Oxidative Cyclisation of *o*-Phenolic Oxime-acid Derivatives using Hypervalent Iodine Reagent: Asymmetric Induction at the γ-Position to the Carbonyl Group of Chiral *o*-Phenolic Oxime-Ester

Masatoshi Murakata, Kohei Yamada and Osamu Hoshino*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Shinjuku-ku, Tokyo 162, Japan

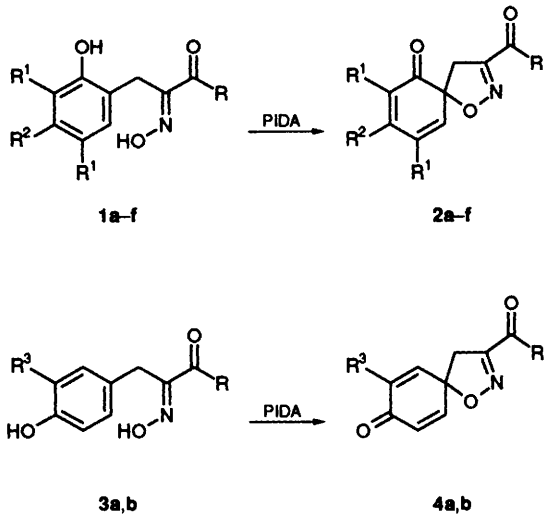
An efficient asymmetric induction at the γ-position to the carbonyl group of the chiral ester took place in 82% diastereoisomeric excess (d.e.) (87% yield) to afford chiral spiroisoxazoline by intramolecular oxidative cyclisation of *o*-phenolic oxime-ester **5** using hypervalent iodine reagent.

The oxidative cyclisation of *o*-phenolic oxime-acid derivatives has been well known as a powerful tool for the synthesis of bromotyrosine derived marine metabolites[1] having a spirocyclohexadienylisoxazoline moiety.[2] Various oxidising agents have been used to synthesise spiroisoxazolines,[3,4] but there is no method for the synthesis of chiral spiroisoxazoline ring system.

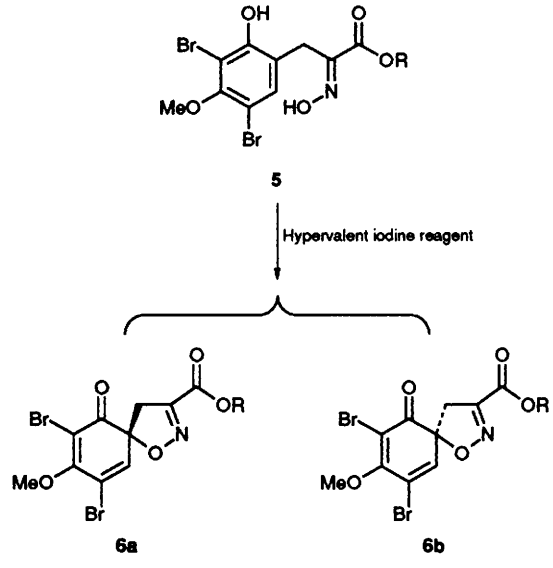
We describe here efficient formation of spiroisoxazoline ring system by the oxidative cyclisation of the *o*-phenolic oxime-acid derivatives using hypervalent iodine reagent and the first example of asymmetric synthesis of spiroisoxazoline ring system by its application.

At first, oxidising agents for construction of spiroisoxazoline ring system were explored. Among them, phenyliodonium diacetate (PIDA)[5] was found to be a suitable oxidant for its formation.† The reaction of *o*-phenolic oxime-ester **1a**[1b] with PIDA in MeCN at 0 °C proceeded smoothly to afford spiroisoxazoline **2a**[1b] (mp 102–104 °C) in 70% yield.‡ We found that the oxidative cyclisation of various *o*-phenolic oxime-acid derivatives with PIDA gave desired spiroisoxazolines as shown in Table 1.§

These findings focused our attention on the asymmetric synthesis of the spiroisoxazoline ring system by its application to *o*-phenolic oxime-ester having a chiral auxiliary group. Therefore, we chose *o*-phenolic oxime-ester **5** {amorphous mass; $[\alpha]_D^{25}$ + 54.7 (*c* 2.04, EtOH)} derived from oxime-acid and (−)-8-phenylmenthol[7] as the chiral ester. As expected, oxidation with PIDA took place in 33% d.e. Furthermore, the diastereoselectivity was improved dramatically to 67% by use of phenyliodonium bis(trifluoroacetate) (PIFA),[5] and the most efficient asymmetric induction (82% d.e.) was achieved by the combination of iodosylbenzene (PhIO) and (−)-camphorsulfonic acid (CSA)[8] as oxidant. The results are shown in Table 2.¶ Interestedly, the sense and degree of asymmetric induction (runs 3 and 4 in Table 2) was essentially independent on the chirality of CSA used.



Scheme 1



Scheme 2 R = (−)-8-phenylmenthyl

Table 1 Intramolecular oxidative cyclisation of **1a–f** and **3a,b** using PIDA[a]

Run	Oxime	R^1	R^2	R^3	R	Product	Mp/°C	Yield (%)[b]
1	**1a**	Br	OMe	—	OMe	**2a**	102–104	70
2	**1b**	Br	OMe	—	OBu^t	**2b**	174–176	72
3	**1c**	Br	OMe	—	$NH(CH_2)_3OMe$	**2c**	98–100	64[c]
4	**1d**	Br	H	—	OMe	**2d**[d]	Oil	46[e]
5	**1e**	H	OMe	—	OMe	**2e**	Oil	40
6	**1f**	H	OMe	—	$NH(CH_2)_3OMe$	**2f**	Oil	45[c]
7	**3a**	—	—	OMe	OMe	**4a**	179–180	39
8	**3b**	—	—	H	OEt	**4b**	Oil	68

[a] Reaction was carried out using PIDA (1.1 equiv.) in MeCN at 0 °C. [b] Isolated yield. [c] Reaction was carried out using PIDA (2.2 equiv.). [d] Unstable product. [e] The yield of a product (mp 130–132 °C), which was reduced by $NaBH_4$.

Table 2 Diastereoselective oxidative cyclisation of **5** using hypervalent iodine[a]

Run	Oxidant	Yield (%)[b]	D.e. (%)[c]
1	PIDA	31	33
2	PIFA	88	67
3	PhIO/(+)-CSA	70	82
4	PhIO/(−)-CSA	87	82

[a]All reactions were carried out using oxidants (1.1 equiv.) in CH_2Cl_2 at −55 to 0 °C. [b] Isolated yield. [c] The diastereoisomeric ratios were determined by 500 MHz ^1H NMR spectral analysis.

It is also noteworthy that oxidative asymmetric induction occurred effectively even at the γ-position to the carbonyl group adjacent to the chiral auxiliary group.

A typical procedure (run 4 in Table 2) is as follows. Iodosylbenzene (0.33 mmol) was suspended in CH_2Cl_2 (3 cm^3). (−)-CSA (0.36 mmol) was added at room temp. and the mixture stirred for 2 h. The resulting clear solution was cooled to −55 °C. A solution of *o*-phenolic oxime-ester **5** (0.3 mmol) in CH_2Cl_2 (15 cm^3) was added to the solution above, and the whole was warmed to 0 °C. After addition of water, the mixture was stirred for 30 min at room temp. Extractive work-up followed by chromatography (silica gel, benzene) afforded spirocyclohexadienylisoxazoline **6a** or **6b** in 87% (82% d.e.). The d.e. was estimated on the basis of the 500 MHz ^1H NMR ($CDCl_3$) spectrum, in which a peak due to vinyl proton (10-H) of each diastereoisomer appears as singlet at δ 6.71 and 6.67 (91 : 9).‖

The present method provides a new and efficient approach to asymmetric synthesis of spiroisoxazoline, which should be useful as a synthon for synthesis of bromotyrosine derived marine metabolites.

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Footnotes

† More recently, McKillop *et al.*[4] have reported that oxidation of a *p*-phenolic oxime derivatives with PIFA gives the corresponding spirocyclohexa-2,5-dienones, while that of an *o*-regioisomer does not produce a desired product.

‡ All new compounds described in the text provided satisfactory analytical and/or spectroscopic data.

§ The oxidation of unsubstituted *o*-phenolic oxime-ester ($R^1 = R^2 =$ H, R = OMe) gave a [4 + 2] dimer.[4,6]

¶ The absolute configuration was not determined.

‖ A 1 : 1 diastereoisomeric mixture of **6a** and **6b** was prepared from **2b** [CF_3CO_2H, CH_2Cl_2, at room temp., 30 min, mp 175–177 °C, 83%; (−)-8-phenylmenthol, DCC, DMAP (0.5 equiv.), CH_2Cl_2, at 0 °C, 30 min, solid, 43%].

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