Synthesis of the Interferon-α Inducer Imiquimod by Thermal Electrocyclic Reactions of 1- and 2-Azahexatriene Systems

Haruyuki YOSHIOKA, Yuhji MATSUYA, Tominari CHOSHI, Eiichi SUGINO, and Satoshi HIBINO*

Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729–02, Japan.
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The interferon-α inducer imiquimod (1), possessing an imidazo[4,5-*c*]quinoline ring, has been newly synthesized by two routes based on thermal electrocyclic reactions of 1- and 2-azahexatriene systems involving the imidazole 4,5-bond.

Key words imiquimod; thermal electrocyclic reaction; azahexatriene system; imidazo[4,5-*c*]quinoline; synthesis

In connection with synthetic studies on condensed heteroaromatic compounds, especially fused pyridine ring systems, based on thermal electrocyclic reactions[1] of conjugated hexatriene or monoazahexatriene systems including one double bond of the aromatic or heteroaromatic portion,[2,3] we have achieved a total synthesis of the interferon-α (INF-α) inducer imiquimod (**1**) (R-837).[4] Imiquimod is a potent inducer of INF-α in many animal species, as well as humans, and is a potent antiviral and antitumor agent.[5] Efforts have been made to synthesize **1** and its analogs. However, nearly all the procedures for the preparation of imidazo[4,5-*c*]quinolines have consisted of reacting 3,4-diaminoquinolines with either carboxylic acids or their equivalents.[4] We describe here a new approach to the synthesis of 4-amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline, imiquimod (**1**).

We accessed the tricyclic imidazoquinoline ring of **1** by using two types of pyrido-annelation based on the thermal electrocyclic reactions of the 1-azahexatriene system (**2** and/or **3**) (route A) in which the 5,5a-bond of **1** is cleaved and the 2-azahexatriene system (**4**) (route B) in which the 3a,4-bond is cleaved, as depicted in the retro-synthetic scheme (Chart 1).

We first attempted to synthesize tricyclic imidazo[4,5-*c*]-quinoline (**13**) *via* route A (Chart 2). To synthesize a type of 1-azahexatriene system (**2**), readily available 1-isobutylimidazole (**6**)[6] was used as a starting material. Treatment of **6** with *n*-BuLi at −78 °C followed by the addition of dimethyl disulfide yielded the 2-methylthioimidazole (**7**) (95%) which occupies the most reactive position of the imidazole ring.[7] Bromination of **7** with *N*-bromosuccinimide (NBS) at room temperature by the reported method[8] produced the 5-bromoimidazole (**8**) (83%). This compound **8** was then subjected to the Suzuki cross-coupling reaction[9] with phenylboronic acid[10] in the presence of $Pd(PPh_3)_4$ to yield the 5-phenylimidazole (**9**) (98%). Subsequent bromination of **9** with NBS[8] yielded the 4-bromoimidazole (**10**) (98%). Treatment of **10** with *n*-BuLi at −78 °C followed by introduction of carbon dioxide gas produced the imidazole-4-carboxylic acid (**11**) (77%). Reaction of 11 with hydroxylamine methyl ether, followed by the addition of triphenylphosphine-carbon tetrachloride gave the oxime ether (**12**) (49%), the so-called 1-azahexatriene system (**2**), according to the previously reported one-pot procedure.[11] Electrocyclic reaction of **12** was examined under various conditions (temperature range: 110—220 °C), but the proposed reaction did not proceed. This may have been due to the stable aromaticity of the phenyl ring. It may be necessary to conduct the experiment at a higher temperature or at a higher temperature under vacuum conditions.[12]

Therefore, we turned to the synthesis of a type of 1-azahexatriene system (**3**) for the electrocyclic reaction (Chart 3). 2,4,5-Tribromoimidazole (**14**)[13] was alkylated with isobutyl bromide to give the isobutylimidazole (**15**) (88%), which was then converted to the methylthioimid-

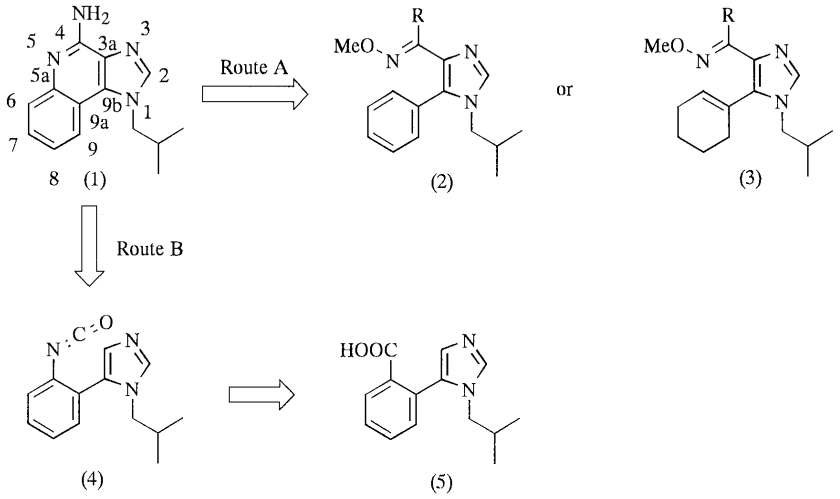

Chart 1

* To whom correspondence should be addressed.

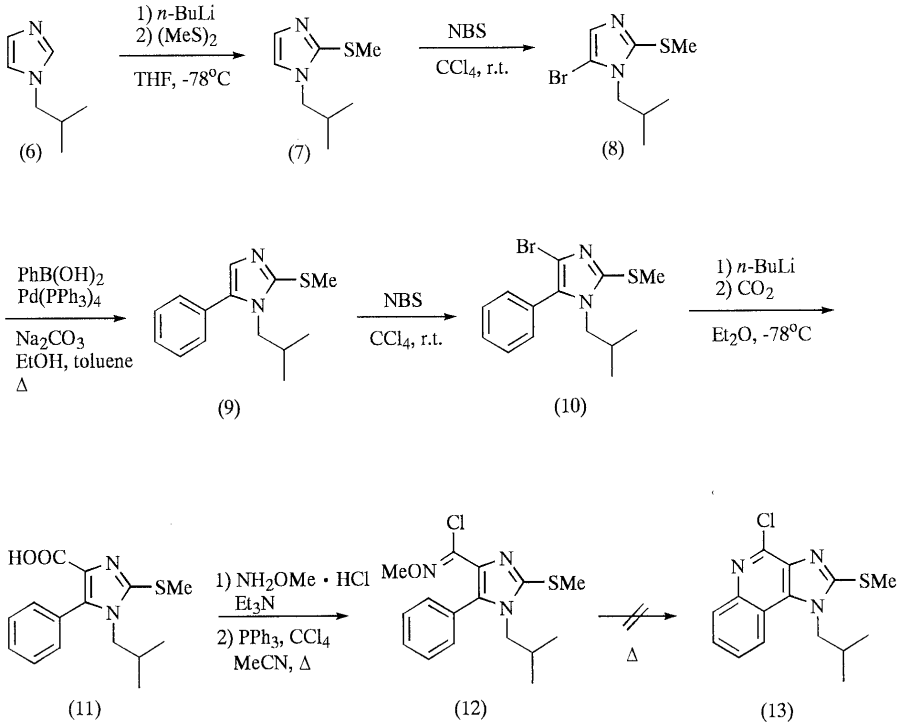

Chart 2

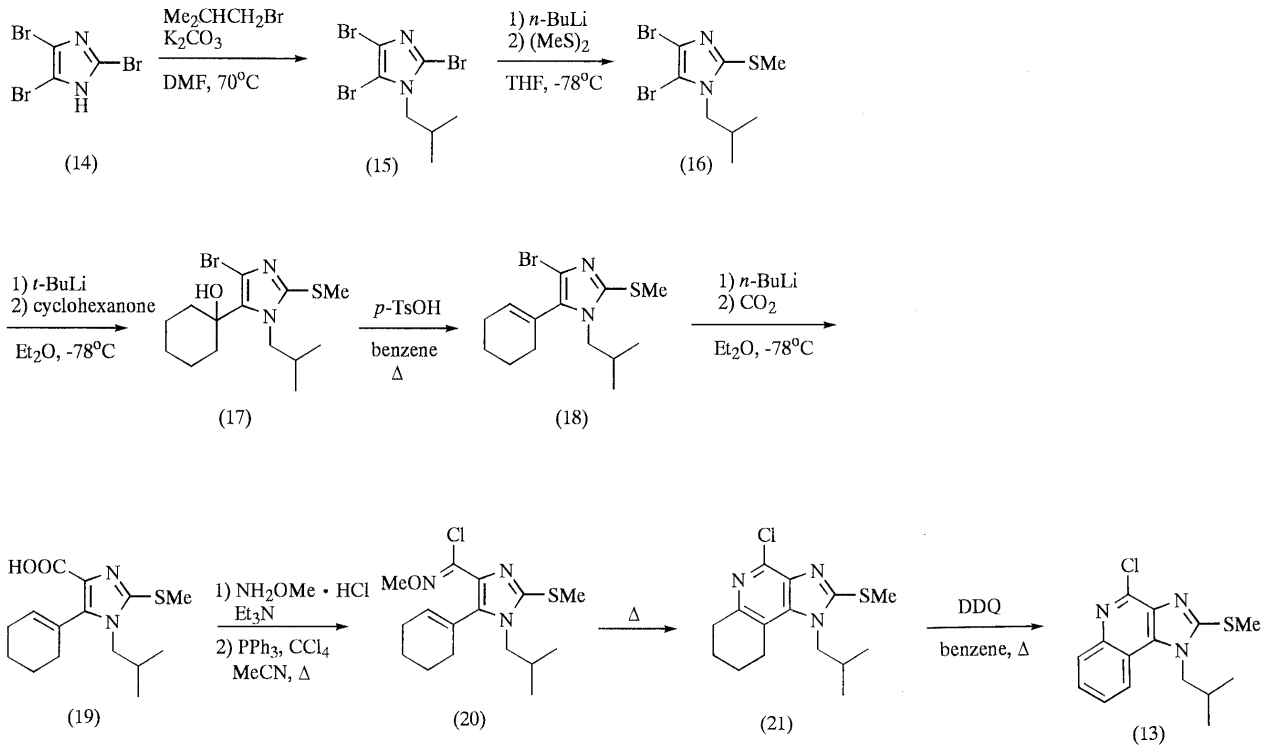

Chart 3

azole (**16**) by treatment with *n*-BuLi at −78 °C, followed by the addition of dimethyl disulfide (85%). Halogen-lithium exchange reaction of **16** with *tert*-BuLi at −78 °C and subsequent addition of cyclohexanone produced the cyclohexyl alcohol (**17**) (51%) regioselectively.[3a,7,14] Heating of **17** in the presence of *p*-toluenesulfonic acid in benzene yielded the cyclohexenylimidazole (**18**) (97%), which was then treated with *n*-BuLi, followed by the introduction of carbon dioxide gas at −78 °C to afford the corresponding carboxylic acid (**19**) (51%). Reaction of **19** with hydroxylamine methyl ether, followed by the addition of triphenylphosphine-carbon tetrachloride gave the α-chloro-oxime ether (**20**), with a 1-azahexatriene system (**3**) (46%). The electrocyclic reaction of **20** was carried out in *o*-dichlorobenzene, yielding the cyclized tetrahydroimidazo[4,5-*c*]quinoline (**21**) (62%), which was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide the desired imidazo[4,5-*c*]quinoline (**13**)

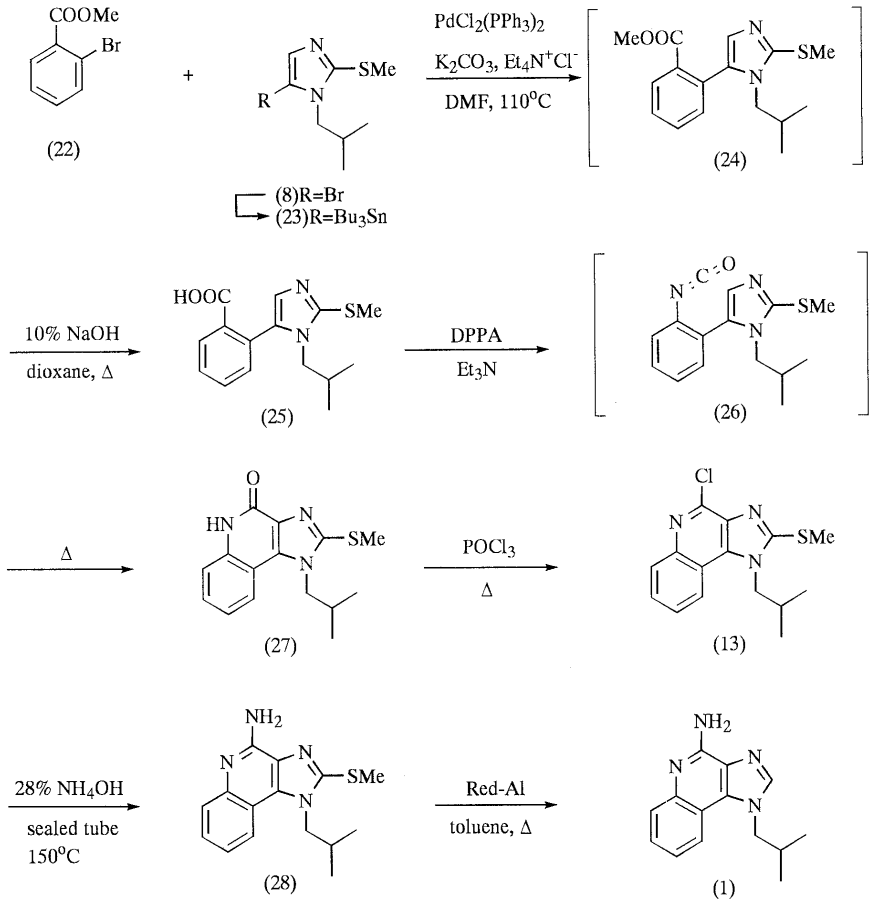

Chart 4

(41%).

We further attempted to synthesize the imidazo[4,5-*c*]quinoline ring (**13**) through route B (Chart 4) using the thermal electrocyclic reaction of the 2-azahexatriene system (**4**) (Chart 1). We tried a cross-coupling reaction between methyl 2-bromobenzoate (**22**) and 5-stannylimidazole (**23**). Treatment of the 5-bromoimidazole (**8**) with *n*-BuLi, followed by the addition of tributyltin chloride gave the stannylimidazole (**23**), which was then subjected to a cross-coupling reaction[15] with methyl 2-bromobenzoate (**22**) in the presence of $PdCl_2(PPh_3)_2$ to yield the 5-phenylimidazole derivative (**24**). Hydrolysis of the crude **24** with 10% NaOH yielded the carboxylic acid (**25**) (79% from **22**) as a precursor to the isocyanate (**26**), having the required 2-azahexatriene system (**4**). Compound **25** was treated with diphenylphosphoryl azide (DPPA)[16] at 50 °C in benzene and then the solvent was replaced with *o*-dichlorobenzene for the thermal electrocyclic reaction. The reaction progressed to give the desired imidazo-[4,5-*c*]quinoline (**27**) (90% from **25**). This compound was converted to the 4-chloro-1*H*-imidazo[4,5-*c*]quinoline (**13**) by treatment with $POCl_3$ (88%). The product was identical to the previously synthesized compound (**13**) (route A), based on a comparison of the spectral data.

Finally, treatment of **13** with 28% NH_4OH in a sealed tube produced the amine derivative (**28**) (93%) and subsequent desulfurization of **28** with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in toluene afforded imiquimod (**1**) (80%). Its physical data were consistent with reported data.[4b]

Thus, total synthesis of imiquimod (**1**) was achieved using two types of thermal electrocyclic reactions of a 1-azahexatriene system (**3**) and a 2-azahexatriene system (**4**) involving the imidazole 4,5-bond for construction of the framework.

Experimental

Melting points were determined with a Yanagimoto micro-melting point apparatus MP-500D without correction. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8500 spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were taken on JEOL PMX60Si, FX100 and JNM A500 spectrometers with Me_4Si as an internal standard unless otherwise stated. Mass spectra and high-resolution mass spectra (HRMS) were measured with a Shimadzu 9020DF instrument at 70 eV (EI). All air-sensitive reactions were run under an argon atmosphere. NBS was recrystallized from water, and dried in a desiccator under vacuum before use. Silica gel (60—100 mesh, Merck) was used for column chromatography.

1-Isobutyl-2-methylthioimidazole (7) A solution of *n*-BuLi (9.6 ml of 1.63 M in hexane, 15.7 mmol) was added dropwise to a stirred solution of *N*-isobutylimidazole (**6**)[6] (1.95 g, 15.7 mmol) in anhydrous tetrahydrofuran (THF) (15 ml) at −78 °C. The mixture was stirred for 30 min at −78 °C, then a solution of MeSSMe (1.4 ml, 15.7 mmol) in anhydrous THF (5 ml) was added and the reaction temperature was gradually raised at room temperature. The solution was stirred for 12 h, and then poured into water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (silica gel, 30 g) with EtOAc–hexane (3:7, v/v) to give **7** (2.54 g, 95%), bp 96—97 °C/2.5 Torr. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=6 Hz, $CH_3\times2$), 1.78—2.31 (1H, m, CH), 2.56 (3H, s, SCH_3), 3.67 (2H, d, J=7 Hz, NCH_2), 6.82 (1H, d, J=2 Hz, imidazole C_4 or C_5-H), 6.97(1H, d,

$J=2$ Hz, imidazole C_4 or C_5-H). MS *m/z*: 170 (M^+). HRMS Calcd for $C_8H_{13}N_2S$: 170.0877. Found: 170.0865.

5-Bromo-1-isobutyl-2-methylthioimidazole (8) NBS (1.15 g, 6.46 mmol) was added to a solution of **7** (1.0 g, 5.87 mmol) in CCl_4 (30 ml) and the mixture was stirred for 1 h at room temperature. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, 20 g) with EtOAc–hexane (1 : 19, v/v) to give **8** (1.21 g, 83%), bp 98—99 °C/1 Torr. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, $J=6$ Hz, $CH_3\times2$), 1.90—2.44 (1H, m, CH), 2.57 (3H, s, SCH_3), 3.70 (2H, d, $J=7$ Hz, NCH_2), 6.96 (1H, s, imidazole C_4-H). MS *m/z*: 250 (M^++2), 248 (M^+). HRMS Calcd for $C_8H_{13}{}^{79}BrN_2S$: 247.9982. Found: 247.9996.

1-Isobutyl-2-methylthio-5-phenylimidazole (9) A stirred mixture of **8** (220 mg, 0.883 mmol), phenylboronic acid[10] (161 mg, 1.32 mmol), Pd $(PPh_3)_4$ (31 mg, 0.026 mmol) and Na_2CO_3 (1.8 ml of 2 M aqueous solution, 3.53 mmol) in anhydrous toluene (5 ml) and anhydrous EtOH (0.5 ml) was heated at 110 °C for 4 h. The reaction mixture was poured into water, and then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) with EtOAc–hexane (1 : 4, v/v) give **9** (213 mg, 98%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.66 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.39—2.07 (1H, m, CH), 2.63 (3H, s, SCH_3), 3.78 (2H, d, $J=7$ Hz, NCH_2), 6.99 (1H, s, imidazole C_4-H), 7.26 (5H, s, C_6H_5). MS *m/z*: 246 (M^+). HRMS Calcd for $C_{14}H_{18}N_2S$: 246.1190. Found: 246.1213.

4-Bromo-1-isobutyl-2-methylthio-5-phenylimidazole (10) NBS (200 mg, 1.13 mmol) was added to a stirred solution of **9** (185 mg, 0.751 mmol) in CCl_4 (5 ml). After having been stirred for 1 h, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, 10 g) with EtOAc–hexane (1 : 19, v/v) give **10** (239 mg, 98%), mp 68—70 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.67 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.35—2.06 (1H, m, CH), 2.06 (3H, s, SCH_3), 3.66 (2H, d, $J=7$ Hz, NCH_2), 7.29 (5H, s, C_6H_5). MS *m/z*: 326 (M^++2), 324 (M^+). *Anal.* Calcd for $C_{14}H_{17}BrN_2S$: C, 51.70; H, 5.27; N, 8.61. Found: C, 51.93; H, 5.39; N, 8.65.

1-Isobutyl-2-methylthio-5-phenylimidazole-4-carboxylic Acid (11) A solution of *n*-BuLi (2.1 ml of 1.61 M hexane solution, 3.38 mmol) was added to a solution of **10** (500 mg, 1.54 mmol) in anhydrous Et_2O (15 ml) at −78 °C. The mixture was stirred at −78 °C for 1 h, then CO_2 gas was introduced into the solution. The reaction temperature was gradually raised to ambient temperature and stirring was continued for 12 h. The mixture was extracted with 1% NaOH aqueous solution. The water layer was adjusted to pH 4 with AcOH, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from MeOH to give **11** (342 mg, 76.6%), mp 238—241 °C. IR (KBr) cm^{-1}: 2968 (OH), 1677 (C=O). ^{1}H-NMR ($CDCl_3$/MeOH-d_4) δ: 0.69 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.41—2.20 (1H, m, CH), 2.68 (3H, s, SCH_3), 3.63 (2H, d, $J=7$ Hz, NCH_2), 7.35 (5H, s, C_6H_5). MS *m/z*: 290 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.92; H, 6.42; N, 9.48.

1-Isobutyl-2-methylthio-4-(*N*-methoxyimino-1-chloromethyl)imidazole (12) A mixture of $NH_2OMe\cdot HCl$ (104 mg, 1.24 mmol) and Et_3N (0.17 ml, 1.24 mmol) in anhydrous MeCN (7 ml) was stirred at ambient temperature for 10 min. After the addition of **11** (300 mg, 1.03 mmol) in anhydrous MeCN (4 ml) and PPh_3 (1.35 g, 5.17 mmol) to the above mixture, CCl_4 (795 mg, 5.17 mmol) in MeCN (4 ml) was added gradually. The reaction mixture was stirred at ambient temperature for 1 h, refluxed for 3 h and then quenched with water. The whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) with EtOAc–hexane (3 : 7, v/v) to afford **12** (189 mg, 49%). ^{1}H-NMR ($CDCl_3$) δ: 0.68 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.51—2.28 (1H, m, CH), 2.68 (3H, s, SCH_3), 3.57 (2H, d, $J=7$ Hz, NCH_2), 3.79 (3H, s, OCH_3), 7.28 (5H, s, C_6H_5). MS *m/z*: 339 (M^++2), 337 (M^+). HRMS Calcd for $C_{16}H_{20}{}^{35}ClN_3OS$: 337.1015. Found: 337.1032

2,4,5-Tribromo-1-isobutylimidazole (15) A mixture of **14**[13] (5.0 g, 16.4 mmol) and K_2CO_3 (3.17 g, 23.0 mmol) in *N,N*-dimethylformamide (DMF) (25 ml) was stirred at room temperature for 30 min and then isobutyl bromide (1.9 ml, 17.2 mmol) was added. The reaction mixture was heated at 70 °C for 3 h. After removal of the solvent under reduced pressure, the residue was taken up in water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 70 g) with EtOAc–hexane (1 : 19, v/v) to give **15** (5.19 g, 88%), bp 128—129 °C/0.7 Torr. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.91—2.51 (1H, m, CH), 3.77 (2H, d, $J=7$ Hz, NCH_2). MS *m/z*: 363 (M^++6), 361 (M^++4), 359 (M^++2), 357 (M^+). HRMS Calcd for $C_7H_9{}^{79}Br_3N_2$: 357.8315. Found: 357.8291.

4,5-Dibromo-1-isobutyl-2-methylthioimidazole (16) *n*-BuLi (6.7 ml of 1.63 M hexane solution, 10.9 mmol) was added to a stirred solution of **15** (3.93 g, 10.9 mmol) in anhydrous THF (60 ml) at −78 °C and the mixture was further stirred at −78 °C for 30 min. The reaction temperature was gradually raised to ambient temperature and stirring was continued for 12 h. The mixture was poured into water, and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 70 g) with EtOAc–hexane (1 : 9, v/v) to give **16** (3.05 g, 85%), bp 148—149 °C/3 Torr. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.87—2.40 (1H, m, CH), 2.58 (3H, s, SCH_3), 3.69 (2H, d, $J=7$ Hz, NCH_2). MS *m/z*: 330 (M^++4), 328 (M^++2), 326 (M^+). HRMS Calcd for $C_8H_{12}{}^{79}Br_2N_2S$: 325.9087. Found: 325.9059.

4-Bromo-1-isobutyl-5-(1-hydroxycyclohexyl)-2-methylthioimidazole (17) *tert*-BuLi (2.8 ml of 1.62 M pentane solution, 3.05 mmol) was added to a stirred solution of **16** (1.08 g, 3.05 mmol) in anhydrous Et_2O (30 ml) at −78 °C and the mixture was stirred for 30 min. Cyclohexanone (0.9 ml, 9.14 mmol) in anhydrous Et_2O (2 ml) was added at −78 °C. The reaction temperature was gradually raised to ambient temperature and stirring was continued for 12 h. The mixture was poured into water, and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 30 g) with EtOAc–hexane (1 : 9, v/v) to afford **17** (544 mg, 51%) as an oil. IR (neat) cm^{-1}: 3340 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.10—2.39 (11H, m, $CH_2\times5$ and CH), 2.53 (3H, s, SCH_3), 4.01(2H, d, $J=7$ Hz, NCH_2). MS *m/z*: 348 (M^++2), 346 (M^+). HRMS Calcd for $C_{14}H_{23}{}^{79}BrN_2OS$: 346.0713. Found: 346.0733.

4-Bromo-5-(1-cyclohexenyl)-1-isobutyl-2-methylthioimidazole (18) A solution of **17** (260 mg, 0.75 mmol) and *p*-toluenesulfonic acid (*p*-TsOH·H_2O) (142 mg, 0.75 mmol) in benzene (10 ml) was refluxed for 1 h and then cooled to room temperature. It was treated with aqueous $KHCO_3$ solution (saturated), and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) with EtOAc–hexane (1 : 19, v/v) to give **18** (239 mg, 97%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.35—2.40 (9H, m, $CH_2\times4$ and CH), 2.58 (3H, s, SCH_3), 3.60 (2H, d, $J=7$ Hz, NCH_2). MS *m/z*: 330 (M^++2), 328 (M^+). HRMS Calcd for $C_{14}H_{21}{}^{79}BrN_2S$: 328.0608. Found: 328.0635.

5-(1-Cyclohexenyl)-1-isobutyl-2-methylthioimidazole-4-carboxylic Acid (19) *n*-BuLi (7.3 ml of 1.63 M hexane solution, 11.8 mmol) was added to a stirred solution of **18** (1.30 g, 3.95 mmol) in anhydrous Et_2O (50 ml) at −78 °C. The mixture was stirred at −78 °C for 1 h, then CO_2 gas was introduced at the same temperature. The temperature of the mixture was gradually raised to ambient temperature and stirring was continued for 12 h. The reaction mixture was extracted with aqueous 1% NaOH solution and the water layer was adjusted to pH 4 with AcOH. The mixture was reextracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was recrystallized from EtOAc–hexane to give **19** (591 mg, 51%), mp 165—167 °C. IR (KBr) cm^{-1}: 2932 (OH) 1669 (C=O). ^{1}H-NMR (100 MHz, DMSO-d_6) δ: 0.18 (6H, d, $J=7$ Hz, $CH_3\times2$), 1.36—1.77(4H, m, $CH_2\times2$), 1.84—2.31 (5H, m, $CH_2\times2$ and CH), 2.57 (3H, s, SCH_3), 3.62 (2H, d, $J=7$ Hz, NCH_2), 5.58—5.83 (1H, m, =CH). MS *m/z*: 294 (M^+). *Anal.* Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7.53; N, 9.51. Found: C, 61.38; H, 7.63; N, 9.32.

5-(1-Cyclohexenyl)-1-isobutyl-4-(*N*-methoxyimino-1-chloromethyl)-2-methylthioimidazole (20) A mixture of $NH_2OMe\cdot HCl$ (68 mg, 0.815 mmol) and Et_3N (82 mg, 0.815 mmol) in anhydrous MeCN (4 ml) was stirred at room temperature for 10 min. After addition of PPh_3 (445 mg, 1.70 mmol), a solution of **19** (200 mg, 0.68 mmol) in anhydrous MeCN (3 ml) and a solution of CCl_4 (261 mg, 1.70 mmol) in anhydrous MeCN (3 ml) were added. The reaction mixture was stirred at ambient temperature for 1 h and further stirred at reflux temperature for 3 h. It was cooled to room temperature, then mixed water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) with EtOAc–hexane (1 : 9, v/v) to give **20** (106 mg, 46%)

as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=7 Hz, $CH_3\times2$), 1.35—2.39 (9H, m, $CH_2\times4$ and CH), 2.62 (3H, s, SCH_3), 3.61 (2H, d, J=7 Hz, NCH_2), 4.00 (3H, s, OCH_3), 5.60—5.87 (1H, m, =CH). MS m/z: 343 (M^++2), 341 (M^+). HRMS Calcd for $C_{16}H_{24}{}^{35}ClN_3OS$: 341.1327. Found: 341.1340.

4-Chloro-1-isobutyl-2-methylthio-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline (21) A stirred solution of **20** (34 mg, 0.099 mmol) in *o*-dichlorobenzene (2 ml) was heated at reflux temperature for 8 h. After removal of the solvent, the residue was purified by column chromatography (silica gel, 7 g) with EtOAc–hexane (1 : 9, v/v) to give **21** (19 mg, 62%), mp 177.5—180 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, d, J=7 Hz, $CH_3\times2$), 1.61—2.48 (5H, m, $CH_2\times2$ and CH), 2.76—3.19 (4H, m, $CH_2\times2$), 2.81 (3H, s, SCH_3), 3.99 (2H, d, J=7 Hz, NCH_2). MS m/z: 311 (M^++2), 309 (M^+). *Anal.* Calcd for $C_{15}H_{20}ClN_3S$: C, 58.14; H, 6.51; N, 13.56. Found: C, 57.85; H, 6.73; N, 13.29.

4-Chloro-1-isobutyl-2-methylthio-1*H*-imidazo[4,5-*c*]quinoline (13) A solution of **21** (20 mg, 0.065 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (32 mg, 0.142 mmol) in benzene (1 ml) was heated at reflux temperature for 4 h. It was mixed with water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 7 g) with EtOAc–hexane (1 : 9, v/v) to give **13** (8 mg, 41%), mp 187—189 °C (Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, d, J=7 Hz, $CH_3\times2$), 1.98—2.62 (1H, m, CH), 2.85 (3H, s, SCH_3), 4.19 (2H, d, J=7 Hz, NCH_2), 7.35—7.67 (2H, m, $C_6H_4\times1/2$), 7.78—8.15 (2H, m, $C_6H_4\times1/2$). MS m/z: 307 (M^++2), 305 (M^+). *Anal.* Calcd for $C_{15}H_{16}ClN_3S$: C, 58.91; H, 5.27; N, 13.74. Found: C, 58.62; H, 4.99; N, 14.01.

5-(2-Carboxyphenyl)-1-isobutyl-2-methylthioimidazole (25) *n*-BuLi (2.4 ml of 1.63 M hexane solution, 3.84 mmol) was added to a stirred solution of **8** (869 mg, 3.49 mmol) in anhydrous Et_2O (40 ml) at −78 °C. Stirring was continued at −78 °C for 1 h, then tri-*n*-butyltin chloride (1.9 ml, 3.84 mmol) was added. The reaction temperature was raised to ambient temperature for 12 h. The mixture was treated with aqueous NH_4Cl solution (saturated), and then extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness to give **23**. A solution of the crude **23** in anhydrous DMF (5 ml) was added to a stirred mixture of methyl 2-bromobenzoate (**22**) (500 mg, 2.33 mmol), $PdCl_2(PPh_3)_2$ (49 mg, 0.07 mmol), K_2CO_3 (321 mg, 2.33 mmol) and $Et_4N^+Cl^-$ (385 mg, 2.33 mol) in anhydrous DMF (10 ml). The whole was heated at 110 °C for 2 h, then treated with aqueous 30% KF solution (10 ml) and stirring was continued for 1 h. The mixture was filtered with the aid of Celite and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 15 g) with EtOAc–hexane (1 : 4, v/v) to give **24**, together with the debrominated imidazole (**7**). Aqueous 10% NaOH solution (3 ml) was added to a solution of the crude **24** in dioxane (10 ml) and the mixture was heated at reflux temperature for 12 h. After removal of the solvent, EtOAc was added to the residue. The mixture was extracted with aqueous 1% NaOH solution and the water layer was adjusted to pH 4 with AcOH, then reextracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from MeOH to give **25** (535 mg, 79%), mp 235—237 °C. IR (KBr) cm^{-1}: 3103 (OH), 1647 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.67 (6H, d, J=7 Hz, $CH_3\times2$), 1.34—2.01 (1H, m, CH), 2.58 (3H, s, SCH_3), 3.67 (2H, d, J=7 Hz, NCH_2), 7.06 (1H, s, C_4-H), 7.14—8.27 (4H, m, C_6H_4). MS m/z: 290 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.11; H, 6.10; N, 9.55.

1-Isobutyl-2-methylthio-1*H*,5*H*-imidazo[4,5-*c*]quinolin-4-one (27) A mixture of **25** (300 mg, 1.03 mmol), Et_3N (0.43 ml, 3.10 mmol) and DPPA (0.69 ml, 3.10 mmol) in anhydrous benzene (10 ml) was stirred at 50 °C for 1 h. The solvent was replaced with *o*-dichlorobenzene (10 ml) and the mixture was heated at reflux temperature for 1 h. After removal of the solvent under reduced pressure, the residue was recrystallized from EtOAc to give **27** (148 mg, 49.8%). The mother liquor was concentrated and the residue was purified by column chromatography (silica gel, 20 g) with EtOAc to give **27** (119 mg, 40.1%) (total 90%), mp >300 °C. IR (KBr) cm^{-1}: 1668 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.06 (6H, d, J=7 Hz, $CH_3\times2$), 2.25—2.35 (1H, m, CH), 2.84 (3H, s, SCH_3), 4.37 (2H, d, J=7 Hz, NCH_2), 7.39 (1H, t, J=8 Hz, aromatic H), 7.56 (1H, t, J=8 Hz, aromatic H), 7.58 (1H, d, J=8 Hz, aromatic H), 8.05 (1H, d, J=8 Hz, aromatic H). MS m/z: 287 (M^+). *Anal.* Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.84; H, 6.03; N, 14.36.

4-Chloro-1-isobutyl-2-methylthio-1*H*-imidazo[4,5-*c*]quinoline (13) A solution of **27** (400 mg, 1.39 mmol) in $POCl_3$ (1 ml) was heated at reflux temperature for 1 h, then poured into ice-water, and neutralized with aqueous 28% NH_4OH solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 15 g) with EtOAc–hexane (1 : 9, v/v) to give **13** (376 mg, 88%), mp 187—189 °C (Et_2O). The NMR spectrum of this compound was identical with that of the previously synthesized sample (**13**).

4-Amino-1-isobutyl-2-methylthio-1*H*-imidazo[4,5-*c*]quinoline (28) A mixture of **13** (200 mg, 0.654 mmol) in MeOH (2 ml) and 28% NH_4OH (8 ml) was heated at 150 °C for 48 h in a sealed tube. The mixture was diluted with water, and then extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 15 g) with MeOH–$CHCl_3$ (1 : 99, v/v) to give **28** (175 mg, 93%), mp 205—208 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, d, J=7 Hz, $CH_3\times2$), 1.92—2.64 (1H, m, CH), 2.75 (3H, s, SCH_3), 4.18 (2H, d, J=7 Hz, NCH_2), 5.46 (2H, br s, NH_2), 7.15—7.55 (2H, m, aromatic H×2), 7.63—7.96 (2H, m, aromatic H×2). MS m/z: 286 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_4S$: C, 62.91; H, 6.33; N, 19.56. Found: C, 62.71; H, 6.54; N, 19.61.

4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline (Imiquimod) (1) Red-Al (1.15 ml of 3.46 M toluene solution, 1.52 mmol) was added to a solution of **28** (30 mg, 0.11 mmol) in anhydrous toluene (3 ml). The mixture was heated at reflux temperature for 30 min, then poured into water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) with MeOH–$CHCl_3$ (1 : 60, v/v) to give imiquimod (**1**) (20 mg, 80%), mp 292—294 °C (sublimed at about 230 °C) (EtOH) (lit.,[4b] mp 288—291 °C). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.05 (6H, d, J=7 Hz, $CH_3\times2$), 2.25—2.35 (1H, m, CH), 4.54 (2H, d, J=7 Hz, NCH_2), 7.14 (2H, br s, NH_2), 7.46 (1H, t, J=8 Hz, aromatic H), 7.62 (1H, t, J=8 Hz, aromatic H), 7.79 (1H, d, J=8 Hz, aromatic H), 8.17 (1H, d, J=8 Hz, aromatic H). MS m/z: 240 (M^+). *Anal.* Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 70.25; H, 6.68; N, 23.07.

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