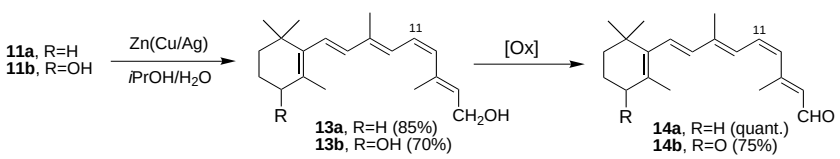
In contrast to the attempted conversions outlined above, the following conditions finally gave satisfactory results. Zinc-mediated semi-hydrogenation of acetylenic compounds has been reported, but in most cases α-branched acetylenes are not reduced or are reduced at low yields with elevated temperatures (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.

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 tetrapropylammonium 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 MnO_2.

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 [^{3}H-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. ^{1}H NMR spectra were obtained on a Bruker DMX500 instrument and the residual protic solvent ($CDCl_3$ or C_6D_6) was used as internal reference. ^{13}C NMR was recorded at 75 MHz on a Bruker DMX300 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 perfomed 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 *n*BuLi (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**[24] (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 NH_4Cl and extracted with Et_2O (2×). The combined organic phases were washed with saturated NaCl and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (hexanes/EtOAc, 4:1) to yield **7b** (2.14 g, 97%; 5:1 *E*:*Z* at C9). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.21$ (s, 9H), 0.64 (dd, 6H, $J = 7.9$, 15.9 Hz), 0.98 (t, 9H, $J = 7.9$ Hz), 1.00 (s, 3H), 1.02 (s, 3H), 1.38 (m, 1H), 1.64 (m, 2H), 1.72 (s, 3H), 1.82 (m, 1H), 2.05 (s, 3H), 4.04 (t, 1H, $J = 5.5$ Hz), 5.44 (s, 1H), 6.09 (d, 1H, $J = 16.1$ Hz), 6.21 (d, 1H, $J = 16.1$ 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 nBu$_4$NF (16.4 mL, 1 M in THF, 16.35 mmol) and then stirred at room temperature for 2 h. The mixture was quenched with aqueous NH_4Cl and extracted with Et_2O (2×). The combined organic phases were washed with saturated NaCl and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (hexanes/EtOAc, 3:1) to yield **8b** (929 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.00$ (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, $J = 2.3$ Hz), 4.00 (t, 1H, $J = 4.6$ Hz), 5.43 (s, 1H), 6.11 (d, 1H, $J = 16.1$ Hz), 6.23 (d, 1H, $J = 16.1$ Hz);

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^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.0, 18.5, 27.4, 28.4, 29.0, 34.4, 34.7, 70.1, 82.1, 83.9, 108.3, 129.3, 130.4, 136.1, 141.3, 148.8$; $C_{16}H_{22}O$: calcd 230.1671; found 230.1678 (HRMS).

Compound 10b: Vinyl iodide **9**[26] (268 mg, 0.86 mmol) was dissolved in *i*PrNH$_2$ (3 mL), and tetrakis(triphenylphosphine)palladium (8.2 mg, 0.007 mmol) was then added. The solution was stirred at room temperature for 5 min, following which CuI (1.4 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 Et_2O, extracted with aqueous NH_4Cl, washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (EtOAc/hexanes, 1:19) to yield **10b** (271 mg, 91 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.91(s, 9H), 1.00 (s, 3H), 1.03 (s, 3H), 1.43 (m, 1H), 1.63 (m, 1H), 1.69 (m, 1H), 1.81 (s, 3H), 1.84 (s, 3H), 1.90 (m, 1H), 2.05 (s, 3H), 4.00 (dd, 1H, $J = 4.8, 5.0$ Hz), 4.28 (d, 2H, $J = 6.2$ Hz), 5.55 (s, 1H), 5.93 (t, 1H, $J = 6.2$ Hz), 6.17 (d, 1H, $J = 16.1$ Hz), 6.20 (d, 1H, $J = 16.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.2$, 15.0, 17.7, 18.3, 18.6, 25.9, 27.5, 28.5, 29.0, 34.5, 34.7, 42.8, 60.1, 69.9, 85.8, 99.2, 109.6, 119.2, 128.3, 130.4, 136.2, 136.5, 141.2, 146.5; $C_{26}H_{42}O_2Si$: calcd 414.2954; found 414.2954 (HRMS).

Compound 12: Activated Zn dust was prepared as described by Boland et al.[30] Argon was bubbled through a suspension of Zn dust (10 g) in distilled H_2O (60 mL) for 15 min. $Cu(OAc)_2$ (1 g) was added and the flask was sealed immediately. The mixture was stirred vigorously for 15 min. $AgNO_3$ (1 g) was then added (exothermic reaction), and the solution was stirred for 30 min. The activated Zn was then filtered as it was washed successively with H_2O, MeOH, acetone, and Et_2O. The moist activated Zn was transferred immediately to a flask of the reaction solvents (H_2O, 20 mL; MeOH, 20 mL). Compound **10b** (170 mg, 0.41 mmol) was added to this mixture, which was then stirred at room temperature in the dark for 21 h. The Zn dust was filtered through Celite with Et_2O and H_2O. The organic phases were separated, washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield **12** (159 mg, 93 %) with 100 % stereoselectivity. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.91 (s, 9H), 1.01 (s, 3H), 1.04 (s, 3H), 1.43 (m, 1H), 1.64 (m, 1H), 1.70 (m, 1H), 1.83 (s, 3H), 1.84 (s, 3H), 1.88 (m, 1H), 1.92 (s, 3H), 4.00 (t, 1H, $J = 4.6$ Hz), 4.32 (d, 2H, $J = 6.3$ Hz), 5.63 (t, 1H, $J = 6.2$ Hz), 5.89 (d, 1H, $J = 11.7$ Hz), 6.13 (s, 2H), 6.32 (t, 1H, $J = 11.9$ Hz), 6.57 (d, 1H, $J = 12.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.1$, 12.2, 17.2, 18.3, 18.6, 26.0, 27.5, 28.5, 29.1, 34.5, 34.8, 60.4, 70.2, 124.4, 125.7, 127.4, 129.5, 132.0, 133.5, 133.9, 136.3, 139.1, 142.0; $C_{26}H_{44}O_2Si$: calcd 416.3110; found 416.3111 (HRMS).

Compound 13a: Activated Zn dust was prepared as described above. The activated Zn was transferred immediately into the reaction solvent of water (2 mL) and *i*PrOH (2 mL). A solution of enyne **11a** (14 mg, 0.05 mmol) in *i*PrOH (2 mL) was added to this activated Zn suspension, and the mixture was stirred at room temperature for 21 h. The Zn was then filtered through Celite with Et_2O and H_2O. The organic phases were separated, washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield **13a** (12 mg, 85 %; 13:1 *Z*:*E* at C11). All spectroscopic measurements were consistent with reported data.[15] ^{1}H NMR (500 MHz, C_6D_6): $\delta = 1.09$ (s, 6H), 1.46 (m, 2H), 1.57 (m, 2H), 1.66 (s, 3H), 1.73 (s, 3H), 1.86 (s, 3H), 1.92 (m, 2H), 3.94 (d, 1H, $J = 6.6$ Hz), 5.69 (t, 1H, $J = 6.6$ Hz), 5.87 (d, 1H, $J = 11.7$ Hz), 6.29 (d, 1H, $J = 16.3$ Hz), 6.35 (d, 1H, 16.3 Hz), 6.38 (t, 1H, $J = 11.9$ Hz), 6.83 (d, 1H, $J = 12.1$ Hz).

Acknowledgments

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[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.
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