HETEROCYCLES, Vol. 99, No. 1, 2019, pp. 716 - 723. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 27th August, 2018, Accepted, 13th September, 2018, Published online, 17th October, 2018
DOI: 10.3987/COM-18-S(F)44

CONCISE SYNTHESIS OF ANTICANCER ACTIVE *trans*-4-(4-OCTYLPHENYL)PROLINOL

Junki Ando,[1,2] Aoi Tazawa,[1] Kohei Ishizawa,[1] Minoru Tanaka,[1]* and Hiroyoshi Takamura[2]*

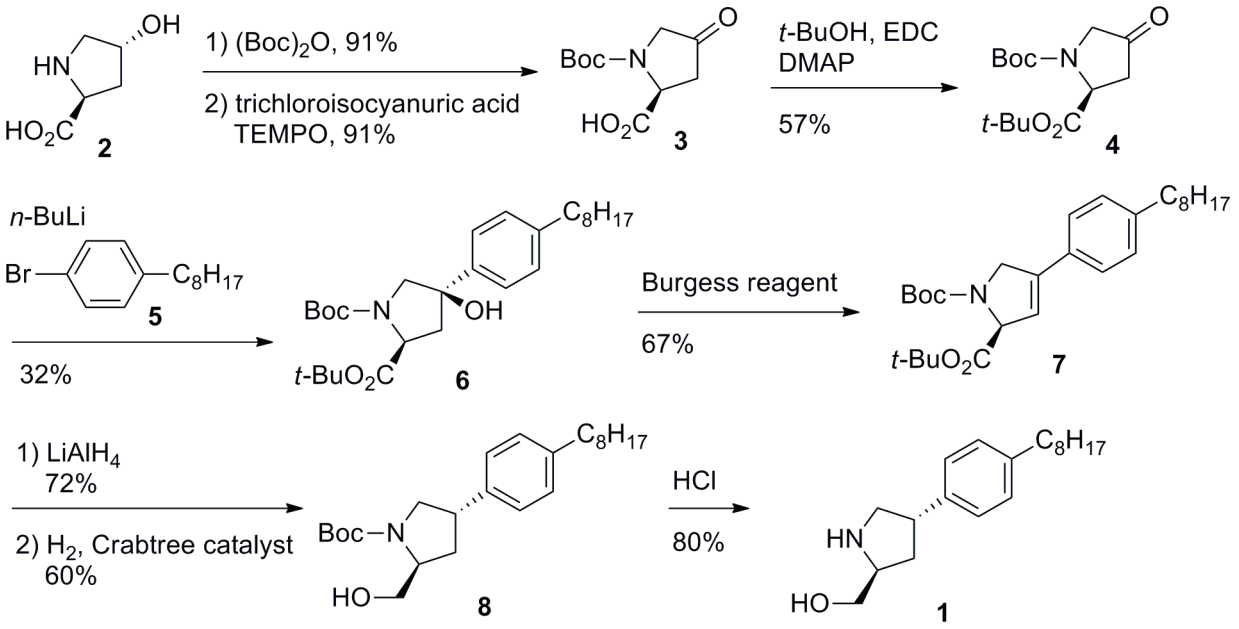
[1] Sohyaku Innovative Research Division, Mitsubishi Tanabe Pharma Corporation, 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan. [2] Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan. E-mail: tanaka.minoru@mw.mt-pharma.co.jp (M.T.), takamura@cc.okayama-u.ac.jp (H.T.)

Abstract – Concise synthesis of anticancer active *trans*-4-(4-octylphenyl)prolinol has been achieved. Regioselective iodination of aromatic compound and subsequent Suzuki–Miyaura cross-coupling with *trans*-1-octen-1-ylboronic acid produced the desired coupling product. Further transformation of this product afforded *trans*-4-(4-octylphenyl)prolinol. The synthesis of this anticancer compound has been performed with 23% overall yield and six steps, which have been improved in comparison with those (3.5% overall yield and eight steps) previously reported.

The substituted prolinols have been recognized as key and versatile synthetic intermediates for the total synthesis of natural products[1] and other biologically active compounds.[2] In addition, the prolinol is a central structural feature which is found in drug candidates such as anticancer compounds,[3] antivirus compounds,[4] CCR3 receptor antagonists,[5] and sphingosine-1-phosphate agonists.[6]

Hanessian's research group found that *trans*-4-(4-octylphenyl)prolinol (**1**, Scheme 1) exhibited the anticancer activity against PC3 (IC_{50} = 9.8 μM) and DU145 (IC_{50} = 10.6 μM) cell lines in their research of FTY720 analogues which limit nutrient transporter expression but lack sphingosine-1-phosphate activity.[3b,7] The synthetic route of **1**, which was reported by Hanessian and co-workers, is depicted in Scheme 1. Protection of *trans*-4-hydroxy-L-proline (**2**) with $(Boc)_2O$ and subsequent TEMPO oxidation gave ketone **3**. The carboxylic acid **3** was treated with *t*-BuOH/EDC/DMAP to afford ester **4**. The ketone **4** reacted with aryllithium species, derived from 4-octyl-1-bromobenzene (**5**) and *n*-BuLi, to provide the

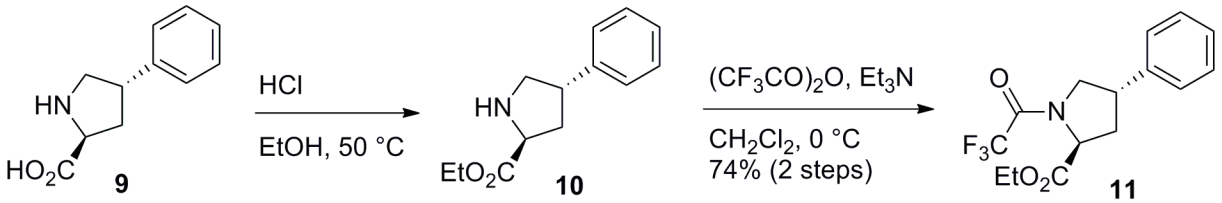
desired adduct **6** in 32% yield. The alcohol **6** was subjected to Burgess dehydration conditions to give alkene **7**, which was converted to alcohol **8** by reduction of the ester moiety with $LiAlH_4$ and hydroxy-directed hydrogenation with Crabtree catalyst. Finally, deprotection of the carbamate **8** with HCl produced *trans*-4-(4-octylphenyl)prolinol (**1**).[8,9] Overall yield and the number of sequence for the synthesis of **1** from the starting material **2** were 3.5% and eight steps, respectively. Herein, we report the alternative synthetic route toward the anticancer active compound **1** via regioselective iodination and subsequent Suzuki–Miyaura cross-coupling[10] as key transformations.



Scheme 1. Synthesis of anticancer compound **1** by Hanessian's research group[3b,7]

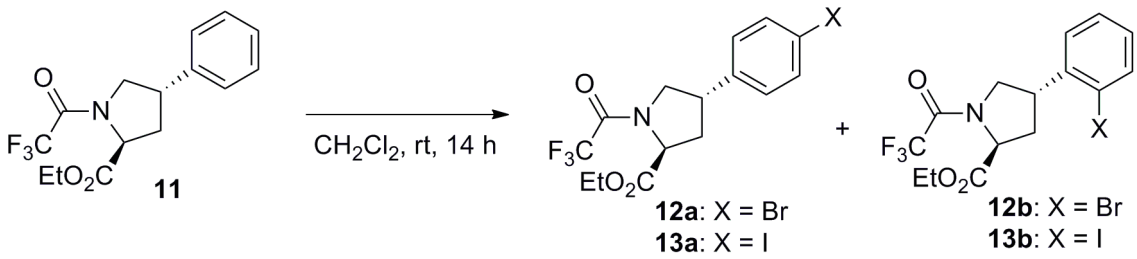
Our synthesis of **1** commenced from commercially available *trans*-4-phenyl-L-proline (**9**) as shown in Scheme 2. Ethyl esterification of **9** with HCl in EtOH afforded ester **10**, which was treated with $(CF_3CO)_2O/Et_3N$ to provide trifluoroacetamide **11** in 74% yield in two steps. Next, we investigated the regioselective halogenation of the aromatic compound **11** (Table 1). When we treated **11** with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide[11] in CH_2Cl_2 at room temperature for 14 h, the reaction did not proceed and the starting material **11** was recovered (entry 1). The use of combination of Br_2 and $FeBr_3$[12] provided trace amounts of brominated products **12a** and **12b** (entry 2). Changing the brominating reagent from Br_2 to NBS[13] was effective and the desired *p*-brominated product **12a** and undesired *o*-brominated product **12b** were obtained in 24% combined yield with a ratio of 70:30 (entry 3). Because the starting material **11** was partially recovered in these reaction conditions, the amount of reagents was increased to 4.0 equiv of NBS and 4.5 equiv of $FeBr_3$ respectively and the combined yield of **12a** and **12b** was improved to 80% (entry 4). We next surveyed the iodination

conditions of **11** to reach the desired product **13a**. Thus, when the iodination of **11** using the $I_2/AgNO_3$ combination[14] was performed, *p*- and *o*-iodinated products **13a** and **13b** were produced in 54% combined yield (entry 5). Although the combined yield of **13a** and **13b** was decreased in comparison with 80% yield of **12a** and **12b** obtained in the bromination (entry 4), regioselectivity of the desired *p*-halogenated products was increased to 80:20 from 70:30. The aromatic compound **11** was iodinated with I_2 (1.2 equiv)/$PhI(OCOCF_3)_2$ (1.5 equiv)[15] to produce **13a** and **13b** in 66% combined yield with 81:19 regioselectivity (entry 6). The chemical yield and regioselectivity of **13a** were increased to 80% and 87:13, respectively, by using 2.5 equiv of I_2 and 3.0 equiv of $Ph(OCOCF_3)_2$ (entry 7).



Scheme 2. Synthesis of halogenation precursor **11**

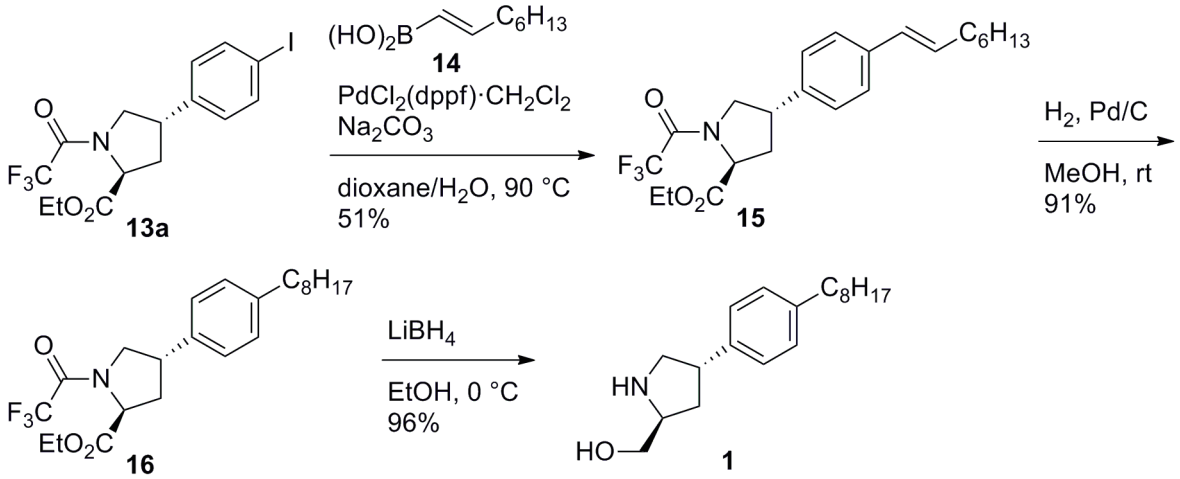
Table 1. Halogenation of aromatic compound **11**



Entry	Conditions	Yield (%)[a]	Ratio (**a**:**b**)[b]
1	NBS (1.2 equiv), benzoyl peroxide (1.5 equiv)	N.D.[c]	N.D.[c]
2	Br_2 (1.2 equiv), $FeBr_3$ (1.5 equiv)	N.D.[d]	N.D.[d]
3	NBS (1.2 equiv), $FeBr_3$ (1.5 equiv)	24 (**12a** + **12b**)	70:30
4	NBS (4.0 equiv), $FeBr_3$ (4.5 equiv)	80 (**12a** + **12b**)	70:30
5	I_2 (1.2 equiv), $AgNO_3$ (1.5 equiv)	54 (**13a** + **13b**)	80:20
6	I_2 (1.2 equiv), $PhI(OCOCF_3)_2$ (1.5 equiv)	66 (**13a** + **13b**)	81:19
7	I_2 (2.5 equiv), $PhI(OCOCF_3)_2$ (3.0 equiv)	80 (**13a** + **13b**)	87:13

[a]Isolated combined yield. [b]Determined by ^1H NMR spectra of the mixture of *p*- and *o*-halogenated products. [c]Not determined. No reaction was observed. [d]Not determined. Formation of trace amounts of **12a** and **12b** was observed.

Having succeeded in the regioselective *p*-halogenation of the arene compound **11**, we next tried to transform **13a** to the target compound **1** (Scheme 3). The aryl iodide **13a**[16] reacted with *trans*-1-octen-1-ylboronic acid (**14**)[17] in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2/Na_2CO_3$ to produce the Suzuki–Miyaura cross-coupling[10] product **15** in 51% yield. The alkene **15** was hydrogenated with Pd/C to give octylaromatic compound **16** in 91% yield. Finally, reduction of the ester moiety and removal of the trifluoroacetyl group of **16** took place simultaneously with $LiBH_4$ to furnish the target compound **1** in 96% yield.



Scheme 3. Synthesis of anticancer compound **1**

In conclusion, we examined the regioselective halogenation of the arene compound **11** and found that treatment of **11** with I_2 (2.5 equiv)/$PhI(OCOCF_3)_2$ (3.0 equiv) provided the *p*- and *o*-iodinated products **13a** and **13b** in 80% combined yield with 87:13 regioselectivity. The octyl substituent on the aromatic part was introduced by Suzuki–Miyaura cross-coupling of **13a** and *trans*-1-octen-1-ylboronic acid (**14**) and subsequent hydrogenation to produce the anticancer compound **1**. Our synthesis of **1** described herein was achieved in 23% overall yield and six total steps from *trans*-4-phenyl-L-proline (**9**), which were improved over those reported by Hannesian and co-workers: 3.5% overall yield and eight total steps from *trans*-4-hydroxy-L-proline (**2**). Further synthetic study of other (4-substituted phenyl)prolinol derivatives by using the combination of regioselective iodination and Suzuki–Miyaura cross-coupling is currently underway.

EXPERIMENTAL

General Methods. Reagents were used as received from commercial suppliers unless otherwise indicated. All reactions were carried out under an atmosphere of argon. Reaction solvents were purchased as dehydrated solvents and stored with active 4 Å molecular sieves under argon prior to use for reactions.

All solvents for workup procedure were used as received. IR spectra were recorded on PerkinElmer Spectrum One FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 UltraShield Plus. Chemical shifts in the NMR spectra are reported in ppm with reference to the internal residual solvent (^{1}H NMR, $CDCl_3$ 7.26 ppm; ^{13}C NMR, $CDCl_3$ 77.0 ppm). The following abbreviations are used to designate the multiplicities: d = doublet, t = triplet, m = multiplet. Coupling constants (*J*) are in hertz. High resolution mass spectra were recorded on LTQ Orbitrap Velos Pro mass spectrometer equipped with an ESI Lockspray source.

Trifluoroacetamide 11. To a solution of *trans*-4-phenyl-L-proline (**9**, 3.00 g, 15.7 mmol) in EtOH (58 mL) was added 4N HCl (20 mL) at room temperature. The mixture was stirred at 50 °C for 20 h. Concentration gave ethyl ester **10**, which was used for the next step without further purification.

To a solution of ethyl ester **10** obtained above in CH_2Cl_2 (52 mL) were added Et_3N (6.5 mL, 47.1 mmol) and $(CF_3CO)_2O$ (2.8 mL, 20.4 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 h and the reaction was quenched with H_2O. The mixture was extracted with $CHCl_3$ and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 1:1) gave trifluoroacetamide **11** (3.67 g, 74% in two steps, 80:20 mixture of rotamers): IR 2984, 1742, 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.39–2.57 (m, 2H), 3.63–3.72 (m, 2H), 4.23–4.34 (m, 3H), 4.74–4.76 (m, 1H), 7.21–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 35.3, 42.8, 53.2, 60.4, 61.8, 127.0, 127.7, 129.0, 138.5, 170.4; HRMS (ESI) calcd for $C_{15}H_{17}F_3NO_3$ $[M + H]^+$ 316.1161, found 316.1157.

Aryl Bromides 12a and 12b (Table 1, Entry 4). To a solution of trifluoroacetamide **11** (100 mg, 0.317 mmol) in CH_2Cl_2 (1.6 mL) were added $FeBr_3$ (422 mg, 1.43 mmol) and NBS (226 mg, 1.27 mmol) at room temperature. The mixture was stirred at room temperature for 14 h. Column chromatography (hexane/EtOAc = 9:1, 7:3) gave a mixture of aryl bromides **12a** and **12b** (100 mg, 80%, **12a**:**12b** = 70:30). Aryl Bromide **12a** (80:20 mixture of rotamers): IR 2983, 1741, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.30–2.57 (m, 2H), 3.57–3.69 (m, 2H), 4.21–4.32 (m, 3H), 4.72–4.75 (m, 1H), 7.10–7.12 (m, 2H), 7.47–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 35.2, 42.4, 52.9, 60.3, 61.9, 116.1 (q, *J* = 285.7 Hz), 121.5, 128.7, 132.1, 137.5, 155.8 (q, *J* = 37.5 Hz), 170.2; HRMS (ESI) calcd for $C_{15}H_{16}F_3NO_3{}^{79}Br$ $[M + H]^+$ 394.0266, found 394.0263. Aryl Bromide **12b** (80:20 mixture of rotamers): IR 2982, 1742, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.37–2.49 (m, 2H), 3.65–3.73 (m, 1H), 3.94–4.14 (m, 1H), 4.22–4.36 (m, 3H), 4.71–4.74 (m, 1H), 7.13–7.18 (m, 1H), 7.21–7.23 (m, 1H), 7.31–7.35 (m, 1H), 7.58–7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 34.3, 42.1, 51.8, 60.0, 61.9, 116.1 (q, *J* = 284.9 Hz), 124.9, 126.6, 128.1, 129.1, 133.6, 137.9, 155.9 (q, *J* = 37.6 Hz), 170.1; HRMS (ESI) calcd for $C_{15}H_{16}F_3NO_3{}^{79}Br$ $[M + H]^+$ 394.0266, found 394.0262.

Aryl Iodides 13a and 13b (Table 1, Entry 7). To a solution of trifluoroacetamide **11** (100 mg, 0.317 mmol) in CH_2Cl_2 (1.6 mL) were added $PhI(OCOCF_3)_2$ (409 mg, 0.952 mmol) and I_2 (201 mg, 0.793

mmol) at room temperature. The mixture was stirred at room temperature for 14 h. Column chromatography (hexane/EtOAc = 9:1, 7:3) gave a mixture of aryl iodides **13a** and **13b** (112 mg, 80%, **13a**:**13b** = 87:13). Aryl Iodide **13a** (80:20 mixture of rotamers): IR 2981, 1740, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 2.29–2.56 (m, 2H), 3.57–3.67 (m, 2H), 4.18–4.32 (m, 3H), 4.72–4.75 (m, 1H), 6.96–7.00 (m, 2H), 7.66–7.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 35.1, 42.4, 52.9, 60.3, 61.9, 92.9, 116.1 (q, J = 284.9 Hz), 128.9, 138.1, 138.6, 155.8 (q, J = 37.8 Hz), 170.2; HRMS (ESI) calcd for $C_{15}H_{16}F_3NO_3I$ $[M + H]^+$ 442.0127, found 442.0120. Aryl Iodide **13b** (80:20 mixture of rotamers): IR 2981, 1741, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 2.31–2.49 (m, 2H), 3.62–3.70 (m, 1H), 3.95–4.03 (m, 1H), 4.21–4.34 (m, 3H), 4.71–4.74 (m, 1H), 6.96–7.01 (m, 1H), 7.17–7.19 (m, 1H), 7.34–7.38 (m, 1H), 7.86–7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 34.7, 47.1, 52.0, 60.0, 61.9, 101.3, 125.9, 129.0, 129.4, 140.3, 141.2, 170.1; HRMS (ESI) calcd for $C_{15}H_{16}F_3NO_3I$ $[M + H]^+$ 442.0127, found 442.0122.

Alkene 15. To a solution of aryl iodide **13a** (101 mg, 0.230 mmol) in dioxane (4.2 mL) and H_2O (1.4 mL) were added *trans*-1-octen-1-ylboronic acid (**14**, 54.0 mg, 0.340 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (9.3 mg, 11.0 μmol), and Na_2CO_3 (72.3 mg, 0.690 mmol) at room temperature. The mixture was stirred at 90 °C for 1 h and the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 9:1, 4:1) gave alkene **15** (50.0 mg, 51%, 80:20 mixture of rotamers): IR 2925, 1743, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 3H), 1.24–1.36 (m, 9H), 1.37–1.49 (m, 2H), 2.17–2.34 (m, 2H), 2.34–2.41 (m, 2H), 3.60–3.69 (m, 2H), 4.18–4.32 (m, 3H), 4.72–4.75 (m, 1H), 6.22 (dt, J = 15.6, 6.7 Hz, 1H), 6.35 (d, J = 15.6 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 28.9, 29.3, 31.7, 33.1, 35.3, 39.4, 42.6, 53.2, 60.4, 61.8, 126.4, 127.1, 128.9, 131.9, 136.8, 137.5, 170.4; HRMS (ESI) calcd for $C_{23}H_{31}F_3NO_3$ $[M + H]^+$ 426.2256, found 426.2250.

Octylbenzene 16. A mixture of alkene **15** (35.0 mg, 82.0 μmol) and Pd/C (7.0 mg) in MeOH (1.0 mL) was stirred at room temperature under H_2 atmosphere for 2 h. Celite filtration and concentration gave octylbenzene **16** (32.0 mg, 91%, 80:20 mixture of rotamers): IR 2925, 2855, 1744, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.26–1.32 (m, 15H), 2.33–2.42 (m, 2H), 2.58 (t, J = 7.7 Hz, 2H), 3.60–3.69 (m, 2H), 4.18–4.31 (m, 3H), 4.72–4.75 (m, 1H), 7.11–7.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 29.2, 29.5, 31.5, 31.9, 35.4, 35.5, 38.8, 39.3, 42.5, 53.3, 60.4, 61.8, 116.1 (q, J = 285.7 Hz), 126.8, 129.0, 135.6, 142.5, 155.9 (q, J = 37.5 Hz), 170.4; HRMS (ESI) calcd for $C_{23}H_{33}F_3NO_3$ $[M + H]^+$ 428.2413, found 428.2407.

***trans*-4-(4-Octylphenyl)prolinol (1).** To a solution of ethyl ester **16** (20.0 mg, 47.0 μmol) in EtOH (1.0 mL) was added $LiBH_4$ (4.1 mg, 0.190 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h and the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with

EtOAc and dried over Na_2SO_4. Concentration and HPLC (XBridge C18 column) purification (10 mM aqueous $(NH_4)_2CO_3$/MeCN = 3:7, MeCN) gave *trans*-4-(4-octylphenyl)prolinol (**1**, 13.0 mg, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.22–1.34 (m, 10H), 1.54–1.63 (m, 2H), 1.94–2.01 (m, 2H), 2.57 (t, J = 8.2 Hz, 2H), 2.93–3.00 (m, 1H), 3.26–3.35 (m, 2H), 3.40–3.44 (m, 1H), 3.54–3.61 (m, 2H), 7.10–7.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 29.3, 29.4, 29.5, 31.5, 31.9, 35.5, 35.8, 44.4, 54.6, 59.1, 65.2, 127.0, 128.5, 140.6, 141.0; HRMS (ESI) calcd for $C_{19}H_{32}NO$ $[M + H]^+$ 290.2484, found 290.2478.

ACKNOWLEDGEMENTS

We thank Dr. Masayuki Watanabe, Mr. Kazunari Shimooka, and Ms. Kaoru Marukawa for valuable discussions. We also thank Ms. Kaori Murakoshi for technical support of LC-MS/MS analysis, Ms. Saori Tahara for technical support of IR analysis, and Mr. Iwao Takamuro for helpful advice. This research was supported by Mitsubishi Tanabe Pharma Corporation.

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