PII: S0040-4039(96)00857-X

# Two-step Conversion of 2-Substituted Furans into γ-Oxo-α,β-unsaturated Carboxylic Acids. Formal Synthesis of (+)-Patulolide A and (-)-Pyrenophorin

Yuichi Kobayashi,* Kiyonobu Kishihara, and Kengo Watatani

Department of Biomolecular Engineering, Tokyo Institute of Technology,
4259 Nagatsuta-cho, Midori-ku, Yokohama 226, Japan

Abstract: NBS oxidation of 2-substituted furans 9 and 15 followed by further oxidation of the enals with NaClO$_2$ afforded the acids 11 and 17 in good yields, which are the intermediates of (+)-patulolide A and (-)-pyrenophorin, respectively. Copyright © 1996 Elsevier Science Ltd

The *trans* γ-oxo-α,β-unsaturated carboxylic moiety is a common structural unit of biologically important natural products such as A26771B, patulolide A, pyrenophorin, vermiculine, *etc.*[1] For synthesis of these molecules, a promising method appears to be oxidation of 2-substituted furans 1 to *trans* γ-oxo-α,β-unsaturated aldehydes 2 followed by further oxidation to the acids 3 because of the ready availability of 2-substituted furans (eq. 1). Another advantage of this approach is chemical stability of furans 1 under basic,

(1)

(+)-Patulolide A   (-)-Pyrenophrin
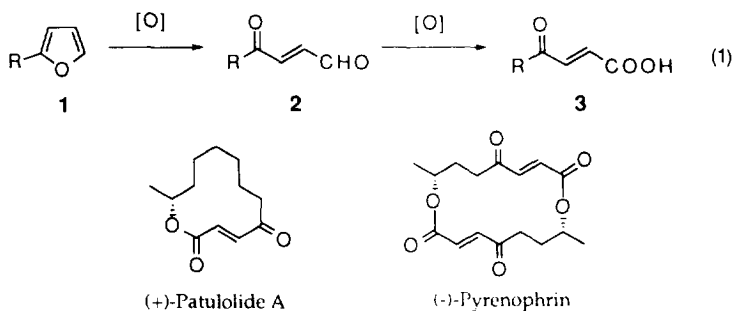
mild oxidative, and weakly acidic conditions, thus promising easy transformation of an initially introduced simple substituent to the desired one through carbon-carbon bond formations and/or functional group inter-conversions. Although a number of furan oxidations have been published so far,[2] surprisingly Br$_2$ in MeOH followed by hydrolysis,[3] PCC,[4] and CrO$_3$/H$_2$SO$_4$[5] have been used for this purpose.[6] Except in one case,[3c] however, these methods suffer from prolonged reaction time, strongly acidic conditions, low yield, and/or contamination of the *cis* isomer. To circumvent these disadvantages methods using reactive but unstable alkoxy furans have recently been devised.[1b,7]

During the synthesis of brefeldin A, we found that NBS oxidizes the furan 1a into *trans* γ-oxo-α,β-unsaturated aldehyde 2a efficiently.[8] Slightly acidic conditions (pH 5-6) and short reaction time (4 h) coupled with easy handling

for **1a,2a**
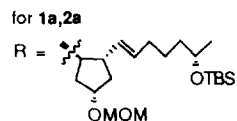
seem to meet the present purpose. Thus, to test the feasibility of the reaction we carried out asymmetric syntheses of (+)-patulolide A[9] and (-)-pyrenophorin.[3b,5,7c,9d,10] Herein we report the results of this experimentation.

The synthesis of (+)-patulolide A is revealed in Scheme 1. Our goal is the acid 12, from which (+)-patulolide A is synthesized by macrocyclization followed by deprotection.[9b] Alkylation of 1-bromo-5-chloro-pentane with furyllithium (4) generated from furan (n-BuLi, 0 °C, 1 h) afforded the chloride 5 in 95% yield. Since our attempt to prepare the Grignard reagent from 5 failed due to instability of the reagent under preparatory conditions (THF, reflux), 5 was converted to the bromide 6 with LiBr (2 equiv) under P.T.C.[11] in 94% yield (97% conversion by NMR). The Grignard reagent could be prepared from 6 in the usual way and was used for the reaction with optically active (S)-epichlorohydrin (7) (98.9% e.e.) to afford 8 in good yield.[12] Reduction of 8 with LiAlH$_4$ afforded the key intermediate 9 in excellent yield. The alcohol 9 without protection of the hydroxyl group was subjected to NBS (1.5 equiv) in the presence of pyridine (2 equiv) in acetone-THF-H$_2$O (5 : 4 : 2) at -20 °C for 1 h and then at room temperature for 4 h to furnish *trans* γ-keto aldehyde 10 in 73% yield. No *cis* isomer was found by ^{1}H NMR spectroscopy.[13] Further oxidation of 10 with NaClO$_2$ in the presence of 2-methyl-2-butene[14] under slightly acidic conditions afforded the *trans* acid 11 in 87% yield. During the conversions the hydroxyl group was unaffected by these reagents. Finally, protection of the γ-keto group and hydrolysis of the ethyl ester partially formed during ketalization furnished the acid 12, whose ^{1}H NMR and IR spectra were in accord with the data reported.[9b]

The next target molecule was the acid 18, the intermediate for synthesis of (-)-pyrenophorin,[10c,d] and its synthesis is summarized in Scheme 2. Commercially available 13 (86% e.e.)[15] was converted by the three-step sequence in 80% yield to the iodide 14, which upon alkylation with furyllithium (4) afforded 15 in good yield. NBS oxidation of 15 was carried out under the same conditions mentioned above for 9 to afford the enal 16 in 64% yield, which upon oxidation with NaClO$_2$ (83% yield) and subsequent ketalization furnished the intermediate 18, whose spectra (^{1}H NMR, IR) were in good agreement with the published data.[10c]

To obtain more examples of the conversion, furans 1b-d were then examined. Reactions were carried out as mentioned above. As shown in Table 1, the corresponding *trans* enals 2b-d and acids 3b-d were obtained in good yields.

Table 1. Two-step Conversion of 1b-d

1-3	R	1→2, %	2→3, %
b	OAc CH$_3$-CH(CH$_2$)$_6$	87	70
c	OTHP CH$_3$-CH(CH$_2$)$_2$	62	78
d	Ph(CH$_2$)$_3$	65	77

In summary, we have presented the usefulness of the two-step conversion of 2-substituted furans 1 into *trans* γ-oxo-α,β-unsaturated carboxylic acids 3. Under the given conditions phenyl, ester, THP, siloxy, and even free OH groups are all tolerated. Usually 1 can be prepared quite easily by alkylation with furyllithium
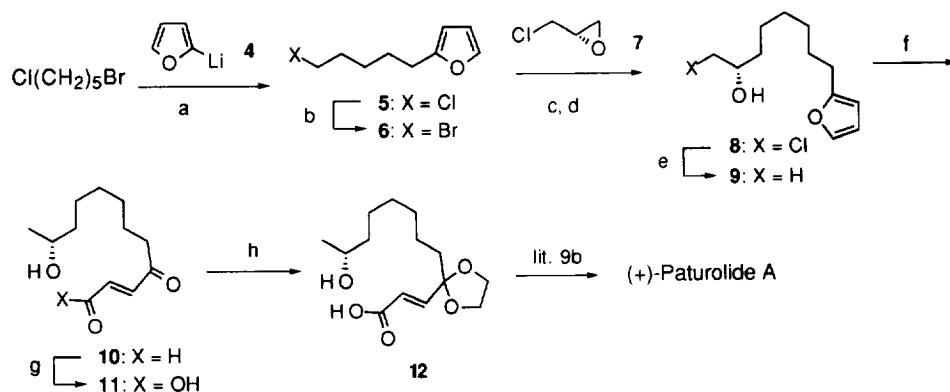
Scheme 1. (a) **4**, THF, room temp., 95%; (b) LiBr, (C$_8$H$_{17}$)$_3$NMe (cat.), 100 °C, 94%; (c) **6**, Mg, THF; (d) **7** (98.9% e.e.), CuCN (cat.), THF, 90%; (e) LiAlH$_4$, THF, room temp., 93%; (f) NBS (1.5 equiv), pyridine (2 equiv), THF/acetone/H$_2$O = 5:4:2; -20 °C, 1 h then room temp., 4 h, 73%; (g) NaClO$_2$, 2-methyl-2-butene, t-BuOH/phosphate buffer (pH 3.6)/H$_2$O = 2:1:1, 87%; (h) HO(CH$_2$)$_2$OH, p-TsOH (cat.), C$_6$H$_6$ then LiOH, MeOH/H$_2$O, 62%.
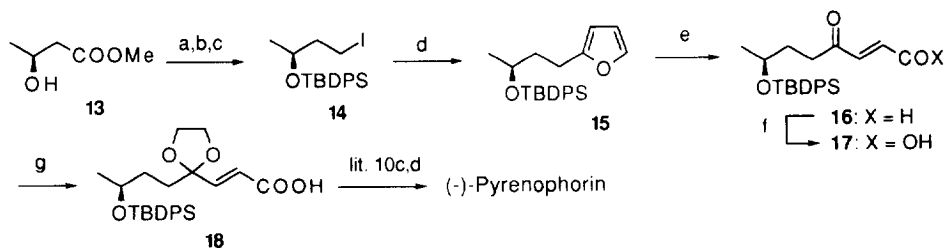
Scheme 2. (a) TBDPSCl, imidazole, DMF, 100%; (b) DIBAL, THF, -50 ~ -15 °C, 3 h, 91%; (c) I$_2$, PPh$_3$, C$_6$H$_6$, 88%; (d) **4**, THF, room temp., 94%; (e) NBS (1.2 equiv), pyridine (4 equiv), THF/acetone/H$_2$O = 5:4:2; -20 °C, 1 h then room temp., 5 h, 64%; (f) NaClO$_2$, 2-methyl-2-butene, t-BuOH/phosphate buffer (pH 3.6)//H$_2$O = 2:1:1, 83%; (g) HO(CH$_2$)$_2$OH, p-TsOH (cat.), C$_6$H$_6$ then LiOH, MeOH/H$_2$O, 70%.

(**4**) and are stable under various conditions necessary for manipulation of the substituent as exemplified above. Thus, furyl anion is now a synthetic equivalent to the supposed anion **19** (Fig. 1).[16]
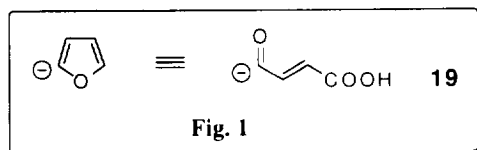
Fig. 1

REFERENCES AND NOTES

1. (a) Boeckman, R. H. Jr.; Goldstein, S. W.: In *The Total Synthesis of Natural Products*; ApSimon, J. Ed.; John Wiley and Sons, Inc.: New York, 1988; Vol. 7, Chapter 1. (b) Asaoka, M.; Takei, H. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 819-828.

2. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795-819.

3. (a) Hirsch, J. A.; Szur, A. J. *J. Heterocycl. Chem.* **1972**, *9*, 523-529. (b) Hase, T. A.; Nylund, E.-L. *Tetrahedron Lett.* **1979**, 2633-2636. (c) Gunn, B. P. *Tetrahedron Lett.* **1985**, *26*, 2869-2872.

4. (a) Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661-663. (b) Petrini, M.; Ballini, R.; Rosini, G.; Marotta, E. *Tetrahedron* **1986**, *42*, 151-154.

5. Ngooi, T. K.; Scilimati, A.; Guo, Z.-w.; Sih, C. J. *J. Org. Chem.* **1989**, *54*, 911-914.

6. Oxidative conversions of 2,5-disubstituted furans to *trans* and/or *cis* 2-ene-1,4-diones have been reported: (a) Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143-4147. (b) Jurczak, J.; Pikul, S. *Tetrahedron Lett.* **1985**, *26*, 3039-3040. (c) Pikul, S.; Raczko, J.; Ankner, K.; Jurczak, J. *J. Am. Chem. Soc.* **1987**, *109*, 3981-3987.

7. (a) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269-4270. (b) Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 4611-4614. (c) Asaoka, M.; Yanagida, N.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061-1064. (d) Gunn, B. P.; Brooks, D. W. *J. Org. Chem.* **1985**, *50*, 4417-4418.

8. Watatani, K.; Kikori, Y.; Mizojiri, R.; Kobayashi, Y.: Unpublished result.

9. (a) Rodphaya, D.; Sekiguchi, J.; Yamada, Y. *J. Antibiot.* **1986**, *39*, 629-635. (b) Makita, A.; Yamada, Y.; Okada, H. *J. Antibiot.* **1986**, *39*, 1257-1262. (c) Mori, K.; Sakai, T. *Liebigs Ann. Chem.* **1988**, 13-17. (d) Solladié, G.; Gerber C. *Synlett* **1992**, 449-450.

10. (a) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860-2865. (b) Seuring, B.; Seebach, D. *Liebigs Ann. Chem.* **1978**, 2044-2073. (c) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634-4642. (d) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 841-844. (e) Matsushita, Y.; Furusawa, H.; Matsui, T.; Nakayama, M. *Chem. Lett.* **1994**, 1083-1084. (f) Nokami, J.; Taniguchi, T.; Gomyo, S.; Kakihara, T. *Chem. Lett.* **1994**, 1103-1106. (g) Bonete, P.; Nájera, C. *J. Org. Chem.* **1994**, *59*, 3202-3209. (h) Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1995**, *51*, 7721-7726, and references cited therein.

11. Loupy, A.; Pardo, C. *Synth. Commun.* **1988**, *18*, 1275-1281.

12. Although (*R*)-propylene oxide is the best choice for preparation of **8**, we selected **7** because it had been kindly provided by Daiso Co. Ltd.

13. Several hours at room temp. was necessary to isomerize the initially formed *cis* isomer to the *trans* one.

14. (a) Lindgren B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888-890. (b) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825-4830.

15. Synthesis of enantiopure **13**: Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.

16. Representative procedure is as follows: To a solution of the furan **9** (190 mg, 0.968 mmol) and pyridine (156 μL, 1.93 mmol) in THF/acetone/H_2O (5:4:2, 7 mL) was added NBS (259 mg, 1.46 mmol) in THF/acetone/H_2O (5:4:2, 3 mL) at -20 °C. The solution was stirred for 1 h at -20 °C and for 4 h at room temperature, and then poured into a mixture of AcOEt and aq. $Na_2S_2O_3$ with vigorous stirring. The organic layer was separated and the aqueous solution was extracted with AcOEt. The combined organic layers were dried and concentrated to afford the residue, which was purified by chromatography on SiO_2 to afford the aldehyde **10** (150 mg, 73 % yield). To a solution of the aldehyde **10** (299 mg, 1.41 mmol) and 2-methyl-2-butene (1.5 μL, 14 mmol) in *t*-BuOH (10 mL) and phosphate buffer (pH 3.6, 5 mL) was added $NaClO_2$ (225 mg, purity 85%, 2.49 mmol) in H_2O (5 mL) and the resulting mixture was stirred for 1.5 h at room temperature. Most of the solvent was removed under reduced pressure and the residue was poured into a mixture of AcOEt and brine. The aqueous layer was acidified to pH ca 4 by addition of 1 N HCl. The organic layer was separated and the aqueous layer was extracted with AcOEt. Usual purification gave the title acid **11** (281 mg, 87% yield).