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A UNIQUE AND SIMPLE PREPARATIVE METHOD FOR α -ARYL-PIPECOLINIC ACID ESTERS VIA BASE-INDUCED SOMMELET–HAUSER REARRANGEMENT

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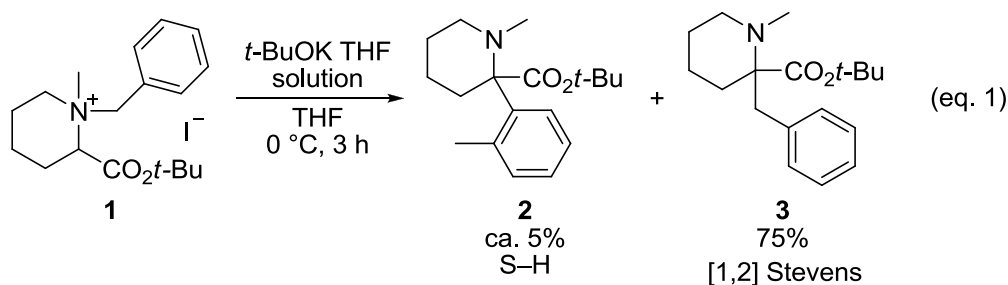
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Abstract – A unique and simple preparative method for *N*-cyano- α -aryl-pipecolinic acid esters via base-induced Sommelet–Hauser rearrangement, the von Braun reaction, and intramolecular α -alkylation is reported. The removal of the *N*-cyano substituent was achieved by hydrogenation and hydride reduction.

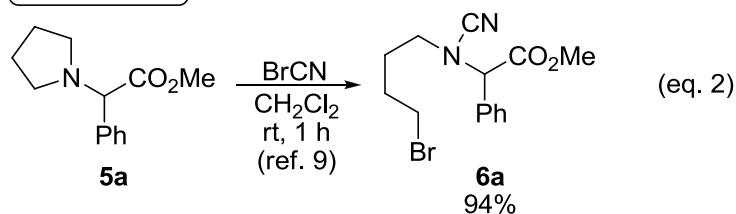
Six-membered cyclic α -amino acid derivatives, such as pipecolinic acid, occur in numerous biologically important natural products and are pharmacologically interesting as building blocks for synthetic drugs.¹ Various synthetic methods, including asymmetric synthesis, have been reported; however, preparative methods for α -substituted (quaternary) pipecolinic acids are limited,² especially for α -aryl derivatives^{3,4} because of the difficulty of C–C bonds formation between aromatic (sp^2) and piperidinyll (sp^3) carbons. Previously, we reported the base-induced Sommelet–Hauser (S–H) rearrangement⁵ of *N*-benzylic amino acid-derived ammonium ylides, which enables the formation of C(sp^2)–C(sp^3) bonds under mild conditions and affords various types of α -aryl amino acids such as α -arylproline, α -arylglycine, and α -arylalanine derivatives.^{6,9} In the course of our study of the S–H rearrangement, we carried out a reaction involving *N*-benzylpipecolinic acid-derived tetraalkylammonium salt **1** to prepare α -(*o*-tolyl)pipecolinic acid ester **2** to expand the synthetic scope of the rearrangement. However, our attempt failed because the cooperative [1,2] Stevens rearrangement proceeded to afford exclusively α -benzylated **3** (eq. 1).⁷ Recently, we reported that the von Braun reaction⁸ of methyl 2-phenyl-2-pyrrolidinylacetate **5a** gave the corresponding ring-opening product **6a** in a 94% yield (eq. 2).⁹ Substrate **5a** appears to be a model S–H rearrangement product, and product **6a** may be a good synthetic intermediate for the synthesis of α -arylpipecolinic acid derivatives because only a simple

intramolecular α -alkylation (cyclization) would be required. In fact, the previous synthetic route to α -arylpipicolinic acids mainly involves intramolecular α -alkylation (cyclization) of *N*- or α -(4-halobutyl)- α -arylglycine derivatives.³ Thus, we started to investigate a new synthetic route for synthetically valuable α -arylpipicolinic acid esters **7** from easily accessible tetraalkylammonium salts **4** via S-H rearrangement, the von Braun reaction, and intramolecular α -alkylation (eq. 3).

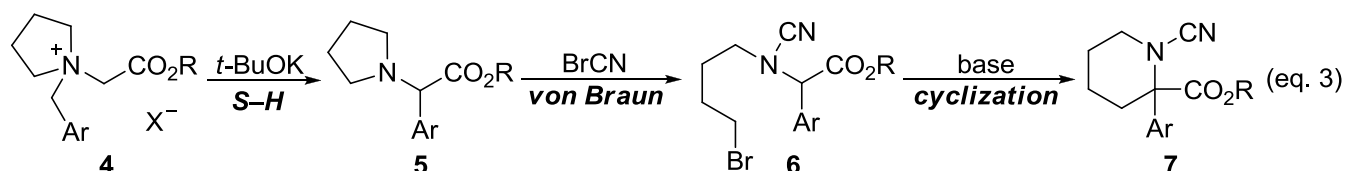
Unsuccessful result



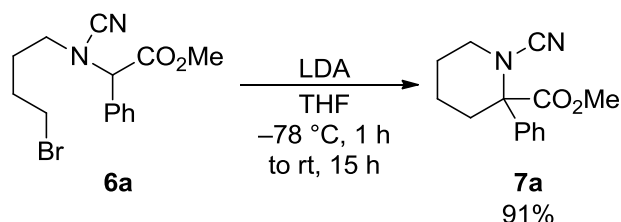
Recent result



This work



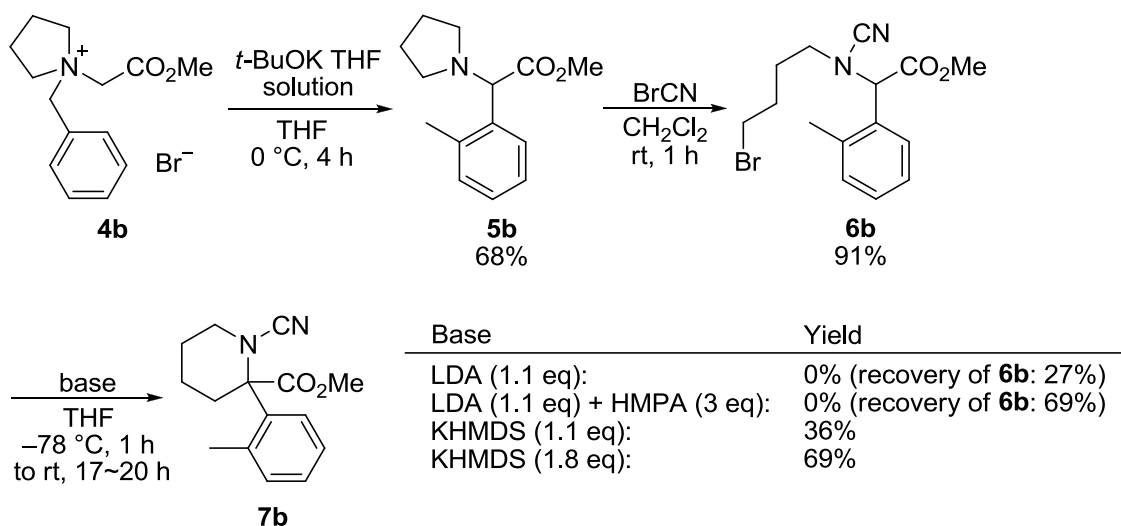
First, we examined the cyclization of **6a** by treatment with 1.1 equivalents of LDA (Scheme 1). The desired *N*-cyano- α -arylpipicolinic acid ester **7a** was obtained in a 91% yield.



Scheme 1

With this reaction in hand, we prepared *N*-benzylglycine-derived tetraalkylammonium salt **4b** and analyzed the reactions to investigate the possibility of obtaining α -arylpipicolinic acid derivatives **7** from **4** via S-H rearrangement (Scheme 2). The corresponding *o*-tolyl derivative **6b** was obtained via the

S–H rearrangement of **4b** (68%) and the von Braun reaction of **5b** (91%). However, **6b** did not cyclize to **7b** after treatment with LDA. The addition of HMPA did not result in any improvement. Thus, we used potassium bis(trimethylsilyl)amide (KHMDs) as a base to generate the reactive potassium enolate. The desired product **7b** was obtained in a 69% yield when 1.8 equivalents of KHMDs was used.

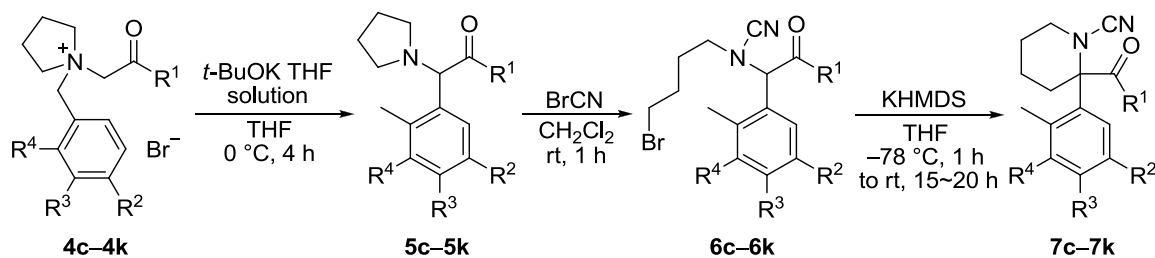


Scheme 2

To define the scope and limitations of the present method, we prepared *ortho*-, *meta*-, and *para*-methyl- or chloro-substituted *N*-benzylic salts **4c–4k** and used them to obtain various types of *N*-cyano- α -arylpipicolinic acid derivatives (Table 1). In most cases, the S–H rearrangement of **4** and following the von Braun reaction of **5** proceeded, giving reasonable yields (entries 1–9, 1st and 2nd step). One exception was the ring-opening reaction of 2,4-dimethylphenyl derivative **5g**, which resulted in a low yield of **6g** (20%) because of a competing α -bromo substitution reaction⁹ ($R^3 = \text{Me}$, entry 5, 2nd step). The cyclization of isopropyl or *tert*-butyl ester-derived substrates **6c–6j** proceeded smoothly to give **7c–7j** in the presence of 1.1 equivalents of KHMDs (entries 1–8, 3rd step). The amide derivative **6k** did not cyclize at all because of the poorer reactivity of the amide enolate (entry 9, 3rd step).

Next, we applied this method to the preparation of an α -benzylpipicolinic acid ester, **7d'**, and a seven-membered cyclic α -amino acid ester, **7l**, via a base-induced [1,2] Stevens rearrangement⁵ (Scheme 3). When the reaction of **4d** and **4l** was carried out in dichloromethane using sodium *tert*-butoxide as a base, the [1,2] Stevens rearrangement proceeded preferably to afford α -benzylated **5d'** and **5l**.¹⁰ Procedures similar to those described in Table 1 gave the desired products **7d'** and **7l**, respectively.

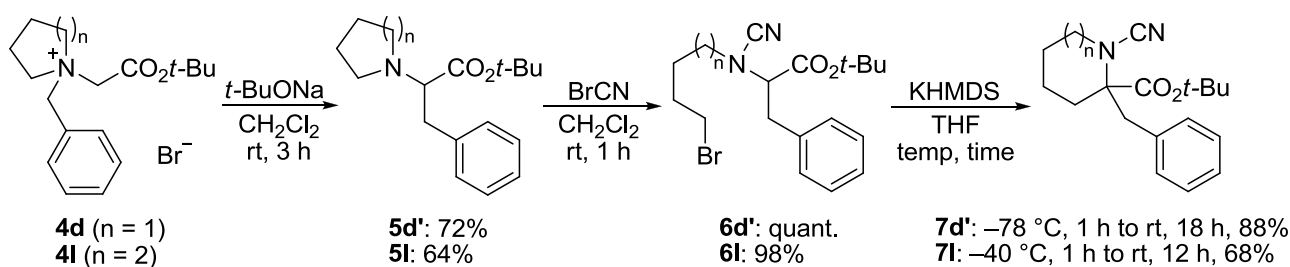
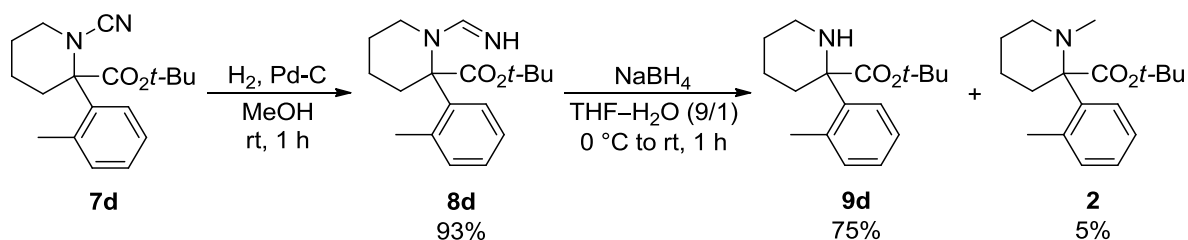
Finally, we attempted to remove the *N*-cyano substituent, as in **7d**, to obtain *N*-free α -substituted pipicolinic acid ester **9d** (Scheme 4). The hydrogenation of **7d** under a hydrogen atmosphere afforded the corresponding amidine **8d** in a 93% yield. Treatment of **8d** with sodium borohydride gave the desired secondary amine **9d** in a 75% yield with a side product of *N*-methyl derivative **2**.

Table 1. Preparation of various types of α -arylpipercolinic acid derivatives **7** from **4**

Entry	R ¹	R ²	R ³	R ⁴		1st Step: 5 (%) ^a	2nd Step: 6 (%) ^a	3rd Step: 7 (%) ^{a,b}
1	<i>Oi</i> -Pr	H	H	H	c	75	89	94
2	<i>Ot</i> -Bu	H	H	H	d	82	89	87
3	<i>Ot</i> -Bu	Me	H	H	e	63	75	89
4	<i>Ot</i> -Bu	Cl	H	H	f	81	96	84
5	<i>Ot</i> -Bu	H	Me	H	g	62	20 ^c	84
6	<i>Ot</i> -Bu	H	Cl	H	h	56	73	57
7	<i>Ot</i> -Bu	H	H	Me	i	74	74	67
8	<i>Ot</i> -Bu	H	H	Cl	j	94	87	75
9	NEt ₂	H	H	H	k	79	56	0

^a Isolated yields. ^b Reactions were carried out in the presence of 1.1 equivalents of KHMDS.

^c *tert*-Butyl 2-bromo-2-(2,4-dimethylphenyl)acetate prepared by α -bromo-substitution was obtained as a main product.

**Scheme 3****Scheme 4**

In conclusion, we have developed a new synthetic method for the preparation of *N*-cyano- α -aryl-pipecolinic acid esters **7** from tetraalkylammonium salts **4** via rearrangement (Sommelet–Hauser or [1,2] Stevens), the von Braun reaction, and intramolecular α -alkylation. The *N*-cyano substituent, as in **7**, can be removed via hydrogenation and hydride reduction. The method presented herein is a unique and simple preparative method for α -arylpipecolinic acid esters.¹¹

EXPERIMENTAL

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. ¹H and ¹³C NMR spectra were measured on a Varian 400 MHz spectrometer (¹H: 400 MHz, ¹³C: 100 MHz) and a 700 MHz spectrometer (¹H: 700 MHz, ¹³C: 175 MHz). The splitting patterns are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak. High-resolution mass spectra were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with a magnetic stirring bars under an argon atmosphere. Tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc., Japan as an anhydrous solvent. Cyanogen bromide was purchased from KANTO Chemical Co., Inc., Japan. A 0.5 M potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene and a 1.0 M potassium *tert*-butoxide solution in THF were purchased from Tokyo Chemical Industry Co., Ltd (TCI). For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F₂₅₄), or Fuji Silysia Chemical TLC plates (NH, Fuji Silysia Chemical Ltd., Japan) for amidine **8d** were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan) or pH-controlled silica gel (Chromatorex NH–DM1020, Fuji Silysia Chemical Ltd., Japan) for amidine **8d**.

Representative procedure for the preparation of *tert*-butyl 2-(pyrrolidin-1-yl)-2-(*o*-tolyl)acetate (**5d**).

A 1.0 M THF solution of potassium *tert*-butoxide (4.9 mL, 4.9 mmol) was added to a solution of **4d** (1.58 g, 4.43 mmol) in THF (44 mL) at 0 °C. The mixture was stirred for 4 h at the same temperature under an argon atmosphere. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/EtOAc = 5/1 to 2/1 as the eluent) gave **5d** (1.00 g, 82% yield) as a colorless oil; IR (film) 3051, 2972, 2874, 2785, 2722, 1741, 1603, 1483, 1459, 1391, 1367, 1334, 1253, 1214, 1146, 1038, 977, 940, 906, 845, 815, 751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (1H, dd, *J* = 7.4, 1.2 Hz, ArH), 7.20–7.09 (3H, m, ArH), 4.12 (1H, s, CHCO), 2.63–2.53 (2H, m, NCH₂), 2.53–2.44 (2H, m, NCH₂), 2.43 (3H, s, ArCH₃), 1.83–1.71 (4H, m, CH₂), 1.36 (9H, s, *t*-Bu); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 136.3, 135.9, 130.0, 128.0, 127.1, 125.9, 80.5, 69.5, 52.0,

27.7, 23.3, 19.6; HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958. Found: 276.1955.

Representative procedure for the preparation of *tert*-butyl 2-(*N*-(4-bromobutyl)cyanamido)-2-(*o*-tolyl)acetate (6d**).** A solution of cyanogen bromide (95%, 1.22 g, 11 mmol) in CH_2Cl_2 (2 mL) was added to a solution of **5d** (1.00 g, 3.63 mmol) in CH_2Cl_2 (18 mL) at room temperature under an argon atmosphere and the solution was stirred for 1 h. The resulting solution was treated with saturated aqueous sodium hydrogen carbonate and extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium bromide, dried over sodium sulfate, and concentrated by evaporation. Purification of the residue by chromatography on silica gel (hexane/EtOAc = 5/1 to 1/1 as the eluent) afforded **6d** (1.23 g, 89% yield) as a white solid; IR (film) 3067, 2977, 2935, 2880, 2212, 1738, 1605, 1491, 1460, 1393, 1369, 1342, 1255, 1221, 1155, 1074, 1041, 955, 881, 861, 826, 754 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.20 (4H, m, ArH), 4.84 (1H, s, CHCO), 3.37 (1H, dt, $J = 12.6, 6.4$ Hz, CH_2), 3.35 (1H, dt, $J = 12.6, 6.4$ Hz, CH_2), 3.10 (2H, t, $J = 6.8$ Hz, CH_2), 2.42 (3H, s, Ar CH_3), 1.94–1.77 (4H, m, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 137.5, 131.3, 131.1, 129.6, 128.0, 126.4, 115.6, 83.4, 64.1, 49.6, 32.6, 29.4, 27.9, 26.3, 19.3; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{25}N_2O_2BrNa$: 403.0992. Found: 403.0990.

Representative procedure for the preparation of *tert*-butyl 1-cyano-2-(*o*-tolyl)piperidine-2-carboxylate (7d**).** A solution of **6d** (0.61 g, 1.6 mmol) in THF (8.1 mL) was cooled at -78 °C and treated with a 0.5 M KHMDS solution in toluene (3.6 mL, 1.8 mmol). The solution was stirred for 1 h at the same temperature and allowed to warm to room temperature. After stirring for 15 h for room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel to obtain **7d** (0.42 g, 87% yield) as a white solid; IR (film) 3061, 2964, 2928, 2862, 2210, 1730, 1454, 1392, 1367, 1332, 1286, 1250, 1143, 1112, 1085, 1060, 1006, 971, 944, 865, 837, 755, 746, 729 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.13 (4H, m, ArH), 3.55–3.39 (2H, m, N CH_2), 2.62 (3H, s, Ar CH_3), 2.40 (1H, ddd, $J = 13.6, 3.6, 3.6$ Hz, CH_2), 2.13 (1H, ddd, $J = 13.6, 13.6, 3.6$ Hz, CH_2), 1.92–1.83 (1H, m, CH_2), 1.82–1.69 (2H, m, CH_2), 1.62–1.42 (1H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 137.0, 136.0, 133.2, 128.7, 127.2, 126.0, 117.0, 83.4, 70.6, 49.4, 32.0, 27.9, 23.5, 21.2, 20.9; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_2Na$: 323.1730. Found: 323.1727.

Preparation of *tert*-butyl 1-(iminomethyl)-2-(*o*-tolyl)piperidine-2-carboxylate (8d**).** A mixture of **7d** (153 mg, 0.509 mmol) and palladium on activated carbon (loading: 10 wt.%, 29 mg) in MeOH (5 mL) was stirred for 1 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by

chromatography on pH-controlled silica gel (Chromatorex NH-DM1020)(hexane/EtOAc = 3/1 to 2/1 as the eluent) to obtain **8d** (143 mg, 93% yield) as a white solid; IR (KBr) 3427, 3287, 3057, 2978, 2947, 2869, 2822, 1725, 1620, 1454, 1392, 1356, 1285, 1244, 1150, 1125, 1005, 973, 956, 897, 845, 820, 778, 756, 723 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.57 (1H, s, CH=N), 7.24-7.11 (3H, m, ArH), 7.08 (1H, dd, $J = 8.2, 1.2$ Hz, ArH), 4.45-4.35 (1H, m, NH), 2.58-2.45 (1H, m, NCH_2), 2.50 (3H, s, ArCH_3), 2.37-2.29 (1H, m, NCH_2), 2.00 (1H, ddd, $J = 13.3, 13.3, 3.8$ Hz, CH_2), 1.86-1.76 (2H, m, CH_2), 1.73-1.46 (2H, m, CH_2), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 161.3, 138.5, 136.0, 133.3, 127.7, 127.3, 126.1, 82.7, 71.9, 40.3, 33.3, 27.9, 23.3, 22.0, 21.7; HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_2$: 303.2067. Found: 303.2063.

Preparation of *tert*-butyl 2-(*o*-tolyl)piperidine-2-carboxylate (9d) and *tert*-butyl 1-methyl-2-(*o*-tolyl)piperidine-2-carboxylate (2). Sodium borohydride (32 mg, 0.85 mmol) was added to a solution of **8d** (45.8 mg, 0.151 mmol) in THF (1.35 mL) and water (0.15 mL) at 0 °C. After stirring for 1 h at room temperature, the resulting mixture was diluted with water and extracted with EtOAc. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 15/1 to 10/1 as the eluent) to obtain **9d** (31.3 mg, 75%) as a colorless oil and **2** (2.4 mg, 5% yield) as a colorless oil. **9d**: colorless oil; IR (film) 3427, 3333, 3059, 2932, 2867, 2827, 2783, 2690, 1724, 1601, 1479, 1453, 1391, 1366, 1239, 1161, 1121, 1059, 1030, 969, 930, 898, 838, 755 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.57 (1H, m, ArH), 7.18-7.06 (3H, m, ArH), 2.89 (1H, dddd, $J = 12.2, 4.5, 4.5, 0.8$ Hz, NCH_2), 2.82 (1H, ddd, $J = 12.2, 9.5, 3.6$ Hz, NCH_2), 2.47 (3H, s, ArCH_3), 2.32-2.21 (1H, m, CH_2), 2.18 (1H, br, NH), 1.90-1.67 (3H, m, CH_2), 1.63-1.47 (2H, m, CH_2), 1.44 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 142.0, 136.0, 132.2, 126.8, 126.2, 125.6, 80.9, 65.7, 42.7, 32.9, 27.9, 25.4, 21.7, 21.0; HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_2$: 276.1958. Found: 276.1958. **2**: colorless oil; IR (film) 3059, 2974, 2928, 2804, 2719, 1716, 1477, 1453, 1391, 1366, 1291, 1238, 1212, 1158, 1135, 1099, 1056, 1033, 1004, 956, 894, 847, 773, 754, 722 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.30 (1H, br, ArH), 7.15-7.06 (3H, m, ArH), 2.79 (1H, d, $J = 11.2$ Hz, NCH_2), 2.66 (1H, dd, $J = 11.2, 11.2$ Hz, NCH_2), 2.55 (3H, br, ArCH_3), 2.30 (3H, s, NCH_3), 2.16 (1H, d, $J = 11.2$ Hz, CH_2), 1.85-1.50 (5H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 141.7, 136.6, 132.4, 127.1, 126.5, 125.4, 81.2, 72.3, 50.8, 40.9, 34.5, 28.4, 25.4, 22.1, 21.0; HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2$: 290.2115. Found: 290.2113.

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7. Even if the reaction was carried out at $-40\text{ }^{\circ}\text{C}$ for 15 h, the almost same results were obtained.
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9. E. Tayama, R. Sato, K. Takedachi, H. Iwamoto, and E. Hasegawa, *Tetrahedron*, 2012, **68**, 4710.
10. The Sommelet–Hauser and [1,2] Stevens rearrangement are competitive. The selectivity of these rearrangements is determined by the base, solvent, temperature, and the structure of the substrate. For an example, the use of a sodium base (sodium *tert*-butoxide) and a nonpolar solvent (dichloromethane) preferred to give the [1,2] Stevens rearrangement product. Other examples: see, ref. 6.
11. We attempted the reactions of 2-methyl- and 3-methoxy-pyrrolidinyl derivatives to obtain the corresponding substituted pipercolinic acid esters. However, the reactions were unsuccessful because of the formation of a mixture of four isomers after von Braun reaction.