Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 2943–2952
Tetrahedron

Syntheses of the antibiotic alkaloids renierone, mimocin, renierol, renierol acetate, renierol propionate, and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione

Nagako Kuwabara, Hiroyuki Hayashi, Noriko Hiramatsu, Tominari Choshi, Teppei Kumemura, Junko Nobuhiro and Satoshi Hibino*

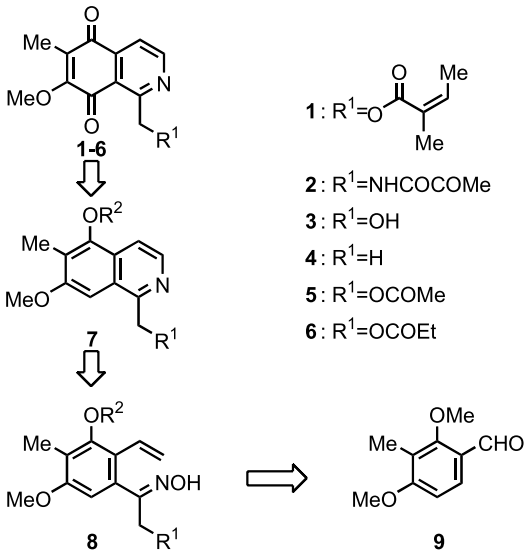
Graduate School of Pharmacy and Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan

Received 29 January 2004; revised 6 February 2004; accepted 6 February 2004

Abstract—The total synthesis of renierone, mimocin, renierol, renierol acetate, renierol propionate, and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione was successfully achieved by the regioselective oxidation of 5-oxygenated isoquinoline. The synthetic method of the 5-oxygenated isoquinoline is based on the thermal electrocyclic reaction of 1-azahexatriene system involving the benzene 1,2-bond.

1. Introduction

Many naturally occurring isoquinoline-5,8-diones have been isolated both from marine sponges and from *Actinomycetes*.[1] The isoquinolinequinones possess significant biological activity,[2] which suggests their potential value as promising structures for the development of new pharmaceuticals. In 1979, renierone (**1**) was isolated from the major metabolite of *Reniera* sp.[3] Mimocin (**2**), isolated from a metabolite of *Streptomyces lavendulae*, contains a pyruvamide side chain in place of the angelate ester side chain of **1**.[4] Renierol (**3**) was isolated from the hard blue sponge *Xestospongia caycedoi*.[6] Further studies of the metabolites of *Reniera* sp. have resulted in the isolation of 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**),[3b,5] which was also found in a blue Philippine marine sponge of the genus *Xestospongia* sp.[6] In addition, renierol acetate (**5**) and renierol propionate (**6**) were isolated from the marine sponge *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*[7] (Scheme 1).



Scheme 1.

Synthetic studies of these antibiotic alkaloids have been conducted by five groups. The total synthesis of renierone (**1**) was established by the groups of Danishefsky[8] and Kubo.[2d,9] Mimocin (**2**) was totally synthesized by the groups of Matsuo[10] and Kubo.[11] The total syntheses of renierol (**3**), renierol acetate (**5**), and renierol propionate (**5**) were reported by the Kubo group.[2d,7c,9a,c] 7-Methoxy-1,6-dimethyl-5,8-dihydro-isoquinoline-5,8-dione (**4**) was synthesized by the groups of Kubo,[9a,c] Liebskind,[12] and Molina.[13] Among these efforts, two regioselective syntheses of the isoquinoline-5,8-dione system have been reported that employ either the oxidation of an 8-aminoisoquinoline derivative with Fremy's salt (Kubo group)[2d,9] or the oxidative demethylation of a 5,7,8-trimethoxyisoquinoline derivative with Ag_2O (Liebskind group).[12] However, it remains difficult to estimate the regioselectivity of oxidative demethylation from the 5,7,8-trimethoxyisoquinoline to

Keywords: Antibiotic alkaloids; Isoquinoline-5,8-diones; Electrocyclic reaction; Azahexatriene system.
* Corresponding author. Tel.: +81-84-936-2111; fax: +81-84-936-2024; e-mail address: hibino@fupharm.fukuyama-u.ac.jp

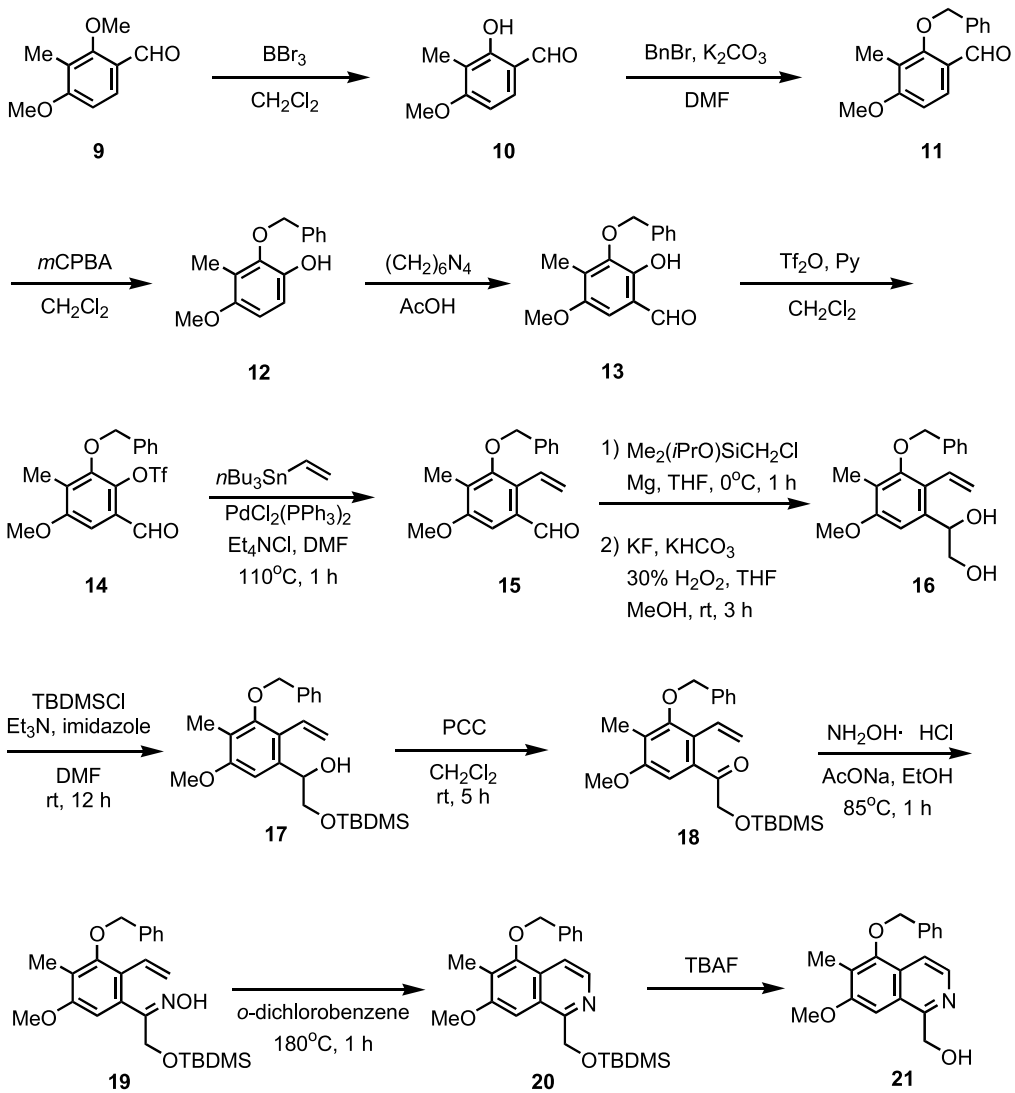
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.02.010

either the isoquinoline-5,8-dione or isoquinoline-7,8-dione using the above synthetic works.

In the course of our studies directed towards the synthesis of biologically active, condensed nitrogen-containing heterocyclic compounds including natural products based on the electrocyclic reaction of a 6π-electron system,[14] we developed thermal electrocyclic reactions using either hexatriene[14c,15] or azahexatriene[14c,16] systems incorporating one double bond of the aromatic or heteroaromatic ring. Recently, we preliminarily reported the total syntheses of renierol (**3**), renierol acetate (**5**), and renierol propionate (**6**) based on the application of our methodology.[17] In this paper, we describe the details of these former studies[17] and the additional total syntheses of renierone (**1**), mimocin (**2**), and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**6**). All of these alkaloids have a common skeleton, 1-hydroxymethyl (or methyl)-7-methoxy-6-methylisoquinoline-5,8-dione, and they differ only in terms of the side chain at C-1 of the isoquinoline ring. There are several classical methods currently used for the synthesis of this type of isoquinoline, e.g., the Bischler-Napieralski reaction. However, we adopted our methodology for the present syntheses, because it has been shown to be advantageous over other approaches due to the cleanliness of the reaction associated with the loss of water.[16] As shown in a retro-synthetic analysis (Scheme 1), we initially planned the synthesis of the common precursor, 5-oxygenated 7-methoxy-6-methylisoquinoline (**7**), in order to achieve the regioselective syntheses of six isoquinoline-5,8-dione antibiotic alkaloids. Namely, a required precursor (**7**) would be obtained by a thermal electrocyclic reaction of *o*-alkenylbenzketoxime (**8**) as a 1-aza-6π-electron system, which would be derived from the known 2,4-dimethoxy-3-methylbenzaldehyde (**9**).[18]

2. Results and discussion

For the preparation of a required precursor (**7**), we began as follows (Scheme 2). The benzaldehyde (**9**) was treated with boron tribromide to produce the 2-hydroxybenzaldehyde (**10**) (88%), which was converted into the benzyl ether (**11**) (99%). The benzaldehyde (**11**) was subjected to the Baeyer–Villiger reaction with *m*-chloroperbenzoic acid (*m*CPBA) to give the phenol (**12**) (88%). The Duff reaction



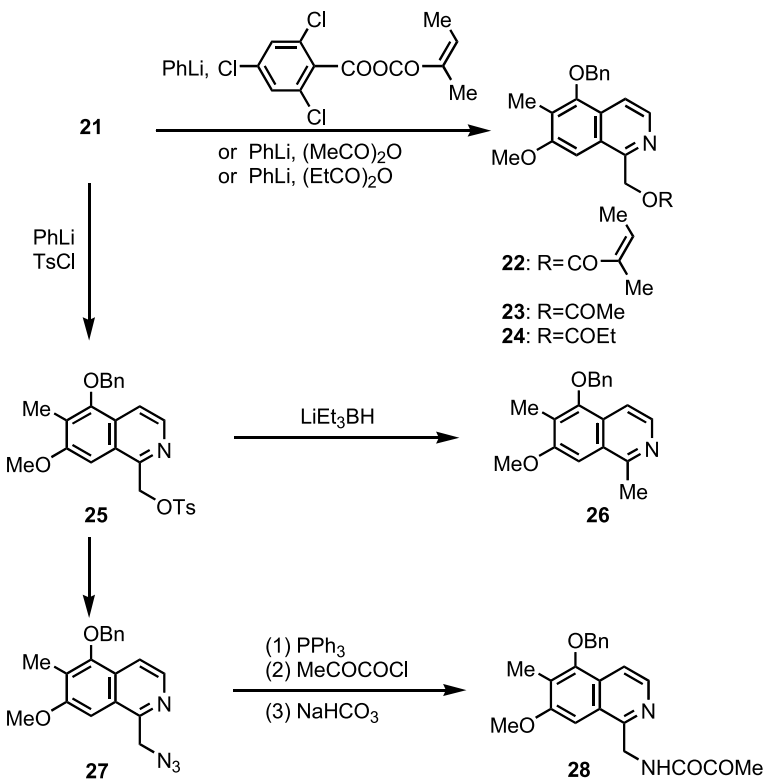
Scheme 2.

of **12** was carried out by hexamethylenetetramine in acetic acid to yield the 2-hydroxybenzaldehyde (**13**) (53%), which was treated with trifluoromethanesulfonic anhydride (Tf_2O) to yield the triflate (**14**) (81%). The cross-coupling reaction of **14** with vinyl tributyltin in the presence of palladium dichlorobistriphenylphosphine [$PdCl_2(PPh_3)_2$] gave the *o*-ethenylbenzaldehyde (**15**) (90%). The Grignard reaction of **15** with dimethylisopropyloxysilylmethylmagnesium chloride,[19] followed by treatment with potassium fluoride and 30% hydrogen peroxide, afforded the 1,2-diol (**16**) (87%). Selective protection of **16** with *tert*-butyldimethylsilyl chloride (TBDMSCl) produced the TBDMS ether (**17**) (92%), which was oxidized with pyridinium chlorochromate (PCC) to obtain the ketone (**18**). Subsequent treatment of **18** with hydroxylamine afforded the ketoxime (**19**) as a 1-azahexatriene system (**8**) (57%), which was subjected to a thermal electrocyclic reaction in *o*-dichlorobenzene at 180 °C to furnish the desired 5-benzyloxyisoquinoline (**20**) (42%). Although the electrocyclic reaction of the highly substituted substrate (**19**) also proceeded, the yield of **20** was only marginally better than that of the simple *o*-alkenylbenzaldoxime.[20] Deprotection of the TBDMS group of **20** was carried out using tetrabutylammonium fluoride (TBAF) to provide the expected 5-benzyloxy-1-hydroxymethylisoquinoline (**21**) as the common precursor, 5-oxygenated isoquinoline (**7**), with the appropriate substitutents (Scheme 2).

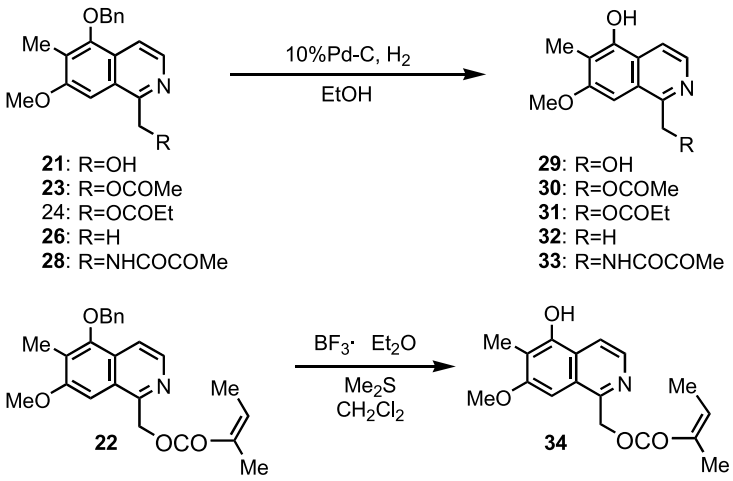
For the next step, the 1-hydroxymethylisoquinoline (**21**) was converted to the corresponding esters; angelate (**22**) (78%), acetate (**23**) (83%), and propionate (**24**) (80%) by treatment of **21** with phenyllithium, followed by the addition of the mixed anhydride[21] of angelic acid with 2,4,6-trichlorobenzoyl chloride, acetic anhydride, and propionic anhydride, respectively. For the conversion of **21** into the 1-methylisoquinoline (**26**), 1-hydroxymethylisoquinoline (**21**) was tosylated by treatment with phenyllithium, followed by the addition of *p*-toluenesulfonyl chloride (*p*-TsCl) (64%). Subsequent reduction of the tosylate (**25**) with lithium triethylborane ($LiEt_3BH$)[9] afforded the 1-methylisoquinoline (**26**) (85%). Furthermore, the nucleophilic substitution reaction of tosyloxymethylisoquinoline (**25**) was carried out by sodium azide to obtain the azide derivative (**27**) (81%), which was treated with triphenylphosphine (PPh_3) in situ, followed by the addition of pyruvoyl chloride,[22] prepared from pyruvic acid and α,α-dichloromethyl methyl ether at 50 °C,[23] to furnish the 1-pyruvoylaminomethylisoquinoline (**28**) (45%). Thus, all of the side chains at the C-1 position of these isoquinoline-5,8-dione alkaloids (**1**–**6**) could be arranged (Scheme 3).

The sequential cleavage of the benzyl groups of **21**, **23**, **24**, **26**, and **28** was carried out by 10% Pd–C and hydrogen in ethanol to give the phenols (**29**–**33**) in excellent yields (91–99%). However, these conditions could not be utilized for **22** because of the reduction of the alkene of the C-1 side chain. Debenzylation of 5-benzyloxyisoquinoline (**22**) successfully proceeded using Fuji's conditions of $BF_3{\cdot}Et_2O$ and Me_2S in dichloromethane[24] to obtain the phenol (**34**) (98%) (Scheme 4).

At the final stage, the oxidation of all of the 5-hydroxyisoquinolines (**29**–**34**) was attempted using two types of oxidizing agents, ceric ammonium nitrate (CAN; Method A),[25] and a combination of salcomine with oxygen (Method

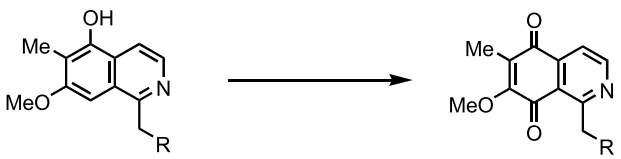


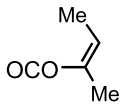
Scheme 3.



Scheme 4.

Table 1. Oxidation of phenols to isoquinoline-5,8-diones



Phenols compounds No.	R	Quinones compounds No.	Oxidizing agents CAN (%)[a]	Salcomine+O_2 (%)[b]
29	OH	**3**	52	78
30	OCOMe	**5**	91	96
31	OCOEt	**6**	87	99
32	H	**4**	81	85
33	NHCOCOMe	**2**	79	85
34		**1**	90	95

[a] Method A.
[b] Method B.

B)[26] to exclusively provide the corresponding isoquinoline-5,8-diones (**1**–**6**) in excellent yields, as shown in Table 1. It was demonstrated that both oxidizing agents produced similar results for the same substrate. The physical data for these isoquinoline-5,8-dione derivatives (**1**–**6**) were consistent with those of natural[3–7] and synthetic[2d,8–13]products in all respects.

3. Conclusions

The total syntheses of the isoquinolinequinone antibiotics, renierone (**1**), mimocin (**2**), renierol (**3**), renierol acetate (**5**), renierol propionate (**6**), and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**) were newly established through the construction of 5-oxygenated isoquinoline (**7**) based on the thermal electrocyclic reaction of 1-aza-6π-electron system (**8**), followed by the regioselective oxidation with both oxidizing agents. Based on this result, it was found that the 5-oxygenated isoquinoline (**7**) is an effective precursor of isoquinoline-5,8-diones (**1**–**6**).

4. Experimental

4.1. General

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Horiba FT-720 spectrophotometer. ^{1}H NMR spectra were taken by JEOL PMX60Si and JNM AL-300 spectrometers using $SiMe_4$ as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on Shimadzu QP-5050 and GC–MS 9020DF spectrometers (EI). Silica gel (60–100 mesh, Merck Art 7734) was used for the column chromatography.

4.1.1. 2-Hydroxy-4-methoxy-3-methylbenzaldehyde (10). A solution of benzaldehyde **9** (6 g, 33.3 mmol) in CH_2Cl_2 (30 mL) was slowly added to a stirred solution of BBr_3 (3.7 mL, 40 mmol) in CH_2Cl_2 (40 mL) at −78 °C under N_2 atmosphere. After gradually being warmed to rt, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated.

The residue was purified by column chromatography (silica gel, 100 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the phenol **10** (4.6 g, 83%), mp 60.5–61.5 °C (Et_2O). IR (KBr) ν: 3400, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.05 (3H, s), 3.92 (3H, s), 6.56 (1H, d, J=9 Hz), 7.37 (1H, d, J=9 Hz), 9.71 (1H, s), 11.44 (1H, s); MS m/z: 166 (M^+). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.36; H, 6.35.

4.1.2. 2-Benzyloxy-4-methoxy-3-methylbenzaldehyde (11). A mixture of phenol **10** (6 g, 54.2 mmol), benzyl bromide (6.4 mL, 54.2 mmol) and K_2CO_3 (10 g, 72.2 mmol) in DMF (60 mL) was heated at 60 °C for 4 h under N_2 atmosphere. After being cooled to an ambient temperature, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 100 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the benzyl ether **11** (9.2 g, 99%), mp 57.5–58.5 °C (Et_2O). IR (KBr) ν: 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.19 (3H, s), 3.92 (3H, s), 4.95 (2H, s), 6.77 (1H, d, J=9 Hz), 7.75 (1H, d, J=9 Hz), 10.13 (1H, s); MS m/z: 256 (M^+). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.23; H, 6.52.

4.1.3. 2-Benzyloxy-4-methoxy-3-methylphenol (12). A mixture of benzaldehyde **11** (250 mg, 0.98 mmol), and *m*CPBA (252 mg, 1.46 mmol) in CH_2Cl_2 (15 mL) was heated at 60 °C for 1 h under N_2 atmosphere. After being cooled to an ambient temperature, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, and concentrated. A solution of the residue in EtOH (5 mL) was added an aqueous KOH solution (10%, 5 mL), and then stirred at rt for 1 h. The mixture was acidified with 1 M HCl, which was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily phenol **12** (209 mg, 88%). IR (neat) ν: 3528 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (3H, s), 3.79 (3H, s), 4.88 (2H, s), 6.55 (1H, d, J=9 Hz), 6.74 (1H, d, J=9 Hz), 7.45–7.55 (5H, m); MS m/z: 244 (M^+). HRMS calcd for $C_{15}H_{16}O_3$: 244.1099; observed: 244.1105.

4.1.4. 3-Benzyloxy-2-hydroxy-5-methoxy-4-methylbenzaldehyde (13). Hexamethyltetramine (688 mg, 4.91 mmol) was added to a solution of the phenol **12** (200 mg, 0.82 mmol) in AcOH (10 mL), which was heated at 110 °C for 3 h. After being cooled to an ambient temperature, the solution was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the benzaldehyde **13** (118 mg, 53%), mp 73–74 °C (Et_2O). IR (KBr) ν: 3528, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.13 (3H, s), 3.82 (3H, s), 5.09 (2H, s), 6.70 (1H, s), 7.32–7.49 (5H, m), 9.83 (1H, s); MS m/z: 272 (M^+). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.85; H, 6.18.

4.1.5. 3-Benzyloxy-5-methoxy-4-methyl-2-(trifluoromethylsulfonyloxy)benzaldehyde (14). Tf_2O (93 μL, 0.55 mmol) was added to an ice-cooled solution of benzaldehyde **13** (100 mg, 0.37 mmol), and pyridine (59 μL, 0.73 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere. After being stirred at the same temperature for 1 h, an aqueous $NaHCO_3$ solution (saturated) was added to the reactant, and then the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the triflate **14** (120 mg, 81%), mp 72–73 °C (Et_2O). IR (KBr) ν: 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.13 (3H, s), 3.89 (3H, s), 4.96 (2H, s), 7.17 (1H, s), 7.32–7.45 (5H, m), 10.18 (1H, s); MS m/z: 404 (M^+). Anal. Calcd for $C_{17}H_{15}F_3O_6S$: C, 50.50; H, 3.74. Found: C, 50.75; H, 3.90.

4.1.6. 3-Benzyloxy-2-ethenyl-5-methoxy-4-methylbenzaldehyde (15). A mixture of the triflate **14** (843 mg, 2.08 mmol), vinyl *n*-tributyltin (913 mL, 3.13 mmol), Et_4NCl (345 mg, 2.08 mmol) and $PdCl_2(PPh_3)_2$ in DMF (5 mL) was heated at 110 °C for 1.5 h under Ar atmosphere. After being cooled to an ambient temperature, an aqueous KF solution (30%) was added to the reactant, and then the mixture was stirred at rt for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the benzaldehyde **15** (530 mg, 90%), mp 87–87.5 °C (Et_2O). IR (KBr) ν: 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (3H, s), 3.90 (3H, s), 4.81 (2H, s), 5.35 (1H, d, J=18 Hz), 5.72 (1H, d, J=12 Hz), 7.03 (1H, d, J=12, 18 Hz), 7.35–7.47 (6H, m), 10.18 (1H, s); MS m/z: 282 (M^+). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.88; H, 6.59.

4.1.7. 1-(3-Benzyloxy-2-ethenyl-5-methoxy-4-methylphenyl)ethane-1,2-diol (16). A solution of the benzaldehyde **15** (60 mg, 0.21 mmol) in THF (3 mL) was added to the Grignard reagent [prepared from chloromethyldimethylisopropoxysilane (191 μL, 1.06 mmol), 1,2-dibromoethane (20 μL, 0.23 mmol), and Mg (26 mg, 1.06 mmol) in THF (2 mL) according to the Tamao's procedure[19]] under N_2 atmosphere. After being stirred at rt for 2 h, the mixture was quenched with an aqueous NH_4Cl solution (10%), and then the mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4, and concentrated at 0 °C. A solution of H_2O_2 (28%, 216 mL, 1.19 mmol) was added to the mixture of the residue, $KHCO_3$ (64 mg, 0.64 mmol), and KF (37 mg, 0.64 mmol) in THF (2 mL) and MeOH (2 mL). After being stirred at rt for 3 h, an aqueous $Na_2S_2O_3$ solution (50%) was added slowly to the mixture. Et_2O was added to the mixture, which was filtered through a pad of Celite. The filtrate was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the diol **16** (58 mg, 87%), mp 79–80 °C (Et_2O). IR (KBr) ν: 3279 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09 (3H, s), 3.50–3.67 (2H, m), 3.84 (3H, s), 4.72 (2H, s), 5.07–5.11 (1H, m), 5.50 (1H, dd, J=2, 12 Hz), 5.55 (1H, dd, J=2, 18 Hz), 6.82 (1H,

d, J=12, 18 Hz), 6.97 (1H, s), 7.28–7.43 (5H, m); MS m/z: 314 (M^+). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.81; H, 7.32.

4.1.8. 1-(3-Benzyloxy-2-ethenyl-5-methoxy-4-methylphenyl)-2-(*tert*-butyldimethylsilyloxy)ethanol (17). *tert*-Butyldimethylsilyl chloride (57 mg, 0.38 mmol) was added to a solution of the diol **16** (100 mg, 0.32 mmol) and imidazole (65 mg, 0.96 mmol) in DMF (10 mL) at rt under N_2 atmosphere. The mixture was stirred at the same temperature for 1 h. After being quenched with water, the mixture was extracted with EtOAc. The EtOAc layer was washed with an aqueous $NaHCO_3$ solution (saturated), water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the alcohol **17** (126 mg, 92%), mp 68.5–69.5 °C (Et_2O). IR (KBr) ν: 3470 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.92 (9H, s), 2.15 (3H, s), 3.48 (1H, d, J=9 Hz), 3.78 (1H, dd, J=3, 9 Hz), 3.86 (3H, s), 4.68 (1H, d, J=11 Hz), 4.76 (1H, d, J=11 Hz), 5.08 (1H, dd, J=3, 9 Hz), 5.50 (1H, dd, J=2, 12 Hz), 5.57 (1H, dd, J=2, 18 Hz), 6.75 (1H, dd, J=12, 18 Hz), 6.95 (1H, s), 7.32–7.46 (5H, m); MS m/z: 428 (M^+). Anal. Calcd for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47. Found: C, 70.29; H, 8.68.

4.1.9. 2-Benzyloxy-4-[α-(*tert*-butyldimethylsilyloxy)-acetyl]-3-ethenyl-6-methoxytoluene (18). A solution of the alcohol **17** (432 mg, 2.02 mmol) in CH_2Cl_2 (5 mL) was added to an ice-cooled mixture of PCC (434 mg, 2.02 mmol) and Celite (800 mg) in CH_2Cl_2 under N_2 atmosphere. After being stirred at rt for 10 h, the reaction mixture was diluted with Et_2O, and then the mixture was filtrated through a pad of Celite. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily ketone **18** (365 mg, 85%). IR (neat) ν: 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 2.17 (3H, s), 3.83 (3H, s), 4.56 (2H, s), 4.75 (2H, s), 5.41 (1H, dd, J=1.5, 12 Hz), 5.39 (1H, dd, J=1.5, 18 Hz), 6.62 (1H, s), 6.96 (1H, dd, J=12, 18 Hz), 7.30–7.45 (5H, m); MS m/z: 426 (M^+). HRMS calcd for $C_{25}H_{34}O_4Si$: 426.2226; observed: 426.2233.

4.1.10. 2-Benzyloxy-4-[2-(*tert*-butyldimethylsilyloxy)-1-(hydroxyimino)ethyl]-3-ethenyl-6-methoxytoluene (19). A mixture of the ketone **18** (240 mg, 0.56 mmol), NH_2-OH·HCl (196 mg, 2.82 mmol) and AcONa (231 mg, 2.82 mmol) in EtOH (10 mL) were heated at 85 °C for 1 h. After being cooled to an ambient temperature, the mixture was concentrated. The water was added to the resulting residue, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the gummy oxime **19** (141 mg, 57%). IR (neat) ν: 3250, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: −0.06 (4H, s), −0.04 (2H, s), 0.71 (6H, s), 0.83 (3, s), 2.16 (2/3H, s), 2.17 (1/3H, s), 3.82 (3H, s), 4.73 (4/3H, s), 4.74 (2/3H, s), 5.31 (1/3H, dd, J=2, 12 Hz), 5.36 (2/3H, dd, J=2, 12 Hz), 5.61 (2/3H, dd, J=2, 18 Hz), 5.69 (1/3H, dd, J=2, 18 Hz), 6.49 (1/3H, s), 6.59 (2/3H, s), 6.75 (1/3H, dd, J=12, 18 Hz), 6.84 (2/3H, dd, J=12, 18 Hz), 7.33–7.47 (5H, m); MS m/z: 441 (M^+). HRMS calcd for $C_{25}H_{35}NO_4Si$: 441.2335; observed: 441.2321.

4.1.11. 1-(*tert*-Butyldimethylsilyloxymethyl)-5-benzyloxy-7-methoxy-6-methylisoquinoline (20). A solution of the oxime **19** (141 mg, 0.32 mmol) in *o*-dichlorobenzene (5 mL) was heated at 180 °C for 1 h. After being cooled to an ambient temperature, the solvent was evaporated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily isoquinoline **20** (66 mg, 49%). ^1H NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (9H, s), 2.34 (3H, s), 3.98 (3H, s), 4.98 (2H, s), 5.22 (2H, s), 7.38–7.55 (6H, m), 7.74 (1H, d, J=6 Hz), 8.29 (1H, dd, J=6 Hz); MS m/z: 423 (M^+). HRMS calcd for $C_{25}H_{33}NO_3Si$: 463.2230; observed: 463.2228.

4.1.12. 5-Benzyloxy-1-hydroxymethyl-7-methoxy-6-methylisoquinoline (21). A solution of TBAF (1.0 M in THF, 107 μL, 0.11 mmol) was added to an ice-cooled solution of the isoquinoline **20** (45.5 mg, 0.11 mmol) in THF (3 mL). After being stirred at rt for 1 h, the reaction mixture was treated with water. The mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3:7 v/v) as an eluent to give the alcohol **21** (30 mg, 89%), mp 144.5–146.5 °C (Et_2O). IR (KBr) ν: 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.98 (3H, s), 4.98 (2H, s), 5.15 (2H, s), 6.85 (1H, s), 7.36–7.54 (5H, m), 7.74 (1H, d, J=6 Hz), 8.33 (1H, dd, J=6 Hz); MS m/z: 309 (M^+). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.97; H, 6.35; N, 4.49.

4.1.13. (5-Benzyloxy-7-methoxy-6-methylisoquinol-1-yl)methyl angelate (22). A solution of PhLi (0.88 M in cyclohexane–Et_2O, 771 μL, 0.68 mmol) was added dropwise to an ice-cooled solution of the alcohol **21** (100 mg, 0.32 mmol) in dioxane (5 mL) and Et_2O (5 mL) under N_2 atmosphere. After being stirred at the same temperature for 10 min, the mixed anhydride (angelic 2,4,6-trichlorobenzoic anhydride) [prepared from 2,4,6-trichlorobenzoyl chloride (202 μL, 1.29 mmol), triethylamine (244 μL, 1.62 mmol) and angelic acid (136 mg, 1.36 mmol) in toluene (10 mL) under N_2 atmosphere, according to the Greene's procedure[21]] was added to the mixture. After being stirred at rt for 12 h, the mixture was quenched with water, which was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily ester **22** (98 mg, 78%). IR (neat) ν: 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.90 (3H, dq, J=1.5, 1.5 Hz), 1.98 (3H, dq, J=1.5, 7.2 Hz), 2.34 (3H, s), 3.95 (3H, s), 4.98 (2H, s), 5.77 (2H, s), 6.09 (1H, qq, J=1.5, 7.2 Hz), 7.20 (1H, s), 7.36–7.54 (5H, m), 7.81 (1H, d, J=5.5 Hz), 8.40 (1H, d, J=5.5 Hz); MS m/z: 391 (M^+). HRMS calcd for $C_{24}H_{25}NO_4$: 391.1784; observed: 391.1795.

4.1.14. (5-Benzyloxy-7-methoxy-6-methylisoquinol-1-yl)methyl acetate (23). A solution of PhLi (0.88 M in cyclohexane–Et_2O, 154 μL, 0.14 mmol) was added dropwise to an ice-cooled solution of the alcohol **21** (20 mg,

0.06 mmol) in dioxane (2 mL) and Et_2O (2 mL) under N_2 atmosphere. After being stirred at the same temperature for 10 min, $(MeCO)_2O$ (7 μL, 0.07 mmol) was added to the mixture. The mixture was stirred at ambient temperature for 30 min, which was quenched with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the acetate **23** (19 mg, 83%), mp 112.5–113.5 °C (Et_2O). IR (KBr) ν: 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.34 (3H, s), 3.98 (3H, s), 4.97 (2H, s), 5.70 (2H, s), 7.15 (1H, s), 7.38–7.54 (5H, m), 7.80 (1H, d, J=6 Hz), 8.40 (1H, d, J=6 Hz); MS m/z: 351 (M^+). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.98; H, 4.30; N, 3.86.

4.1.15. (5-Benzyloxy-7-methoxy-6-methylisoquinol-1-yl)methyl propionate (24). The same procedure as above was carried out using the alcohol **21** (50 mg, 0.16 mmol), PhLi (0.88 M in cyclohexane–Et_2O, 386 μL, 0.34 mmol) and $(EtCO)_2O$ (23 μL, 0.18 mmol) to give the propionate **24** (47.5 mg, 80%), mp 97.5–98.5 °C (Et_2O). IR (KBr) ν: 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.18 (3H, t, J=8 Hz), 2.34 (3H, s), 2.44 (2H, q, J=8 Hz), 3.97 (3H, s), 4.97 (2H, s), 5.70 (2H, s), 7.15 (1H, s), 7.37–7.54 (5H, m), 7.80 (1H, d, J=6 Hz), 8.39 (1H, d, J=6 Hz); MS m/z: 365 (M^+). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.59; H, 6.33; N, 3.74.

4.1.16. 5-Benzyloxy-7-methoxy-6-methyl-1-(4-toluenesulfonyloxymethyl)isoquinoline (25). The same procedure as above was carried out using the alcohol **21** (77 mg, 0.33 mmol), PhLi (0.88 M in cyclohexane–Et_2O, 830 μL, 0.73 mmol) and *p*-TsCl (69 mg, 0.36 mmol) to give the oily tosylate **25** (82 mg, 64%). IR (neat) ν: 1371, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.36 (3H, s), 3.95 (3H, s), 4.88 (2H, s), 5.50 (2H, s), 7.22–7.72 (10H, m), 7.75 (1H, d, J=6 Hz), 8.20 (1H, d, J=6 Hz); MS m/z: 463 (M^+). HRMS calcd for $C_{26}H_{25}NO_5S$: 463.1453; observed: 463.1466.

4.1.17. 5-Benzyloxy-1,6-dimethyl-7-methoxyisoquinoline (26). A solution of $LiEt_3BH$ (1.0 M in THF, 470 mL, 0.48 mmol) was added dropwise to an ice-cooled solution of the tosylate **25** (110 mg, 0.24 mmol) in THF (1 mL). After being stirred at the same temperature for 10 min, the reaction mixture was quenched with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the 1-methylisoquinoline **26** (59 mg, 85%), mp 123–124 °C (Et_2O). ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.92 (3H, s), 4.00 (3H, s), 4.97 (2H, s), 7.09 (1H, s), 7.39–7.55 (5H, m), 7.67 (1H, d, J=6 Hz), 8.27 (1H, d, J=6 Hz); MS m/z: 293 (M^+). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.93; H, 6.49; N, 4.65.

4.1.18. 1-Azidomethyl-5-benzyloxy-7-methoxy-6-methylisoquinoline (27). A solution of NaN_3 (24 mg, 0.37 mmol) in water (3 mL) was added dropwise to an ice-cooled solution of the tosylate **25** (115 mg, 0.25 mmol) in dioxane (15 mL), and then the mixture was stirred at 60 °C for 1 h. After being cooled to an ambient temperature, the mixture was diluted with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the azide **27** (67 mg, 81%), mp 82–83 °C (Et_2O). IR (KBr) ν: 2100, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.99 (3H, s), 4.86 (2H, s), 4.97 (2H, s), 7.10 (1H, s), 7.36–7.53 (5H, m), 7.79 (1H, d, J=6 Hz), 8.36 (1H, d, J=6 Hz); MS m/z: 334 (M^+). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.46; H, 5.54; N, 16.63.

4.1.19. 5-Benzyloxy-7-methoxy-6-methyl-1-(pyruvoylaminomethyl)isoquinoline (28). A solution of PPh_3 (54 mg, 0.21 mmol) in benzene (3 mL) was added dropwise to a solution of the azide **27** (63 mg, 0.19 mmol) in benzene (2 mL) under N_2 atmosphere, and then the solution was stirred at rt for 12 h. The pyruvoyl chloride [prepared from pyruvic acid (52 μL, 0.75 mmol) and α,α-dichloromethyl methyl ether (68 μL, 0.75 mmol) at 50 °C for 30 min[22]] was added dropwise to the ice-cooled solution. After being stirred at rt for 5 min, an aqueous $NaHCO_3$ solution (saturated, 30 mL) and MeOH (10 mL) was added to the ice-cooled mixture, which was stirred at the same temperature for 1 h. The mixture was diluted with water, and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the amide **28** (33 mg, 45%), mp 129.5–131 °C (Et_2O). IR (KBr) ν: 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.55 (3H, s), 400 (3H, s), 4.97 (2H, s), 4.99 (2H, s), 7.04 (1H, s), 7.36–7.53 (5H, m), 7.76 (1H, d, J=6 Hz), 8.34 (1H, d, J=6 Hz), 8.90 (1H, br s),; MS m/z: 378 (M^+). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.98; H, 5.97; N, 7.36.

4.1.20. 5-Hydroxy-1-hydroxymethyl-7-methoxy-6-methylisoquinoline (29). A mixture of the alcohol **21** (52 mg, 0.19 mmol) and 10% Pd–C (10 mg) in EtOH (15 mL) was stirred at rt for 2 h under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite, the filtrate was concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3:7 v/v) as an eluent to give the 5-hydroxyisoquinoline **29** (19 mg, 99%), mp 189.5–190 °C (MeOH). IR (KBr) ν: 3017 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.98 (3H, s), 5.09 (2H, s), 7.13 (1H, s), 7.93 (1H, d, J=6 Hz), 8.19 (1H, d, J=6 Hz); MS m/z: 219 (M^+). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.88; H, 6.15; N, 6.22.

4.1.21. (5-Hydroxy-7-methoxy-6-methylisoquinol-1-yl)methyl acetate (30). The same procedure as above was carried out using the acetate **23** (20 mg, 0.057 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **30** (14.5 mg, 98%), mp 204–205 °C (benzene). IR (KBr) ν: 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.23 (3H, s), 3.96 (3H, s), 5.68 (2H, s), 6.95 (1H, s), 7.86 (1H, d, J=6 Hz), 8.40 (1H, d, J=6 Hz); MS m/z: 261 (M^+), 218. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.56; H, 5.98; N, 5.19.

4.1.22. (5-Hydroxy-7-methoxy-6-methylisoquinol-1-yl)methyl propionate (31). The same procedure as above was carried out using the propionate **24** (42 mg, 0.11 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **31** (31 mg, 98%), mp 167.5–168 °C (benzene). IR (KBr) ν: 3450, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.17 (3H, t, J=8 Hz), 2.30 (3H, s), 2.42 (1H, q, J=8 Hz), 3.94 (3H, s), 5.68 (2H, s), 6.95 (1H, s), 7.87 (1H, d, J=6 Hz), 8.37 (1H, d, J=6 Hz); MS m/z: 275 (M^+), 218. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.75; H, 6.34; N, 4.93.

4.1.23. 5-Hydroxy-7-methoxy-1,6-dimethylisoquinoline (32). The same procedure as above was carried out using the 1-methylisoquinoline **26** (52 mg, 0.12 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **32** (33 mg, 91%), mp 238–240 °C (decomp.) (benzene). IR (KBr) ν: 3439 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.78 (3H, s), 3.89 (3H, s), 6.80 (1H, s), 7.73 (1H, d, J=6 Hz), 8.07 (1H, d, J=6 Hz); MS m/z: 203 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.14; H, 6.56; N, 6.73.

4.1.24. 5-Hydroxy-7-methoxy-6-methyl-1-(pyruvoylaminomethyl)isoquinoline (33). The same procedure as above was carried out using the 1-methylisoquinoline **28** (62 mg, 0.16 mmol) and 10% Pd–C (10 mg) to give the 5-hydroxyisoquinoline **33** (42 mg, 91%), mp 174.5–175.5 °C (Et_2O). IR (KBr) ν: 3302, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.30 (3H, s), 2.55 (3H, s), 3.97 (3H, s), 4.95 (2H, d, J=4 Hz), 6.84 (1H, s), 7.82 (1H, d, J=6 Hz), 8.33 (1H, d, J=6 Hz), 8.75–8.85 (1H, br s); MS m/z: 288 (M^+), 202. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.68; H, 5.80; N, 9.62.

4.1.25. (5-Hydroxy-7-methoxy-6-methylisoquinol-1-yl)methyl angelate (34). $BF_3{\cdot}Et_2O$ (214 μL, 1.69 mmol) and Me_2S (170 μL, 2.32 mmol) were added dropwise to an ice-cooled solution of the angelate **28** (33 mg, 0.084 mmol) in CH_2Cl_2 (8 mL), and then the mixture was stirred at rt for 12 h. In Addition, $BF_3{\cdot}Et_2O$ (214 μL, 1.69 mmol) and Me_2S (170 μL, 2.32 mmol) were added to an ice-cooled mixture, which was stirred at rt for 6 h. The mixture was quenched with water, which was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3:7 v/v) as an eluent to give the 5-hydroxyisoquinoline **34** (25 mg, 96%), mp 154–155 °C (Et_2O). IR (KBr) ν: 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.26 (3H, dq, J=1.5, 1.5 Hz), 1.75 (3H, dq, J=1.5, 7.2 Hz), 1.84 (3H, s), 2.29 (3H, s), 3.92 (3H, s), 5.72 (2H, s), 6.90 (1H, qq, J=1.5, 7.2 Hz), 7.00 (1H, s), 7.86 (1H, d, J=6 Hz), 8.38 (1H, d, J=6 Hz); MS m/z: 301 (M^+), 218. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.97; H, 6.58; N, 4.51.

4.1.26. Renierone (1). *Method A*. A solution of CAN (150 mg, 0.27 mmol) of CH_3CN (2 mL) and H_2O (1 mL) was added dropwise to an ice-cooled solution of the phenol **34** (16.5 mg, 0.055 mmol) of CH_3CN (2 mL) and H_2O (1 mL). After being stirred at the same temperature for 30 min, the mixture was diluted with water, which was neutralized with an aqueous $NaHCO_3$ solution (saturated). The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3:7 v/v) as an eluent to give renierone **1** (15.5 mg, 90%), mp 92–92.5 °C (Et_2O) (lit.,[3a] 91.5–92.5 °C). IR (KBr) ν: 1707, 1666, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.83 (3H, dq, J=1.5, 1.5 Hz), 1.90 (3H, dq, J=1.5, 7.3 Hz), 2.09 (3H, s), 4.14 (3H, s), 5.76 (2H, s), 6.09 (1H, qq, J=1.5, 7.3 Hz), 7.86 (1H, d, J=5 Hz), 8.92 (1H, d, J=5 Hz); MS m/z: 315 (M^+), 83.

Method B. A stirred solution of the phenol **34** (17.3 mg, 0.057 mmol) and salcomine (3.6 mg, 0.011 mmol) in DMF (5 mL) was bubbled with oxygen at rt for 2 h. The reaction mixture was diluted with water, and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3:7 v/v) as an eluent to give renierone **1** (17.2 mg, 95%).

4.1.27. Mimocin (2). *Method A*. The same procedure as above was carried out using the amide **33** (15.7 mg, 0.055 mmol) and CAN (149 mg, 0.27 mmol) to give mimocin **2** (13 mg, 79%), mp 189–191 °C (decomp.) (Et_2O) (lit.,[4] 189–191 °C). IR (KBr) ν: 3391, 1722, 1684, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.53 (3H, s), 4.17 (3H, s), 5.10 (2H, d, J=5.1 Hz), 8.62 (1H, br s), 8.94 (1H, d, J=5 Hz); MS m/z: 302 (M^+).

Method B. The same procedure as above was carried out using the amide **33** (14.8 mg, 0.051 mmol) and salcomine (3.2 mg, 0.01 mmol) with O_2 to give mimocin **2** (13.2 mg, 85%).

4.1.28. Renierol (3). *Method A*. The same procedure as above was carried out using the 1-hydroxymethylisoquinoline **29** (11 mg, 0.05 mmol) and CAN (143 mg, 0.26 mmol) to give renierol **3** (6.2 mg, 52%), mp 128–130 °C (Et_2O) (lit.,[9c] 131–133 °C). IR (KBr) ν: 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10 (3H, s), 4.15 (3H, s), 4.48 (1H, br s), 5.20 (2H, s), 7.92 (1H, d, J=5 Hz), 8.84 (1H, d, J=5 Hz); MS m/z: 233 (M^+), 233.

Method B. The same procedure as above was carried out using the 1-hydroxymethylisoquinoline **29** (11 mg, 0.05 mmol) and salcomine (3 mg, 0.01 mmol) with O_2 to give renierol **3** (9.1 mg, 78%).

4.1.29. 7-Methoxy-1,6-dimethylisoquinoline-5,8-dione (4). *Method A*. The same procedure as above was carried out using the 1-methylisoquinoline **32** (17.2 mg, 0.084 mmol) and CAN (231 mg, 0.42 mmol) to give the compound **4** (14.9 mg, 81%), mp 186–188.5 °C (Et_2O) (lit.,[3b] 188–190 °C). IR (KBr) ν: 1668, 1628, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.98 (3H, s), 4.14 (3H, s), 7.80 (1H, d, J=5 Hz), 8.84 (1H, d, J=5 Hz); MS m/z: 217 (M^+).

Method B. The same procedure as above was carried out using the 1-methylisoquinoline **32** (15.8 mg, 0.078 mmol) and salcomine (4.9 mg, 0.016 mmol) with O_2 to give the compound **4** (14.3 mg, 85%).

4.1.30. Renierol acetate (5). *Method A*. The same procedure as above was carried out using the acetate **30** (3.9 mg, 0.015 mmol) and CAN (41 mg, 0.075 mmol) to give renierol acetate **5** (2.4 mg, 91%), mp 108–109 °C (Et_2O) (lit.,[7c] 118–119 °C). IR (KBr) ν: 1749, 1674, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09 (3H, s), 2.23 (3H, s), 4.15 (3H, s), 5.71 (2H, s), 7.89 (1H, d, J=5 Hz), 8.94 (1H, d, J=5 Hz); MS *m/z*: 275 (M^+), 233.

Method B. The same procedure as above was carried out using the acetate **30** (8.3 mg, 0.032 mmol) and salcomine (2 mg, 0.0064 mmol) with O_2 to give renierol acetate **5** (8.4 mg, 96%).

4.1.31. Renierol propionate (6). *Method A*. The same procedure as above was carried out using the propionate **31** (5.3 mg, 0.019 mmol) and CAN (53 mg, 0.097 mmol) to give renierol propionate **6** (4.9 mg, 87%), mp 88–90 °C (Et_2O) (lit.,[2d] 89–90 °C). IR (KBr) ν: 2960, 1751, 1672, 1653, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.5 Hz), 2.09 (3H, s), 2.52 (2H, d, J=7.5 Hz), 4.15 (3H, s), 5.71 (2H, s), 7.88 (1H, d, J=5 Hz), 8.92 (1H, d, J=5 Hz); MS *m/z*: 289 (M^+), 233.

Method B. The same procedure as above was carried out using the propionate **31** (7.4 mg, 0.027 mmol) and salcomine (3 mg, 0.096 mmol) with O_2 to give renierol propionate **6** (7.7 mg, 99%).

Acknowledgements

This work was in part supported by a Grant-in-Aid for Scientific research of the Ministry of Education, Science, Sports, and Culture of Japan. We would like to thank Professor A. Kubo, Meiji Pharmaceutical University for the information of renierol acetate and renierol propinate.

References and notes

1. (a) Arai, T.; Kubo, A. *The alkaloid*; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, pp 44–100. (b) Christopherson, C. *The alkaloid*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 24, pp 25–111. (c) Thompson, R. H. *Naturally occurring quinones*; Chapman and Hall: London, 1987; Vol. III. pp 633–671. (d) Pettit, G. R.; Collins, J. C.; Herald, D. L.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A.; Tackett, L. P. *Can. J. Chem.* **1992**, *70*, 1170–1175. (e) Venkateswarlu, Y.; Reddy, M. V. K.; Srivas, K. V. N.; Rao, J. V. *Indian J. Chem.* **1993**, 704. (f) Pettit, G. R.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793–798. (g) Pettit, G. R.; Collins, J. C.; Knight, J. C.; Herald, D. L.; Nieman, R. A. *J. Nat. Prod.* **2003**, *66*, 544–547.
2. (a) Take, Y.; Oogose, K.; Kubo, T.; Inouye, Y.; Nakamura, S.; Kitahara, Y.; Kubo, A. *J. Antibiotic.* **1987**, *40*, 679–684. (b) Inouye, Y.; Oogose, K.; Take, Y.; Kubo, A.; Nakamura, S. *J. Antibiotic.* **1987**, *40*, 702–705. (c) Take, Y.; Inouye, Y.; Nakamura, S.; Allaudeen, H. S.; Kubo, A. *J. Anitbiotic.* **1989**, *42*, 107–115. (d) Kubo, A.; Kitahara, Y.; Nakahara, S. *Chem. Pharm. Bull.* **1989**, *37*, 1384–1386.
3. (a) McIntire, D. E.; Faulkner, D. J.; Engen, D. V.; Clardy, J. *Tetrahedron Lett.* **1979**, *20*, 4163–4166. (b) Flinke, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 265–269.
4. Kubo, A.; Nakahara, S.; Iwata, R.; Takahashi, K.; Arai, T. *Tetrahedron Lett.* **1980**, *21*, 3207–3208.
5. McKee, T.; Ireland, C. M. *J. Nat. Prod.* **1987**, *50*, 754–756.
6. Edrada, R. A.; Proksch, P.; Wray, V.; Christ, R.; Witte, L.; Van Soest, R. W. M. *J. Nat. Prod.* **1996**, *59*, 973–976.
7. (a) de Silva, E. D.; Glavita, N. K. 16th IUPAC International Symposium on the Chemistry of Natural Products; Kyoto, May 1988, Abstract Pa 8, p 610. (b) Glavita, N. K. University of Hawaii, PhD Dissertation. (c) Kitahara, Y.; Nakahara, S.; Numata, R.; Inaba, K.; Kubo, A. *Chem. Pharm. Bull.* **1985**, *33*, 823–830.
8. Danishefsky, S.; Berman, E.; Cvetovich, R.; Minamikawa, J. *Tetrahedron Lett.* **1980**, *21*, 4819–4822.
9. (a) Kubo, A.; Nakahara, S. *Chem. Pharm. Bull.* **1981**, *29*, 595–596. (b) Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2582–2584. (c) Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4056–4068.
10. (a) Matsuo, K.; Okumura, M.; Tanaka, K. *Chem. Lett.* **1982**, 1339–1340. (b) Matsuo, K.; Okumura, M.; Tanaka, K. *Chem. Pharm. Bull.* **1982**, *30*, 4170–4174.
11. Kubo, A.; Kitahara, Y.; Nakahara, S.; Iwata, R.; Numata, R. *Chem. Pharm. Bull.* **1988**, *36*, 4355–4363.
12. Iyer, S.; Liebskind, S. *J. Am. Chem. Soc.* **1987**, *109*, 2759–2770.
13. Molina, P.; Vidal, A.; Tover, F. *Synthesis* **1997**, 963–966.
14. (a) Okamura, W. H.; de Lera, A. R. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: New York, 1994; Vol. 5, pp 697–750. (b) Kawasaki, T.; Sakamoto, M. *J. Indian Chem. Soc.* **1994**, *71*, 443–457. (c) Hibino, S.; Sugino, E. *Advances in nitrogen heterocycles*; Moody, C. J., Ed.; JAI: Greenwich CT, 1995; Vol. 1, pp 205–227.
15. (a) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1996**, *37*, 2593–2596. (b) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535–2545. (c) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1998**, *46*, 1948–1949. (d) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Tetrahedron* **2000**, *58*, 5807–5811. (e) Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881–886.
16. (a) Yoshioka, H.; Choshi, T.; Sugino, E.; Hibino, S. *Heterocycles* **1995**, *41*, 161–174. (b) Choshi, T.; Yamada, S.; Sugino, E.; Hibino, S. *Synlett* **1995**, 147–148. (c) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899–5904. (d) Yoshioka, H.; Matsuya, Y.; Chsohi, T.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1996**, *44*, 709–714. (e) Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, E. *Heterocycles* **1996**, *43*, 1847–1854. (f) Choshi, T.; Yamada, S.; Nobuhiro, J.; Mihara, Y.; Sugino, E.; Hibino, S. *Heterocycles* **1998**, *48*, 11–14. (g) Choshi, T.; Matsuya, Y.; Okita, M.; Inada, K.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1998**, *39*, 2341–2344. (h) Sugino, E.; Choshi, T.; Hibino, S. *Heterocycles* **1999**, *50*, 543–559. (i) Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108–113. (j) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S. *Heterocycles* **2000**, *53*,

1877–1880. (k) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793–8798.
17. Kuwabara, N.; Hayashi, H.; Hiramatsu, N.; Choshi, T.; Hibino, S. *Chem. Pharm. Bull.* **1999**, *47*, 1805–1807.
18. Godfrey, I. M.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353–1354.
19. Tamao, R.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245–4248.
20. (a) Hibino, S.; Sugino, E.; Adachi, Y.; Nomi, K.; Sato, K. *Heterocycles* **1989**, *28*, 275–282. (b) Hibino, S.; Sugino, E.; Choshi, T.; Sato, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2429–2432.
21. Hartmann, B.; Kanazawa, A. M.; Depres, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077–5080.
22. Barluenga, N.; Fererro, M.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 3497–3500.
23. Ottenheijm, H. C.; de Man, J. H. M. *Synthesis* **1975**, 163–164.
24. (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662–3664. (b) Miki, Y.; Fujita, R.; Matsushita, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2533–2536.
25. (a) Joseph, J. R., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629. (b) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521–522. (c) Kubo, A.; Kitahara, Y.; Nakahara, S.; Numata, R. *Chem. Pharm. Bull.* **1983**, *31*, 341–343. (d) Kitahara, Y.; Nakai, T.; Nakahara, S.; Akazawa, M.; Shimizu, M.; Kubo, A. *Chem. Pharm. Bull.* **1991**, *39*, 2256–2263.
26. (a) Bailes, R. H.; Calvin, M. *J. Am. Chem. Soc.* **1947**, *69*, 1886–1893. (b) VanDort, H. M.; Geursen, H. J. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 520–526. (c) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 232–236. (d) Wakamatsu, T.; Nishi, T.; Ohnuma, T.; Ban, Y. *Synth. Commun.* **1984**, *14*, 1167–1173.