HETEROCYCLES, Vol. 84, No. 1, 2012, pp. 587 - 595. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 1st June, 2011, Accepted, 20th July, 2011, Published online, 29th July, 2011
DOI: 10.3987/COM-11-S(P)27

IMPROVED SYNTHESIS OF THE NEW FURO[3,2-*h*]ISOQUINOLINE ALKALOIDS TMC-120B AND TMC-120A, AND THEIR INHIBITORY ACTIVITIES AGAINST IFN-γ AND IL-4 PRODUCTION

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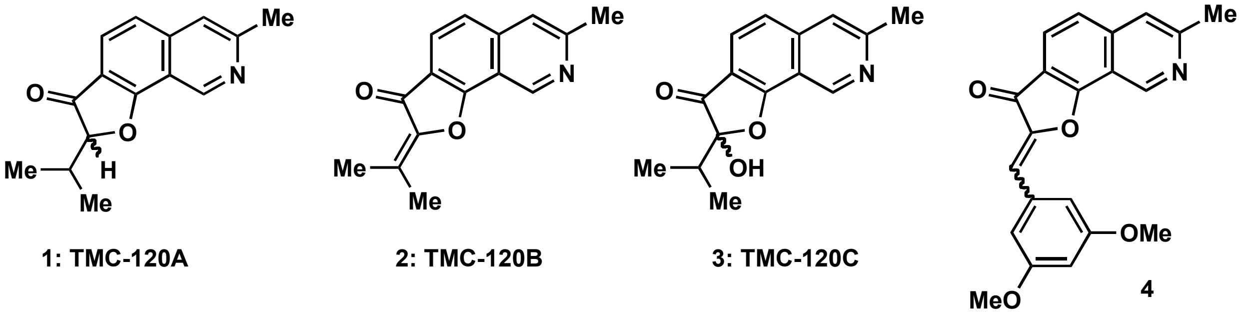
This paper is dedicated to Dr. Albert Padwa, Professor of Emory University on the occasion of his 75th birthday.

Abstract – In our synthetic route of TMC-120B (**2**), the synthetic intermediate, methyl [7-(methoxycarbonyl)-3-methyl-8-isoquinolyloxy]acetate (**8**) was newly synthesized in seven steps along with an improvement of the overall yield. The catalytic hydrogenation of TMC-120B (**2**) was also improved. Inhibition of interferon-γ and interleukin-4 production by TMC-120A (**1**), TMC-120B (**2**), and their derivative **4** was evaluated. The results indicated that these compounds are selective inhibitors of Th1 cell function.

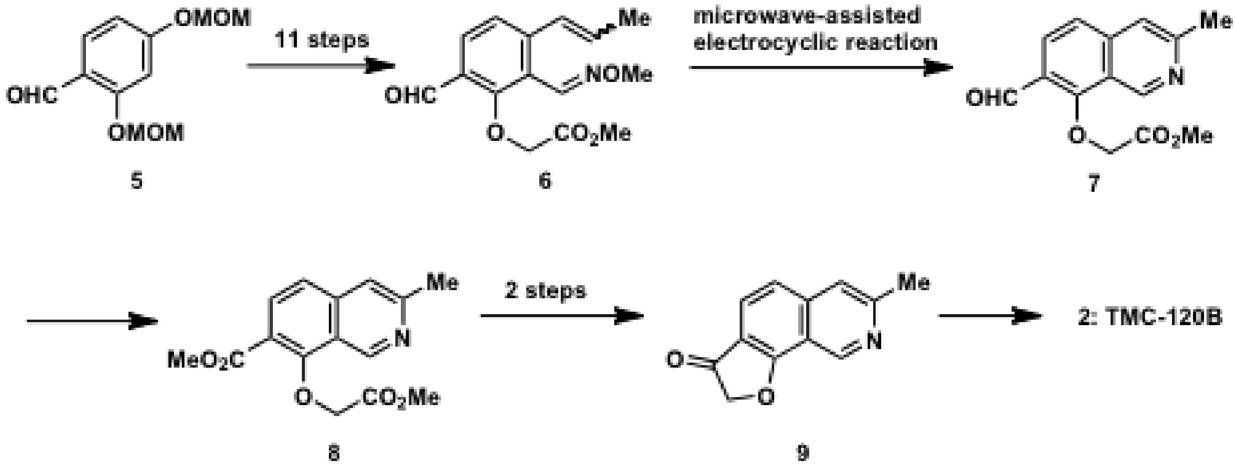
INTRODUCTION

In our research, we have studied the synthesis of biologically active fused heteroaromatic compounds, including natural products, through the construction of functionalized frameworks based on the thermal electrocyclic reaction[1,2] of a 6π-electron system or an aza 6π-electron system incorporating a principal aromatic or heteroaromatic moiety[3-6] Recently, we selected three new furo[3,2-*h*]isoquinoline alkaloids, TMC-120A (**1**), TMC-120B (**2**), and TMC-120C (**3**), isolated from *Aspergillus ustus* TC1118,[7,8] as target compounds (Scheme 1). We performed the first total synthesis of TMC-120B (**2**) by constructing the appropriate 3,7,8-trisubstituted isoquinoline framework **8** in 13 steps (7% overall yield), starting from 2,4-bis(methoxymethyloxy)benzaldehyde (**5**), based on the microwave-assisted thermal electrocyclic reaction[5,6] of the aza 6π-electron system **6**, followed by the formation of a furanone ring **9** and the introduction of an isopropylidene moiety in 16 steps (2.5% overall yield) (Scheme 2).[9,10]



Scheme 1

In the present paper, we describe an improved synthesis of TMC-120B (**2**) through a new synthetic route of methyl [7-(methoxycarbonyl)-3-methyl-8-isoquinolyloxy]acetate **8**, and TMC-120A (**1**) from **2**. In addition, an aromatic benzylidene derivative **4** was synthesized by our reported procedure[10] to examine inhibitory activities against interferon-γ (IFN-γ) and interleukin (IL)-4 production together with aliphatic derivatives **1** and **2**. These results are also described here.



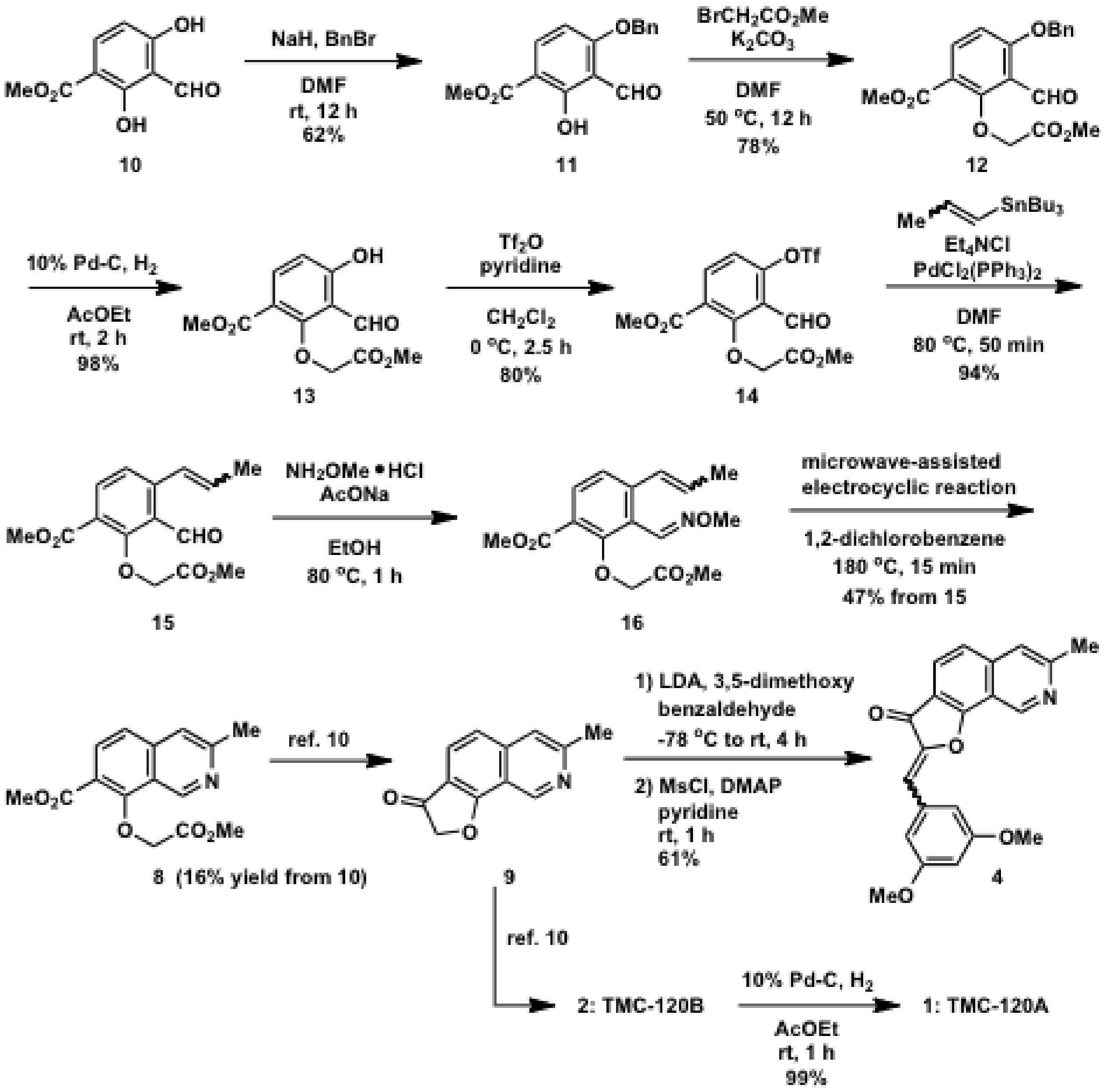
Scheme 2

RESULTS AND DISCUSSION

We attempted a short-step synthesis of the 3,7,8-trisubstituted isoquinoline **8**, starting from the known methyl 3-formyl-2,4-dihydroxybenzoate (**10**)[11] as illustrated in Scheme 3.

Initially, a selective monobenzylation of the benzoate **10** with benzyl bromide and NaH in DMF at room temperature afforded the monobenzyl ether **11** on a less hindered hydroxy group at the 6-position, which was followed by further alkylation with methyl bromoacetate in the presence of K_2CO_3 at 50 °C to give the diester **12**. Debenzylation of **12** with 10% Pd-C under H_2 atmosphere smoothly reproduced the 4-hydroxybenzoate **13**. After conversion of the phenol **13** into the triflate **14** with trifluoromethansulfonic anhydride (Tf_2O) and pyridine at 0 °C, the Stille coupling reaction of the triflate **14** with tributyl propenylstannane and $PdCl_2(PPh_3)_2$ in the presence of Et_4NCl in DMF at 80 °C yielded the

2-propenylbenzaldehyde **15**. Subsequent treatment of **15** with hydroxylamine methyl ether in EtOH at reflux temperature produced the oxime ether **16** as an aza 6π-electron system, which was then subjected to the microwave-assisted electrocyclic reaction[9,10] in 1,2-dichlorobenzene at 180 °C to give the expected 3,7,8-trisubstituted isoquinoline **8** in 47% yield from **15**. The microwave-assisted thermal electrocyclic reaction of **16** without purification was attempted, but it was assumed that the yield of **8** would be almost the same as that of a similar reaction of **7** from **6**, as reported previously.[9,10] The isoquinoline **8** was obtained in seven steps from **10** in 16% yield.



Scheme 3

Although, Kohno and coworkers[7,8] reported that TMC-120A (**1**) was obtained from TMC-120B (**2**) in 36% yield with 10% Pd-C, we further attempted the conversion of TMC-120B (**2**) to TMC-120A (**1**). The catalytic reduction of TMC-120B (**2**) with 10% Pd-C under H$_2$ atmosphere in EtOAc gave the racemic

TMC-120A (**1**) in 99% yield. Asymmetric reduction of **2** with several chiral reagents failed. Furthermore, the benzylidene derivative **4** of TMC-120B (**2**) was synthesized by the reaction of the furanone **9**[9,10] and 3,5-dimethoxybenzaldehyde with LDA, followed by treatment with methanesulfonyl chloride (MsCl) in the presence of DMAP in pyridine, to evaluate the biologic activities.

Table 1. Effects on IFN-γ production from antigen-stimulated T cells

	IFN-γ (ng/mL)			
OVA peptide (μg/mL)	Control	TMC-120A (3μM)	TMC-120B (3μM)	**4** (3μM)
0	0	0	1.55	0.7
0.3	13.65	8.1	6.65	9.55
3	19.95	12.5	8.85	12.35
30	39.3	18.4	9.05	18.75

Data represent means of duplicate cultures.

Table 2. Effects on IL-4 production from antigen-stimulated T cells

	IL-4 (pg/mL)			
OVA peptide (μg/mL)	Control	TMC-120A (3μM)	TMC-120B (3μM)	**4** (3μM)
0	0	0	0	0
0.3	81	103.5	82.5	88.5
3	135	152.5	133	128.5
30	164	166	168	132

Data represent means of duplicate cultures.

Table 3. Effects on cell proliferation

	Thymidine uptake (fold)			
OVA peptide (μg/mL)	Control	TMC-120A (3μM)	TMC-120B (3μM)	**4** (3μM)
0	1	1.23	0.95	0.83
0.3	6.32	8.35	8.79	6.42
3	5.93	7.49	8.02	5.75
30	5.92	7.37	7.78	5.69

Data are presented as means of triplicate cultures and presented as fold increase over untreated cells.

We tested the effect of TMC-120A (**1**), B (**2**), and **4** in several cellular assay systems and found that they have a potent inhibitory effect on IFN-γ production. IFN-γ production was induced by stimulating ovalbumin (OVA)–specific murine T cells with OVA peptide antigen. IFN-γ was detected in a peptide concentration-dependent manner, and was strongly inhibited by TMC-120A (**1**), B (**2**), and **4** at a concentration of 3 μM (Table 1). The peptide stimulation simultaneously induced IL-4 production. The effects of TMC-120A (**1**), B (**2**), and **4** on IL-4 production were relatively weak, in that inhibition was scarce at 3 μM (Table 2). All these compounds at a concentration of 3 μM showed no effect on the proliferative response as assessed by [^{3}H] thymidine uptake, indicating that the suppression of IFN-γ production is not due to toxic effects of the compounds (Table 3).

CONCLUSION

An alternative synthesis of the synthetic intermediate **8** was improved in a seven-step sequence, and the overall yield of **8** increased to 16% from **10** by converting the starting material. In addition, the reduction of the C=C double bond of TMC-120B (**2**) according to the procedure reported by the Kohno group[7,8] was achieved in excellent yield. As a result, the formal total synthesis of TMC-120B (**2**) together with TMC-120A (**1**) was completed.

The characteristic feature of these compounds is the selective inhibition of IFN-γ production compared with IL-4 production. Because IFN-γ and IL-4 represent Th1 and Th2 cytokines, respectively, it is possible that these compounds are selective inhibitors of Th1 cell function.

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-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were taken with a JEOL AL-300 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL MStation 700 spectrometer. The microwave irradiation 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.

Methyl 4-benzyloxy-3-formyl-2-hydroxybenzoate (11)

A solution of the phenol **10** (475 mg, 2.42 mmol) in DMF (5 mL) was added to a suspension of 60% NaH (174 mg, 4.36 mmol) in DMF (12 mL) under cooling with ice-water. After being stirred at the room temperature for 30 min, benzyl bromide (0.35 mL, 2.91 mmol) was added under cooling with ice-water. 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 **11** (430 mg, 62%), mp 90-91 °C (Et_2O-hexane). IR (ATR) ν: 1720, 1619 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 5.23 (3H, s), 6.54 (1H, d, *J*= 8.8 Hz), 7.36-7.43 (5H, m), 8.95 (1H, d, *J*=8.8 Hz), 10.46 (1H, s), 12.77 (1H, s). MS (EI) *m/z*: 286 (M^+). HR-MS (EI) *m/z*: 286.0834 (M^+) (Calcd for $C_{16}H_{14}O_5$: 286.0841).

Methyl [5-benzyloxy-6-formyl-2-(methoxycarbonyl)phenoxy]acetate (12)

A mixture of phenol **11** (535 mg, 1.87 mmol), K_2CO_3 (774 mg, 5.60 mmol), and methyl bromoacetate (0.37 mL, 3.74 mmol) in DMF (15 mL) were heated at 50 °C for 12 h. After being cooled to ambient temperature, 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, 30 g) using EtOAc-hexane (3:7) as an eluent to give the acetate **12** (519 mg, 78%), mp 108-109 °C (Et_2O-hexane). IR (ATR) ν: 1754, 1720, 1681 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 3.87 (3H, s), 4.75 (2H, s), 5.23 (2H, s), 6.89 (1H, d, *J*=9.2 Hz), 7.34-7.45 (5H, m), 8.05 (1H, d, *J*=9.2 Hz), 10.52 (1H, s). MS (EI) *m/z*: 358 (M^+). HR-MS (EI) *m/z*: 358.1053 (M^+) (Calcd for $C_{19}H_{18}O_7$: 358.1053).

Methyl [6-formyl-5-hydroxy-2-(methoxycarbonyl)phenoxy]acetate (13)

A mixture of acetate **12** (100 mg, 0.28 mmol) and 10% Pd-C (10 mg) in EtOAc (10 mL) was stirred at room temperature for 2 h under H_2 atmosphere. The reaction mixture was filtrated through a Celite pad, and the Celite pad was washed with EtOAc. The combined EtOAc was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc-hexane (1:4) as an eluent to give the phenol **13** (73 mg, 98%), mp 96-97 °C (MeOH). IR (ATR) ν: 1751, 1716, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 3.90 (3H, s), 4.78 (2H, s), 6.78 (1H, d, *J*=9.2 Hz), 8.09 (1H, d, *J*= 9.2 Hz), 10.61 (1H, s), 12.38 (1H, s). MS (EI) *m/z*: 268 (M^+). HR-MS (EI) *m/z*: 268.0596 (M^+) (Calcd for $C_{12}H_{12}O_7$: 268.0583).

Methyl [6-formyl-2-(methoxycarbonyl)-5-(trifluoromethanesulfonyloxy)phenoxy]acetate (14)

Tf_2O (1.4 mL, 8.28 mmol) was added to a solution of the phenol **13** (1.9 g, 6.90 mmol) and pyridine (1.67 mL, 20.7 mmol) in CH_2Cl_2 (40 mL) under cooling with ice-water. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. 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, 40 g) using EtOAc-hexane (1:4) as an eluent to give the triflate **14** (2.2 g, 80%), mp 60-61 °C (Et_2O-hexane). IR (ATR) ν: 1727, 1697, 1589, 1430, 1203 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 3.96 (3H, s), 4.79 (2H, s), 7.20 (1H, d, *J*=8.8 Hz), 8.17 (1H, d, *J*=8.8 Hz), 10.55 (1H, s). MS (EI) *m/z*: 400 (M^+). HR-MS (EI) *m/z*: 400.009 (M^+) (Calcd for $C_{13}H_{11}F_3O_9S$: 400.0076).

Methyl [6-formyl-2-(methoxycarbonyl)-5-(prop-1-en-1-yl)phenoxy]acetate (15)

A mixture of the triflate **14** (1.5 g, 3.71 mmol), tributyl(1-propenyl)tin (1.5 g, 4.45 mmol), Et_4NCl (738 mg, 4.45 mmol) and $PdCl_2(PPh_3)_2$ (26 mg, 0.037 mmol) in DMF (20 mL) was heated at 80 ^oC for 50 min. After being cooled to ambient temperature, an aqueous 30% KF solution (20 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, 30 g) using EtOAc-hexane (1:9) as an eluent to give the alkene **15** (1.0 g, 94%), mp 87-88 ^oC (EtOAc-hexane). IR (ATR) ν: 1758, 1724, 1697 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.74 (3/2H, dd, *J*=1.8, 7.3 Hz), 1.96 (3/2H, dd, *J*= 1.6, 6.6 Hz), 3.81 (3/2H, s), 3.82 (3/2H, s), 3.91 (3/2H, s), 3.93 (3/2H, s), 4.71 (2/2H, s), 4.75 (2/2H, s), 5.99 (1/2H, dq, *J*=7.3, 11.7 Hz), 6.31 (1/2H, dq, *J*=6.6, 15.8 Hz), 6.81 (1/2H, dd, 1.8, 11.7 Hz), 7.17 (1/2H, d, *J*=8.1 Hz), 7.20 (1/2H, dd, *J*=1.6, 15.8 Hz), 7.36 (1/2H, d, *J*=8.4 Hz), 7.99 (1/2H, d, *J*=8.4 Hz), 8.02 (1/2H, d, *J*= 8.1 Hz), 10.55 (1/2H, s), 10.65 (1/2H, s). MS (EI) *m/z*: 292 (M^+). HR-MS (EI) *m/z*: 292.0938 (M^+) (Calcd for $C_{15}H_{16}O_6$: 292.0947).

Methyl [7-(methoxycarbonyl)-3-methyl-8-isoquinolyloxy]acetate (8)

A mixture of alkene **15** (1.7 g, 5.86 mmol), $MeONH_2 \cdot HCl$ (734 mg, 8.79 mmol), and AcONa (720 mg, 8.79 mmol) in EtOH (30 mL) was heated at 80 ^oC for 1 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. A solution of the crude oxime ether in 1,2-dichlorobenzene (55 mL) was heated at 180 ^oC for 15 min under microwave irradiation (180 W). After removal of solvent under reduced pressure, the residue was purified by column chromatography (silica gel, 40 g) using EtOAc-hexane (4:1) as an eluent to give the isoquinoline **8** (801 mg, 47%), mp 92-93 ^oC (MeOH). IR (ATR) ν: 1712, 1623 cm^{-1}. ^1H-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). ^{13}C-NMR ($CDCl_3$) δ: 169.0, 165.5, 157.8, 154.8, 149.0, 140.0, 131.5, 122.3, 121.8, 119.0, 118.1, 72.5, 52.5, 52.3, 24.4. MS (EI) *m/z*: 289 (M^+). HR-MS (EI) *m/z*: 289.0919 (M^+) (Calcd for $C_{15}H_{15}NO_5$: 289.0950).

TMC-120A (1)

A mixture of TMC-120B (**2**) (8.5 mg, 0.036 mmol) and 10% Pd-C (2 mg) in EtOAc (3 mL) were stirred at room temperature for 1 h under H_2 atmosphere. The reaction mixture was filtrated through a Celite pad, and the Celite pad was washed with EtOAc. The combined EtOAc was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (2:3) as an eluent to give TMC-120A (**1**) (8.5 mg, 99%), mp 110-112 °C (MeOH) (Lit.,[7,8] mp 115-116 °C). IR (ATR) ν: 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, *J*=7.0 Hz), 1.26 (3H, d, *J*=7.0 Hz), 2.47-2.54 (1H, m), 2.76 (3H, s), 4.69 (1H, d, *J*=3.7 Hz), 7.32 (1H, d, *J*=8.4 Hz), 7.55 (1H, s), 7.72 (1H, d, *J*=8.4 Hz), 9.56 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 199.6, 173.9, 157.5, 146.6, 142.3, 123.9, 120.1, 119.5, 117.5, 115.2, 91.5, 31.1, 24.7, 18.8, 15.7. MS (EI) *m/z*: 241 (M^+). HR-MS (EI) *m/z*: 241.1104 (M^+) (Calcd for $C_{15}H_{15}O_2$: 241.1103).

7-Methyl-2-[(3,5-dimethoxyphenyl)methylidene]furo[3,2-*h*]isoquinoline-3-one (4)

A solution of furanone **9** (20 mg, 0.10 mmol) in THF (1.5 mL) was added to a solution of LDA [prepared from *i*-Pr_2NH (0.070 mL, 0.40 mmol) and *n*-BuLi (2.6 M in Hexane, 0.15 mL, 0.40 mmol) in THF (1.5 mL)] at -78 °C. After stirring at the same temperature for 30 min, 3,5-dimethoxybenzaldehyde (100 mg, 0.60 mmol) in THF (1 mL) was added to the reaction mixture, the mixture was allowed to stand slowly to rt, and further stirred for 4 h. The reaction mixture was quenched with saturated NH_4Cl aqueous solution, and then extracted with EtOAc. The EtOAc was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a mixture of the residue and DMAP (3 mg, 0.015 mmol) in pyridine (2 mL) was added methanesulfonyl chloride (0.077 mL, 1.0 mmol) under cooling with ice-water. After stirring at room temperature for 1 h, the reaction mixture was quenched with water, and then extracted with EtOAc. The EtOAc was washed with water and 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 v/v) as an eluent to give the furoisoquinoline **4** (21 mg, 61%), mp 207-209 °C (MeOH). IR (ATR) ν: 1697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (9/4H, s), 3.42 (3/4H, s), 3.90 (6/4H, s), 3.91 (18/4H, s), 6.58 (3/4H, t, *J*=2.2 Hz), 6.78 (1/4H, t, *J*=2.2 Hz), 6.96 (4/4H, s), 7.18 (6/4H, d, *J*=2.2 Hz), 7.34 (2/4H, d, *J*=2.2 Hz), 7.49 (3/4H, d, *J*=8.4 Hz), 7.61 (3/4H, s), 7.65 (1/4H, s), 7.68 (1/4H, d, *J*=8.8 Hz), 7.89 (3/4H, d, *J*=8.4 Hz), 8.01 (1/4H, d, *J*=8.8 Hz), 9.63 (3/4H, s), 9.69 (1/4H, s). ^{13}C-NMR ($CDCl_3$) δ: 183.5, 182.9, 165.9, 165.6, 161.0, 160.9, 157.3, 155.4, 154.9, 147.3, 147.0, 146.0, 138.2, 138.1, 133.5, 133.5, 124.2, 124.1, 122.9, 119.7, 119.6, 119.3, 119.1, 117.6, 117.5, 114.6, 114.4, 109.8, 109.4, 107.5, 106.5, 103.5, 55.7, 55.56., 24.8, 24.6. MS (EI) *m/z*: 347 (M^+). HR-MS (EI) *m/z*: 347.1175 (M^+) (Calcd for $C_{21}H_{17}NO_4$: 347.1158).

Effect on T cell activation

To evaluate antigen-dependent activation of murine T cells, a mixture of lymph node and spleen cells were prepared from DO11.10 transgenic mice expressing transgenic T cell receptors specific for OVA 323-339 epitope.[12] The cells were incubated with different concentrations of epitope peptide in

RPMI1640 medium supplemented with 10% fetal bovine serum and 50 μM β-mercaptoethanol in a humidified atmosphere containing 5% CO_2 at 37 °C. The test compounds were dissolved in DMSO and added simultaneously with the peptide (final DMSO concentration: 0.2%). Culture supernatants were collected after 48 h of culture and subjected to measurement of IL-4 and IFN-γ concentrations by enzyme-linked immunosorbent assay kit (BD Pharmingen). Cell proliferation was examined by [^{3}H] thymidine uptake during the last 16 h of the 64-h culture.

ACKNOWLEDGEMENT

This work was supported in part by Grant-in Aid for Scientific Research (C) (No.155900333) from Japan Society for the Promotion of Science (JSPS). We thanks to Dr. Mamoru Kiniwa and Dr. Koichi Ikizawa for the assistance of biological evaluation.

REFERENCES AND NOTES

1. E. N. Marvel, "*Thermal Electrocyclic Reactions*," Academic Press, New York, 1980, Chapt. 2.
2. W. H. Okamura and A. R. de Lera, "*Comprehensive Organic Synthesis*," Vol. 5, ed. by B. M. Trost, I. Fleming, and L. A. Paqette, Pergamon Press, New York, 1991, p. 699.
3. S. Hibino and E. Sugino, "*Advances in Nitrogen Heterocycles*," Vol. 5, ed. by C. J. Moody, JAI Press, Greenwich, CT, 1995, p. 205.
4. T. Choshi, *Yakugaku Zasshi*, 2001, **121**, 487.
5. T. Choshi and S. Hibino, *Heterocycles*, 2011, **83**, 1205.
6. Most recent work of a microwave-assisted electrocyclic reaction of aza 6π-electron system: Y. Ishihara, S. Azuma, T. Choshi, K. Kohno, K. Ono, H. Tsutsumi, T. Ishizu, and S. Hibino, *Tetrahedron*, 2011, **67**, 1320.
7. J. Kohno, H. Hiramatsu, M. Nishio, M. Sakurai, T. Okuda, and S. Komatsubara, *Tetrahedron*, 1999, **55**, 11247.
8. J. Kohno, M. Sakurai, N. Kameda, M. Nishio, K. Kawano, N. Kishi, T. Okuda, and S. Komatsubara, *J. Antibiot*., 1999, **52**, 913.
9. T. Kumemura, T. Choshi, A. Hirata, M. Sera, Y. Takahashi, J. Nobuhiro, and S. Hibino, *Heterocycles*, 2003, **61**, 13.
10. T. Kumemura, T. Choshi, A. Hirata, M. Sera, Y. Takahashi, J. Nobuhiro, and S. Hibino, *Chem. Pharm. Bull.*, 2005, **53**, 393.
11. R. C. Shah and M. C. Laiwalla, *J. Chem. Soc.*, 1938, 1828.
12. J. M. Robertson, P. E. Jensen, and B. D. Evavold, *J. Immunol.*, 2000, **164**, 4706.