Synthesis of 3-[4-Acyl-2-(1-methoxy-1-methylethyl)morpholin-3-yl]-benzonitriles as Novel Potassium Channel Openers

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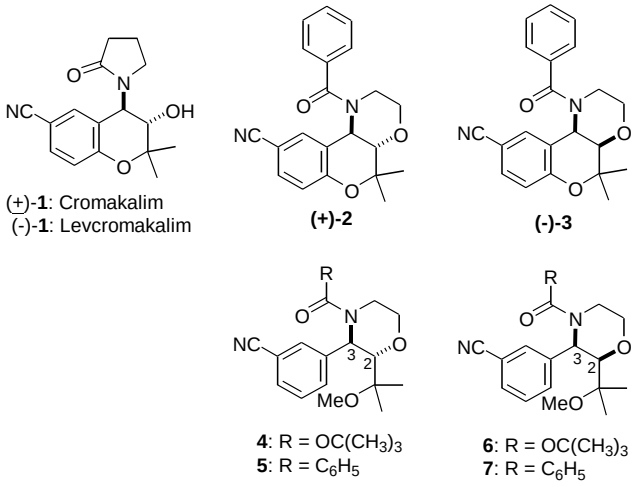
Potassium channel openers (KCO's) have been demonstrated to possess potent relaxant-activity on smooth muscle. Tissue-selective KCO's may find use in the treatment of a variety of diseases, such as hypertension, asthma, and urinary incontinence. We have previously reported a series of 1,9-dioxa-4-aza-phenanthrene-6-carbonitriles, including compounds **2** & **3**, as bladder-selective KCO's. As a continuation of our efforts, we have designed 3-[4-acyl-2-(1-methoxy-1-methylethyl)morpholin-3-yl]-benzonitriles as ring-opened analogs of compounds **2** & **3**. In this report, we describe the efficient construction of the novel 2,3-disubstituted morpholine structure, as represented by the synthesis of compounds **4**-**7**. Compounds **4**-**7** showed potent and selective relaxant-activity on rat bladder detrusor strip preparation. In this series, the most potent derivatives are Boc-substituted analogs **4** & **6** (IC_{50} = 3.9 and 2.9 μM, respectively).

Keywords: Potassium channel opener; Cromakalim; Synthesis; Morpholine; DAST.

INTRODUCTION

The potassium channel openers (KCO's) are chemically heterogeneous agents which relax smooth muscle by opening potassium channels in the cell membrane.[1-4] KCO's hold therapeutic promise as antianginals, cardioprotectives, bronchodilators, and agents against urinary incontinence.[5-12] Some KCO's have been introduced in the clinic as antihypertensive agents. Cromakalim ((±)-**1**) is a prototype KCO,[2] which lacks tissue selectivity, therefore, limiting its clinical potential.[13] Tissue-selective KCO's that selectively activate potassium channels in the bladder may be potential therapeutics for the treatment of urge urinary incontience.[14-18] In our previous study, we synthesized a series of 1,9-dioxa-4-aza-phenanthrene-6-carbonitriles,[19,20] as represented by compounds **2** & **3** (Chart 1). These compounds were designed on the basis of rigidization of the amide function and the 3-hydroxy group in **1**. Compound **2**, the *N*-benzoyl derivative, has been identified as a bladder-selective KCO, while its *cis* isomer **3** was found to be more potent than **2** ($IC_{50,\ bladder}$ = 8.2 μM, $IC_{50,\ portal\ vein}$ = 35 μM). In an effort to further study the structure activity relationship of **3** and related compounds, we synthesized compounds **4**-**7**, which can be viewed as ring-opened analogs of **2** & **3**. The KCO activities and selectivity of target compounds **4**-**7** were determined by in vitro tissue assays, spontaneously contracting rat portal vein and KCl-stimulated rat detrusor strip preparations.

Chart 1



RESULTS AND DISCUSSION

The synthetic strategy for target compounds **4**-**7** was

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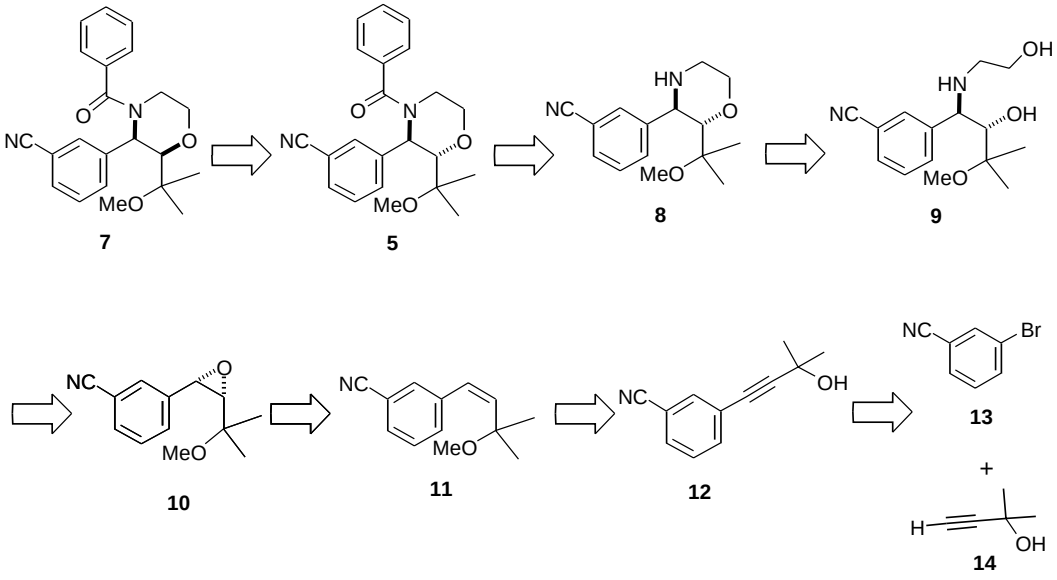
modeled after the synthesis of **2** & **3** as shown in Scheme I. In our previous study, we found that compound **2** can be converted smoothly to its *cis* isomer **3** upon treatment with base.[19,20] Therefore, we expected to obtain the desired *cis* compounds **6** & **7** from their *trans* isomers **4** & **5** *via* base-catalyzed epimerization. The key intermediate morpholine **8** could be derived from *cis*-olefin **11** *via* epoxidation, nucleophilic ring opening, followed by cyclization. Compound **11** could be obtained from alkyne **12** *via* partial hydrogenation, which leads to 3-bromobenzonitrile (**13**) and 2-methyl-3-butyn-2-ol (**14**) as starting materials. Therefore, compound **13** was coupled with **14** under Heck condition[21] to give acetylene **12** in 90% yield (Scheme II). Partial hydrogenation of alkyne **12** with the Lindlar catalyst then provided *cis* alkene **15**, which was methylated with CH_3I/NaH to give methyl ether **11** in good yield. Epoxidation of olefin **11** with *m*-CPBA yielded epoxide **10** in 76% yield.

Initially, epoxide **10** was treated with 2-aminoethanol to construct the desired morpholine ring and provided the diol intermediate **9** in low yield (20%). Furthermore, when compound **9** was subjected to Mitsunobu reaction condition (Et_3P/DEAD),[22] only a trace amount of morpholine **8** was obtained. Thus, an alternative approach using an allyl group as a masked hydroxyethyl moiety was adopted. Epoxide **10** was reacted with allylamine in DMSO to give aminoalcohol **16** in 52% yield. Compound **16** was converted to diol **18** *via* treatment with $(Boc)_2$, ozonolysis, and $NaBH_4$ reduction. Treatment of the *N*-protected **18** with Et_3P/DEAD then provided the desired morpholine **4** in 90% yield. Deprotection of compound **4** with stannic chloride[23] gave the corresponding morpholine **8**, which was acylated with benzoyl chloride/Et_3N to provide target compound **5** in satisfactory yield. The *trans* configuration of **4** & **5** was confirmed by their ^{1}H-NMR spectra, which showed a coupling constant of 9 Hz between the protons at C-2 and C-3.

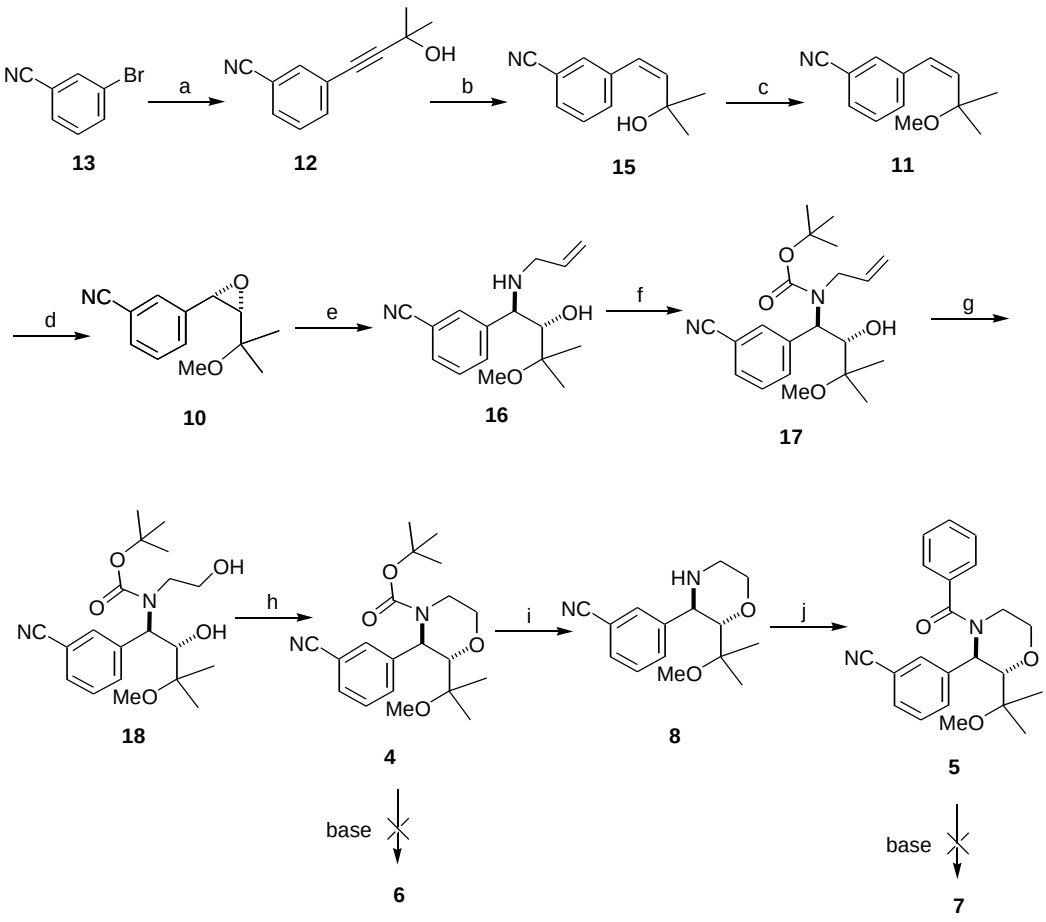
However, unlike what was observed with compounds **2** & **3**, we failed to convert compounds **4** & **5** to the corresponding *cis* isomers **6** & **7** under various basic conditions. Therefore, the alternative approach as shown in Scheme III, with (diethylamino)sulfur trifluoride (DAST)-effected hydroxyl inversion[24] as the key step, was followed. Thus, compound **16** was treated with acetic anhydride in pyridine to afford acetamide **21** in 56% yield. Treatment of **21** with DAST, followed by hydrolysis of the intermediate acetate, then gave aminoalcohol **20** in 31% yield. *cis*-Aminoalcohol **20** was then subjected to the same reaction sequence as described for the synthesis of **5** from **16**, with the successful generation of target compounds **6** & **7** (Scheme IV). The *cis* configuration of **6** & **7** was confirmed by ^{1}H-NMR of **19**, which showed a coupling constant of 3 Hz between the protons at C-2 and C-3.

The KCO activities and selectivity of compounds **4**-**7** were evaluated in vitro with preparations of spontaneously contracting rat portal vein and KCl-stimulated rat detrusor strip by the literature procedures.[16] All new compounds demonstrated potent and selective relaxant-activity on bladder detrusor (Table 1). Unlike the structure-activity relationship (SAR) in the series of compounds (+)-**2** and (-)-**3**, the *trans* isomers **4** & **5** showed quite similar KCO activities and selec-

Scheme I



Scheme II



Reagents and Conditions: (a) **14**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 110 °C, 90%; (b) $Pd/CaCO_3/Pb$, H_2, MeOH, 90%; (c) NaH, CH_3I, THF, 0 °C, 95%; (d) *m*-CPBA, CH_2Cl_2, rt, 76%; (e) allylamine, DMSO, 150 °C, 52%; (f) $(Boc)_2O$, K_2CO_3, THF, 60 °C, 60%; (g) O_3, CH_2Cl_2, -78 °C; then $NaBH_4$, CH_3OH, rt; 70%; (h) Et_3P, DEAD, THF, rt, 90%; (i) $SnCl_4$, CH_2Cl_2, rt, 87%; (j) benzoyl chloride, Et_3N, THF, 0 °C, 52%.

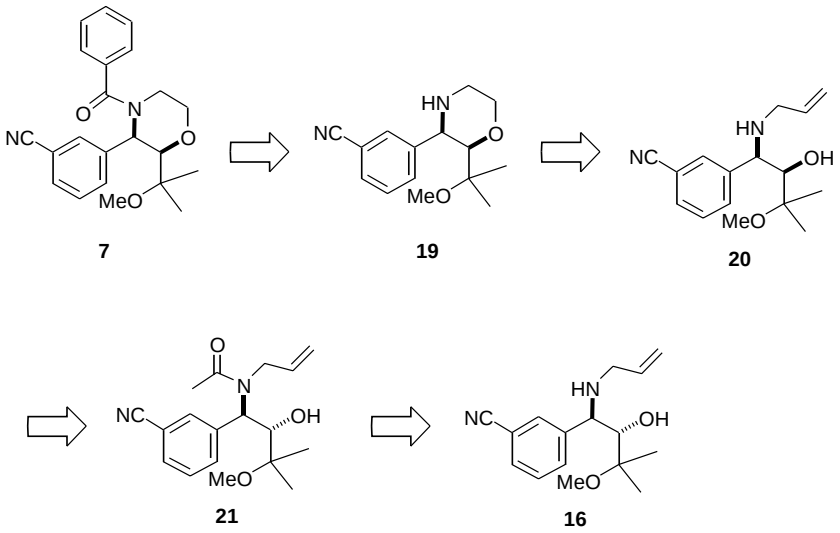
tivity as the *cis* isomers **6** & **7** in this novel series of ring-opened analogs. Replacing the phenyl substituent on compounds **5** & **7** with Boc group significantly increased the relaxant-activity on bladder detrusor and produced the most potent derivatives **4** & **6** in this series of compounds (IC_{50} = 3.9 and 2.9 μM, respectively).

Further pharmacological evaluation and SAR studies are in progress and will be reported in due course.

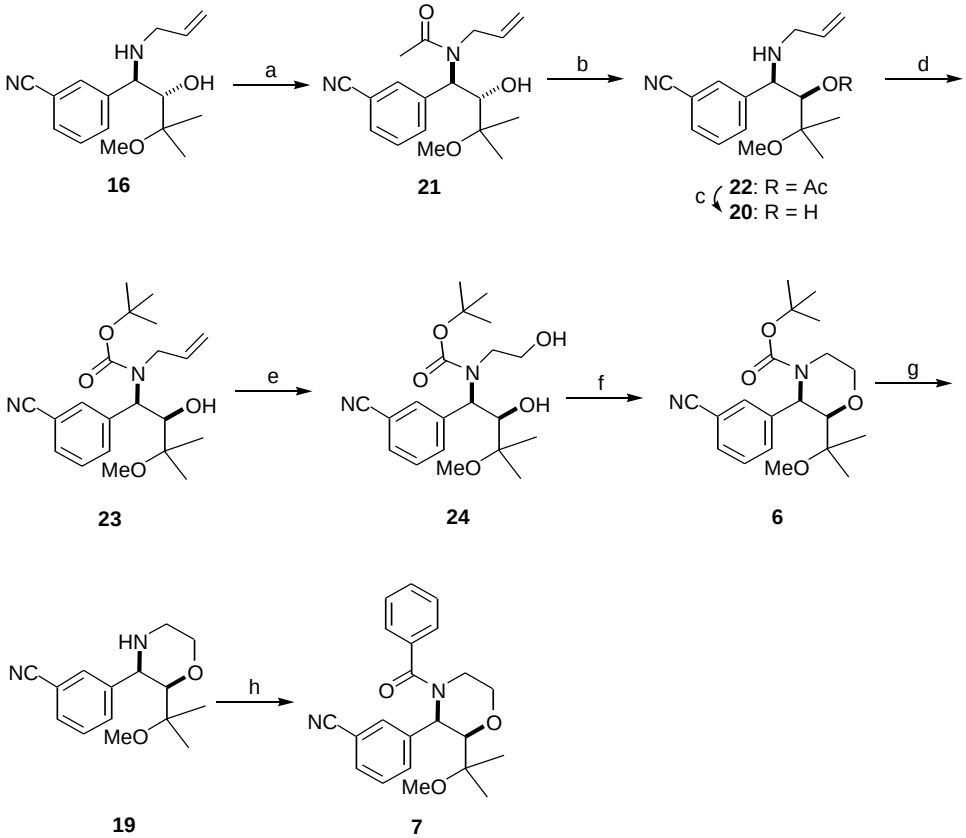
EXPERIMENTAL SECTION

Melting points were taken in a capillary tube by using a MEL-TEMP II melting point apparatus by Laboratory Devices. NMR spectra were recorded on Bruker AMX-200, AMX-400, and DMX-500 FT-NMR spectrometers; chemical shifts were recorded in parts per million downfield from Me_4Si. IR spectra were determined with a Perkin-Elmer 1760-X FT-IR spectrometer. Mass spectra were recorded on Jeol JMS-D300 and FINNIGAN TSQ-46C mass spectrometers; HRMS was obtained with a Jeol JMS-HX110 spectrometer. TLC was performed on Merck (Art. 5715) silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor, or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck (Art. 9385) 40-63 μm silica gel 60. Elemental analyses were carried out on a Perkin-Elmer 240 elemental analyzer and the results were

Scheme III



Scheme IV



Reagents and Conditions: (a) Ac_2O, pyridine, rt, 56%; (b) DAST, CH_2Cl_2, 0 ^oC, 49%; (c) NaOH, CH_3OH, rt, 30 min, 31% (two steps); (d) $(Boc)_2O$, K_2CO_3, THF, 60 ^oC, 47%; (e) O_3, CH_2Cl_2, -78 ^oC; then $NaBH_4$, CH_3OH, rt; 72%; (f) Et_3P, DEAD, THF, rt, 40%; (g) $SnCl_4$, CH_2Cl_2, rt, 87%; (h) benzoyl chloride, Et_3N, THF, 0 ^oC, 80%.

Table 1. Mechanoinhibitory Activities of Compounds **4-7** (IC_{50} ± SD, μM)[a]

Compound	Portal vein[b]	Detrusor[c]	IC_{50} ratio[d]
(+)-**2**	+[e]	66 ± 20	ND[f]
(-)-**3**	35 ± 0.7	8.2 ± 2	4.2
4	+[e]	3.9 ± 0.8	ND[f]
5	+[e]	18 ± 5	ND[f]
6	+[e]	2.9 ± 2	ND[f]
7	+[e]	23 ± 0.1	ND[f]
levcromakalim	0.09 ± 0.01	0.29 ± 0.01	0.31

[a] Data represents the mean of three experiments each performed in duplicate. [b] Spontaneously contracting rat portal vein. [c] Isolated rat detrusor strips exposed to extracellular KCl (20 μM). [d] $IC_{50,\ portal\ vein}/IC_{50,\ bladder}$. [e] The "+" sign indicates no inhibition was observed at the concentration range tested (0.01-100 μM), but an increase in the frequency of the spontaneous contraction was observed at high concentrations (≥ 30 μM). [f] Not determined.

within ± 0.4% of theoretical values. Anhydrous tetrahydrofuran was distilled from sodium-benzophenone prior to use.

3-(3-Hydroxy-3-methyl-1-butynyl)benzonitrile (12)

A mixture of 3-bromobenzonitrile (**13**, 6.00 g, 32.9 mmol), 2-methyl-3-butyn-2-ol (**14**, 4.0 mL, 41.1 mmol), dichlorobis(triphenylphosphine)palladium (1.12 g, 5 mol%), and CuI (0.61 g, 10 mol%) in Et_3N (200 mL) was degassed and then heated to 110 °C in a sealed flask for 3 h. After it cooled, the solution was filtered and evaporated. The residue was dissolved in CH_2Cl_2 (400 mL) and treated with activated charcoal. The mixture was filtered, evaporated, and chromatographed on silica gel (CH_2Cl_2) to afford **12** (5.47 g, 90%) as a colorless oil. R_f 0.18 (CH_2Cl_2); IR (neat) 3200~3600, 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 6H), 2.15 (s, 1H), 7.39 (d, *J* = 6.3 Hz, 1H), 7.56 (d, *J* = 6.3 Hz, 1H), 7.60 (d, *J* = 6.3 Hz, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 65.5, 79.8, 96.3, 112.8, 118.0, 124.4, 129.2, 131.4, 134.9, 135.7; MS (EI, 70 eV) *m*/*z* 185 (M^+), 170 (base peak); HRMS (EI) Calcd. for $C_{12}H_{11}NO^+$: 185.0815, found 185.0828.

***cis*-3-(3-Hydroxy-3-methyl-1-butenyl)benzonitrile (15)**

A solution of **12** (0.68 g, 3.68 mmol) and quinoline (1 mL) in anhydrous CH_3OH (30 mL) was hydrogenated at atmospheric pressure over 5% Pd/$CaCO_3$/Pb (0.3 g) until 1 equiv of H_2 was absorbed. The mixture was filtered, diluted with CH_2Cl_2 (30 mL), and washed with 2M HCl. The CH_2Cl_2 layer was dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 1/10) to afford **15** (0.62 g, 90%) as an oil. R_f 0.68 (EtOAc/*n*-hexane = 1/3); IR (neat) 3200~3600, 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (s, 6H), 1.73 (s, 1H), 5.77 (d, *J* = 12.7 Hz, 1H), 6.30 (d, *J* = 12.8 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.5, 72.5, 112.2, 119.4, 126.3, 128.9, 130.7, 133.3, 134.3, 139.2, 141.4; MS (EI, 70 eV) *m*/*z* 187 (M^+), 154 (base); HRMS (EI) Calcd. for $C_{12}H_{13}NO^+$: 187.1002, found 187.1000.

***cis*-3-(3-Methoxy-3-methyl-1-butenyl)benzonitrile (11)**

To a solution of **15** (1.90 g, 10.2 mmol) in THF (20 mL), NaH (0.81 g, 20.3 mmol) and CH_3I (1.26 mL, 20.3 mmol) were added and stirred at 0 °C for 6 h. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined extract was washed with aqueous 1N NaOH, H_2O, and brine, dried ($MgSO_4$) and evaporated to afford **11** (2.00 g, 98%). R_f 0.70 (EtOAc/*n*-hexane = 1/3); IR (neat) 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 6H), 2.96 (s, 3H), 5.59 (d, *J* = 13.0 Hz, 1H), 6.37 (d, *J* = 13.0 Hz, 1H), 7.31~7.48 (m, 2H), 7.65-7.71 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7, 50.5, 76.0, 112.2, 119.3, 128.4, 128.9, 130.7, 133.4, 134.4, 138.8, 138.9; MS (EI, 70 eV) *m*/*z* 201 (M^+, base); HRMS (EI) Calcd. for $C_{13}H_{15}NO^+$: 201.1154, found 201.1154.

3-[3-(1-Methoxy-1-methyl-ethyl)-oxiranyl]benzonitrile (10)

To a stirred solution of **11** (2.14 g, 11.4 mmol) in CH_2Cl_2 (50 mL) was added *m*-chloroperbenzoic acid (4.23 g, 70% in water) and the mixture was stirred at ambient temperature for 24 h. The precipitate was filtered off and the filtrate was washed with aqueous Na_2SO_3 followed by aqueous $NaHCO_3$. The dried ($MgSO_4$) organic phase was evaporated and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **10** (1.72 g, 75%) as an oil. R_f 0.43 (EtOAc/*n*-hexane = 1/3); IR (neat) 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.71 (s, 3H), 1.02 (s, 3H), 3.19 (s, 3H), 3.22 (d, *J* = 4.5 Hz, 1H), 3.99 (d, *J* = 4.5 Hz, 1H), 7.37~7.62 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0, 24.4, 51.0, 55.2, 65.4, 74.5, 112.6, 118.9, 129.2, 130.6, 131.4, 131.5, 137.5; MS (EI, 70 eV) *m*/*z* 217 (M^+), 186 (base); HRMS (EI) Calcd. for $C_{13}H_{15}NO_2^+$: 217.1103, found 217.1103.

3-[2-Hydroxy-1-(2-hydroxy-ethylamino)-3-methoxy-3-methylbutyl]benzonitrile (9)

A solution of epoxide **10** (0.60 g, 2.76 mmol) and ethanolamine (1.35 mL, 22.1 mmol) in THF (10 mL) was refluxed under N_2 overnight. The reaction mixture was evaporated and chromatographed on silica gel (CH_2Cl_2/CH_3OH/

NH_4OH = 100/10/1) to afford **9** (0.15 g, 20%) as an oil. R_f 0.30 (CH_2Cl_2/CH_3OH/NH_4OH = 100/10/1); IR (neat) 3315, 2228 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.15 (s, 3H), 2.19 (s, 3H), 2.40~2.54 (m, 2H), 3.11 (s, 3H), 3.32 (d, *J* = 3.7 Hz, 1H), 3.55 (m, 2H), 3.86 (d, *J* = 3.7 Hz, 1H), 7.36~7.75 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 21.8, 48.7, 49.2, 61.2, 62.4, 77.8, 79.7, 112.2, 118.8, 129.1, 130.8, 131.6, 132.4, 144.2; MS (FAB) *m*/*z* 279 (MH^+, base); FAB-HRMS Calcd. for $C_{15}H_{23}N_2O_3^+$: 279.1708, found 279.1709.

3-(1-Allylamino-2-hydroxy-3-methoxy-3-methylbutyl)-benzonitrile (16)

A mixture of epoxide **10** (1.00 g, 4.61 mmol), dimethylsulfoxide (DMSO, 5.00 mL) and allylamine (3.50 mL, 46.1 mmol) in a sealed flask was heated to 150 °C under N_2 for 48 h. After it cooled, DMSO was removed by Kugelrohr distillation, and then the residue was treated with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, and brine, dried ($MgSO_4$), evaporated and chromatographed on silica gel (EtOAc) to afford **16** (0.79 g, 65%) as an oil. R_f 0.66 (EtOAc); IR (neat) 3315, 2228 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.18 (s, 3H), 2.81~3.02 (m, 4H), 3.15 (s, 3H), 3.28 (d, *J* = 3.0 Hz, 1H), 3.92 (d, *J* = 3.0 Hz, 1H), 5.01 (s, 1H), 5.07 (s, 1H), 5.76 (m, 1H), 7.35~7.63 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 22.6, 49.8, 53.2, 69.1, 70.0, 78.3, 112.6, 116.9, 119.5, 129.3, 129.6, 130.4, 130.7, 136.3, 147.9; MS (FAB) *m*/*z* 275 (MH^+, base); FAB-HRMS Calcd. for $C_{16}H_{23}N_2O_2^+$: 275.1761, found 275.1754.

Allyl-[1-(3-cyanophenyl)-2-hydroxy-3-methoxy-3-methylbutyl]carbamic acid *tert*-butyl ester (17)

To a solution of **16** (2.56 g, 9.34 mmol) in THF (20 mL), K_2CO_3 (1.94 g, 14.0 mmol) and $(Boc)_2O$ (4.20 g, 18.7 mmol) were added and stirred at 50 °C for 24 h. The mixture was evaporated, treated with H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried ($MgSO_4$), evaporated and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **17** (1.70 g, 50%) as an oil. R_f 0.74 (EtOAc/*n*-hexane = 1/3); IR (neat) 3500~3000, 2230, 1681 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.76 (s, 6H), 1.42 (s, 9H), 3.17 (s, 3H), 3.63~3.82 (m, 2H), 3.98 (s, 1H), 4.87 (s, 1H), 4.94 (s, 1H), 5.13 (s, 1H), 5.59 (m, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0, 22.2, 28.7, 49.4, 50.1, 60.2, 72.3, 78.2, 81.3, 112.7, 117.2, 119.3, 129.4, 131.1, 132.5, 133.5, 135.1, 142.7, 157.6; MS (FAB) *m*/*z* 375 (MH^+, base); FAB-HRMS Calcd. for $C_{21}H_{31}N_2O_4^+$: 375.2283, found 375.2281.

[1-(3-Cyanophenyl)-2-hydroxy-3-methoxy-3-methylbutyl]-(2-hydroxyethyl)carbamic acid *tert*-butyl ester (18)

A solution of **17** (2.7 g, 7.5 mmol) in CH_2Cl_2 (40 mL) was treated with O_3 for 5 min at -78 °C, and then evaporated under reduced pressure. The residue was dissolved in CH_3OH (40 mL), and then $NaBH_4$ (0.34 g, 9.0 mmol) was added to this solution. The mixture was evaporated, treated with H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 1/4) to afford **18** (2.00 g, 70%) as a pale-yellow oil. R_f 0.31 (EtOAc/*n*-hexane = 1/3); IR (neat) 3600~3200, 2230, 1691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.21 (s, 3H), 1.45 (s, 9H), 3.01 (d, *J* = 13 Hz, 2H), 3.18 (s, 3H), 3.55 (s, broad, 1H), 3.60 (s, broad, 1H), 3.91 (s, broad, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 29.0, 49.7, 49.9, 62.1, 77.2, 77.8, 79.6, 81.5, 113.1, 119.3, 129.8, 131.6, 132.7, 133.6, 142.5, 157.5; MS (FAB) *m*/*z* 379 (MH^+); FAB-HRMS Calcd. for $C_{20}H_{31}N_2O_5^+$: 379.2223, found 379.2229.

***trans*-3-(3-Cyanophenyl)-2-(1-methoxy-1-methylethyl)-morpholine-4-carboxylic acid *tert*-butyl ester (4)**

To a stirred solution of **18** (175 mg, 0.46 mmol) and triethylphosphine (0.93 mL, 1 M in THF) in THF (5 mL) was added dropwise diethyl azodicarboxylate (0.41 mL, 40% in toluene) at room temperature under N_2. The resulting mixture was stirred at room temperature for 30 min. The mixture was evaporated and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **4** (133 mg, 80%) as an oil. mp: 76-77 °C (*n*-hexane); R_f 0.78 (EtOAc/*n*-hexane = 1/3); IR (neat) 2229, 1696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (s, 6H), 1.39 (s, 9H), 3.17 (s, 3H), 3.23 (t, *J* = 5.0 Hz, 1H), 3.38~3.43 (m, 1H), 3.69 (d, *J* = 2.0 Hz, 1H), 3.72~3.94 (m, 2H), 5.42 (d, *J* = 2.0 Hz, 1H), 7.33~7.50 (m, 3H), 7.56 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3, 22.6; 28.8, 41.1, 49.5, 51.2, 61.5, 77.6, 80.8, 84.3, 112.8, 119.4, 129.7, 130.6, 130.8, 131.6, 145.7, 155.5; MS (FAB) *m*/*z* 361 (MH^+); FAB-HRMS Calcd. for $C_{20}H_{29}N_2O_4^+$: 361.2127, found 361.2122. Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.30; H, 7.64; N, 7.83.

***trans*-3-[2-(1-Methoxy-1-methylethyl)morpholin-3-yl]-benzonitrile (8)**

To a stirred solution of **4** (0.50 g, 1.4 mmol) in CH_2Cl_2 was added stannic chloride (1.45 g, 5.6 mmol) at room temperature and stirred for 30 min. The solvent and the excess $SnCl_4$ were evaporated. The residue was dissolved in

CH_3OH, and then ether was added to afford the HCl salt of **8** as a white precipitate (0.36 g, 87%). R_f 0.32 (CH_2Cl_2/CH_3OH/NH_4OH = 100/10/1); IR (neat) 2233 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.08 (s, 3H), 1.71 (s, 1H), 2.79 (s, 3H), 2.85 (dd, *J* = 11, 2.0 Hz, 1H), 2.98 (dt, *J* = 11, 3.0 Hz, 1H), 3.40 (d, *J* = 9.0 Hz, 1H), 3.70 (dt, *J* = 11, 3.0 Hz, 1H), 3.82 (d, *J* = 9.0 Hz, 1H), 3.94 (dd, *J* = 11, 2.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 24.0, 46.7, 49.2, 62.0, 68.4, 77.0, 85.5, 112.3, 119.4, 129.1, 131.3, 132.5, 133.6, 144.6; MS (FAB) *m*/*z* 261 (MH^+, base); FAB-HRMS Calcd. for $C_{15}H_{21}N_2O_2^+$: 261.1603, found 261.1601.

trans-3-[4-Benzoyl-2-(1-methoxy-1-methylethyl)morpholin-3-yl]benzonitrile (5)

Compound **8** (100 mg, 0.34 mmol) in THF (6 mL) was reacted with triethylamine (80 μL, 0.58 mmol) and benzoyl chloride (54 μL, 0.46 mmol) at 0 °C under N_2 for 0.5 h and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 10% $NaHCO_3$, 10% HCl, H_2O, and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **5** (64 mg, 52%) as an oil. R_f 0.19 (EtOAc/*n*-hexane = 1/3); IR (CH_2Cl_2) 2229, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.28 (s, 3H), 1.79 (s, broad, 1H), 3.20 (s, 3H), 3.30 (s, broad, 1H), 3.55 (m, 1H), 3.78 (s, 1H), 4.19 (m, 1H), 5.89 (broad, 1H), 7.35 (m, 5H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.80 (d, broad, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 41.9, 49.2, 61.6, 77.3, 78.3, 112.7, 118.8, 126.5, 128.3, 128.5, 129.4, 129.7, 129.9, 130.9, 132.1, 135.8, 143.3, 171.1; MS (FAB) *m*/*z* 365 (MH^+); FAB-HRMS Calcd. for $C_{22}H_{25}N_2O_3^+$: 365.1866, found 365.1883. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.58; H, 6.74; N, 7.62.

***N*-Allyl-*N*-[1-(3-cyanophenyl)-2-hydroxy-3-methoxybutyl]-acetamide (21)**

A solution of compound **16** (5.2 g, 19 mmol) and acetic anhydride (3.2 mL) in pyridine (20 mL) was stirred at 0 °C for 18 h. The mixture was treated with 10% NaOH and extracted with CH_2Cl_2. The organic layer was washed with 2N HCl (100 mL) and then evaporated. The residue was chromatographed (silica gel, EtOAc/*n*-hexane = 2/3) to afford **21** (3.35 g, 56%) as a light-brown oil. R_f 0.25 (EtOAc/*n*-hexane = 2:3); IR (neat) 3500~3200, 2229, 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.21 (s, 3H), 2.13 (s, 3H), 3.21 (s, 3H), 3.90-4.10 (m, 4H), 4.96-5.06 (m, 2H), 5.57 (m, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 20.9, 22.0, 22.6, 22.9, 48.9, 49.1, 60.2, 76.5, 77.3, 112.2, 117.4, 118.7 129.0, 130.9, 131.2, 132.2, 133.0, 133.2, 133.6, 141.7, 173.1; MS (FAB) *m*/*z* 317 (MH^+); FAB-HRMS Calcd. for $C_{18}H_{25}N_2O_3^+$: 317.1865, found 317.1876.

3-(1-Allylamino-2-hydroxy-3-methoxy-3-methylbutyl)-benzonitrile (20)

A solution of **21** (2.9 g, 9.2 mmol), diethylaminosulfur trifluoride (DAST, 1.45 mL, 11.02 mmol) and CH_2Cl_2 (220 mL) was stirred at room temperature under N_2 for 30 min. The mixture was evaporated, dissolved in 2M NaOH in CH_3OH (20 mL), stirred at room temperature for 10 min, and then evaporated. The residue was dissolved in CH_2Cl_2, and the resultant mixture was washed with H_2O and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 2/3) to afford **20** (778 mg, 31%) as an oil. R_f 0.34 (EtOAc/*n*-Hexane = 2/3); IR (neat) 3315, 2228 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.05 (s, 3H), 2.81 (dd, *J* = 14.2, 6.6 Hz, 2H), 2.92 (ddd, *J* = 14.0, 4.0, 1.3 Hz, 1H), 3.09 (s, 3H), 3.60 (d, *J* = 6.0 Hz, 1H), 3.74 (d, *J* = 6.0 Hz, 1H), 4.97 (d, *J* = 1.0 Hz, 1H), 4.99 (m, 1H), 5.72 (m, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 21.9, 48.7, 49.3, 63.0, 77.8, 111.7, 115.9, 118.8, 128.5, 130.6, 132.5, 133.5, 136.2, 143.3; MS (FAB) *m*/*z* 275 (MH^+, base); FAB-HRMS Calcd. for $C_{16}H_{23}N_2O_2^+$: 275.1761, found 275.1762.

Allyl-[1-(3-cyanophenyl)-2-hydroxy-3-methoxy-3-methyl-butyl]carbamic acid *tert*-butyl ester (23)

To a solution of **20** (1.50 g, 5.47 mmol) in THF (60 mL), K_2CO_3 (1.13 g, 8.20 mmol) and $(Boc)_2O$ (2.46 g, 11.0 mmol) were added and stirred at 50 °C for 24 h. The mixture was evaporated, treated with H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **23** (0.94 g, 47%) as an oil. R_f 0.62 (EtOAc/*n*-hexane = 2/3); IR (neat) 3500~3000, 2229, 1685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.17 (s, 3H), 1.42 (s, 9H), 3.18 (s, 3H), 3.65 (m, 1H), 3.86~3.91(m, 2H), 4.08 (s, 1H), 4.86 (d, *J* = 6.0 Hz, 1H), 4.92 (s, 1H), 5.10 (s, 1H), 5.40 (m, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 28.8, 49.6, 50.1, 60.4, 77.7, 77.8, 81.3, 112.3, 116.8, 119.5, 129.2, 131.4, 134.1, 134.8 135.1, 141.4, 156.3; MS (FAB) *m*/*z* 375 (MH^+); FAB-HRMS Calcd. for $C_{21}H_{31}N_2O_4^+$: 375.2283, found 375.2285.

[1-(3-Cyanophenyl)-2-hydroxy-3-methoxy-3-methylbutyl]-(2-hydroxyethyl)carbamic acid *tert*-butyl ester (24)

A solution of **23** (0.94 g, 2.6 mmol) in CH_2Cl_2 (50 mL) was treated with O_3 for 5 min at -78 °C, and then evaporated under reduced pressure. The residue was dissolved in CH_3OH (40 mL), and then $NaBH_4$ (0.42 g, 5.2 mmol) was added to this solution. The mixture was evaporated, treated with H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 1/4) to afford **24** (0.69 g, 72%) as a pale-yellow oil. R_f 0.26 (EtOAc/*n*-hexane = 2/3); IR (neat) 2230, 1691 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 6H), 1.46 (s, 9H), 3.20 (s, 3H), 3.48 (s, broad, 3H), 4.10 (s, 1H), 5.17 (s, broad, 1H), 7.39 (t, *J* = 4.0 Hz, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 22.5, 28.9. 49.6, 49.7, 61.2, 62.5, 77.5, 78.5, 81.7, 112.6, 119.3, 129.3, 129.4, 131.6, 134.2, 135.1, 141.1, 156.6; MS (FAB) *m*/*z* 379 (MH^+); FAB-HRMS Calcd. for $C_{20}H_{31}N_2O_5^+$: 379.2223, found 379.2236.

***cis*-3-(3-Cyanophenyl)-2-(1-methoxy-1-methylethyl)-morpholine-4-carboxylic acid *tert*-butyl ester (6)**

To a stirred solution of **24** (688 mg, 1.82 mmol) and triethylphosphine (3.6 mL, 1 M in THF) in THF (20 mL) was added dropwise diethyl azodicarboxylate (634 μL, 40% in toluene) at room temperature under N_2. The resulting mixture was stirred at room temperature for 30 min. The mixture was evaporated and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **6** (265 mg, 40%) as a solid. mp: 143-144 °C (*n*-hexane); R_f 0.73 (EtOAc/*n*-hexane = 1/3); IR (neat) 2229, 1696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.72~1.06 (m, 6H), 1.35 and 1.39 (s, 9H), 3.02 and 3.04 (s, 3H), 3.32 (m, 1H), 3.61 and 3.62 (s, 1H), 3.67~3.80 (m, 2H), 4.18~4.26 (m, 1H), 4.93 and 5.14 (d, *J* = 3.0 Hz, 1H), 7.36 (m, 1H), 7.52 (m, 1H), 7.79 and 7.84 (d, *J* = 8.0 Hz, 1H), 7.81 and 7.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 21.3; 22.8, 23.7, 28.3, 28.4, 38.5, 39.4, 49.1, 49.2, 53.6, 55.1, 68.0, 68.2, 75.5, 75.6, 80.4, 80.7, 85.3, 85.9, 111.5, 118.9, 119.1, 128.4, 130.9, 133.9, 134.1, 134.7, 135.3, 139.7, 140.4, 154.2, 154.5; MS (FAB) *m*/*z* 361 (MH^+); FAB-HRMS Calcd. for $C_{20}H_{29}N_2O_4^+$: 361.2127, found 361.2124; Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.69; H, 7.88; N, 7.59.

***cis*-3-[2-(1-Methoxy-1-methylethyl)morpholin-3-yl]benzonitrile (19)**

To a stirred solution of **6** (150 mg, 0.42 mmol) in CH_2Cl_2 was added stannic chloride (438 mg, 1.68 mmol) at room temperature and stirred for 30 min. The solvent and the excess $SnCl_4$ were evaporated. The residue was treated with 1N NaOH and extracted with CH_2Cl_2. The extract was washed with H_2O, and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (CH_2Cl_2/CH_3OH/NH_4OH = 100/10/1) to afford **19** as an oil (94 mg, 87%). R_f 0.32 (EtOAc/*n*-hexane = 1/3); IR (neat) 2233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.93 (s, 3H), 2.57 (ddd, *J* = 13, 3.0, 1.0 Hz, 1H), 3.02 (s, 3H), 3.21 (td, *J* = 12, 4.0 Hz, 1H), 3.79 (d, *J* = 3.0 Hz, 1H), 3.80 (dt, *J* = 12, 3.0 Hz, 1H), 3.92 (d, *J* = 3.0 Hz, 1H), 4.15(dd, *J* = 11, 3.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.51 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.77 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.87 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 22.7, 39.3, 49.2, 56.4, 69.1, 75.9, 85.5, 111.6, 119.0, 128.4, 130.5, 133.3, 134.4, 142.7; MS (FAB) *m*/*z* 261 (MH^+); FAB-HRMS Calcd. for $C_{15}H_{21}N_2O_2^+$: 261.1603, found 261.1607.

***cis*-3-[4-Benzoyl-2-(1-methoxy-1-methylethyl)morpholin-3-yl]benzonitrile (7)**

Compound **19** (54 mg, 0.21 mmol) in THF (10 mL) was reacted with triethylamine (45 μL, 0.32 mmol) and benzoyl chloride (29 μL, 0.25 mmol) at 0 °C under N_2 for 0.5 h and evaporated under reduced pressure. To the residue was added CH_2Cl_2, and then the mixture was washed with 10% $NaHCO_3$, 10% HCl, H_2O, and brine, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (EtOAc/*n*-hexane = 1/3) to afford **7** (60 mg, 80%) as an oil. R_f 0.30 (EtOAc/*n*-hexane = 2/3); IR (CH_2Cl_2) 2229, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.09 (s, 3H), 2.95 and 3.06 (s, 3H), 3.43 (d, *J* = 13.6 Hz, 1H), 3.59 and 3.84 (t, *J* = 12.0 Hz, 1H), 3.67 and 4.35 (m, 1H), 3.71 (s, 1H), 4.15 (d, *J* = 8.7 Hz, 1H), 4.90 and 5.85 (s, 1H), 7.21~7.78 (m, 7H), 7.98 (d, *J* = 7.4 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 22.8, 42.9, 49.3, 52.3, 68.3, 75.6, 86.0, 111.8, 118.9, 126.8, 128.5, 128.7, 129.9, 131.3, 124.4, 135.3, 135.6, 139.1, 170.0; MS (FAB) *m*/*z* 365 (MH^+); FAB-HRMS Calcd. for $C_{22}H_{25}N_2O_3^+$: 365.1866, found 365.1871.

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