

HIGHLY CIS-SELECTIVE WITTIG REACTION OF OXIDO-ALLYLIC PHOSPHORANE
WITH ALDEHYDE. AN EFFICIENT SYNTHESIS OF 11-CIS-RETINOIDS

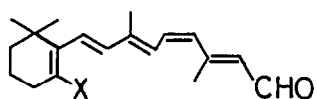
Akihiko Hosoda, Takeo Taguchi, and Yoshiro Kobayashi*

Tokyo College of Pharmacy, 1432-1 Korinouchi, Hachioji, Tokyo 192-03, Japan

Summary: An efficient and highly stereoselective preparation of (2E,4Z)-dienyl alcohols was explored by reactions of (E)-oxido-allylic phosphorane with aldehydes. 11-cis-Retinals could be effectively prepared.

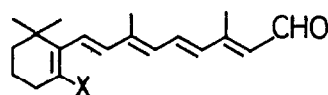
Isomers of retinal serve as chromophores for two classes of biologically important photoreceptor proteins, rhodopsin and bacteriorhodopsin. Investigations on the structures and the mechanism of functions of both proteins have been extensively studied using artificial pigments, among which fluorinated analogs are involved.¹⁾ Recently, we reported the preparation of all-trans-18,18-trifluororetinal(2b)²⁾ and its artificial pigment, trifluorobacteriorhodopsin(F₃-bR).³⁾ The fact that F₃-bR, unlike natural bR, does not translocate protons due to the presence of an electronegative trifluoromethyl group indicates that a proper fit of the chromophore in the binding site is required for proton translocation.³⁾ In visual pigment, rhodopsin, the chromophore is 11-cis-retinal(1a). Although several methods for the preparation of 11-cis isomer have been reported, the low stereoselectivity of the synthetic reactions and difficulty in the separation of the desired 11-cis isomer from the resulting reaction mixture due to its instability are problems that remain to be solved.⁴⁾

We report an efficient and highly selective synthesis of (2E,4Z)-dienyl alcohol(5) by reactions of (E)-oxido-allylic phosphoranes derived from 4a and 4c with aldehydes and its application to the synthesis of 11-cis-retinals including the fluoro analog(1b) through reactions of 4a with β-ionylidene acetaldehyde derivatives(3a and 3b).



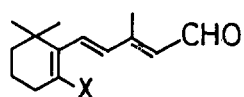
1a X=CH₃

1b X=CF₃



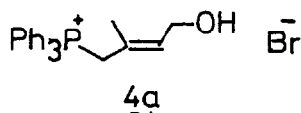
2a X=CH₃

2b X=CF₃



3a X=CH₃

3b X=CF₃



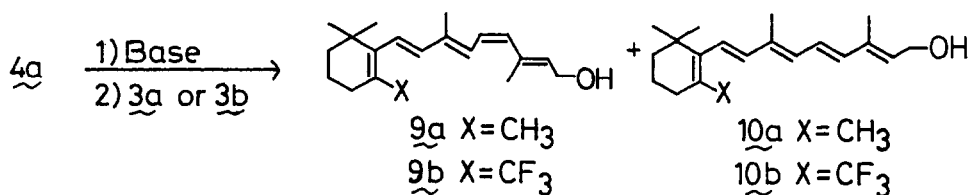
4a

The results of the reactions of the phosphonium salt (4) with aldehydes are summarized in Table 1. In the case of the (E)-phosphonium salt, 4b, a mixture of four possible isomers (5b-8b) was obtained (entry 8,9) as a result of isomerization of the double bond in the phosphorane through resonance and non-selective reaction with aldehyde.⁷⁾ With the oxido-allylic phosphorane derived from 4a, only 5a(2E,4Z) and 7a(2E,4E) were obtained without isomerization of the double bond existing in the phosphorane. When the reaction was conducted using a lithium base in THF, cis-selectivity was moderate with aliphatic aldehyde (entry 1), but trans-isomer was still predominant with aromatic aldehyde (entry 5). No appreciable increase in cis-selectivity was observed in either case by the addition of HMPA as a co-solvent. On using potassium hexamethyldisilazide[KN(TMS)₂] as the base, the desired cis-isomer 5a was obtained with high stereoselectivity (>90%) in the reactions of both aromatic and aliphatic aldehydes.

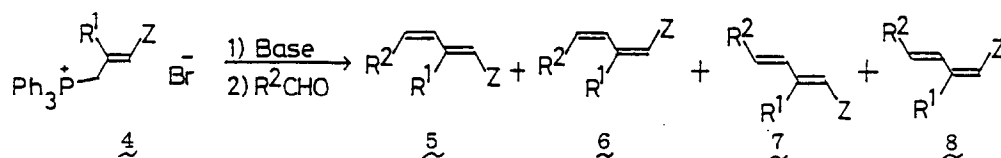
Similar tendencies were also found in reactions of the oxido-allylic phosphorane derived from 4c with aldehydes (entry 10-13).

11-cis-Retinals, 1a and 1b, were effectively prepared through the reactions of the phosphorane derived from 4a with 3a and 3b, respectively. Thus, following the generation of ylid by treating 4a with KN(TMS)₂ in THF for 1h, the addition of aldehyde, 3a, at -78°C and subsequent stirring at room temperature for 1h afforded retinols, 9a and 10a, in 40% yield in a ratio of 83:17 for 11-cis, 9a, and all-trans isomer, 10a as determined by ¹H-nmr(400 MHz). MnO₂ oxidation of the retinol mixture and subsequent purification by hplc afforded 11-cis-retinal, 1a. High stereoselectivity was also found in the reaction with trifluoro derivative, 3b.

The Wittig reaction of aldehydes with salt-free alkylidene triphenylphosphorane is an excellent method for synthesis of cis-alkene.⁹⁾ In contrast, the reaction with oxido-type or allylic-type phosphorane has been reported to proceed with trans-selectivity or non-selectivity.^{10,11)} Both β- and γ-oxido-type phosphorane particularly enhance trans-selectivity through the interconversion of the oxaphosphetane intermediates.¹⁰⁾ Although details of the



X	Base	Yield(%)	11-cis(<u>9</u>) : all-trans(<u>10</u>)
CH ₃	KN(TMS) ₂	40	83 : 17
CH ₃	n-BuLi	31	37 : 63
CF ₃	KN(TMS) ₂	19	88 : 12



4a-8a R¹=CH₃, Z=CH₂OH; 4b-8b R¹=CH₃, Z=COOMe; 4c-8c R¹=H, Z=CH₂OH

Table 1. Reactions of 4a, 4b or 4c with aldehyde^a

entry	P-salt(<u>4</u>) ^b	R ² CHO	Base	Solvent	Yield(%)	<u>5</u> : <u>6</u> : <u>7</u> : <u>8</u> ^e
1	<u>4a</u>	n-C ₅ H ₁₁	n-BuLi	THF	30	78: 0 : 22: 0
2	<u>4a</u>	n-C ₅ H ₁₁	KN(TMS) ₂	THF	67	91: 0 : 9: 0
3	<u>4a</u>	n-C ₅ H ₁₁	KN(TMS) ₂	Et ₂ O	38	96.5: 0 : 3.5: 0
4	<u>4a</u> ^c	n-C ₅ H ₁₁	KN(TMS) ₂	Et ₂ O	42	92: 0 : 8: 0
5	<u>4a</u>	Ph	n-BuLi	THF	33	18: 0 : 82: 0
6	<u>4a</u>	Ph	KN(TMS) ₂	THF	57	83: 0 : 17: 0
7	<u>4a</u> ^d	Ph	KN(TMS) ₂	THF	54	91: 0 : 9: 0
8	<u>4b</u>	Ph	n-BuLi	THF	quant.	16: 33: 28: 23
9	<u>4b</u>	Ph	KN(TMS) ₂	THF	68	10: 20: 43: 27
10	<u>4c</u>	n-C ₅ H ₁₁	n-BuLi	THF	80	81: - : 12: -f
11	<u>4c</u>	n-C ₅ H ₁₁	KN(TMS) ₂	THF	60	95: 0 : 5: 0
12	<u>4c</u>	Ph	n-BuLi	THF	54	49: - : 32: -g
13	<u>4c</u>	Ph	KN(TMS) ₂	THF	35	83: 0 : 17: 0

(a) After treatment of the phosphonium salt with base at -78°C for 5 min, then at room temperature for 1h, aldehyde was added at -78°C and then the mixture was stirred for 1h at -78°C to room temperature.

(b) molar ratio, 4a or 4c/base/aldehyde=1.5/3.2/1, 4b/base/aldehyde=1.5/1.5/1 except for entries 4 and 7 (c) 4a/base/aldehyde=3/6.4/1

(d) 4a/base/aldehyde=0.83/1.8/1 (e) determined by nmr(400 MHz)⁸⁾

(f) 6c+8c(R=n-C₅H₁₁), 7% ratio (g) 6c+8c(R²=Ph), 19% ratio

mechanism of the present reaction are not clear, the results indicate oxido-allylic phosphorane to possibly have a nature distinct from those of oxido-type and allylic-type phosphoranes. Corey reported the non-selective synthesis of 5S,12S-diHETE through reaction of the particular oxido-allylic phosphorane generated by lithium base.¹²⁾ Selection of base for generating phosphorane is of particular importance in the present case.

In conclusion, the Wittig reaction of oxido-allylic phosphorane is an efficient method for the synthesis of (2E,4Z)-dienyl alcohols and this opens a new entry for 11-cis-retinoids.

Acknowledgement: This work was supported in part by a grant-in aid from Toray Foundation for the Promotion of Science and Technics.

References and Notes

- 1) A. E. Asato and R. S. H. Liu, *Tetrahedron Lett.*, 27, 3337(1986) and references cited therein; M. Sheves, A. Albeck, N. Friedman, and M. Ottolenghi, *Proc. Natl. Acad. Sci. USA*, 83, 3262(1986).
- 2) T. Taguchi, A. Hosoda, and Y. Kobayashi, *Tetrahedron Lett.*, 26, 6209(1985)
- 3) V. J. Rao, F. Derguini, K. Nakanishi, T. Taguchi, A. Hosoda, Y. Hanzawa, Y. Kobayashi, C. Pande, and R. H. Callender, *J. Am. Chem. Soc.*, 108, 6077 (1986).
- 4) K. Tsukida, A. Kodama, and M. Ito, *J. Chromatogr.*, 134, 331(1977); R. S. H. Liu and A. E. Asato, *Tetrahedron*, 40, 1931(1984); D. Mead, A. E. Asato, M. Denny, R. S. H. Liu, Y. Hanzawa, T. Taguchi, A. Yamada, N. Kobayashi, A. Hosoda, and Y. Kobayashi, *Tetrahedron Lett.*, submitted.
- 5) 4a was prepared as follows: By treating E/Z mixture of 4-bromo-3-methylbutenoic acid with K_2CO_3 in MeOH was obtained (E)-bromo acid,⁶⁾ which was, in turn, esterified($c-H_2SO_4$, MeOH), reduced(DIBAL, Et_2O) and reacted with triphenylphosphine(benzene, r.t.).
- 6) W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *J. Am. Chem. Soc.*, 90, 6225(1968).
- 7) R. N. Gedye, K. C. Westaway, P. Arora, R. Bisson, and A. H. Khalil, *Can. J. Chem.*, 55, 1218(1977) and references cited therein.
- 8) 5a($R=n-C_5H_{11}$)($CDCl_3$) δ 5.97(d, $J=11.8$ Hz, H-4), 5.54(t, $J=6.9$ Hz, H-2), 5.38(dt, $J=11.8, 7.4$ Hz, H-5), 4.24(d, $J=6.9$ Hz, H-1); 7a($R=n-C_5H_{11}$)($CDCl_3$) δ 6.06(d, $J=15.6$ Hz, H-4), 5.70(dt, $J=15.6, 7$ Hz, H-5), 5.56(t, $J=6.9$ Hz, H-2), 4.26(d, $J=6.9$ Hz, H-1). Reaction of 3-nonyn-2-one with triethylphosphonoacetate(NaH, THF) followed by the separation of the olefin isomers, DIBAL reduction and partial hydrogenation($H_2/Pd-BaSO_4$) afforded 5a.
- 9) I. Gosney and A. G. Rowley, in "Organophosphorous Reagents in Organic Synthesis", J. I. G. Cadogan, Ed., Academic Press, New York, 1979. Chap.2.
- 10) B. E. Maryanoff, A. B. Reitz, and B. A. Duhl-Emswiler, *J. Am. Chem. Soc.*, 107, 217(1985) and references cited therein.
- 11) E. Vedejs and H. W. Fang, *J. Org. Chem.*, 49, 210(1984) and references cited therein.
- 12) E. J. Corey, A. Marfat, and B. C. Laguzza, *Tetrahedron Lett.*, 22, 3339 (1981).

(Received in Japan 7 August 1986)