Synthesis of the New Furo[3,2-*h*]isoquinoline Alkaloid, TMC-120B from *Aspergillus ustus*

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A total synthesis of a new furo[3,2-*h*]isoquinoline alkaloid TMC120-B (2), isolated from *Aspergillus ustus* together with two related compounds, has been completed in sixteen steps. The key step is the synthesis of the appropriate 3,7,8-trisubstituted isoquinoline framework (23) based on a thermal electrocyclic reaction of the 1-aza 6π-electron system involving the benzene double bond. In addition, the microwave assisted electrocyclic reaction of this system was newly performed.

Key words furo[3,2-*h*]isoquinoline; TMC-120B; total synthesis; electrocyclic reaction; 6π-electron system; microwave

In the course of our studies of biologically active condensed heteroaromatic compounds including natural products through the construction of functionalized frameworks based on the thermal electrocyclic reaction[1—3] of either 6π-electron[4—6] or aza 6π-electron[4,5,7] systems incorporating the heteroaromatic or aromatic moiety, we have now selected three new furo[3,2-*h*]isoquinoline alkaloids, TMC-120A (**1**), B (**2**), and C (**3**) as target compounds (Fig. 1), which were isolated from a fermentation broth of *Aspergillus ustus* TC 1118 by Kohno *et al.* in 1999.[8,9] Their structures have been determined by spectroscopic, chemical, and X-ray analyses. TMC-120B (**2**) shows moderate inhibitory activity against the interleukin-5 mediated prolongation of eosinophil survival (IC_{50}=2.0 μM).

We describe here the detailed synthetic work of TMC-120B (**2**) as recently reported.[10] In a retro-synthetic analysis (Chart 1), we planned that TMC-120B (**2**) would be derived from furoisoquinoline (**4**) prepared firstly by the Dieckmann condensation of diester (**5**). Next, we envisioned that a 3,7,8-trisubstituted isoquinoline nucleus (**5**) might be obtained by a thermal electrocyclic reaction of *o*-alkenylbenzaldoxime methyl ether (**6**) derived from the cleavage of the 2,3-bond of isoquinoline (**5**) as an application of the synthesis of isoquinoline frameworks by using the 1-azahexatriene system.[7,11—14] Therefore, we thought that the required 1-aza 6π-electron system (**6**) involving the benzene double bond would be derived from the known 2,4-bismethoxymethyl(bis-MOM)oxybenzaldehyde (**10**)[15,16] with several steps.

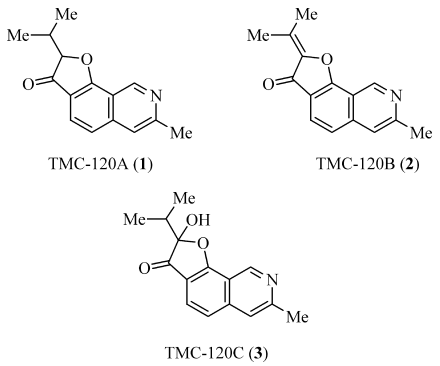

Fig. 1

Results and Discussion

For the synthesis of the required *o*-alkenylbenzaldoxime (**6**) and 3,7,8-trisubstituted isoquinoline nucleus (**5**) (Chart 2), reduction of the aldehyde (**10**) with sodium borohydride in ethanol followed by treatment of the resulting alcohol (**11**) (90%) with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole in DMF gave the TBDMS ether (**12**) in 85% yield. The ether (**12**) was treated with *n*-BuLi in THF at 0 °C to yield the lithio compound, which was quenched with DMF at the same temperature to afford the benzaldehyde (**13**) in 75% yield in spite of the restricted position of space, according to the procedure reported by Pocci group.[17] The reaction of the aldehyde (**13**) with hydroxylamine methyl ether in EtOH gave the oxime methyl ether (**14**) in 89% yield, which was treated with tetrabutylammonium fluoride (TBAF) to afford the benzyl alcohol (**15**) in 92% yield. Oxidation of the alcohol (**15**) with activated manganese dioxide (act. MnO_2) in CH_2Cl_2 furnished the ben-

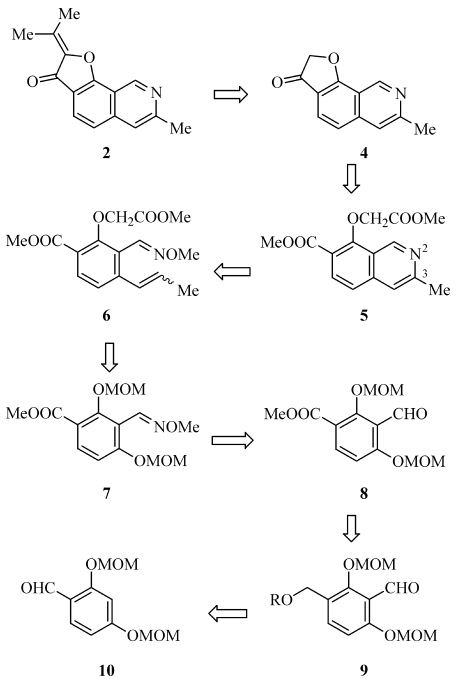

Chart 1

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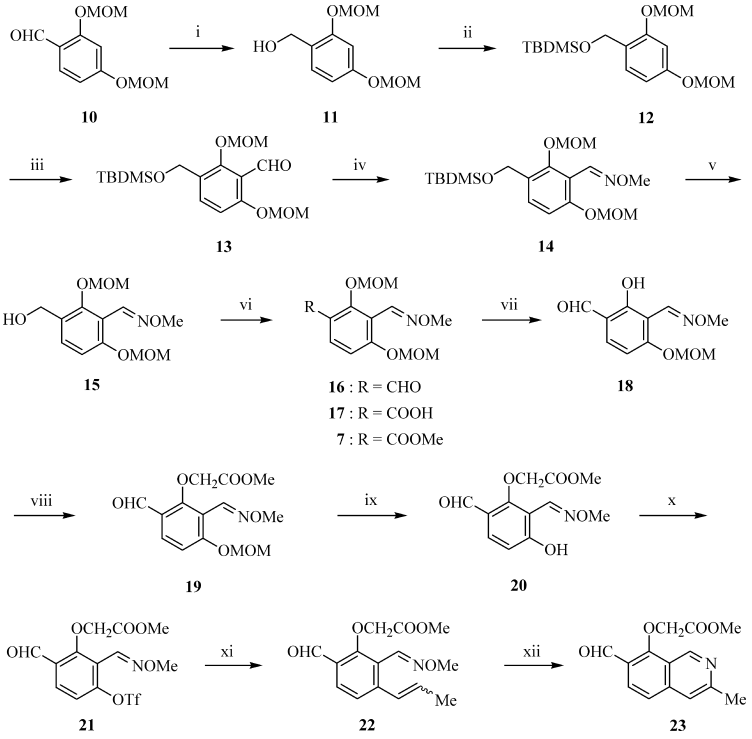


Reagent and conditions: (i) $NaBH_4$, EtOH, rt, 2 h (90%), (ii) TBDMSCl, imidazole, DMF, rt, 12 h (95%), (iii) *n*-BuLi, THF, 40 min, and then DMF, 0 °C, 20 min (75%), (iv) $MeONH_2 \cdot HCl$, AcONa, EtOH, 80 °C, 12 h (89%), (v) TBAF, THF, rt, 1.5 h (91%), (vi) act. MnO_2, CH_2Cl_2, rt, 24 h (89%), (vii) *conc.* HCl, MeOH, 0 °C, 3 h (92%), (viii) NaH, DMF, $BrCH_2COOMe$, rt, 12 h (93%), (ix) AcOH, 90 °C, 12 h (80%), (x) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 4 h (85%), (xi) Me–CH=CH–$SnBu_3$, Et_4NCl, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 4 h (83%), (xii) Table 1.

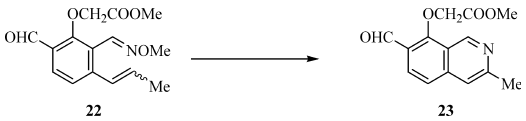
Chart 2

zaldehyde (**16**) in 89% yield, but a conversion of a formyl group of **16** into a carboxylic acid (**17**) with $NaClO_2$ and H_2O_2 in acetonitrile[18] or a methyl ester (**7**) with KOH and I_2 in MeOH[19] both failed. It was difficult to convert the formyl group of benzaldehyde (**16**) into an ester group of a supposed compound **7** in an initial retro-synthetic Chart 1.

We then turned to investigate a synthesis of isoquinoline (**23**) having the formyl group in order to achieve a selective cleavage of MOM-ethers of 2,4-bis(methoxymethyloxy)benzaldehyde (**16**). The treatment of **16** with conc. hydrochloric acid (one equivalent) in MeOH at 0 °C successfully produced the selectively cleavaged 2-hydroxybenzaldehyde (**18**) in an excellent yield (92%). The other conditions, such as 12 N HCl in MeOH at 0 °C,[16] conc. HCl (2 drops) in 2-PrOH at 50 °C,[20] a trace of HCl in MeOH at 62 °C[21] for the cleavage of MOM-ether, and an aqueous acetic acid in THF at 47 °C[22] for the cleavage of tetrahydropyranyl ether, were not suitable for selective deprotection. The resulting phenol (**18**) was then converted into the ether (**19**) by means of methyl bromoacetate with sodium hydride in 93% yield. The cleavage of the MOM-ether at the 4-position of **19** in acetic acid at 90 °C smoothly provided the 4-hydroxybenzaldehyde (**20**) in 80% yield, and sequential treatment of **20** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine at 0 °C gave the triflate (**21**) in 85% yield. The palladium-catalyzed cross-coupling reaction of **21** with tributyl 1-propenyltin in the presence of $PdCl_2(PPh_3)_2$ in DMF at 80 °C afforded the appropriate *o*-propenyl benzaldoxime methyl ether (**22**) in 83% yield as a 1-aza 6π-electron system (Chart 2).

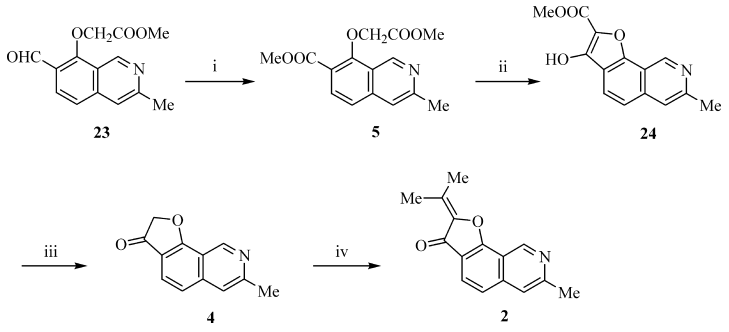
As shown in Table 1, the subsequent thermal electrocyclic reaction of **22** was carried out in *o*-dichlorobenzene under conventional conditions at 150 °C (run 1) and 180 °C (run 2) to produce the desired 3,7,8-trisubstituted isoquinoline (**23**). In this result, the yield of **23** by run 2 was slightly better than that of run 1. On the other hand, the microwave assisted electrocyclic reaction of **22** was performed to study the effect of the microwave irradiation in the same substrate. The effect of the reaction temperature was initially attempted (runs 3—5). From this experiment, the conditions of 150 °C for 20 min in *o*-dichlorobenzene (run 4) was the best result to complete the reaction. In addition, the effects of the other solvents were examined in order to compare with *o*-dichlorobenzene under the same conditions (runs 6—8). Based on this experiment, it was found that *o*-dichlorobenzene was the best solvent for

Table 1



Run	Solvent	MW[a]	Temp (°C)	Time (min)	Yield (%)[b]
1	*o*-Dichlorobenzene	Without MW	150	30	41
2	*o*-Dichlorobenzene	Without MW	180	30	44
3	*o*-Dichlorobenzene	With MW	130	30	30
4	*o*-Dichlorobenzene	With MW	150	20	46
5	*o*-Dichlorobenzene	With MW	180	10	45
6	DMF	With MW	150	20	37
7	2-Methoxyethanol	With MW	150	20	25
8	Bromobenzene	With MW	150	20	32

a) MW: microwave. *b*) %: isolated yields.



Reagent and conditions: (i) NaCN, AcOH, MnO_2, MeOH, rt, 4 h (83%), (ii) NaOMe, MeOH, 80 °C, 12 h (66%), (iii) $LiOH \cdot H_2O$, DMSO–H_2O, 70 °C, 2 h (75%), (iv) LDA, $(CH_3)_2CO$, THF, −40 °C, 4 h, $MeSO_2Cl$, DMAP, pyridine, 0 °C, 2 h (58%).

Chart 3

this substrate (run 4). It has been thought that the microwave irradiated conditions are slightly more effective than the conventional conditions (run 2) for reducing the reaction temperature (run 4) and decreasing the reaction time (runs 4 and 5).

For the preparation of the furanone ring, by the Dieckmann condensation (Chart 3), 7-formylisoquinoline (**23**) was converted into the proposed methyl ester (**5**) using sodium cyanide, MnO_2, and acetic acid in MeOH according to Corey's procedure[22,23] in 83% yield. The cyclization of **5** with sodium methoxide in MeOH at 80 °C gave the β-keto ester (**24**), which was treated with lithium hydroxide in an aqueous DMSO at 70 °C[24] to produce the furanone (**4**) in 50% yield from **24**. Finally, the carbon–carbon bond formation of **4** with acetone in the presence of lithium diisopropylamide (LDA) at −40 °C, followed by treatment with methanesulfonyl chloride (MsCl) and 4-(dimethylamino)-pyridine (DMAP) in pyridine[25] provided TMC-120B (**2**) with the elimination step in 58% yield from **4**. Although this reaction was carried out at −78 and −20 °C, the yields from **4** to **2** were 33 and 35%, respectively, lower than that at −40 °C. The physical and spectroscopic data of synthetic TMC-120B (**2**) agreed with those of natural TMC-120B (**2**) in all respects.

Conclusion

A total synthesis of new type of furo[3,2-*h*]isoquinoline alkaloid TMC-120B (**2**), isolated from *Aspergillus ustus* TC 1118 together with TMC-120A (**1**) and TMC-120C (**3**), was established through the construction of the appropriate 3,7,8-trisubstituted isoquinoline framework based on the thermal electrocyclic reaction of 1-aza 6π-electron system, followed by the formation of furanone ring and the introduction of isopropylidene moiety in sixteen steps (2.5% overall yield). Furthermore, it was demonstrated that the microwave irradiation for the thermal electrocyclic reaction of 1-aza 6π-electron system was a slightly more effective means at least for reducing the reaction temperature and shortening the time.

Experimental

All melting points were measured with a Yanagimoto micro-melting point apparatus MP-500D and are uncorrected. IR spectra were recorded with a Shimadzu FT-IR-8500 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were taken with a JEOL AL-300 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were determined with a Shimadzu QP5050 (EI) and JMS-700 (CI with isobutane) spectrometers by direct inlet system, respectively. The microwave assisted reaction was carried out at 180 W and 2450 MHz with "Discover" of CEM corporation. All air sensitive reactions were run under an argon atmosphere. Solvents were distilled by normal methods (THF dried over sodium benzophenone ketyl, CH_2Cl_2 dried over CaH_2, DMF dried over CaH_2). Silica gel $60PF_{254}$ (60—100 mesh, Merck Art 7744) was used for column chromatography.

2,4-Bis(methoxymethyloxy)benzyl Alcohol (11) $NaBH_4$ (1.8 g, 48.6 mmol) was added gradually to a stirred solution of benzaldehyde (**10**)[15,16] (10 g, 44.2 mmol) in EtOH (50 ml) under cooling with ice-water. After being stirred at room temperature for 2 h, the mixture was concentrated under reduced pressure. After addition of water, the residue was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of solvent gave the oily alcohol (**11**) (9.1 g, 90%), bp 145—147 °C/0.25 torr. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (3H, s), 3.48 (3H, s), 4.62 (2H, s), 5.15 (2H, s), 5.20 (2H, s), 6.68 (1H, dd, J=2.4, 8.2 Hz), 6.80 (1H, d, J=2.4 Hz), 7.19 (1H, d, J=8.2 Hz). MS (CI) *m/z*: 228 (M^+). HR-MS (CI) *m/z*: 228.0994 (M^+) (Calcd for $C_{11}H_{16}O_5$: 228.0998).

1,3-Bis(methoxymethyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)benzene (12) A solution of the alcohol (**11**) (7 g, 30.7 mmol) in DMF (20 ml) was added to a solution of *tert*-butyldimethylsilyl chloride (6.9 g, 46.0 mmol) and imidazole (4.2 g, 61.3 mmol) in DMF (40 ml). After being stirred at room temperature for 12 h, the reaction mixture was quenched with an aqueous $NaHCO_3$ solution (saturated), and then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc–hexane (1 : 9) as an eluent to give the oily silyl ether (**12**) (10 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.94 (9H, s), 3.47 (3H, s), 3.47 (3H, s), 4.71 (2H, s), 5.15 (2H, s), 5.17 (2H, s), 6.71 (1H, dd, J=2.3, 8.4 Hz), 6.77 (1H, d, J=2.3 Hz), 7.34 (1H, d, J=8.4 Hz). MS (CI) *m/z*: 343 $[M+H]^+$. HR-MS (CI) *m/z*: 343.1948 $[M+H]^+$ (Calcd for $C_{17}H_{31}O_5Si$: 343.1941).

2,6-Bis(methoxymethyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)benzaldehyde (13) A solution of *n*-BuLi (2.6 M in hexane, 7.9 ml, 20.6 mmol) was added to a solution of silyl ether (**12**) (4.7 g, 13.7 mmol) in THF (40 ml) under cooling with ice-water. After stirring at the same temperature for 40 min, DMF (3.2 ml, 41.2 mmol) was added. The mixture was further stirred at the same temperature for 20 min, which was quenched with water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc–hexane (1 : 9) as an eluent to give the oily benzaldehyde (**13**) (3.8 g, 75%). IR (neat) ν: 1693 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (6H, s), 0.94 (9H, s), 3.51 (3H, s), 3.56 (3H, s), 4.81 (2H, s), 5.06 (2H, s), 5.27 (2H, s), 7.02 (1H, d, J=8.8 Hz), 7.65 (1H, d, J=8.8 Hz), 10.46 (1H, s). MS (CI) *m/z*: 371 $[M+H]^+$. HR-MS (CI) *m/z*: 371.1897 $[M+H]^+$ (Calcd for $C_{18}H_{31}O_6Si$: 371.1890).

2-(Methoxyiminomethyl)-1,3-bis(methoxymethyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)benzene (14) A mixture of benzaldehyde (**13**) (5.5 g, 14.9 mmol), $MeONH_2 \cdot HCl$ (1.9 g, 22.3 mmol), and AcONa (1.8 g, 22.3 mmol) in EtOH (50 ml) was heated at 80 °C for 12 h. After being cooled to ambient temperature, the mixture was quenched with water. After removal of solvent under reduced pressure, the residue was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc–hexane (1 : 9) as an eluent to give the oily oxime ether (**14**) (5.3 g, 89%). ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.94 (9H, s), 3.48 (3H, s), 3.57 (3H, s), 3.98 (3H, s), 4.83 (2H, s), 5.00 (2H, s), 5.18 (2H, s), 6.95 (1H, d, J=8.6 Hz), 7.44 (1H, d, J=8.6 Hz), 8.39 (1H,

s). MS (CI) *m/z*: 400 $[M+H]^+$. HR-MS *m/z*: 400.2147 $[M+H]^+$ (Calcd for $C_{19}H_{34}NO_6Si$: 400.2155).

3-(Methoxyiminomethyl)-2,4-bis(methoxymethyloxy)benzyl Alcohol (15) Tetrabutylammonium fluoride (1.0 M in THF, 14.5 ml, 14.5 mmol) was added to a solution of the oxime ether (**14**) (5.2 g, 13.0 mmol) in THF (50 ml). The mixture was stirred at room temperature for 1.5 h, which was quenched with water. After removal of solvent under reduced pressure, the residue was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc–hexane (1 : 1) as an eluent to give the oily alcohol (**15**) (3.4 g, 91%). ^{1}H-NMR ($CDCl_3$) δ: 3.47 (3H, s), 3.64 (3H, s), 4.00 (3H, s), 4.57 (2H, s), 5.03 (2H, s), 5.20 (2H, s), 6.95 (1H, d, J=8.4 Hz), 7.33 (1H, d, J=8.4 Hz), 8.41 (1H, s). MS (EI) *m/z*: 285 (M^+); MS (CI) *m/z* 286 $[M+H]^+$. HR-MS (CI) *m/z*: 286.1287 $[M+H]^+$ (Calcd for $C_{13}H_{20}NO_6$: 286.1291).

3-(Methoxyiminomethyl)-2,4-bis(methoxymethyloxy)benzaldehyde (16) A mixture of the alcohol (**15**) (1.8 g, 6.2 mmol) and activated MnO_2 (2.2 g, 21.8 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature for 24 h. The reaction mixture was then filtered through a Celite pad, and the Celite pad was washed with CH_2Cl_2. The combined CH_2Cl_2 was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1 : 9) as an eluent to give the benzaldehyde (**16**) (1.6 g, 89%), mp 84—87 °C (AcOEt–hexane). IR (KBr) ν: 1673 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3H, s), 3.59 (3H, s), 4.01 (3H, s), 5.12 (2H, s), 5.28 (2H, s), 7.05 (1H, d, J=8.8 Hz), 7.87 (1H, d, J=8.8 Hz), 8.36 (1H, s), 10.29 (1H, s). MS (EI) *m/z*: 283 (M^+). *Anal.* Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.15; N, 4.94. Found: C, 55.35; H, 6.29; N, 4.72.

2-Hydroxy-3-(methoxyiminomethyl)-4-(methoxymethyloxy)benzaldehyde (18) *conc.* HCl (0.034 ml, 0.35 mmol) was slowly added to a solution of the benzaldehyde (**16**) (100 mg, 0.35 mmol) in MeOH (4 ml) under cooling with ice-water. After stirring at the same temperature for 3 h, the mixture was concentrated. The resulting residue was adjusted to pH 5 with an aqueous Na_2CO_3 solution (10%). The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 9) as an eluent to give the phenol (**18**) (78 mg, 92%), mp 64—67 °C (MeOH). IR (KBr) ν: 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3H, s), 4.02 (3H, s), 5.28 (2H, s), 6.73 (1H, d, J=8.8 Hz), 7.79 (1H, d, J=8.8 Hz), 8.61 (1H, s), 10.35 (1H, s), 11.21 (1H, s). MS (EI) *m/z*: 239 (M^+). *Anal.* Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.42; H, 5.67; N. 5.77.

Methyl [6-Formyl-2-(methoxyiminomethyl)-3-(methoxymethyloxy)-phenyloxy]acetate (19) A solution of the phenol (**18**) (782 mg, 3.3 mmol) in DMF (8 ml) was added to a suspension of 60% NaH (196 mg, 4.9 mmol) in DMF (12 ml) under cooling with ice-water. After being stirred at the same temperature for 30 min, methyl bromoacetate (0.48 ml, 4.9 mmol) was added. The mixture was stirred at room temperature for 12 h, which was quenched with an aqueous NH_4Cl solution (saturated). The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3 : 7) as an eluent to give the ester (**19**) (942 mg, 93%), mp 98—100 °C (MeOH). IR (KBr) ν: 1751, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3H, s), 3.81 (3H, s), 3.99 (3H, s), 4.69 (2H, s), 5.28 (2H, s), 7.05 (1H, d, J=8.8 Hz), 7.87 (1H, d, J=8.8 Hz), 8.39 (1H, s), 10.42 (1H, s). MS (EI) *m/z*: 311 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.23; H, 5.61; N, 4.45.

Methyl [6-Formyl-3-hydroxy-2-(methoxyiminomethyl)phenyloxy]acetate (20) A solution of the ester (**19**) (189 mg, 0.61 mmol) in AcOH (7 ml) was heated at 90 °C for 12 h. After being cooled to ambient temperature, the reaction mixture was quenched with water. The mixture was stirred at room temperature for 30 min. The resulting precipitate was filtered to give the phenol (**20**) (129 mg, 80%), mp 112—115 °C (AcOEt–hexane). IR (KBr) ν: 1751, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.81 (3H, s), 4.03 (3H, s), 4.68 (2H, s), 6.89 (1H, d, J=8.4 Hz), 7.77 (1H, d, J=8.4 Hz), 8.82 (1H, s), 10.07 (1H, s), 11.09 (1H, s). MS (EI) *m/z*: 267 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.25; H, 5.18; N, 5.37.

Methyl [6-Formyl-2-(methoxyiminomethyl)-3-(trifluoromethanesulfonyloxy)phenyloxy]acetate (21) Trifluoromethanesulfonic anhydride (0.33 ml, 2.0 mmol) was added to a solution of the phenol (**20**) (441 mg, 1.7 mmol) and pyridine (0.40 ml, 5.0 mmol) in CH_2Cl_2 (12 ml) under cooling with ice-water. After stirring at the same temperature for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (saturated). The mixture was extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 9) as an eluent to give the oily triflate (**21**) (560 mg, 85%). IR (neat) ν: 1758, 1697, 1423, 1203, 1137 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 4.07 (3H, s), 4.70 (2H, s), 7.27 (1H, d, J=8.2 Hz), 7.95 (1H, d, J=8.2 Hz), 8.29 (1H, s), 10.47 (1H, s). MS (EI) *m/z*: 399 (M^+) and MS (CI) *m/z*: 400 $[M+H]^+$. HR-MS (CI) *m/z*: 400.0305 $[M+H]^+$ (Calcd for $C_{13}H_{13}F_3NO_8S$: 400.0314).

Methyl [6-Formyl-2-(methoxyiminomethyl)-3-(prop-1-en-1-yl)phenyloxy]acetate (22) A mixture of the triflate (**21**) (84 mg, 0.21 mmol), tributyl(1-propenyl)tin (84 mg, 0.25 mmol), Et_4NCl (42 mg, 0.25 mmol) and $PdCl_2(PPh_3)_2$ (2 mg, 0.021 mmol) in DMF (4 ml) was heated at 80 °C for 4 h. After being cooled to ambient temperature, an aqueous KF solution 30% (8 ml) was added to the reaction mixture. The mixture was stirred at room temperature for 30 min, which was filtered through a Celite pad, and then the Celite pad was washed with EtOAc. The combined filtrate was extracted with EtOAc, which was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 9) as an eluent to give the alkene (**22**) (51 mg, 83%), mp 49—50 °C ($CHCl_3$–hexane). IR (KBr) ν: 1766, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (3/3H, dd, J=1.8, 7.1 Hz), 1.94 (6/3H, dd, J=1.8, 6.6 Hz), 3.80 (9/3H, s), 3.98 (3/3H, s), 4.01 (6/3H, s), 4.63 (4/3H, s), 4.66 (2/3H, s), 5.96 (1/3H, dq, J=7.1, 11.7 Hz), 6.31 (2/3H, dq, J=6.6, 15.4 Hz), 6.57 (1/3H, dd, J=1.8, 11.7 Hz), 6.86 (2/3H, dd, J=1.8, 15.4 Hz), 7.19 (1/3H, d, J=8.1 Hz), 7.40 (2/3H, d, J=8.2 Hz), 7.79 (2/3H, d, J=8.2 Hz), 7.83 (1/3H, d, J=8.1 Hz), 8.27 (1/3H, s), 8.37 (2/3H, s), 10.40 (2/3H, s), 10.49 (1/3H, s). MS (EI) *m/z*: 291 (M^+). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 62.07, H, 6.01; N, 4.60.

Methyl [7-Formyl-3-methyl-8-isoquinolyloxy]acetate (23) Without Microwave Irradiation: A solution of the alkene (**22**) (191 mg, 0.66 mmol) in *o*-dichlorobenzene (7 ml) was heated at 180 °C for 30 min. After being cooled to ambient temperature, the reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 1) as an eluent to give the isoquinoline (**23**) (74 mg, 44%).

With Microwave Irradiation: A solution of **22** (22.5 mg, 0.077 mmol) in *o*-dichlorobenzene (0.8 ml) was heated at 150 °C for 20 min under microwave irradiation (180 W), and then the solution was subjected to the same workup to yield **23** (9.5 mg, 46%), mp 136—138 °C (MeOH). IR (KBr) ν: 1759, 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.74 (3H, s), 3.83 (3H, s), 4.91 (2H, s), 7.53 (1H, s), 7.58 (1H, d, J=8.6 Hz), 8.03 (1H, d, J=8.6 Hz), 9.61 (1H, s), 10.62 (1H, s). MS (EI) *m/z*: 259 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.99; H, 5.23; N, 5.25.

Methyl [7-(Methoxycarbonyl)-3-methyl-8-isoquinolyloxy]acetate (5) AcOH (0.042 ml, 0.73 mmol) was added to a suspension of the isoquinoline (**23**) (125 mg, 0.48 mmol), NaCN (118 mg, 2.4 mmol), and activated MnO_2 (717 mg, 7.3 mmol) in MeOH (8 ml). After being stirred at room temperature for 4 h, the mixture was quenched with water. The mixture was then filtered through a Celite pad and the Celite pad was washed with EtOAc. The combined filtrate was concentrated under reduced pressure and the resulting residue was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 1) as an eluent to give the methyl ester (**5**) (116 mg, 83%), mp 92—96 °C ($CHCl_3$). IR (KBr) ν: 1716, 1624 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.73 (3H, s), 3.86 (3H, s), 3.97 (3H, s), 4.84 (2H, s), 7.48 (1H, s), 7.52 (1H, d, J=8.6 Hz), 8.05 (1H, d, J=8.6 Hz), 9.73 (1H, s). MS (EI) *m/z*: 289 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.57; H, 5.45; N, 4.68.

Methyl 3-Hydroxy-7-methylfuro[3,2-*h*]isoquinoline-2-carboxylate (24) A mixture of methyl ester (**5**) (300 mg, 1.04 mmol) and NaOMe (280 mg, 5.19 mmol) in MeOH (10 ml) was heated at 80 °C for 12 h. After being cooled to ambient temperature, the mixture was concentrated under reduced pressure. The residue was adjusted to pH 4 with 10% HCl solution. The mixture was extracted with EtOAc, which was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 40 g) using MeOH–$CHCl_3$ (1 : 9) as an eluent to give the furanone (**24**) (176 mg, 66%), mp 188—191 °C ($CHCl_3$). IR (KBr) ν: 1697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s), 4.06 (3H, s), 7.55 (1H, d, J=8.8 Hz), 7.59 (1H, s), 7.87 (1H, d, J=8.8 Hz), 9.69 (1H, s). MS *m/z*: 257 (M^+). *Anal.* Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.55; H, 4.42; N, 5.40.

7-Methyl-2-hydrofuro[3,2-*h*]isoquinolin-3-one (4) A solution of the

furanone (**24**) (48 mg, 0.19 mmol), $LiOH \cdot H_2O$ (39 mg, 0.93 mmol), in DMSO (3 ml), and H_2O (3 ml) was stirred at 70 °C for 1 h. After being cooled to ambient temperature, the mixture was quenched with an aqueous NH_4Cl solution (saturated). The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 1) as an eluent to give furoisoquinoline (**4**) (28 mg, 75%), mp 119—122 °C (AcOEt–hexane). IR (KBr) ν: 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s), 4.88 (2H, s), 7.34 (1H, d, J=8.4 Hz), 7.55 (1H, s), 7.74 (1H, d, J=8.4 Hz), 9.53 (1H, s). MS (EI) m/z: 199 (M^+). *Anal.* Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.63; H, 4.76; N, 6.84.

TMC-120B (2) A solution of the furoisoquinoline (**4**) (20 mg, 0.10 mmol) in THF (2 ml) was added to a solution of LDA [prepared from diisopropylamine (0.070 ml, 0.40 mmol) and *n*-BuLi (2.6 M in hexane, 0.15 ml, 0.40 mmol) in THF (1 ml)] at −40 °C. After stirring at the same temperature for 30 min, acetone (0.044 ml, 0.60 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred for further 4 h. The mixture was quenched with an aqueous NH_4Cl solution (saturated), and then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude alcohol was used for the next step without any further purification. Methanesulfonyl chloride (0.017 ml, 0.22 mmol) was added to a solution of alcohol (19 mg, 0.074 mmol) and DMAP (3 mg, 0.015 mmol) in pyridine (2 ml) under cooling with ice-water. After stirring at room temperature for 2 h, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (4 : 1) as an eluent to give TMC-120B (**2**) (14 mg, 58%), mp 175—178 °C (MeOH) (lit.,[8,9] mp 176—178 °C). IR (KBr) ν: 1693 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.45 (3H, s), 2.76 (3H, s), 7.38 (1H, d, J=8.6 Hz), 7.56 (1H, s), 7.83 (1H, d, J=8.6 Hz), 9.57 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 182.3, 164.0, 156.7, 146.2, 145.6, 141.4, 133.9, 124.2, 120.6, 119.6, 119.4, 114.6, 24.7, 20.4, 17.6. MS m/z: 239 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.54; H, 5.50; N, 5.80.

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