

HYDROXIMATE AS A SYNTHETICALLY USEFUL FUNCTIONAL GROUP Part II ¹⁾: SYNTHESIS OF (±)-OXO-PARABENZLACTONE

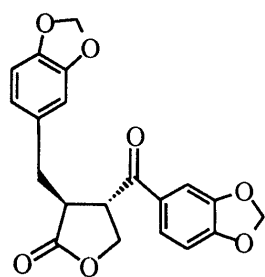
Okiko MIYATA, Atsuko NISHIGUCHI, Ichiya NINOMIYA, and Takeaki NAITO *

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658, Japan

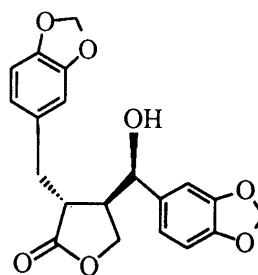
A stereoselective route to (±)-oxo-parabenzlactone has been developed by the combination of thiyl radical addition-cyclization of dienyhydroximate and subsequent conversion of the resulting cyclic hydroximate to lactone.

KEY WORDS oxo-parabenzlactone; thiyl radical cyclization; thiophenol, lignan; hydroximate

A new lignan of the dibenzylbutyrolactone type, (+)-oxo-parabenzlactone (**1**),²⁾ was recently isolated from the wood of *Protium tenuifolium* (Burseraceae). Previously, the enantiomer of **1** was obtained as an oxidation product of a lignan, (-)-parabenzlactone, which had been isolated from *Parabenzoin trilobum* Nakai.^{3,4)} The lignans of the dibenzylbutyrolactone type exhibit various biological activities such as antitumor and platelet-activating factor (PAF) antagonistic activities in addition to inhibitory effects on microsomal monooxygenase in insects.^{5,6)} We focused our attention on developing a practical method for the synthesis of (±)-oxo-parabenzlactone via the route involving the thiyl radical addition-cyclization of hydroximates and for the evaluation of pharmacological activities of the lactones prepared.



(+)-oxo-parabenzlactone (**1**)



(-)-parabenzlactone

Our synthetic strategy consists of two key steps: [1] construction of 3,4-disubstituted cyclic hydroximate by thiyl radical addition-cyclization and [2] conversion of cyclic hydroximate to lactone.⁷⁾

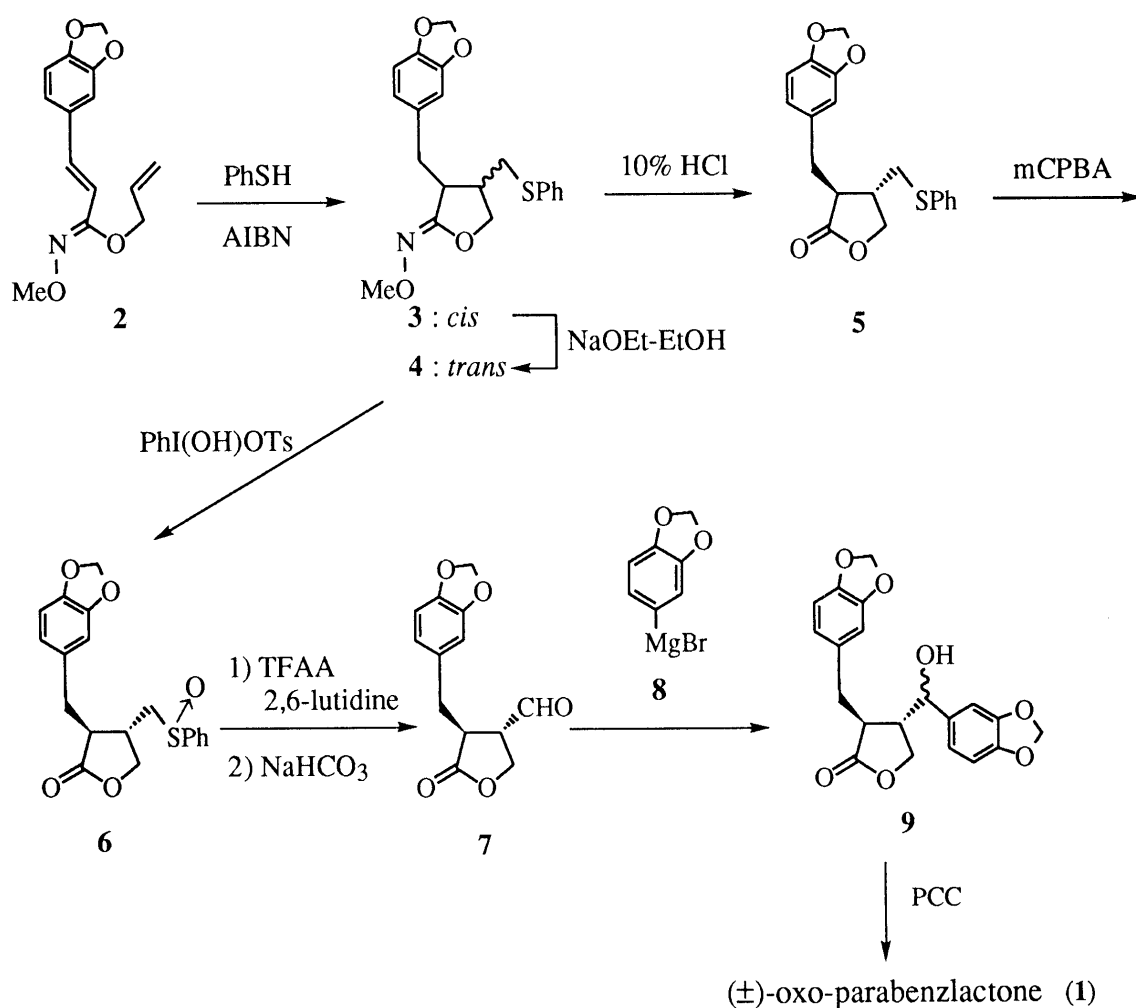
Thiyl radical addition-cyclization of the readily available allyl hydroximate **2**^{1,8)} in the presence of thiophenol (1 equiv.) and AIBN (0.5 equiv.) proceeded smoothly to give a ca. 2 : 1 mixture of the cyclized products **3** and **4** in 73% combined yield, which was separated. The unstable *cis*-**3** was readily isomerized into the *trans*-isomer **4** upon treatment with sodium ethoxide in ethanol.⁹⁾

* To whom correspondence should be addressed.

According to the previous method,¹⁾ hydrolytic conversion of the cyclic hydroxamate **4** into the lactone **5** was readily achieved in 96% yield by treatment with 10% HCl in methanol.

Introduction of the benzyl alcohol moiety into the 4-position of the γ -lactone ring was readily achieved according to the conventional route involving Pummerer rearrangement and the subsequent Grignard reaction. Oxidation of the *trans*-sulfide **5** with *m*-chloroperbenzoic acid (mCPBA) at 0°C gave the corresponding sulfoxide **6** in 81% yield while oxidative conversion of the cyclic hydroxamate **4** to the desired sulfinyl lactone **6** proceeded ineffectively to give the lactone **6** in only 19% yield under the conditions using [hydroxy(tosyloxy)iodo]benzene^{10,11)} as an oxidant. The *trans*-sulfoxide **6** was subjected to the Pummerer reaction and the subsequent hydrolysis to obtain the desired *trans*-aldehyde **7** in 84% yield.

Treatment of the aldehyde **7** with the Grignard reagent **8** gave a diastereomeric mixture of the adducts **9**, which without separation was converted into the ketone **1** (mp. 138-139 °C (lit.²⁾ (+)-**1**: 105-106 °C) by oxidation with pyridinium chlorochromate (PCC) in 45% yield. The ketone **1** obtained was identical with oxo-parabenzlactone²⁾ upon comparisons of the spectral data with those of the authentic sample.

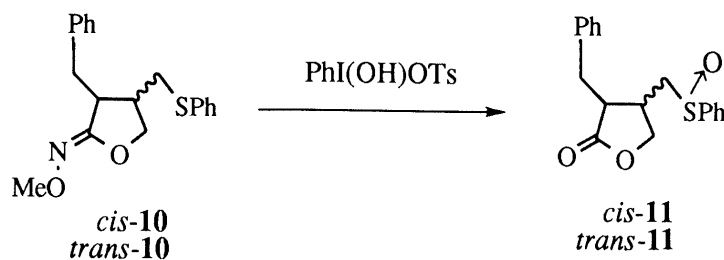


In conclusion, thiyl radical addition-cyclization of the hydroximate was successfully applied to the practical synthesis of (\pm)-oxo-parabenzlactone and the related lignans, and evaluation of their biological activities is now in progress.

ACKNOWLEDGMENTS We are grateful to Dr. M. G. B. Zoghbi (Instituto Nacional de Pesquisas da Amazônia, Manaus, Brazil) for providing us the spectral data of the authentic sample and the Ministry of Education, Science and Culture (Japan) and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants.

REFERENCES AND NOTES

- 1) Part I: Miyata O., Nishiguchi A., Ninomiya I., Naito T., Aoe K., Okamura K., *Tetrahedron Lett.*, **37**, 229-232 (1996).
- 2) Siqueira J. B. G., Zoghbi M. G. B., Cabral J. A., Filho W. W., *J. Nat. Prod.*, **58**, 730-732 (1995).
- 3) Wada K., Munakata K., *Tetrahedron Lett.*, **1970**, 2017-2019.
- 4) Niwa M., Iguchi M., Yamamura S., Nishibe S., *Bull. Chem. Soc. Jpn.*, **49**, 3359-3360 (1976).
- 5) Van Oeveren A., Jansen J. F. G. A., Feringa B. L., *J. Org. Chem.*, **59**, 5999-6007 (1994).
- 6) a) Whiting D. A., *Nat. Prod. Rep.*, **1985**, 191-211. b) Whiting D. A., *Nat. Prod. Rep.*, **1987**, 499-525. c) Ward R. S., *Nat. Prod. Rep.*, **1993**, 1-28.
- 7) Radical cyclization of the allyl esters is known to proceed to give the 2,3-disubstituted butyrolactones in low yield. a) Belletire J. L., Mahmoodi N. O., *Tetrahedron Lett.*, **30**, 4363-4366 (1989). b) Belletire J. L., Mahmoodi N. O., *J. Nat. Prod.*, **55**, 194-206 (1992).
- 8) According to the reported procedure, the *Z*-dienylhydroximate **2** was prepared from the acid chloride *via* the the corresponding hydroxamate without formation of the *E*-isomer. Johnson J. E., Springfield J. R., Hwang J. S., Hayes L. J., Cunningham W. C., McClaugherty D. L., *J. Org. Chem.*, **36**, 284-294 (1971).
- 9) a) Naito T., Honda Y., Miyata O., Ninomiya I., *J. Chem. Soc., Perkin Trans. I*, **1995**, 19-26. b) Sato T., Wada Y., Nishimoto M., Ishibashi H., Ikeda M., *J. Chem. Soc., Perkin Trans I*, **1989**, 879-886.
- 10) Moriarty R. M., Vaid R. K., Koser G. F., *Synlett*, **1990**, 365-383.
- 11) As a preliminary experiment, we have found that treatment of the *cis*- and *trans*-hydroximates **10** with 3 equiv. of [hydroxy(tosyloxy)iodo]benzene gave the *cis*- and *trans*-lactones **11** having a sulfinyl group in 77-79% yield.



(Received April 22, 1996; accepted May 14, 1996)