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

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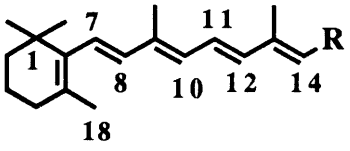
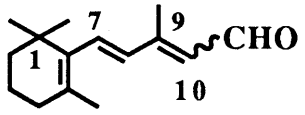
Stereoselective synthesis of 7*E*,9*E*- and 7*E*,9*Z*-β-ionylideneacetaldehydes was accomplished from the β-ionone tricarbonyl iron complex, and the latter was converted to 9*Z*-retinoic acid.

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*-retinal[1] 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=CH_2OH retinol
b: R=CHO retinal
c: R=CO_2H retinoic acid



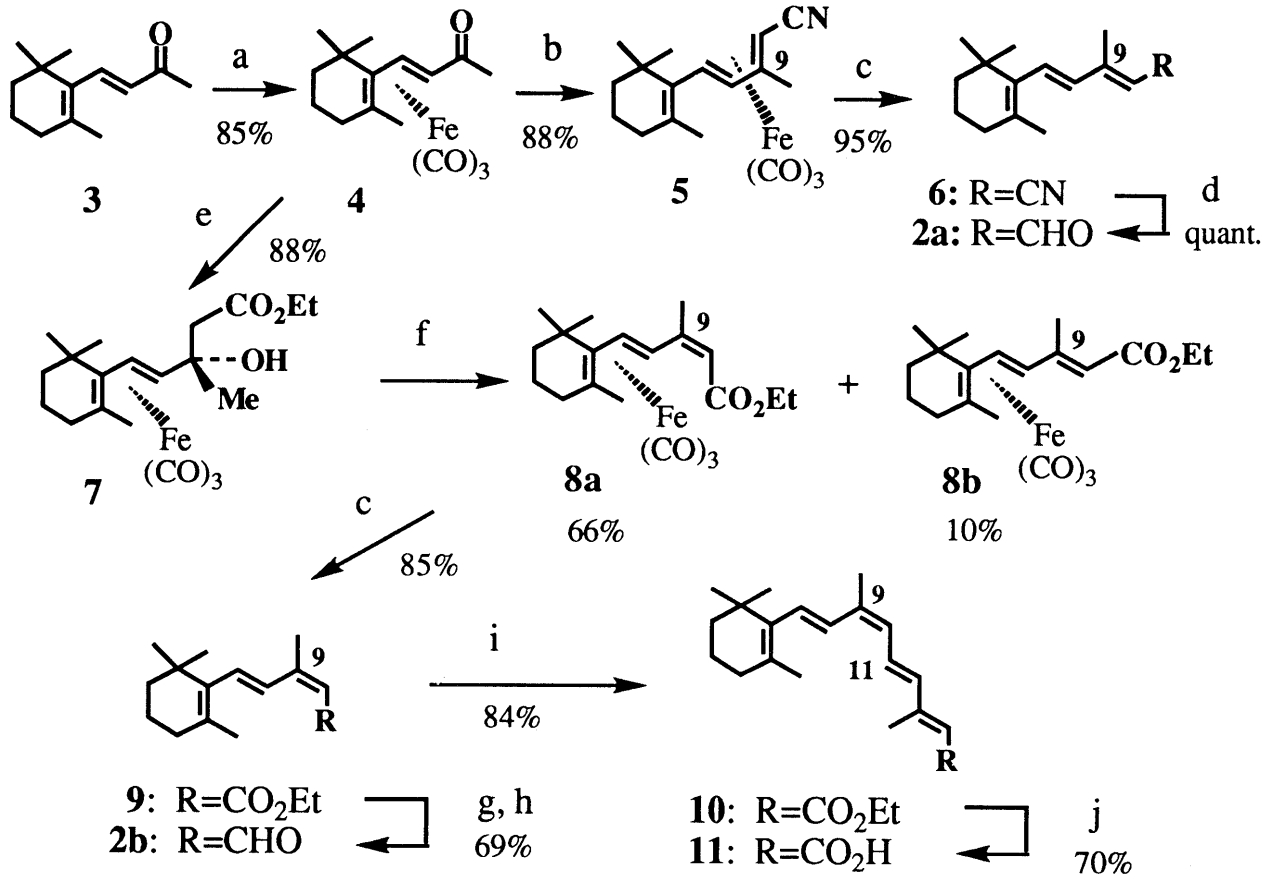
2a: 9*E*
b: 9*Z*

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℃ 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.

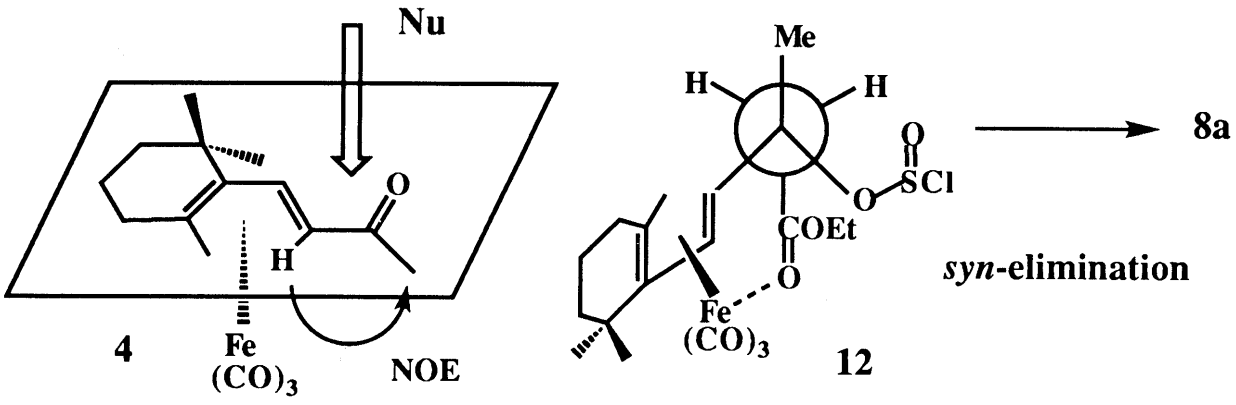
Subsequently, we focused our attention on the stereoselective synthesis of 7*E*,9*Z*-aldehyde **2b**. The reaction of **4** with lithium enolate of ethyl acetate in THF at -70℃ gave the adduct **7**[5,10] as a single product in 88% yield. The structure of **7** was deduced from the reaction mechanism 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 stereochemisry 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 $LiAlH_4$ reduction and following MnO_2 oxidation.



a) $Fe_3(CO)_{12}$ / C_6H_6, reflux, b) LDA, MeCN / THF, -70°C, c) $CuCl_2$ / EtOH, r.t., d) DIBAL / CH_2Cl_2, r.t., e) LDA, AcOEt / THF, -70°C, f) $SOCl_2$ / pyridine, 0°C, g) $LiAlH_4$ / Et_2O, r.t., h) MnO_2 / CH_2Cl_2, r.t., i) *n*-BuLi, $(EtO)_2P(O)CH_2(CH_3)C{=}CHCO_2Et$ / 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℃ 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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5) Satisfactory ^{1}H-NMR, IR and MS spectral data were obtained.
6) ^{1}H-NMR data for compounds **4** and **5** are as follows:
For **4** : (200 MHz, $CDCl_3$) δ 1.22 (3H, s, Me), 1.41 (3H, s, Me), 1.46 (3H, s, Me), 1.5-1.7 (4H, m, $CH_2 \times 2$), 1.8-2.1 (2H, m, CH_2), 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, $CDCl_3$) δ 0.48 (1H, s, 10-H), 1.13 (3H, s, Me), 1.24 (3H, s, Me), 1.4-1.6 (4H, m, $CH_2 \times 2$), 1.83 (3H, s, Me), 1.95 (1H, d, J = 11 Hz, 7-H), 2.02 (2H, br t, J = 7.5 Hz, CH_2), 2.51 (3H, s, Me), 5.89 (1H, d, J = 11 Hz, 8-H).
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10) ^{1}H-NMR data for compounds **7**, **8a** and **8b** are as follows:
For **7** : (200 MHz, $CDCl_3$) 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, $CH_2 \times 2$), 1.7-2.0 (2H, m, CH_2), 2.12 (1H, d J=9 Hz, 8-H), 2.63 (2H, s, CH_2), 3.67 (1H, s, OH disappeared with D_2O), 4.21 (2H, q, J=7 Hz, OCH_2), 5.17 (1H, d, J = 9 Hz, 7-H); For **8a** : (200 MHz, $CDCl_3$) 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, $CH_2 \times 2$), 1.79 (3H, s, Me), 1.8-2.0 (2H, m, CH_2), 4.18 (2H, q, J=7 Hz, OCH_2), 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, $CDCl_3$) 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, $CH_2 \times 2$), 1.8-2.0 (2H, m, CH_2), 2.27 (3H, s, Me), 2.67 (1H, d, J = 9 Hz, 8-H), 4.18 (2H, q, J=7 Hz, OCH_2), 5.38 (1H, d, J = 9 Hz, 7-H), 5.79 (1H, s, 10-H).
11) R. Grée, *Synthesis*, **1989**, 341.
12) The further mechanistic study is now in progress.
13) 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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