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

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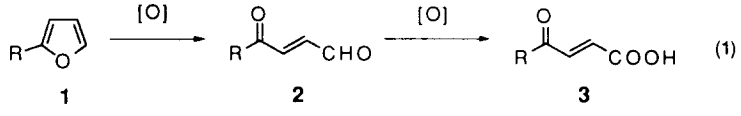
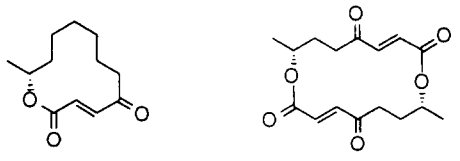
Abstract: *NBS oxidation of 2-substituted furans* ***9*** *and* ***15*** *followed by further oxidation of the enals with* $NaClO_2$ *afforded the acids* ***11*** *and* ***17*** *in good yields, which are the intermediates of (+)-patulolide A and (-)-pyrenophorin, respectively.* Copyright © 1996 Elsevier 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 **2** **3** (1)

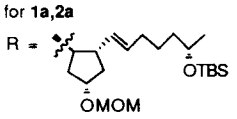


(+)-Patulolide A (-)-Pyrenophrin

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 interconversions. 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_2SO_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-chloropentane 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_2O (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 ^1H 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 ^1H NMR and IR spectra were in accord with the data reported.[9b]

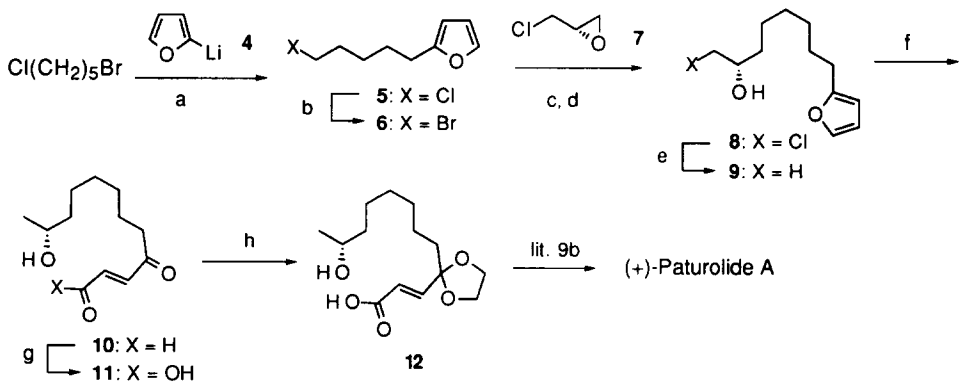
The next target molecule was the acid **18**, the intermediate for synthesis of (-)-pyrenophorin,[10c,d] and its synthesis is summarized in Scheme 2. Commercially available **13** (86% e.e.)[15] was converted by the three-step sequence in 80% yield to the iodide **14**, which upon alkylation with furyllithium (**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 (^1H 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.

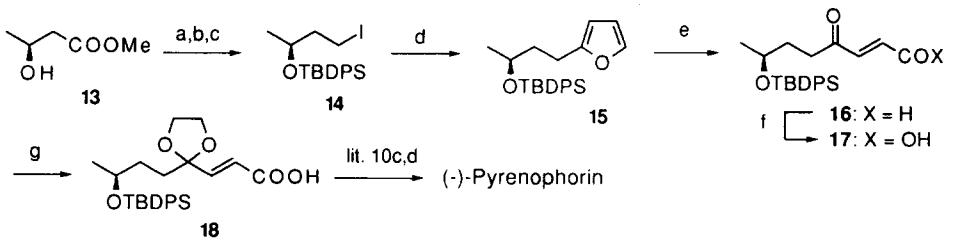
Table 1. Two-step Conversion of **1b-d**

1-3	R	1→2, %	2→3, %
b	CH_3-CH(OAc)$(CH_2)_6$	87	70
c	CH_3-CH(OTHP)$(CH_2)_2$	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, $(C_8H_{17})_3NMe$ (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_2O = 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_2O = 2:1:1, 87%; (h) $HO(CH_2)_2OH$, *p*-TsOH (cat.), C_6H_6 then LiOH, MeOH/H_2O, 62%.



Scheme 2. (a) TBDPSCl, imidazole, DMF, 100%; (b) DIBAL, THF, -50 ~ -15 °C, 3 h, 91%; (c) I_2, PPh_3, C_6H_6, 88%; (d) **4**, THF, room temp., 94%; (e) NBS (1.2 equiv), pyridine (4 equiv), THF/acetone/H_2O = 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_2O = 2:1:1, 83%; (g) $HO(CH_2)_2OH$, *p*-TsOH (cat.), C_6H_6 then LiOH, MeOH/H_2O, 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]

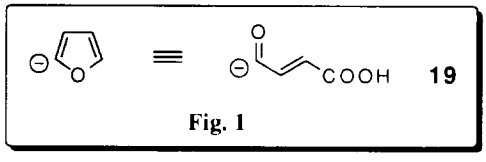


Fig. 1

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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).

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