

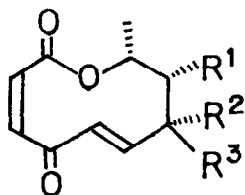
TOTAL SYNTHESIS OF (+)-PYRENOLIDE B

Morio ASAOKA, Satoru NAITO, and Hisashi TAKEI
Department of Life Chemistry, Tokyo Institute of Technology,
Nagatsutacho, Midori-ku, Yokohama 227, Japan

Summary: Synthesis of the title compound is described.

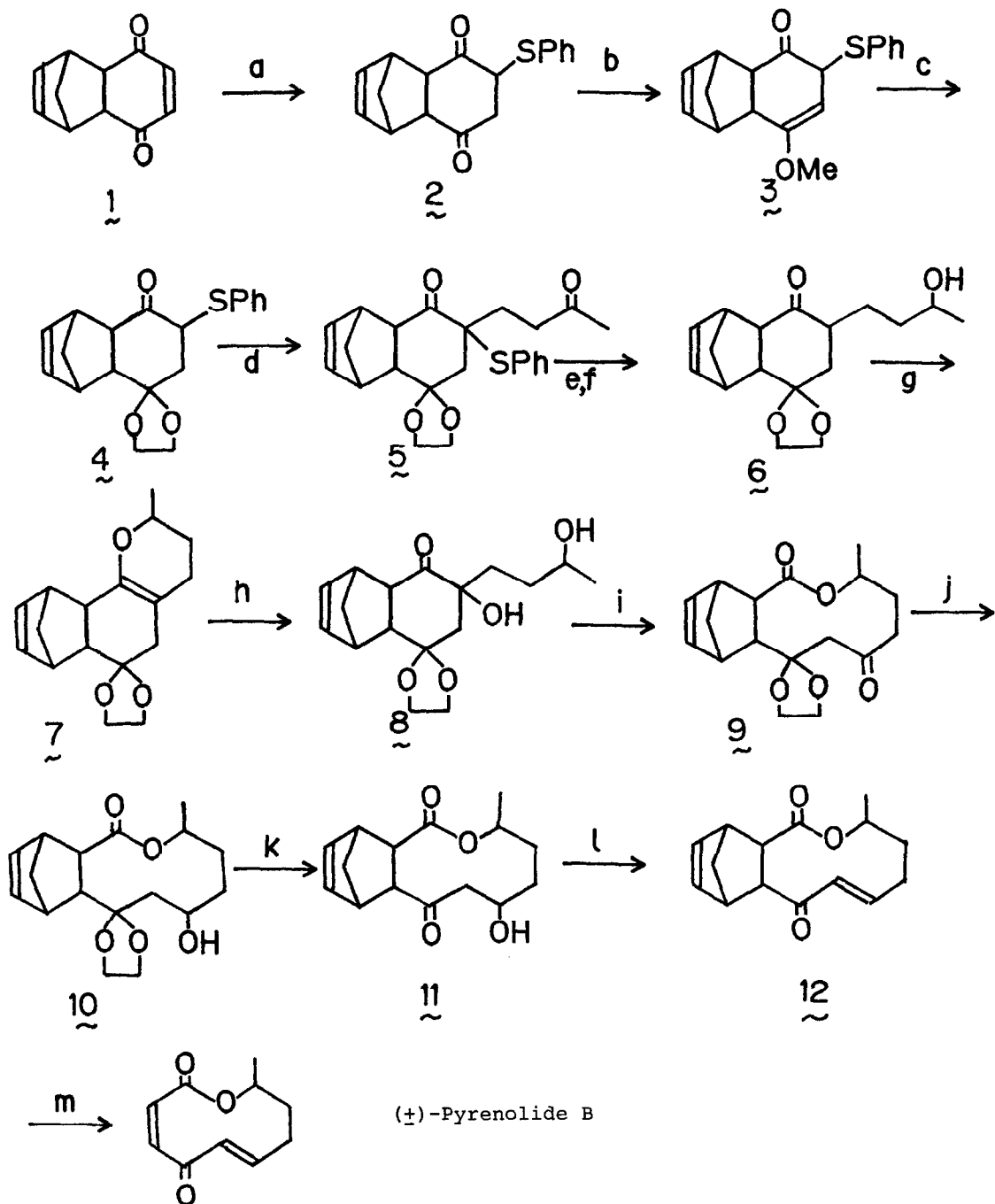
Recently novel 10-membered keto lactones, pyrenolides A, B, and C, which possess a characteristic Z-diacylated olefin (RCOCH=CHCOOR) moiety, were isolated from pyrenophora teres, and they show interesting antifungal activities.¹⁾

In this paper we will report the first total synthesis of (+)-pyrenolide B.



Pyrenolide A: $R^1, R^2 = -O-, R^3 = H$
B: $R^1, R^2, R^3 = H$
C: $R^1, R^2 = H, R^3 = OH$
or $R^1, R^3 = H, R^2 = OH$

As diacyl olefin derivatives are known to be very reactive toward nucleophiles, and those with Z-configuration seem easy to change into E-isomers, we planned to protect the olefin part as a Diels-Alder adduct with cyclopentadiene and to regenerate it by retro Diels-Alder reaction at a final stage. Thus the enone 1 which is easily obtained by Diels-Alder reaction of p-quinone with cyclopentadiene was chosen as a starting material. Triethylamine catalyzed Michael addition of thiophenol to the enone 1 at r.t. gave the adduct 2 (86%, mp 98-9°C). Since direct monoacetalization of 2 with ethylene glycol or its bis(trimethylsilyl) ether derivative in the presence of various acid catalysts resulted in a failure, 2 was treated with excess MeOH and HC(OMe)₃ in the presence of a catalytic amount of TsOH (reflux 1.5 h) to give the enol ether 3 (mp 106-7°C), which were converted into desired acetal derivative 4 (73% from 2, oil) by treatment with ethylene glycol and chlorotrimethylsilane (dichloromethane r.t., 2 h). Treatment of 4 with 3-buten-2-one in the presence of a catalytic amount of potassium tertbutoxide in tert-BuOH-THF at r.t. gave 5 (84%, mp 114-6°C). Reduction of 5 with sodium borohydride at 0°C followed by desulfurization with sodium amalgam²⁾ afforded a diastereomeric mixture of the keto alcohol 6 (93% from 5, oil), which was converted to the cyclic enol ether 7 (85%, oil) by PPTS catalyzed dehydration in benzene with azeotropical removal of water formed (reduced pressure, temperature lower than 40°C).



- (a) PhSH, cat. Et₃N, (b) MeOH, HC(OMe)₃, cat. PTS, (c) (CH₂OH)₂, TMSCl,
 (d) MVK, cat. t-BuOK, (e) NaBH₄, THF-MeOH, (f) Na-Hg, Na₂HPO₄, (g) cat. PPTS,
 (h) m-CPBA, Et₂O-H₂O, (i) Pb(OAc)₄, (j) NaBH₄, (k) PPTS, acetone-H₂O,
 (l) Et₃N, MsCl, (m) Δ

As for the synthesis of 10-membered keto lactones, several methods involving C=C fusion bond cleavage of bicyclic enol ethers are known.³⁾ One-pot methods, namely, treatment of the cyclic enol ether 7 with alkyl nitrite under acidic conditions or oxidation of 7 with 2 equivalents of m-CPBA gave the corresponding 10-membered lactone only in a poor yield. However, 2-step method, oxidation of 7 with 1 equivalent of m-CPBA (wet ether 0°C, 5 h) and subsequent treatment with lead tetraacetate (benzene r.t. 4 h), furnished the desired 10-membered keto lactone 9 (65% from 7, mp 140-2°C). Sodium borohydride reduction of 9 gave a diastereoisomeric mixture of hydroxy derivatives in 91% yield which was separated into two products, 10a (35%, mp 147-8°C) and 10b (56%, mp 153-7°C), by column chromatography. Deacetalization of 10a (wet acetone, PPTS, reflux 3 h) followed by dehydration (CH₂Cl₂, Et₃N, MsCl, 0°C-r.t. 1 day) afforded the enone 12a (81% from 10a, mp 135-8°C). The same transformation of 10b gave 12b (86% from 10b, mp 54-9°C) which was composed of two diastereoisomers. Retro Diels-Alder reaction of 12a at 430°C under reduced pressure (1 mmHg) gave (+)-pyrenolide B (78%, mp 84.0-84.5°C), which was also obtained by the same treatment of 12b in 75% yield. The structure of (+)-pyrenolide B was confirmed by spectroscopical and chromatographical comparison with (-)-pyrenolide B.⁴⁾ Synthesis of chiral pyrenolides A, B, and C according to a slightly modified method is now in progress.

Acknowledgements: We would like to thank Professor M. Nukina and Professor T. Sassa (The Yamagata University) for providing us the natural (-)-pyrenolide B and its spectra.

References and Notes

- 1) a) M. Nukina, T. Sassa, and M. Ikeda, *Tetrahedron Lett.*, 21, 301 (1980).
b) M. Nukina, M. Ikeda, and T. Sassa, *Agric. Biol. Chem.*, 44, 2761 (1980).
- 2) B. M. Trost, H. C. Arndt, P. E. Strega, and T. R. Verhoeven, *Tetrahedron Lett.*, 1976, 3477.
- 3) a) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, 31, 3032 (1966).
b) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, 33, 2013 (1968).
c) T. Wakamatsu, K. Akasaka, and Y. Ban, *J. Org. Chem.*, 44, 2008 (1979), *idem*, *Tetrahedron Lett.*, 1977, 2751.
d) J. R. Mahajan, G. A. L. Ferreira, and H. C. Araujo, *J. Chem. Soc., Chem. Commun.*, 1972, 1078.
- 4) The NMR and IR data of some intermediates and (+)-pyrenolide B are shown below.

(±)-pyrenolide B: NMR(CDCl₃): δ =1.30 (3H, d, J=6Hz), 1.60-2.80 (4H, m), 5.18 (1H, m), 5.90 (1H, dd, J=2, 16Hz), 6.00 (1H, d, J=12Hz), 6.60 (1H, d, J=12Hz), 6.20-7.00 (1H, m); IR (KBr): 1720, 1660 cm⁻¹ (C=O).

12a: NMR(CDCl₃): δ =1.23 (3H, d, J=6Hz), 1.20-1.50 (2H, m), 1.50-2.70 (4H, m), 2.80-3.90 (4H, m), 4.70 (1H, m), 5.70 (1H, dd, J=2, 17Hz), 6.10 (1H, m), 6.40 (1H, m), 6.00-6.90 (1H, m); IR (KBr): 1725, 1655 cm⁻¹ (C=O).

12b: NMR(CDCl₃): δ =1.10-2.80 (9H, m), 2.90-3.80 (4H, m), 4.20-5.30 (1H, m), 5.40-6.90 (4H, m); IR (KBr): 1725, 1700, 1660, 1640 cm⁻¹ (C=O).

10a: NMR(CDCl₃): δ =1.25 (3H, d, J=6Hz), 1.00-2.50 (9H, m), 2.70-3.45 (4H, m), 3.60-4.35 (5H, m), 4.70 (1H, m), 6.00 (1H, m), 6.35 (1H, m); IR (KBr): 3450 cm⁻¹ (OH), 1740 cm⁻¹ (C=O).

10b: NMR(CDCl₃): δ =1.16 (3H, d, J=6Hz), 1.00-3.40 (13H, m), 3.50-4.40 (5H, m), 4.75 (1H, m), 5.80-6.60 (2H, m); IR (KBr): 3500 cm⁻¹ (OH), 1710 cm⁻¹ (C=O).

9: NMR(CDCl₃): δ =1.26 (3H, d, J=6Hz), 1.30-1.50 (2H, m), 1.70-3.40 (10H, m), 3.75-4.10 (4H, m), 4.20-5.10 (1H, m), 5.80-6.50 (2H, m); IR (KBr): 1740, 1710 cm⁻¹ (C=O).

7: NMR(CDCl₃): δ =1.25 (3H, d, J=6Hz), 1.20-3.10 (8H, m), 2.55 (2H, m), 3.00 (2H, m), 3.55-4.15 (5H, m), 6.00 (2H, t); IR(NaCl): 1700 cm⁻¹ (O=C=C).

5: NMR(CDCl₃): δ =1.28 (2H, m), 1.50-3.50 (10H, m), 2.15 (3H, s), 3.90 (4H, m), 5.82 (2H, m), 7.33 (5H, m); IR (KBr): 1710 cm⁻¹ (C=O).

(Received in Japan 12 February 1985)