Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7107–7109

Synthesis to determine the absolute configuration of (−)-pyricuol, a phytotoxin isolated from rice blast disease fungus *Magnaporthe grisea*

Yoko Nakamura, Hiromasa Kiyota,* Rumi Ueda and Shigefumi Kuwahara

Department of Applied Bioorganic Chemistry, Division of Bioscience and Biotechnology for Future Bioindustry, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

Received 27 July 2005; revised 18 August 2005; accepted 22 August 2005
Available online 6 September 2005

Dedicated to Professor Steven V. Ley, FRS CBE, on the occasion of his 60th birthday

Abstract—The absolute configuration of (−)-pyricuol, a phytotoxin isolated from rice blast disease fungus *Magnaporthe grisea*, was determined to be *R* by synthetic studies.

(−)-Pyricuol (**1**) was isolated from the culture filtrate of rice blast disease fungus, *Magnaporthe grisea* (Hebert) Barr, which induced a typical disease symptom stronger than pyriculol (**2**).[1] Compound **1** possesses a unique branched side chain, which was confirmed by our racemic synthesis,[2] however, the stereochemistry had remained unknown. Determination of the absolute configuration was essential for its biosynthetic studies and for further pest managements. In this letter, we describe a synthesis and the absolute configuration of **1** (Fig. 1).

As for the synthesis, we targeted (*S*)-**1** and evolved a new scheme because of the low reproducibility of our previous one (Scheme 1).[2] (*R*)-α,β;γ,δ-Dienol **C** is a key intermediate of the racemic synthesis. Since the semi-reduction of the triple bond of **D** was troublesome, metal-mediated coupling reactions of **E** and **F** are suitable to construct *E*,*Z*-diene. The chirality of **F** is derived from (*R*)-lactate.

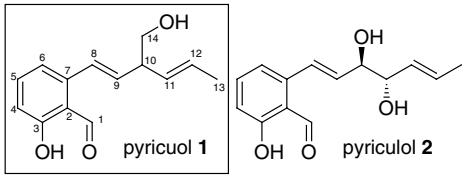
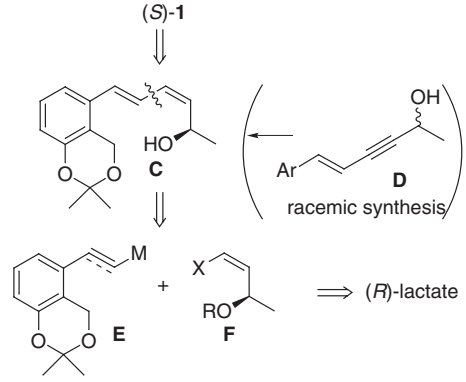


Figure 1. Pyricuol (**1**) and pyriculol (**2**).

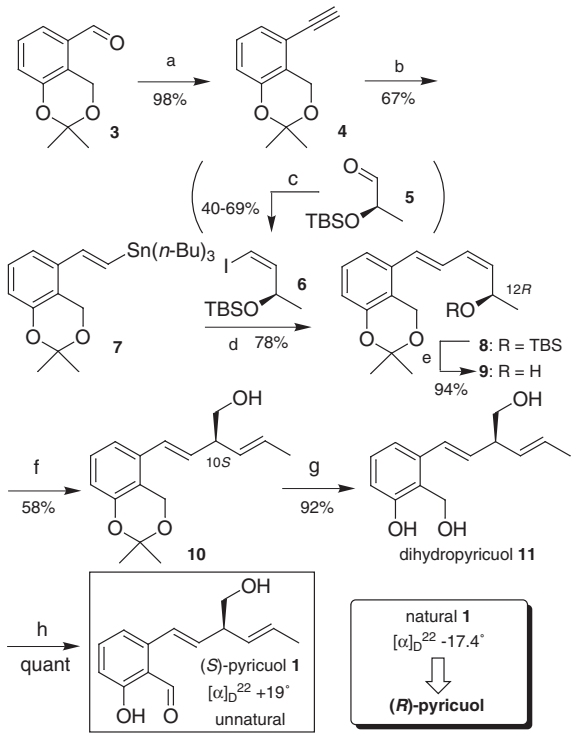


Scheme 1. Retrosynthetic analysis of (*S*)-**1**.

As shown in Scheme 2, the known aldehyde **3**,[3] also the starting compound of racemic synthesis, was converted to alkyne **4** (= **E**) using Ohira–Bestmann reagent[4] in 98% yield. While *Z*-alkenyl iodide **6** (= **F**)[5] was prepared from aldehyde **5**[6] by *Z*-selective Wittig reaction (*Z*/*E* = 25:1).[7] *E*-Isomer of **6** was removed by silica gel column chromatography.

Keywords: (−)-Pyricuol; *Magnaporthe grisea*; Stille reaction; [2,3]-Wittig rearrangement; Total synthesis; Natural products.
* Corresponding author. Tel.: +81 22 717 8785; fax: +81 22 717 8783; e-mail: kiyota@biochem.tohoku.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.099



Scheme 2. Synthesis of (*S*)-pyricuol: (a) dimethyl 1-diazo-2-oxopropylphosphonate (2 equiv), K_2CO_3 (2.5 equiv), MeOH; (b) (n-Bu)$_3$SnH (2.3 equiv), CuCN (1.16 equiv), n-BuLi (2.3 equiv), THF −76 °C; then **4**, −37 °C; (c) $(Ph_3P^+CH_2I)I^-$ (4 equiv), NaHMDS (4 equiv), HMPA (1 equiv), THF, −78 °C; (d) **7** (4 equiv), Pd_2dba_3 (0.05 equiv), $AsPh_3$ (0.1 equiv), CuI (0.1 equiv), DMF, rt; (e) TBAF (excess), THF, rt, 2 h; (f) (i) KH (2.5 equiv), $ICH_2Sn(n\text{-}Bu)_3$ (1.5 equiv), THF, rt; (ii) n-BuLi (1.5 equiv), THF, −79 °C; (g) p-TsOH (cat.), MeOH–dil HCl; (h) MnO_2 (10 equiv), DMSO, 60 °C, 1 h.

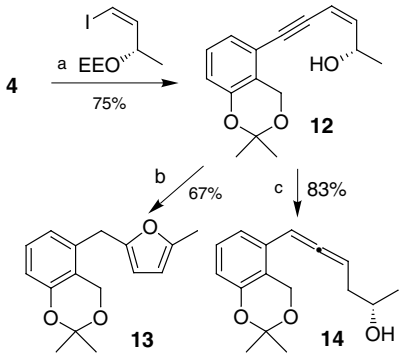
Then, metal-mediated coupling reactions were examined. Although Sonogashira coupling reaction[8] gave an enyne product in good yield, trials of its transformation were unsuccessful.[9] Then, we chose Stille coupling reaction. Hydrostannylation of **4** by stannylcuprate[10] gave *E*-alkenylstannane **7**. This compound was partly decomposed to the corresponding stylene derivative during silica gel column chromatography. Stille reaction[11] with *Z*-vinyl iodide **6** gave the desired *E*,*Z*-diene **8** in 78% yield. Deprotection of TBS group afforded alcohol **9** (= **C**), which was the intermediate of our racemic synthesis. The following steps were done according to our previous report.[2] [2,3]-Wittig rearrangement of an intermediate stannyl ether gave the desired **10** in 58% yield accompanied by 8% of [1,2]-rearranged product. The corresponding *Z*-isomer was not detected by ^{1}H NMR. The *R*-chirality of lactate was to be exclusively transferred to the 10*S*-position according to Still and Mitra.[12] Acetonide group of **10** was removed to afford dihydropyricuol **11**, which would be the biosynthetic precursor, and selective oxidation of benzyl hydroxyl group with MnO_2 gave (*S*)-pyricuol **1**.[13] Overall yield was 25% from **3** in seven steps. The ^{1}H NMR spectral datum was in good agreement with that reported,[1] however, the sign of optical rotation value {$[\alpha]_D^{22}$ +19 (*c* 0.070, $CHCl_3$)} was reversed to that of natural compound[1] {$[\alpha]_D^{22}$ −17.4 (*c* 0.03, $CHCl_3$)}. Accordingly, the absolute configuration of the natural pyricuol is determined to be *R*. Synthesis of natural (*R*)-**1** and comparison of the biological activities of both enantiomers are underway.

Acknowledgements

We thank Professor J.-C. Kim (KRICT) for kindly sending us the natural sample. This work was partially supported by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (No. 14760069 and 17580092), The Agricultural Chemical Research Foundation, Intelligent Cosmos Foundation and The Naito Foundation.

References and notes

1. Kim, J.-C.; Min, J.-Y.; Kim, H.-T.; Cho, K.-Y.; Yu, S.-H. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 173–174.
2. Kiyota, H.; Ueda, R.; Oritani, T.; Kuwahara, S. *Synlett* **2003**, 219–220.
3. Suzuki, M.; Sugiyama, T.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1986**, *50*, 2159–2160, and a reference cited therein; Suzuki, M.; Sugiyama, T.; Watanabe, M.; Murayama, T.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 1121–1127.
4. Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564; Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.
5. Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D. *J. Org. Chem.* **1999**, *64*, 1932–1940.
6. Wakabayashi, S.; Ogawa, H.; Ueno, N.; Kunieda, N.; Mandai, T.; Nokami, J. *Chem. Lett.* **1987**, 875–878.
7. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.
8. Crisp, G. T.; Turner, P. D. *Tetrahedron* **2000**, *56*, 407–415.
9. In our preliminary studies, alkaline treatment of Sonogashira coupling product **12** gave furan **13**, or reduction afforded allene **14**.



(a) (i) $Pd(PPh_3)_4$, Et_3N, CuI, DMF; (ii) PPTS, MeOH, (b) KH, THF; (c) Red Al, THF.
10. Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768–7780, and references cited therein.
11. The conditions were modifications of the reported procedures: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595; Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. *J. Org. Chem.* **1994**, *59*, 5905–5911; Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.;

Gilmore, T. D.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 3267–3270; Kuwahara, S.; Imada, S. *Tetrahedron Lett.* **2005**, *46*, 547–549.

12. Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1987**, *100*, 1927–1928. For a recent review of the [2,3]-Wittig rearrangement, see: Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105–209.
13. (*S*)-Pyricuol, a pale yellow oil, $[\alpha]_D^{22}$ +19 (*c* 0.30, $CHCl_3$) {lit.[1] $[\alpha]_D^{25}$ −17.4 (*c* 0.7, $CHCl_3$)}. IR (ATR, ZnSe) ν_{max} cm^{-1}: 3390 (s, O–H), 3025 (w), 2923 (s), 2854 (s), 1642 (s, C═O), 1609 (s), 1569 (m, Ar), 1450 (s), 1327 (m), 1311 (m), 1193 (m), 1163 (m), 967 (m), 722 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76 (3H, dd, $J = 6.4$, 1.0 Hz, H-13), 3.15 (1H, pseudo-quint, $J = 7.3$ Hz, H-10), 3.63 (1H, m, H-14), 3.68 (1H, m, H-14), 5.43 (1H, ddq, $J = 15.1$, 7.8, 1.5 Hz, H-11), 5.68 (1H, dq, $J = 15.1$, 6.3 Hz, H-12), 6.04 (1H, dd, $J = 15.6$, 7.3 Hz, H-9), 6.87 (1H, d, $J = 8.3$ Hz, H-6), 6.93 (1H, d, $J = 7.3$ Hz, H-4), 6.96 (1H, d, $J = 15.6$ Hz, H-8), 7.44 (1H, t, $J = 8.0$ Hz, H-5), 10.31 (1H, s, CHO), 11.87 (1H, s, ArOH). HRMS (FAB^+): *m*/*z* calcd for $C_{14}H_{17}O_3$, 233.1178; found, 233.1179.