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

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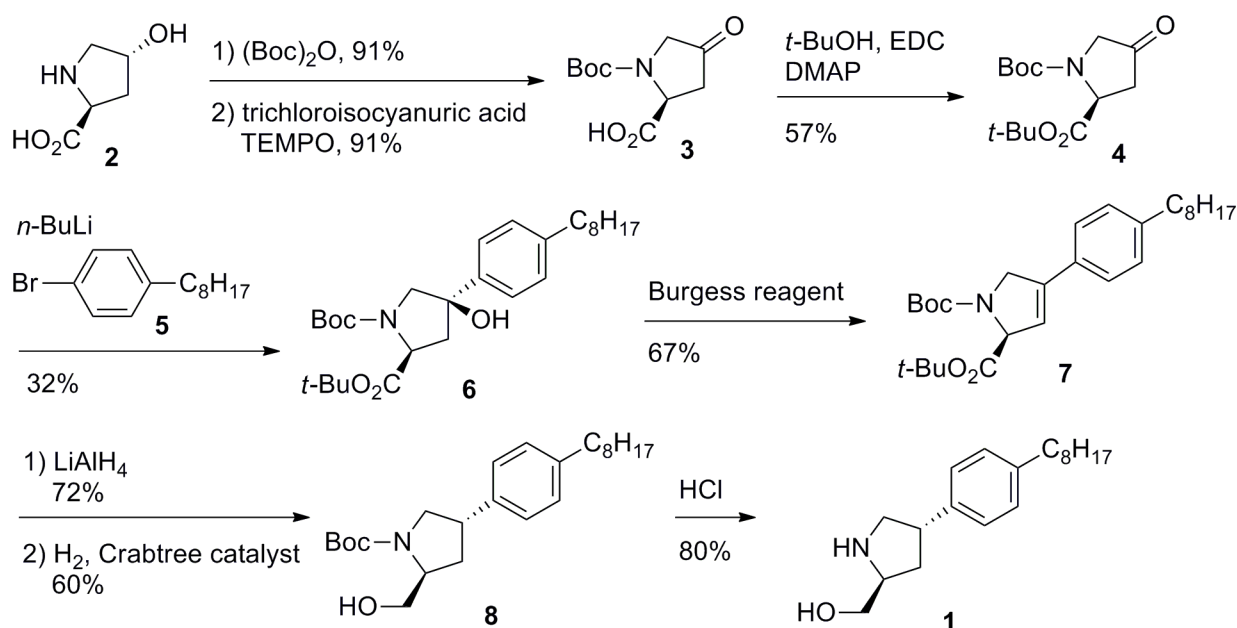
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Abstract – Concise synthesis of anticancer active *trans*-4-(4-octylphenyl)prolinol has been achieved. Regioselective iodination of aromatic compound and subsequent Suzuki–Miyaura cross-coupling with *trans*-1-octen-1-ylboronic acid produced the desired 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 products¹ 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 antiviral 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 (IC₅₀ = 9.8 μM) and DU145 (IC₅₀ = 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

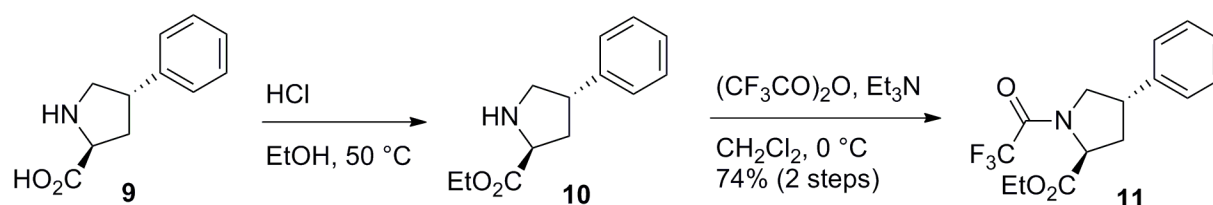
desired adduct **6** in 32% yield. The alcohol **6** was subjected to Burgess dehydration conditions to give alkene **7**, which was converted to alcohol **8** by reduction of the ester moiety with LiAlH_4 and hydroxy-directed hydrogenation with Crabtree catalyst. Finally, deprotection of the carbamate **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-coupling¹⁰ as key transformations.



Scheme 1. Synthesis of anticancer compound **1** by Hanessian's research group^{3b,7}

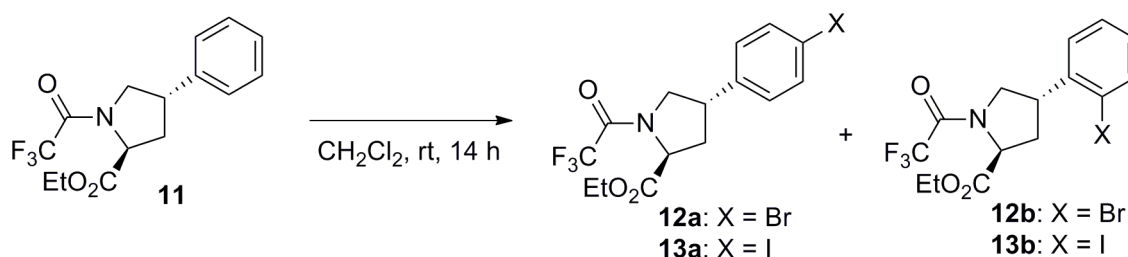
Our synthesis of **1** commenced from commercially available *trans*-4-phenyl-L-proline (**9**) as shown in Scheme 2. Ethyl esterification of **9** with HCl in EtOH afforded ester **10**, which was treated with $(\text{CF}_3\text{CO})_2\text{O}/\text{Et}_3\text{N}$ to provide trifluoroacetamide **11** 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 peroxide¹¹ 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 NBS¹³ 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 I₂/AgNO₃ combination¹⁴ 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 I₂ (1.2 equiv)/PhI(OCOCF₃)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 I₂ and 3.0 equiv of Ph(OCOCF₃)₂ (entry 7).



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

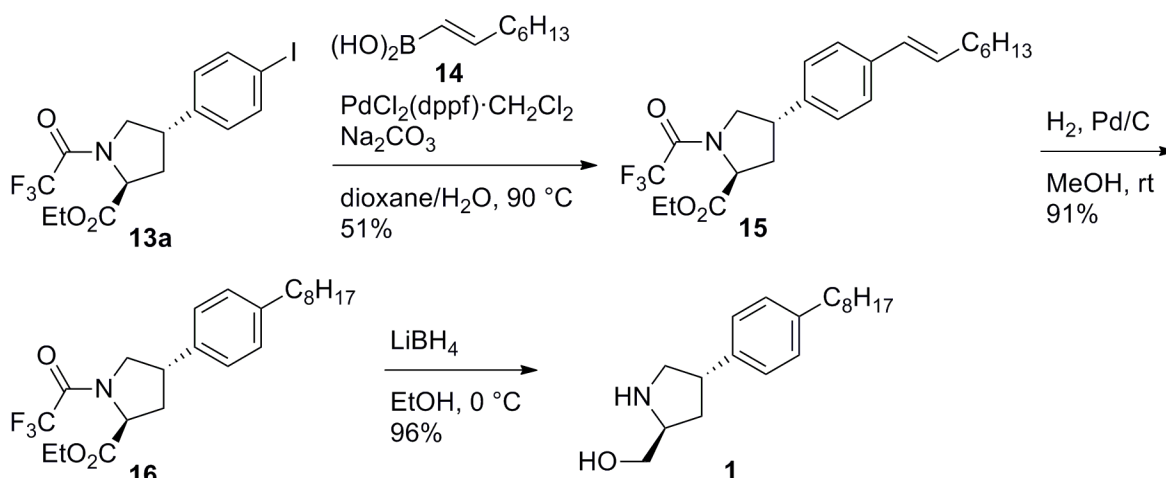
Table 1. Halogenation of aromatic compound **11**



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

^aIsolated combined yield. ^bDetermined by ¹H NMR spectra of the mixture of *p*- and *o*-halogenated products. ^cNot determined. No reaction was observed. ^dNot 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 PdCl₂(dppf)·CH₂Cl₂/Na₂CO₃ to produce the Suzuki–Miyaura cross-coupling¹⁰ 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 LiBH₄ 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 I₂ (2.5 equiv)/PhI(OCOCF₃)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. ^1H 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 (^1H 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 $(\text{CF}_3\text{CO})_2\text{O}$ (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} ; ^1H 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 $\text{C}_{15}\text{H}_{17}\text{F}_3\text{NO}_3$ [$\text{M} + \text{H}$] $^+$ 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} ; ^1H 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 $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_3^{79}\text{Br}$ [$\text{M} + \text{H}$] $^+$ 394.0266, found 394.0263. Aryl Bromide **12b** (80:20 mixture of rotamers): IR 2982, 1742, 1691 cm^{-1} ; ^1H 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 $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_3^{79}\text{Br}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{PhI}(\text{OCOCF}_3)_2$ (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 $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_3\text{I}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_3\text{I}$ [$\text{M} + \text{H}$] $^+$ 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), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (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 $^\circ\text{C}$ 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 $\text{C}_{23}\text{H}_{31}\text{F}_3\text{NO}_3$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{23}\text{H}_{33}\text{F}_3\text{NO}_3$ [$\text{M} + \text{H}$] $^+$ 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 $^\circ\text{C}$. 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 Na₂SO₄. Concentration and HPLC (XBridge C18 column) purification (10 mM aqueous (NH₄)₂CO₃/MeCN = 3:7, MeCN) gave *trans*-4-(4-octylphenyl)prolinol (**1**, 13.0 mg, 96%): ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₃₂NO [M + H]⁺ 290.2484, found 290.2478.

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REFERENCES AND NOTES

- (a) A. M. P. Koskinen and J. M. Paul, *Tetrahedron Lett.*, 1992, **33**, 6853; (b) S. Hanessian and S. Ninkovic, *J. Org. Chem.*, 1996, **61**, 5418.
- (a) N. B. Westwood and R. T. Walker, *Tetrahedron*, 1998, **54**, 13391; (b) J. Cossy, O. Mirguet, D. G. Pardo, and J.-R. Desmurs, *Eur. J. Org. Chem.*, 2002, 3543.
- (a) R. Fransson, A. N. McCracken, B. Chen, R. J. McMonigle, A. L. Edinger, and S. Hanessian, *ACS Med. Chem. Lett.*, 2013, **4**, 969; (b) B. Chen, S. G. Roy, R. J. McMonigle, A. Keebaugh, A. N. McCracken, E. Selwan, R. Fransson, D. Fallegger, A. Huwiler, M. T. Kleinman, A. L. Edinger, and S. Hanessian, *ACS Chem. Biol.*, 2016, **11**, 409.
- M. Sunagawa, M. Itoh, K. Kubota, A. Sasaki, Y. Ueda, P. Angehrn, A. Bourson, E. Goetschi, P. Hebeisen, and R. L. Then, *J. Antibiot.*, 2002, **55**, 722.
- D. J. Kertesz and M. G. Roepel, WO2002050064 A1, 20020627.
- S. Hanessian, G. Charron, A. Billich, and D. Guerini, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 491.
- They describe hydrochloride salt of **1** as the structure in reference 3b.
- For selected examples of the synthesis of 4-substituted proline and prolinol derivatives by other groups, see: (a) J. Krapcho, C. Turk, D. W. Cushman, J. R. Powell, J. M. DeForrest, E. R. Spitzmiller, D. S. Karanewsky, M. Duggan, G. Rovnvak, J. Schwartz, S. Natarajan, J. D. Godfrey, D. E. Ryono, R. Neubeck, K. S. Atwal, and E. W. Petrillo, Jr., *J. Med. Chem.*, 1988, **31**, 1148; (b) J. R. Del Valle and M. Goodman, *J. Org. Chem.*, 2003, **68**, 3923; (c) T. Kondo, I. Sugimoto, T. Nekado, K. Ochi, T. Ohtani, Y. Tajima, S. Yamamoto, K. Kawabata, H. Nakai, and M. Toda, *Bioorg. Med.*

- [Chem.](#), 2007, **15**, 2715; (d) D. Antonow, M. Kaliszczak, G.-D. Kang, M. Coffils, A. C. Tiberghien, N. Cooper, T. Barata, S. Heidelberger, C. H. James, M. Zloh, T. C. Jenkins, A. P. Reszka, S. Neidle, S. M. Guichard, D. I. Jodrell, J. A. Hartley, P. W. Howard, and D. E. Thurston, [J. Med. Chem.](#), 2010, **53**, 2927; (e) C. Klöck, Z. Herrera, M. Albertelli, and C. Khosla, [J. Med. Chem.](#), 2014, **57**, 9042; (f) H. L. Perez, C. Chaudhry, S. L. Emanuel, C. Fanslau, J. Fargnoli, J. Gan, K. S. Kim, M. Lei, J. G. Naglich, S. C. Traeger, R. Vuppungalla, D. D. Wei, G. D. Vite, R. L. Talbott, and R. M. Borzilleri, [J. Med. Chem.](#), 2015, **58**, 1556.
9. For our report of the synthesis of 4-substituted prolinol derivatives, see: J. Ando, A. Tazawa, K. Ishizawa, M. Tanaka, and H. Takamura, *Heterocycles*, **99**, 188.
 10. For reviews, see: (a) N. Miyaura and A. Suzuki, [Chem. Rev.](#), 1995, **95**, 2457; (b) S. R. Chemler, D. Trauner, and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2001, **40**, 4544; (c) A. Suzuki, [Angew. Chem. Int. Ed.](#), 2011, **50**, 6722.
 11. V. Brancato, A. Peduto, S. Wharton, S. Martin, V. More, A. Di Mola, A. Massa, B. Perfetto, G. Donnarumma, C. Schiraldi, M. A. Tufano, M. de Rosa, R. Filosa, and A. Hay, [Antiviral Res.](#), 2013, **99**, 125.
 12. Z.-K. Chen, W. Huang, L.-H. Wang, E. T. Kang, B. J. Chen, C. S. Lee, and S. T. Lee, [Macromolecules](#), 2000, **33**, 9015.
 13. K. Tanemura, T. Suzuki, Y. Nishida, K. Satsumabayashi, and T. Horiguchi, [Chem. Lett.](#), 2003, **32**, 932.
 14. (a) B. A. Hathaway, B. E. Taylor, and J. S. Wittenborn, *Synth. Commun.*, 1998, **28**, 4629; (b) M. S. Yusubov, E. N. Tveryakova, E. A. Krasnokutskaya, I. A. Perederyna, and V. V. Zhdankin, [Synth. Commun.](#), 2007, **37**, 1259.
 15. (a) J. R. Tagat, R. W. Steensma, S. W. McCombie, D. V. Nazareno, S.-I. Lin, B. R. Neustadt, K. Cox, S. Xu, L. Wojcik, M. G. Murray, N. Vantuno, B. M. Baroudy, and J. M. Strizki, [J. Med. Chem.](#), 2001, **44**, 3343; (b) K. Knott, Y. Kharel, M. R. Raje, K. R. Lynch, and W. L. Santos, [Bioorg. Med. Chem. Lett.](#), 2012, **22**, 6817.
 16. After the detailed investigation of separation of the structural isomers **12a,b** and **13a,b**, it was turned out that **12a,b** and **13a,b** were partially separable by chiral HPLC (CHIRALPAK IE-3 column, hexane/EtOH = 17:3), respectively. The aryl iodides **13a** and **13b** were separated by chiral HPLC prior to Suzuki–Miyaura cross-coupling with **14**.
 17. (a) A. N. Thadani and R. A. Batey, [Tetrahedron Lett.](#), 2003, **44**, 8051; (b) M. Musiejuk, J. Doroszuk, and D. Witt, *RSC Adv.*, 2018, **8**, 9718.