Pergamon

*Bioorganic & Medicinal Chemistry Letters*, Vol. 6, No. 17, pp. 2049-2052, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00369-1

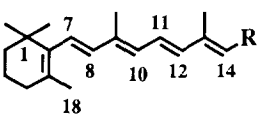
# STEREOSELECTIVE SYNTHESIS OF 11*Z*-RETINAL BY USE OF TRICARBONYLIRON COMPLEX

Akimori Wada, Yukiko Tanaka, Naoko Fujioka and Masayoshi Ito*

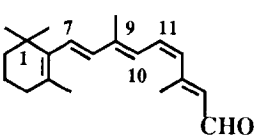
*Kobe Pharmaceutical University, 4-19-1, Motoyamakita-machi, Higashinada, Kobe 658, Japan*

**Abstract:** Peterson reaction of 7*E*,9*E*-β-ionylideneacetaldehyde-tricarbonyliron complex with ethyl trimethylsilyl acetate afforded *Z*-olefin in high stereoselectivity, which was converted to the corresponding 11*Z*-retinal in excellent yield. Copyright © 1996 Elsevier Science Ltd

It is well known that retinoids **1** exhibit the different biological activities depending upon their stereochemistry. For example, the chromophore of the visual pigment rhodopsin is 11*Z*-retinal **2**[1,2] and the ligands of RAR and RXR, which are nuclear regulators to control gene transcription, are all-*E*- and 9*Z*-retinoic acids, respectively.[1,3] Although there were a number of papers on dealing with the synthesis of retinoids,[1] only a few of the stereoselective synthesis has been reported.[4] In connection with our study on the stereoselective synthesis of retinoids and carotenoids,[5] we wish to describe here the first stereoselective synthesis of 11*Z*-retinal by Peterson reaction from the β-ionylideneacetaldehyde-tricarbonyliron complex.



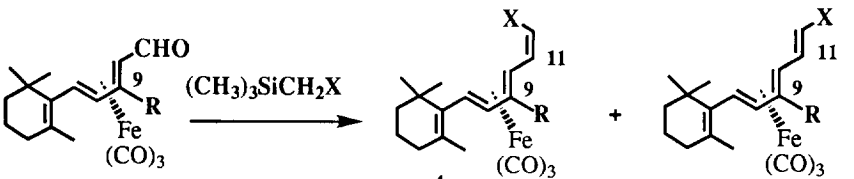

**1a: R=$CH_2OH$** Retinol
**b: R=CHO** Retinal
**c: R=$CO_2H$** Retinoic acid



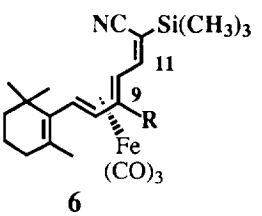

**2**

Treatment of the β-ionylideneacetaldehyde-tricarbonyliron complex **3a**,[5] prepared from the reaction of β-ionone-tricarbonyliron complex with lithium acetonitrile followed by DIBAL reduction, with lithium enolate of ethyl trimethylsilylacetate in THF at -70℃ afforded the 11*Z*-isomer **4a** (X=$CO_2Et$)[6,7] predominantly (77%) accompanied by 11*E*-isomer **5a** (X=$CO_2Et$)[6,7] (15%). The

geometry of the newly produced double bond at the 11 position in **4a** and **5a** was determined from the coupling constant in their NMR spectra. Similarly, in the reaction of trimethylsilylacetonitrile the 11*Z*-nitrile **4a** (X=CN)[6] was obtained as a major product in addition to the 11*E*-isomer **5a** (X= CN)[6] and trimethylsilylnitrile **6**[6] (16%), which was seemed to be produced by dehydration from the reaction intermediate. In order to certain the generality of this *Z*-selectivity, we prepared β-ionylideneacetaldehyde-tricarbonyliron complex derivatives (**3b-d**)[8] and their Peterson reaction was carried out (Table). In the case of 9-demethyl derivative, *Z*-selectivity was decreased dramatically (run 5). The bulky 9-substituent group caused slightly the decrease of yield, however, *Z*-selectivity was not affected seriously. In contrast to these results, *E*-selectivity was observed in the reaction of uncomplexed β-ionylideneacetaldehyde of **3a** with ethyl trimethylsilylacetate (*E*-isomer, 60%: *Z*-isomer, 32%).




**3** **a: R=$CH_3$**
**b: R=$CH_2CH_3$**
**c: R=$CH(CH_3)_2$**
**d: R=H**



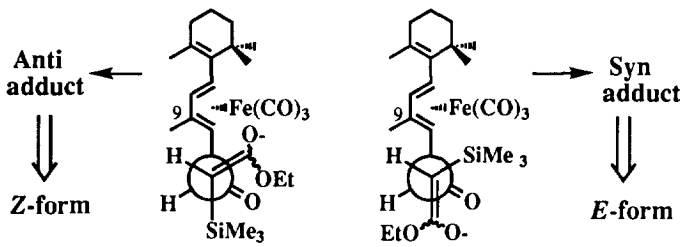

**6**

Table. Peterson Reaction of Aldehyde-tricarbonyliron Complexes.

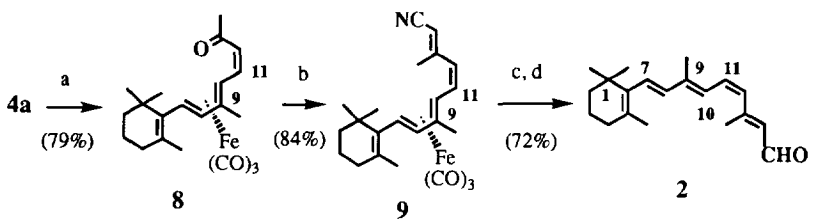
| Runs | Aldehydes R | X | Yield of **4** (%) | Yield of **5** (%) |
|---|---|---|---|---|
| 1 | $CH_3$ | $CO_2CH_2CH_3$ | 77 | 15 |
| 2 | $CH_3$ | CN | 59 | 19 |
| 3 | $CH_2CH_3$ | $CO_2CH_2CH_3$ | 63 | 17 |
| 4 | $CH(CH_3)_2$ | $CO_2CH_2CH_3$ | 56 | 13 |
| 5 | H | $CO_2CH_2CH_3$ | 51 | 43 |

The mechanism of this highly *Z*-selective Peterson reaction is not clear yet. However, the above facts suggest that both tricarbonyliron complexation and the 9-substituent group are essential

for this selectivity. Among the six possible transition states,[9] transition states **7a** and **7b** may be favorable due to the consideration of steric repulsion between the 9-alkyl group and the substituents on the enolate. In these two transition states, **7b** has a serious interaction between the trimethylsilyl group and the diene-ticarbonyliron complex compared with that of **7a**. Therefore, the transition state **7a** was preferred to afford the Z-olefin *via* syn elimination from the β-hydroxysilyl adduct.




The 11Z-ester **4a** was transformed to the C18-ketone-tricarbonyliron complex **8**[6,10] using triphenylstannylmethyllithium[11] in excellent yield. The Emmons-Horner reaction of **8** with diisopropyl cyanomethylphosphonate gave the nitrile **9**[6,10] as a sole product, which was converted to the 11Z-retinal **2**[12] by the sequence of decomplexation and DIBAL reduction. The stereochemistry of an 11 position was unchanged during these transformations.




**Reagents**: (a) $Ph_3SnCH_2I$, *n*-BuLi; (b) $(i\text{-PrO})_2P(O)CH_2CN$, NaH; (c) $CuCl_2$; (d) DIBAL

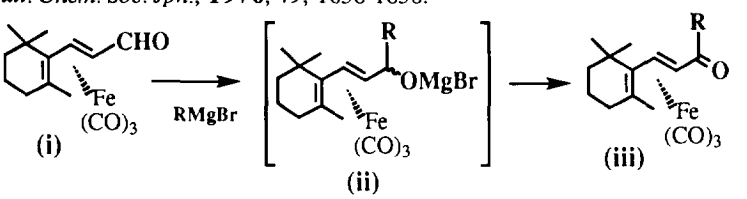
In summary, we developed the new method for the stereoselective Z-olefin synthesis using the Peterson reaction of tricarbonyliron complex and also achieved the stereoselective synthesis of 11Z-retinal **2** for the first time applying this methodology. This method would provide the novel route for the preparation of stereoselective vitamin A and related compounds.

**Acknowledgment:** This work was supported in part by the Science Research Promotion Found from Japan Private School Promotion Foundation.

**References and Notes**

1. "The Retinoids", 2nd ed., Sporn, M. B.; Roberts, A. B.; Goodman, D. S.; Eds; Raven Press, Ltd, New York, 1994.
2. Recent review: Rando, R. R. *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 461-480.

3. Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichele, G.; Evans, R. M.; Thaller, C. *Cell*, **1992**, *68*, 397-406, and references cited therein.
4. Although several methods for the formation of 11Z-olefin have been reported, the low yield and the low stereoselectivity are disadvantages that remain to be solved, see; Hosoda, A.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.*, **1987**, *28*, 65-68; Mead, D.; Asato, A. E.; Denny, M.; Liu, R. S. H.; Hanzawa, Y., Taguchi, T.; Yamada, A.; Kobayashi, N.; Hosoda, A.; Kobayashi, Y. *Tetrahedron Lett.*, **1987**, *28*, 259-262; Trehan, A.; Liu, R. S. H. *Tetrahedron Lett.*, **1988**, *29*, 419-422.
5. Wada, A.; Hiraishi, S.; Ito, M. *Chem. Pharm. Bull.*, **1994**, *42*, 757-759.
6. Satisfactory $^1$H-NMR, IR and MS spectral data were obtained.
7. $^1$H-NMR data for compounds **4** and **5** are as follows:
For **4a** : (300 MHz, $CDCl_3$) δ 1.17 (3H, s, 1- Me), 1.28 (3H, s, 1-Me), 1.29 (3H, t, *J*=7, Me), 1.4 -1.7 (4H, m, 2,3-$H_2$), 1.86 (3H, s, 5-Me), 2.01 (2H, t, *J*=7, 4-$H_2$), 2.34 (1H, d *J*=11, 7-H), 2.36 (3H, s, 9-Me), 3.36 (1H, d, *J*=11, 10-H), 4.18 (2H, q, *J*=7, $CH_2$), 5.50 (1H, d, *J*=11, 8-H), 5,70 (1H, d, *J*=11, 12-H), 6.39 (1H, t, *J*=11, 11-H); For **5a** : (300 MHz, $CDCl_3$) δ 1.15 (3H, s, 1- Me), 1.26 (3H, s, 1-Me), 1.29 (3H, t, *J*=7, Me), 1.4 -1.6 (4H, m, 2,3-$H_2$), 1.56 (1H, d, *J*=11, 10-H), 1.81 (3H, s, 5-Me), 2.01 (2H, t, *J*=7, 4-$H_2$), 2.11 (1H, d, *J*=11, 7-H), 2.40 (3H, s, 9-Me), 4.19 (2H, q, *J*=7, $OCH_2$), 5.72 (1H, d, *J*=11, 8-H), 5.98 (1H, d, *J*=15, 12-H),7.09 (1H, dd, *J*=15,11, 11-H).
8. These compounds were prepared from β-ionone-tricarbonyliron complex analogs (**iii**) in the same manner described for **3a** and the analogs (**iii**) were obtained from dienylaldehyde-tricarbonyliron complex (**i**) by Grignard reaction followed by oxidation using diazocarbonyl-dipiperidine without decomplexation. For oxidation, see; Saigo, K.; Morikawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1976**, *49*, 1656-1658.



(i) (ii) (iii)

9. A similar mechanistic consideration of metalcarbonyl complex has already been reported; Davis, S, G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 393-406; Mukai, C.; Cho, W. J.; Kim, I. J.; Kido, M.; Hanaoka, M. *Tetrahedron*, **1991**, *47*, 3007-3036.
10. $^1$H-NMR data for compounds **8** and **9** are as follows,
For **8** : (300 MHz, $C_6D_6$) δ 1.21 (3H, s, 1-Me), 1.33 (3H, s, 1-Me), 1.3-1.5 (4H, m, 2,3-$H_2$), 1.80 (2H, t, *J*=6.5, 4-$H_2$), 1.83 (6H, s, 5,13-Me), 1.90 (3H, s, 9-Me), 2.59 (1H, d, *J*=11, 7-H), 3.80 (1H, d, *J*=11, 10-H), 5.53 (1H, *J*=11, 8-H), 5.60 (1H, d, *J*=11, 12-H), 6.05 (1H, t, J=11, 11-H); For **9** : (300 MHz, $C_6D_6$) δ 1.16 (3H, s, 1-Me), 1.27 (3H, s, 1-Me), 1.3-1.5 (4H, m, 2,3-$H_2$), 1.68 (3H, s, 5-Me), 1.74-1.82 (2H, m, 4-$H_2$), 1.88 (3H, s, 13-Me), 1.95 (3H, s, 9-Me), 2.02 (1H, d, *J*=11, 7-H), 4.82 (1H, s, 14-H), 5.28 (1H, d, *J*=12, 12-H), 5.51 (1H, d, *J*=11, 8-H), 5.58 (1H, br t, *J*=12, 11-H).
11. Sato, T.; Matsuoka, H.; Igarashi, T.; Minomura, M.; Murayama, E. *J. Org. Chem.*, **1988**, *53*, 1207-1212.
12. Liu, R. S. H.; Asato, A. E. *Tetrahedron*, **1984**, *40*, 1931-1969; Katsuta, Y.; Sakai, M.; Ito, M. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2185-2192.

(*Received in Japan* 20 *June* 1996; *accepted* 23 *July* 1996)