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

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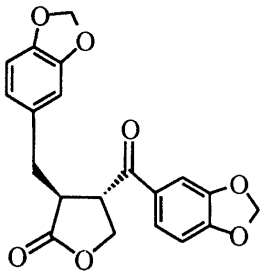
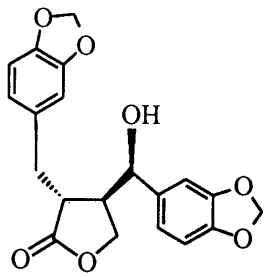
A stereoselective route to (±)-oxo-parabenzlactone has been developed by the combination of thiyl radical addition-cyclization of dienylhydroximate and subsequent conversion of the resulting cyclic hydroximate to lactone.

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]

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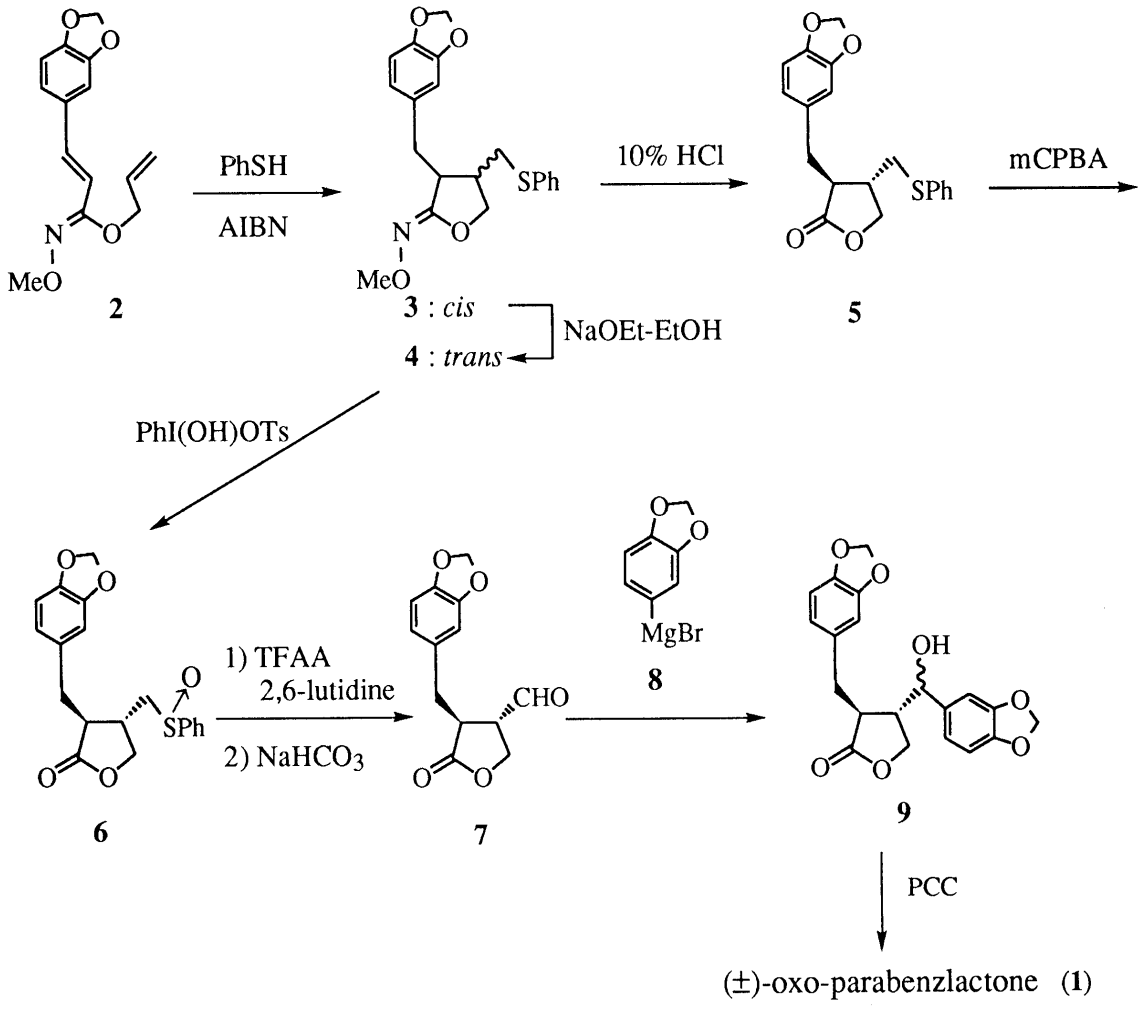
According to the previous method,[1] hydrolytic conversion of the cyclic hydroximate **4** into the lactone **5** was readily achieved in 96% yield by treatment with 10% HCl in methanol.

Introduction of the benzyl alcohol moiety into the 4-position of the γ-lactone ring was readily achieved according to the conventional route invloving 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 hydroximate **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-parabenzlactone[2] 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 (±)-oxo-parabenzlactone and the related lignans, and evaluation of their biological activities is now in progress.

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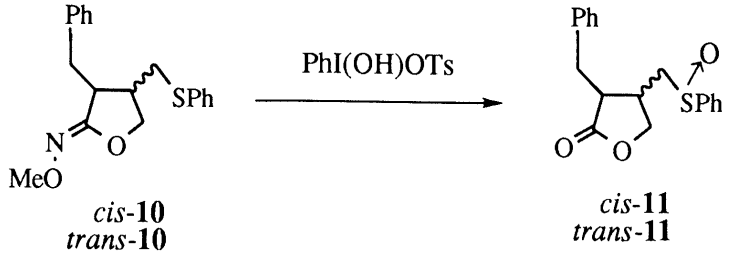
REFERENCES AND NOTES

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. 1*, **1995**, 19-26. b) Sato T., Wada Y., Nishimoto M., Ishibashi H., Ikeda M., *J. Chem. Soc., Perkin Trans 1*, **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.



cis-**10**
trans-**10**

cis-**11**
trans-**11**

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