

STERESELECTIVE SYNTHESIS OF 7*E*,9*E*- AND 7*E*,9*Z*- β -IONYLIDENE-ACETALDEHYDES BY USE OF TRICARBONYL IRON COMPLEX

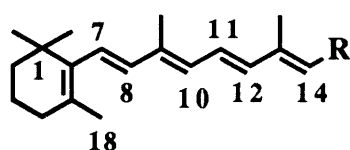
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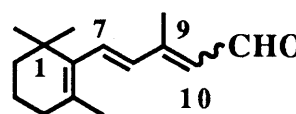
Stereoselective synthesis of 7*E*,9*E*- and 7*E*,9*Z*- β -ionylideneacetaldehydes was accomplished from the β -ionone tricarbonyl iron complex, and the latter was converted to 9*Z*-retinoic acid.

KEYWORDS β -ionylideneacetaldehyde; tricarbonyl iron complex; stereoselective synthesis; retinoid

It is well known that retinoids **1** exhibit different biological activities according to their stereochemistry. For example, the chromophore of the visual pigment rhodopsin is 11*Z*-retinal¹⁾ and the ligands of RAR and RXR, which are nuclear regulators to control gene transcription, are all-*E*- and 9*Z*-retinoic acids respectively.²⁾ β -Ionylideneacetaldehyde **2** is a very important compound for the synthesis of retinoids and carotenoids.³⁾ Although there have been a number of reports on dealing with the synthesis of **2**,⁴⁾ none of the stereoselective syntheses of **2** has been reported. In this paper we wish to describe the stereoselective synthesis of 9*E*- and 9*Z*-isomers of **2** from the β -ionone tricarbonyl iron complex.



- 1a:** R=CH₂OH retinol
b: R=CHO retinal
c: R=CO₂H retinoic acid



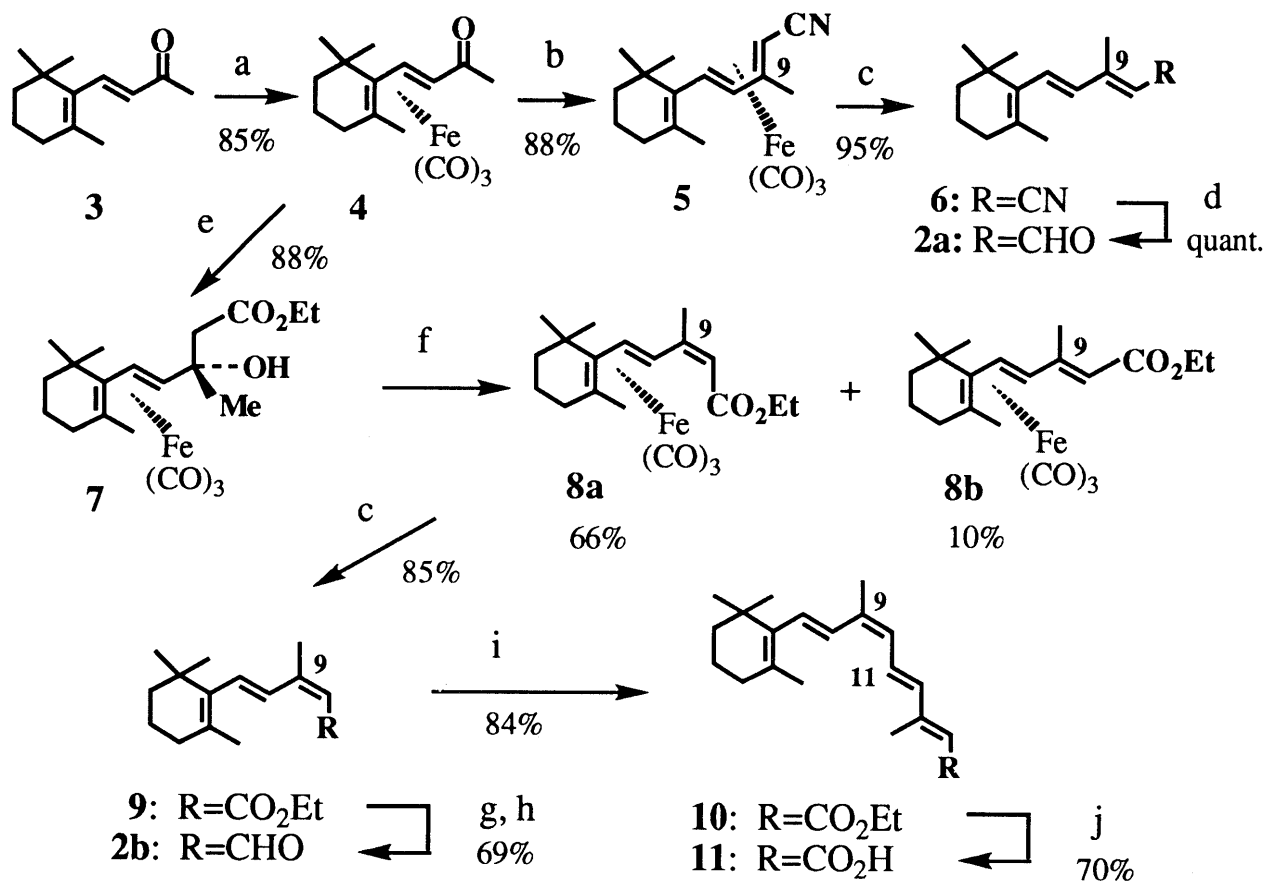
- 2a:** 9*E*
b: 9*Z*

Treatment of the β -ionone tricarbonyl iron complex **4**,^{5,6)} prepared from the reaction of β -ionone **3** with triiron dodecacarbonyl in benzene, with lithium acetonitrile in THF at -70°C afforded **5**^{5,6)} in 88% yield. This reaction involves addition of acetonitrile, dehydration, and migration of tricarbonyl iron.⁷⁾ The geometry of the double bond at 9 position in **5** was determined as *E* compared to the corresponding β -ionylideneacetonitrile **6**⁸⁾ after oxidative decomplexation using copper(II) chloride in ethanol.⁹⁾ The transformation of **6** to the 7*E*,9*E*-aldehyde **2a** was achieved by DIBAL reduction quantitatively.

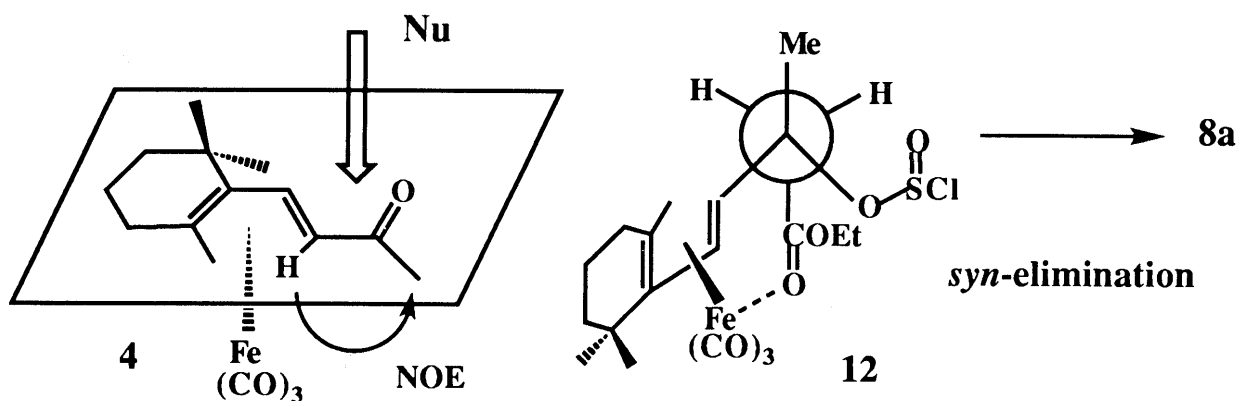
Subsequently, we focused our attention on the stereoselective synthesis of 7*E*,9*Z*-aldehyde **2b**. The reaction of **4** with lithium enolate of ethyl acetate in THF at -70°C gave the adduct **7**^{5,10)} as a single product in 88% yield. The structure of **7** was deduced from the reaction mechanism of *E*-dienone complex having the *s-cis* conformation of enone.¹¹⁾ Dehydration of **7** by thionyl chloride afforded the 9*Z*-ester **8a** predomi-

This paper is dedicated to Professor Yasumitsu Tamura on the occasion of his 70th birthday.

nantly (66%) accompanied by the 9*E*-isomer **8b** (10%).^{5,10} The stereochemistry of the newly produced double bond of these compounds was determined by the transformation to the corresponding β -ionylidene-esters^{4b} after oxidative decomplexation. We speculated that the chelation between the iron and ester group in a reaction intermediate such as **12** plays an important role in the predominant formation of the 9*Z*-isomer.¹² The ester **9** derived from **8a** was converted to the aldehyde **2b** by LiAlH₄ reduction and following MnO₂ oxidation.



a) Fe₃(CO)₁₂ / C₆H₆, reflux, b) LDA, MeCN / THF, -70°C, c) CuCl₂ / EtOH, r.t., d) DIBAL / CH₂Cl₂, r.t., e) LDA, AcOEt / THF, -70°C, f) SOCl₂ / pyridine, 0°C, g) LiAlH₄ / Et₂O, r.t., h) MnO₂ / CH₂Cl₂, r.t., i) *n*-BuLi, (EtO)₂P(O)CH₂(CH₃)C=CHCO₂Et / THF, 0°C, j) 25% NaOH / MeOH, 50°C.



The Emmons-Horner reaction of **2b** with C5-phosphonate was carried out in the presence of *n*-BuLi to give the ester **10**,^{5,13} in which the geometry of the 11,12 double bond was determined as *E* from the coupling constant of 11-H signal in its NMR. The final transformation of **10** to the corresponding acid **11**¹⁴ was achieved by hydrolysis using sodium hydroxide at 50°C in 70% yield.

In summary, we developed the stereoselective synthesis of **2** for the first time, which includes the first predominant synthesis of the *Z*-trisubstituted olefin in the polyene chain. This method will provide a novel route for the preparation of all-*E*- or 9*Z*-vitamin A and related compounds.

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- Satisfactory ¹H-NMR, IR and MS spectral data were obtained.
- ¹H-NMR data for compounds **4** and **5** are as follows:
For **4** : (200 MHz, CDCl₃) δ 1.22 (3H, s, Me), 1.41 (3H, s, Me), 1.46 (3H, s, Me), 1.5-1.7 (4H, m, CH₂ × 2), 1.8-2.1 (2H, m, CH₂), 2.17 (3H, s, COMe), 2.40 (1H, d, *J* = 9 Hz, 8-H), 5.66 (1H, d, *J* = 9 Hz, 7-H); For **5** : (200 MHz, CDCl₃) δ 0.48 (1H, s, 10-H), 1.13 (3H, s, Me), 1.24 (3H, s, Me), 1.4-1.6 (4H, m, CH₂ × 2), 1.83 (3H, s, Me), 1.95 (1H, d, *J* = 11 Hz, 7-H), 2.02 (2H, br t, *J* = 7.5 Hz, CH₂), 2.51 (3H, s, Me), 5.89 (1H, d, *J* = 11 Hz, 8-H).
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- ¹H-NMR data for compounds **7**, **8a** and **8b** are as follows:
For **7** : (200 MHz, CDCl₃) δ 1.07 (3H, s, Me), 1.28 (3H, t, *J* = 7 Hz, Me), 1.37 (3H, s, Me), 1.43 (3H, s, Me), 1.42 (3H, s, Me), 1.4-1.6 (4H, m, CH₂ × 2), 1.7-2.0 (2H, m, CH₂), 2.12 (1H, d, *J* = 9 Hz, 8-H), 2.63 (2H, s, CH₂), 3.67 (1H, s, OH disappeared with D₂O), 4.21 (2H, q, *J* = 7 Hz, OCH₂), 5.17 (1H, d, *J* = 9 Hz, 7-H); For **8a** : (200 MHz, CDCl₃) δ 1.28 (3H, t, *J* = 7 Hz, Me), 1.37 (3H, s, Me), 1.39 (3H, s, Me), 1.43 (3H, s, Me), 1.4-1.7 (4H, m, CH₂ × 2), 1.79 (3H, s, Me), 1.8-2.0 (2H, m, CH₂), 4.18 (2H, q, *J* = 7 Hz, OCH₂), 4.72 (1H, d, *J* = 10 Hz, 8-H), 5.33 (1H, d, *J* = 10 Hz, 7-H), 5.64 (1H, s, 10-H); For **8b** : (200 MHz, CDCl₃) δ 1.28 (3H, s, Me), 1.30 (3H, t, *J* = 7 Hz, Me), 1.43 (3H, s, Me), 1.49 (3H, s, Me), 1.5-1.8 (4H, m, CH₂ × 2), 1.8-2.0 (2H, m, CH₂), 2.27 (3H, s, Me), 2.67 (1H, d, *J* = 9 Hz, 8-H), 4.18 (2H, q, *J* = 7 Hz, OCH₂), 5.38 (1H, d, *J* = 9 Hz, 7-H), 5.79 (1H, s, 10-H).
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- The further mechanistic study is now in progress.
- Although we used C5-phosphonate as a mixture of double bond [*ca.* 1:1], the product obtained in the condensation was a single isomer; see R. N. Gedye, K. C. Westaway, P. Arora, R. Bisson, A. H. Khalil, *Can. J. Chem.*, **55**, 1218 (1977).
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