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Stereoselective synthesis of retinoid isomers using tricarbonyliron complex and its application*

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Abstract: In order to establish the stereoselective synthesis of retinoid isomers, the reaction of β-ionone–tricarbonyliron complex **2** with carbanions was investigated. Treatment of **2**, prepared from the reaction of β-ionone and dodecacarbonyltriiron, with the lithium salt of acetonitrile afforded **3**. In contrast, the reaction of **2** with the lithium enolate of ethyl acetate, and subsequent dehydration by thionyl chloride, provided the ethyl 9*Z*-β-ionylideneacetate **7** predominantly. These compounds (**3** and **7**) were converted to the corresponding β-ionylideneacetaldehydes (**4** and **8**) in excellent yields. The Emmons–Horner reaction of these aldehydes with C5-phosphonate, followed by the sequence of decomplexation and alkaline hydrolysis, gave the corresponding all-*E*- and 9*Z*-retinoic acids (**12** and **15**). The Peterson reaction of **4** with ethyl trimethylsilylacetate provided the 11*Z*-isomer **17** preferentially, accompanied by the 11*E*-isomer. The ester **17** was transformed into 11*Z*-retinal **26**. Applying this synthetic methodology, various 9-demethyl-9-substituted 11*Z*-retinals **36** were prepared.

INTRODUCTION

Retinoids **1** (Scheme 1) are half molecules of β-carotene and are called retinol, retinal and retinoic acid according to their terminal functional groups. It is well known that retinoids, covalently or non-covalently bound to proteins, play an important role as retinoid proteins in vital cells. The most characteristic feature of these compounds is that the biological activities depend upon the stereochemistry of retinoid in the protein. For example, the chromophore of the visual pigment rhodopsin is 11*Z*-retinal and those of bacteriorhodopsin and retinochrome, which function as a light-driven proton pump and for the regeneration of rhodopsin, are 13*Z*- and all-*E*-retinal, respectively [1]. In addition, it has recently been established that retinoic acids play fundamental roles in cell differentiation and proliferation through modulation of their intracellular retinoid receptors. These receptors comprise two distinct classes, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), which have all-*E* and 9*Z*-retinoic acids as ligand molecules, respectively [2].

In contrast to the recognition of the significance of the configuration of retinoids, little is known about the stereoselective synthesis of geometrical isomers of retinoids. Therefore, there is an increasing need for geometrically pure isomers in the retinoid field. High performance liquid chromatography (HPLC) is a powerful tool for obtaining pure stereoisomers from an isomeric mixture of retinoids. However, it is not suitable for large-scale preparation. We describe herein the stereoselective synthesis of retinoid isomers using a tricarbonyliron complex and its application to the synthesis of 11*Z*-retinal.

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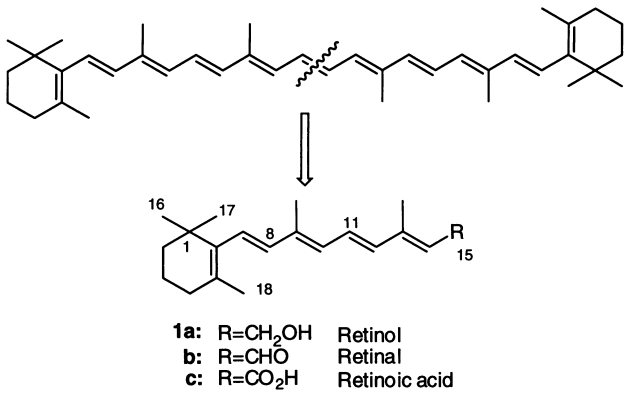


Scheme 1

STEREOSELECTIVE SYNTHESIS OF RETINOID ISOMERS

The conversion of carbonyl compounds to α,β-unsaturated aldehydes is an important reaction in organic synthesis. For this conversion there are a number of methods, such as aldol condensation [3], Wittig reaction [4], Emmons–Horner reaction [5], Peterson olefination [6], etc. However, there are few methods that can be applied to the stereoselective synthesis of retinoids and related compounds, except for all-*E*-isomers. In contrast, diene–tricarbonyliron complexes have been used not only for the protection of the diene moiety, but also for the synthesis of biologically interesting compounds containing polyolefins in the molecule due to their ease of preparation, optical resolution and diastereoselective reactivity [7]. In view of the characteristic structure of retinoids, having five conjugated carbon–carbon double bonds, we investigated the possibility of utilizing diene–tricarbonyliron complexes for this study.

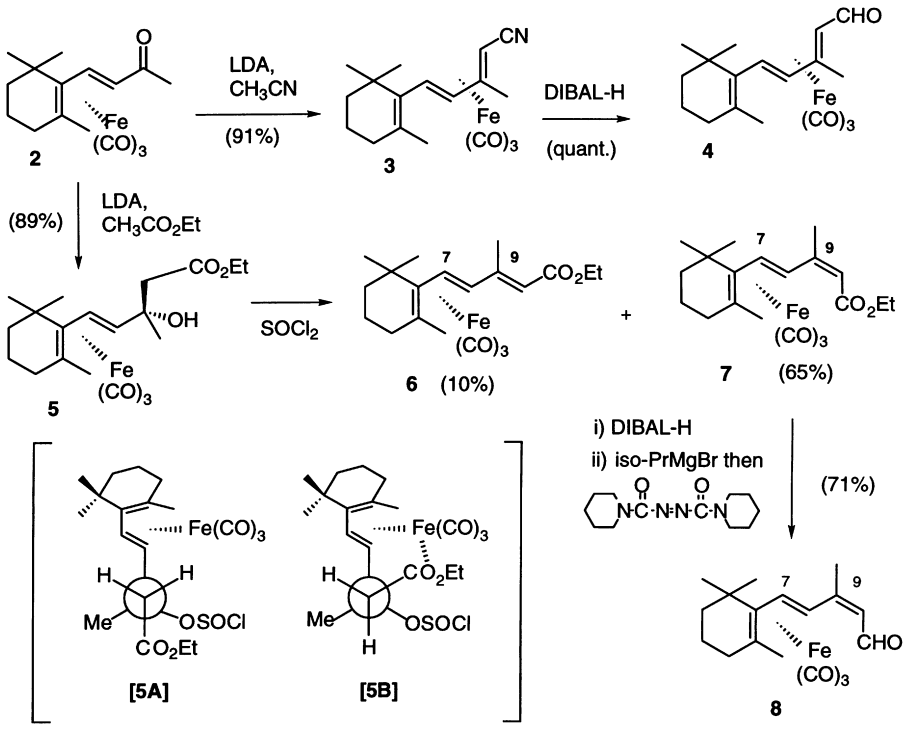
All-*E*- and 9*Z*-retinoic acids

β-Ionylideneacetaldehydes, possessing a trisubstituted olefin, are very important synthons for the synthesis of retinoids and carotenoids [8]; therefore, initially, we tried the stereoselective synthesis of the β-ionylideneacetaldehyde–tricarbonyliron complexes **4** and **8**, and then these compounds were converted to the corresponding retinoic acids (Scheme 2) [9]. Although β-ionone–tricarbonyliron complex **2** is a known compound, we obtained **2** more efficiently from β-ionone by replacement of the metallating reagent pentacarbonyl-iron(0) (20%) with dodecacarbonyl-triiron(0) (98%). Treatment of **2** with the lithium salt of acetonitrile in tetrahydrofuran (THF) at −70° afforded **3** in 91% yield via addition, dehydration and successive migration of tricarbonyliron. A similar migration of tricarbonyliron has already been reported by Salzer and Coworkers [10] in the reaction of sorbaldehyde–tricarbonyliron with carbanions. The geometry of the double bond at the 9 position of **3** was determined as *E* after derivation to the corresponding β-ionylideneacetonitrile by oxidative decomplexation using copper(II) chloride in ethanol. The transformation of **3** to the corresponding aldehyde **4** was achieved quantitatively by diisobutylaluminum hydride (DIBAL-H) reduction.

Next, we focused our attention on the stereoselective synthesis of 9*Z*-aldehyde–tricarbonyliron complex **8**. The reaction of **2** with the lithium enolate of ethyl acetate in THF at −70 °C gave the adduct **5** as a single product in 89% yield. In contrast to the reaction of the acetonitrile, in this case dehydration and subsequent migration of the tricarbonyliron complex were not observed. Although the structure of **5** was deduced from the reaction mechanism, i.e. the carbonyl group of **2** has the s-*cis*-conformation and the nucleophile attacks the other side of the tricarbonyliron complex [7], the confirmation was achieved by single-crystal X-ray analysis [9].

Dehydration of **5** by thionyl chloride afforded the 9*Z*-ester **6** predominantly (65%), accompanied by its 9*E*-isomer **7** (10%). The stereochemistry of the newly produced double bond of these compounds was determined by their transformation to the corresponding β-ionylidene esters [11] after oxidative decomplexation.

It is well known that dehydration with thionyl chloride proceeds via an E_1 mechanism to provide the



Scheme 2

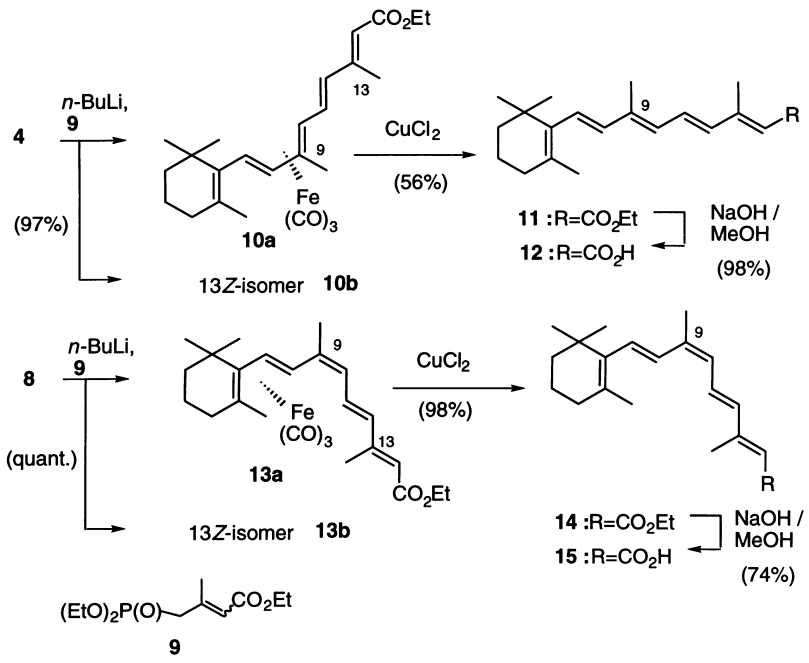
most stable product [12]. However, in the case of **5**, the unstable *Z*-olefin **7** was obtained as the major product. The high stereoselectivity of this dehydration can be understood by a chelation mechanism between the iron and the ester group in the reaction intermediate as shown in the Newman projections (Scheme 2). In the favoured transition state [**5B**], the tricarbonyliron group plays an important role in regulating the formation of the double bond. A similar chelation mechanism between iron and a carbonyl group has already been reported in the hydroxylation of a phenoxo ferric complex to a catecholate complex with *m*-chloroperoxy-benzoic acid [13]. In addition, the significance of the chelation between the iron and the ester is supported by the fact that, in the dehydration of the adducts prepared from the reaction of **2** with nucleophiles not having a heteroatom, such as ethylmagnesium bromide or vinylmagnesium bromide, the *Z*-olefin was not isolated at all. Transformation of **7** to the aldehyde **8** was easily accomplished by DIBAL-H reduction and subsequent mild oxidation using Mukaiyama's method [**14**].

Finally, the aldehydes **4** and **8** were converted to the corresponding retinoic acids (Scheme 3). The Emmons–Horner reaction of **4** with the C5-phosphonate **9** was carried out using n-BuLi to give the ester **10a** and its 13*Z*-isomer **10b**. The stereochemistry (*E*-form) of the 11,12 double bond in **10a,b** was determined on the basis of the coupling constants of the 11-H signal in the nuclear magnetic resonance (NMR) spectrum. It is noteworthy that, although the C5-phosphonate **9** was used as a mixture of double bonds ($\approx 4:1$) in the condensation, the ratio of the all-*E*-isomer in the products increased dramatically (all-*E* : 13*Z* $\approx 12:1$). After decomplexation of **10a**, the final transformation of **11** to the corresponding acid **12** [15] was achieved by hydrolysis using sodium hydroxide at 50 °C in 98% yield. In the same manner, the aldehyde **8** was converted to the corresponding 9*Z*-retinoic acid **15** [16] in good yield.

We have developed a stereoselective synthesis of trisubstituted olefins in the polyene chain, and this method will provide a novel route for the preparation of vitamin A and related compounds.

11*Z*-retinal

Construction of the *Z*-stereochemistry in a disubstituted olefin is essential for the preparation of 11*Z*-retinal. To achieve this, there are various methods, such as selective hydrogenation of the acetylene



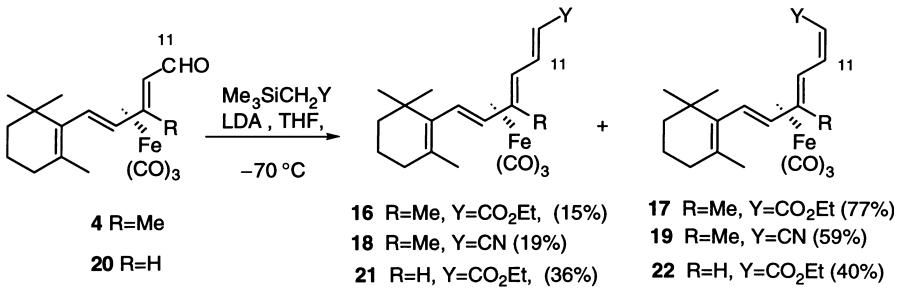
Scheme 3

compounds [17], olefination of the aldehyde using a phosphonate reagent having a fluorine atom [18] and the cross-coupling reaction of vinyl halides with metal olefins in the presence of a palladium catalyst [19]. However, these methods are not satisfactory for the preparation of 11*Z*-retinal **2** due to the low yield, low stereoselectivity and difficulty in synthesis of the starting materials. Recently, it was shown that the aldol condensation of aldehyde, containing the arene–tricarbonylchromium complex [20] or alkyne–hexacarbonyldicobalt complex [21], with silyl enol ether or silyl ketene acetal exhibited a different stereoselectivity compared with that of the uncomplexed aldehydes. These findings suggested that the aldehyde–tricarbonyliron complex is a strong candidate for the construction of disubstituted *Z*-olefin, and it was found that the aldehyde–tricarbonyliron complex **4** was a useful substrate for the preparation of 11*Z*-retinal **26** [22].

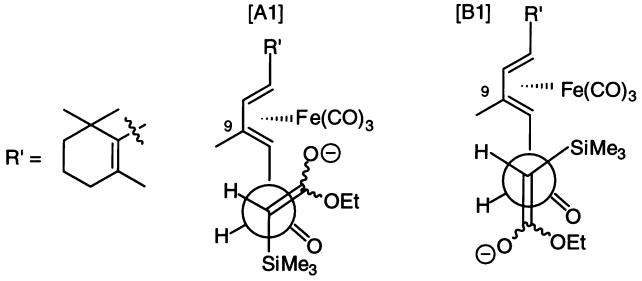
After many trials, we found that the Peterson reaction of **4** afforded the *Z*-olefin selectively (Scheme 4). Thus, treatment of **4** with the lithium enolate of ethyl trimethylsilylacetate in THF at −70 °C afforded the *Z*-isomer **17** (77%) predominantly, accompanied by the 11*E*-isomer **16** (15%). Similarly, in the reaction of trimethylsilylacetonitrile, the 11*Z*-nitrile **18** (59%) was obtained as the major product in addition to the 11*E*-isomer **17** (19%). In the Peterson reaction of **20**, which had no alkyl substituent at the 9 position, the *Z*-stereoselectivity was dramatically decreased, and almost the same amounts of *E*- and *Z*-isomers were obtained. Furthermore, when the non-complexed β-ionylideneacetaldehyde was treated with ethyl trimethylsilylacetate, the *E*-olefin was obtained as the major product (60%), accompanied by the *Z*-olefin (38%). These facts strongly suggest that both the tricarbonyliron complex and the 9 substituent are essential for *Z*-stereoselectivity during these Peterson reactions.

Although the mechanism of this high *Z*-selectivity is not yet clear, we propose the following explanation (Scheme 5). It is well known that, in the dienylaldehyde–tricarbonyliron complex, the carbonyl group of the aldehyde exists in both the s-*cis*- and s-*trans*-conformations around the C_{10}—C_{11} single bond [7]. However, if there is a substituent at the 9 position, such as **4**, the carbonyl group would have the s-*trans*-conformation in order to avoid the steric interaction between the carbonyl group of the aldehyde with the C9 substituent.

Among the six possible transition states, in which the lithium enolate approaches the aldehyde from the opposite side of the tricarbonyliron complex [23], transition states [**A1**] and [**B1**] may be favourable due to the steric repulsion between the 9-alkyl group and the substituent on the enolate. Thus, in these transition states, the hydrogen occupies the least-hindered position in the reaction intermediate. In these



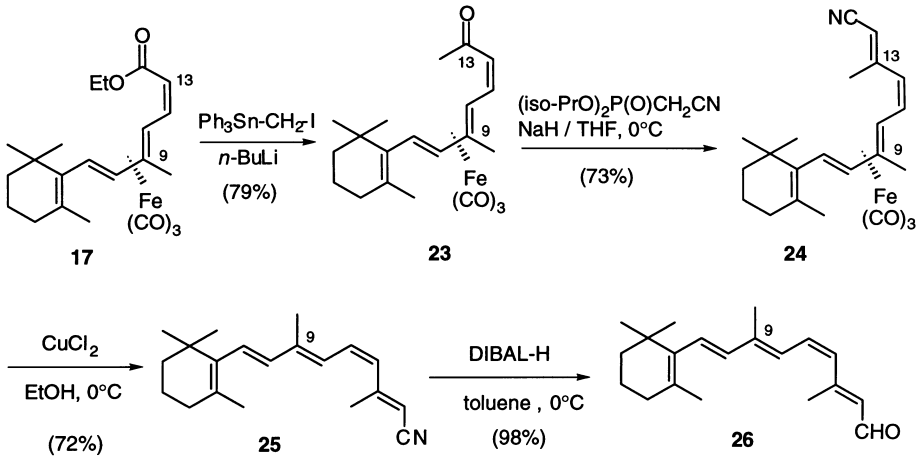
Scheme 4



Scheme 5

two transition states, [**B1**] has a more serious interaction between the trimethylsilyl group and the diene–tricarbonyliron complex compared with that of [**A1**]. Therefore, the transition state [**A1**] was preferred to afford the *Z*-olefin via syn elimination [24] from the β-hydroxysilyl adduct.

Subsequently, we focused our attention on the transformation of the ester **17** to 11*Z*-retinal **26** (Scheme 6). The conversion of the ester **17** to the C18-ketone–tricarbonyliron complex **23** by the reported method using triphenylstannylmethyllithium [25] smoothly proceeded to give the desired ketone **23** in excellent yield. The Emmons–Horner reaction of **23** with diisopropyl cyanomethylphosphonate using sodium hydride as a base gave the nitrile **24** as the single product. After decomplexation of **24** with copper(II) dichloride, the final transformation of **25** to 11*Z*-retinal **26** was achieved by DIBAL-H reduction.

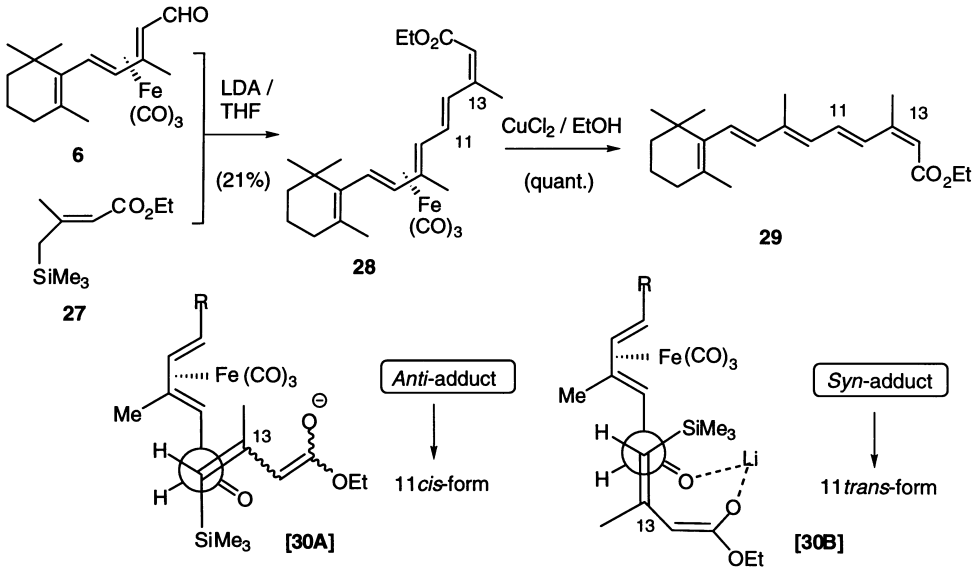


Scheme 6

Ethyl 13*Z*-retinoate

In the Peterson reaction of the aldehyde–tricarbonyliron complex, if we use the vinylouges silyated ester, such as **27** [26], the 11*Z*-ester is expected to be produced in a single step. However, the reaction of **4**

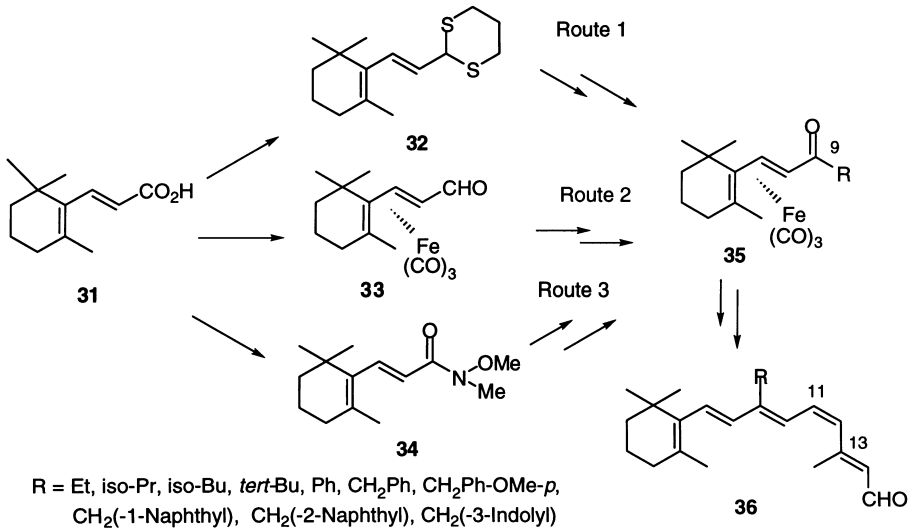
with the lithium enolate of **27** gave the 13*Z*-retinoate–tricarbonyliron complex **28** in low yield. The structure of this compound was determined after decomplexation. We speculated that the chelation intermediate [**30B**] plays an important role for the formation of this compound as shown in Scheme 7.



Scheme 7

SYNTHESIS OF 11*Z*-DEMETHYL-9-SUBSTITUTED RETINALS

The visual transduction process in rhodopsin is initiated by isomerization of the 11*Z*-retinylidene chromophore in rhodopsin to the all-*E*-isomer, accompanied by the conformational change of the apoprotein. Recently, it was suggested that an interaction between the 9-methyl group of retinal and the amino acid residues of the apoprotein had a strong effect on the biological function [27]. In order to clarify the effect of 9 substituents in the rhodopsin chromophore, we synthesized the 11*Z*-9-demethyl-9-substituted retinals (Scheme 8) [28,29].



Scheme 8

As mentioned in the previous section, a stereoselective synthesis of 11*Z*-retinal was developed from the β-ionone–tricarbonyliron complex. Therefore, β-ionone analogue–tricarbonyliron complexes (**35**), in

which the methyl group at the 9 position is replaced by other substituents, are the key intermediates for the synthesis of 11*Z*-9-substituted retinals. We have prepared these analogues by three methods from the acid **31**; (i) the alkylation of the SS-acetal **32**; (ii) the alkylation of the aldehyde–tricarbonyliron complex **33** by Grignard reagent and subsequent oxidation; (iii) the conversion of *N*-methoxy-*N*-methylamide **34** to the ketone derivatives using organometallic reagents. These β-ionone analogue–tricarbonyliron complexes **35** were all transformed to the corresponding 11*Z*-retinal analogues by our developed method in good yields.

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