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DEVELOPMENT OF A PRACTICAL SYNTHESIS OF 7-BROMO-8-METHOXYCARBONYL-3,3-DIMETHYL-3,4-DIHYDRO-1*H*-QUINOXALIN-2-ONE

Kazuhiro Kudo,[a, b, c]* Takahiro Honda,[a, b] and Noriyoshi Yamamoto[b]

[a]Graduate School of Materials Sciences, Nara Institute of Science and Technology, Ikoma, Nara, Japan

[b]Nara Research & Development Center, Santen Pharmaceutical Co., Ltd, 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101, Japan

[c]Product Supply Division, Santen Pharmaceutical Co., Ltd, 348-3, Aza Suwa Oaza Shide Taga-cho Inukami-gun, Shiga 522-0314. Tel: +81-749-48-2924; E-mail: kazuhiro.kudou@santen.co.jp

Abstract – Synthesis of 7-bromo-8-methoxycarbonyl-3,3-dimethyl-3,4-dihydro-1*H*-quinoxalin-2-one from 5-amino-2-bromobenzoic acid was achieved in an overall yield of 27% over four steps. This is a significant improvement from the previous six-step process, which afforded only a 12% yield. The previous process was optimized by adding a high-yielding alkylation step under mild conditions as well as by reducing the number of isolation steps and eliminating purification by column chromatography.

INTRODUCTION

Glucocorticoids are commonly used to treat inflammatory diseases. Apart from their potent anti-inflammatory activities, long-term and high dose treatment may lead to serious adverse effects.[1] Selective glucocorticoid receptor agonists (SEGRA) that can separate an anti-inflammatory activity, and their adverse effects are reported in recent years.[1,2] SEGRA compounds with 3,3-dimethyl-3,4-dihydro-1*H*-quinoxalin-2-one framework (Figure 1) have been developed as candidates for SEGRA and show a remarkable anti-inflammatory effect after topical dosing to the eye and side-effect dissociation by in vivo assay.[2b-e] The structure of SEGRA compounds was not a steroid framework and was reportedly the most desirable example of drug efficacy to have dimethyl functions in 3, 3-position and carbonyl function at 2-position. To evaluate their activities in preclinical and clinical studies, an efficient, reliable, and cost-effective synthetic method is required. Thus, a practical synthesis of a 3,3-dimethyl-3,4-dihydro-

1*H*-quinoxalin-2-one framework must be developed for the construction of SEGRA compounds.

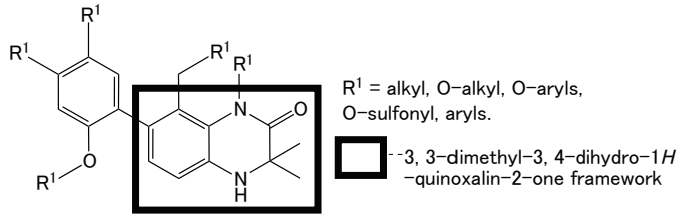
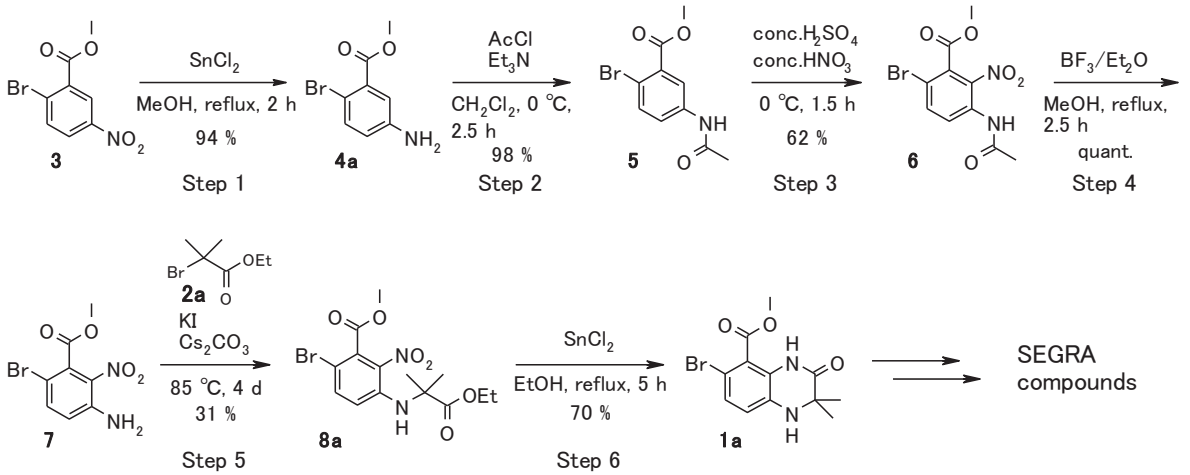


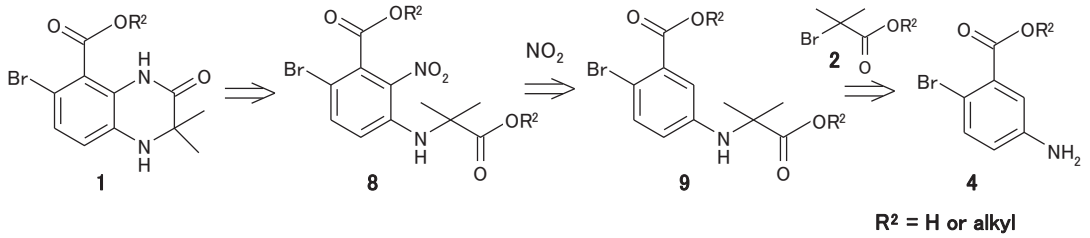
Figure 1. SEGRA compounds with 3,3-dimethyl-3,4-dihydro-1*H*-quinoxalin-2-one framework

In the conventional synthetic route, a number of SEGRA compounds were synthesized from key intermediate **1a** (Scheme 1).[2b-e] A six-step procedure was used to synthesize **1a**, the first step was the reduction of the nitro group on **3** by $SnCl_2$ (94% yield). This was followed by the protection of the amino group on **4a** (98% yield), nitration of **5**, and purification by silica gel column chromatography to afford **6** in 62% yield. Deacetylation afforded **7** in quantitative yield, and alkylation with ethyl 2-bromoisobutyrate (**2a**) and isolation by silica gel column chromatography afforded **8a** in 31% yield. Finally, reduction of the nitro group and successive intramolecular cyclization and column chromatography provided **1a** in 70% yield. Although **1a** was successfully synthesized in an overall 12% yield over six steps, this method has many disadvantages, such as low yield, use of a halogenated solvent, and several purification steps using silica gel column chromatography. Step 5 was particularly problematic as it resulted in a low yield (31%), excess use of **2a** as a solvent, use of expensive Cs_2CO_3, high temperature, and long reaction time (85 °C, 4 d). Purification after this step was also difficult and required two consecutive purifications by silica gel column chromatography. Since this synthetic method was found to be very difficult, an inexpensive, stable, and more efficient synthetic route for **1a** is desirable.



Scheme 1. Conventional synthetic route for key intermediate **1a**

The reason for the resultant low yield in step 5 was assumed to be that the tertiary bromide **2a** is a hindered electrophile and **7** shows low nucleophilicity due to the presence of a strong electron withdrawing group in the *o*-position. To improve the yield of alkylation, we selected **4** as a starting material, which does not have a strong electron withdrawing group and was easy to procure. Alkylation with **2** was investigated under mild conditions. We also explored the nitration of **8** to afford **1**, completing this new synthetic route (Scheme 2).

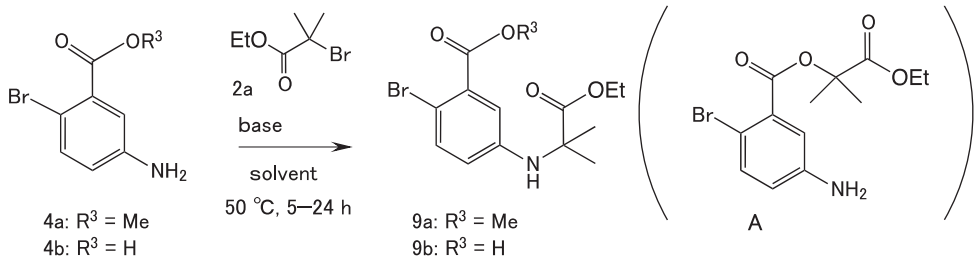


Scheme 2. Retrosynthesis of key intermediate **1**

RESULTS AND DISCUSSION

Alkylation of tertiary, hindered electrophile **2** with **4** was investigated.[3] In the case of **4a** and **2a**, base/solvent combinations of K_2CO_3/DMF, Et_3N/DMF, and Et_3N/2-PrOH at 50 °C did not proceed at all and only the starting material **4a** was recovered (Table 1, entries 1–3). When carboxylic acid **4b** was reacted in K_2CO_3/DMF, **4b** and O-alkylation product **A** were found in a ratio of 59:41, with no detection of target material **9b** (entry 4). In the case of Et_3N/DMF, the conversion was relatively high (76%) and the remaining **4b**, **9b**, and **A** were found in a ratio of 24:41:35 (entry 5).[4] In Et_3N/2-PrOH, the conversion was low and mainly recovered **4b**, a small amount of **9b**, and **A** (85:12:3, entry 6).

Table 1. Alkylation of **4a** and **4b** with **2a**[a]



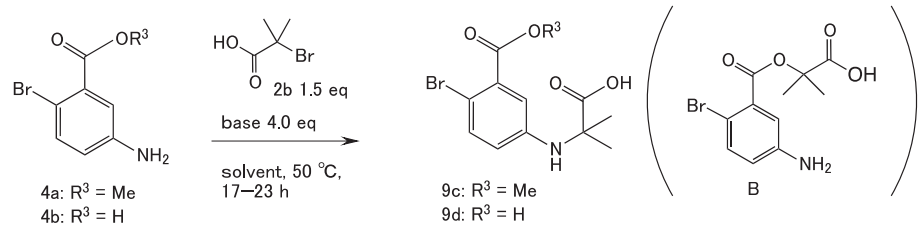
entry	R^3	base	solvent	ratio of **4**:**9**:**A**	conversion (%)
1	Me	K_2CO_3	DMF	100:N.D.:N.D.	0
2		Et_3N	DMF	100:N.D.:N.D.	0

3		Et_3N	2-PrOH	100:N.D.:N.D.	0
4	H	K_2CO_3	DMF	59:N.D.:41	41
5		Et_3N	DMF	24:41:35	76
6		Et_3N	2-PrOH	85:12:3	15

[a]Molar ratio and conversion were determined from ^{1}H NMR spectra of the reaction mixture.[5]

Conversely, alkylation of **4b** and carboxylic acid **2b** in K_2CO_3/DMF showed low conversion to **9d** (44%). However, mainly **4b** and **9d** were observed in the reaction mixture, with **4b** being converted to target material **9d** in high amounts (Table 2, entry 1). In the case of Et_3N/DMF, 99% conversion was observed; however, only 15% was target material **9d**, while the rest were impurities (entry 2). The use of 2-PrOH as the solvent and Et_3N as the base gave high conversion with few impurities, affording **9d** in 85% yield (entry 3). In the case of methyl ester **4a**, 85% conversion was confirmed and the yield of target material **9c** slightly decreased to 68% (entry 4). The use of EtOH as the solvent resulted in a decreased yield of 48% due to residual unreacted **4b** (entry 5). When MeOH was used as the solvent, a further decrease in conversion was observed (24%) and only the remaining **4b** and **9d** were confirmed. In the reaction mixtures in Table 2, impurity **B** was not observed through ^{1}H NMR spectroscopic analysis.

Table 2. Optimization of alkylation

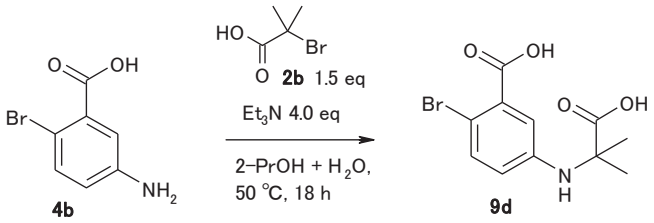


entry	R^3	base	solvent	yield (%) of **9**	conversion (%)[a]	time (h)
1	H	K_2CO_3	DMF	[b]	44	17
2		Et_3N	DMF	15[c]	99[d]	23
3		Et_3N	2-PrOH	85[c]	89[d]	20
4	Me	Et_3N	2-PrOH	68[e]	85	19
5	H	Et_3N	EtOH	48[e]	65	23
6		Et_3N	MeOH	[f]	24	21

[a]Conversion was determined by ^{1}H NMR spectroscopy. [b]Not isolated, but mainly **9d** and **4b** were confirmed in approximately 1:1 molar ratio by ^{1}H NMR spectroscopy of the reaction mixture. [c]HPLC assay yield. [d]Determined by HPLC. [e]Isolated yield. [f]Not isolated.

The lower yield of the alkylation reaction shown in Table 2 was due to the decreased steric effect of the alcohol, which was investigated through the addition of H_2O to 2-PrOH. The reaction was performed at 50 °C for 18 h and with the same equivalents of reagents. Under these conditions, the ratio of the remaining **4b** increased in proportion to H_2O addition and the conversion decreased (Table 3).

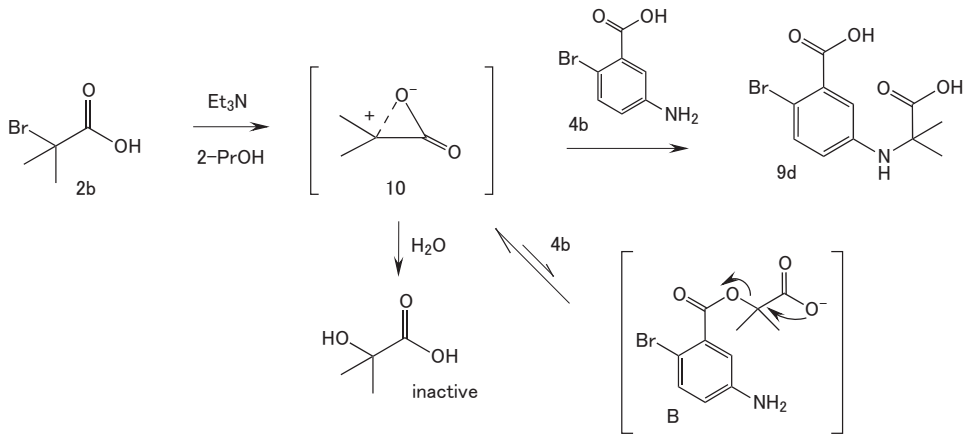
Table 3. Investigation of the influence of H_2O on alkylation



entry	solvent	ratio of **4b**:**9d** [a]	conversion (%)
1	2-PrOH (dry)	8:92	93
2	2-PrOH/H_2O (95:5)	18:82	84
3	2-PrOH/H_2O (90:10)	27:73	77

[a]Confirmed by HPLC.

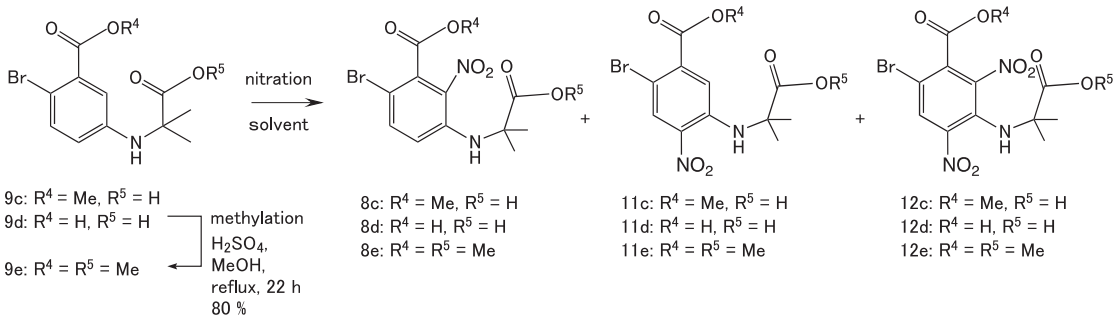
Therefore, the combination of carboxylic acid **2b** and **4b** in Et_3N/2-PrOH afforded the best results, with high conversion and high yield of **9d**. Furthermore, it was found that the addition of H_2O or a low steric effect solvent decreased the yield of **9d**. The mechanism was believed to involve **2b** forming highly active intermediate **10**, which could then react with the amino group on **4b** (Scheme 3). Active intermediate **10** was able to react with H_2O and low steric effect alcohols, resulting in low yields.[6] In the case of *O*-alkylation to yield **B**, the retro-*O*-alkylation proceeds intramolecularly due to the vicinal effect of the carboxylic acid, making **B** unstable.



Scheme 3. Plausible mechanism of alkylation

The nitration reaction of **9** was subsequently investigated (Table 4). Reaction of dicarboxylic acid **9d** in both HNO_3/H_2SO_4 and $NaNO_3$/TFA[7] yielded a complex mixture with a small amount of remaining **9d** (entries 1 and 2). Nitration of **9c**, where R^4 is a methyl ester, in $NaNO_3$/TFA also yielded a complex mixture and no remaining **9c** (entry 3). The reaction mixture of dimethyl ester **9e** in HNO_3/H_2SO_4 contained not only remaining **9e** and target material **8e** but also regioisomer **11e** and a slight amount of dinitration product **12e** (27:42:23:8, entry 4).[8] For the reaction of **9e** in $NaNO_3$/TFA, no **9e** remained and the reaction progress was confirmed as the ratio of target material **8e**, **11e**, and **12e** was 62:22:16, with a 57% HPLC assay yield of **8e**.[9] Impurities were removed through recrystallization in 2-PrOH, affording **8e** in 38% yield and 99% purity. It was found that dimethyl esterification from **9d** to **9e** was necessary for the nitration reaction and was accomplished in 80% yield by stirring **9d** in MeOH in the presence of H_2SO_4.

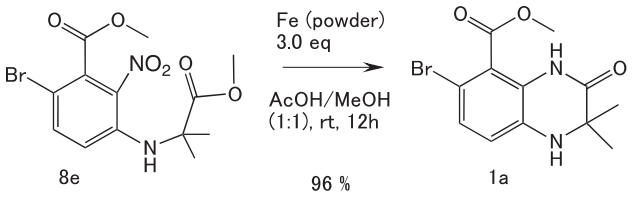
Table 4. Investigation of nitration of **9**



entry	R^4	R^5	nitro agent	equiv.	solvent	temp. (°C)	time (h)	yield of **8e** (%)	ratio of **9**:**8e**:**11**:**12**
1	H	H	HNO_3	15 v/w[a]	H_2SO_4	0	3	complex mixture[b]	-
2			$NaNO_3$	1.05	TFA	25	4	complex mixture[b]	-
3	Me	H	$NaNO_3$	1.05	TFA	25	5	complex mixture[c]	-
4	Me	Me	HNO_3	15 v/w[a]	H_2SO_4	0	3	[d]	27:42:23:8[e]
5			$NaNO_3$	1.0	TFA	50	5	57(38)[f]	N.D.:62:22:16[g]

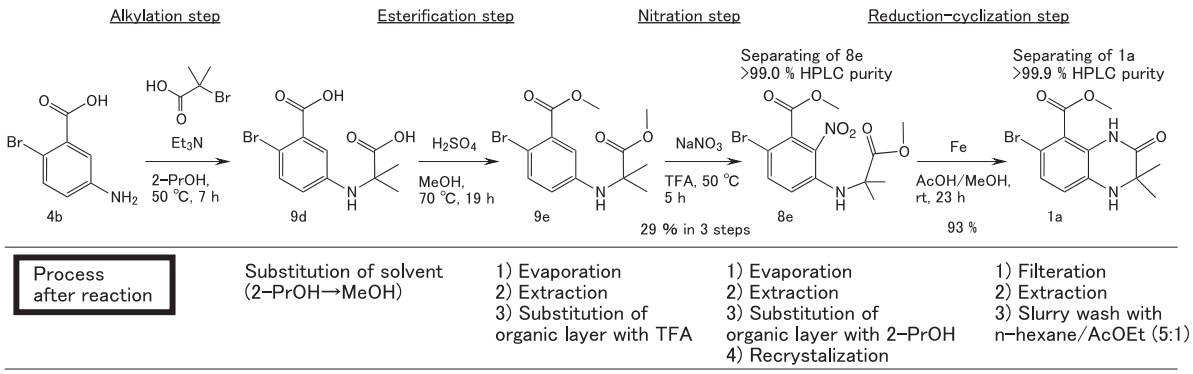
[a]Weight of **9**. [b]Confirmed a small amount of remaining **9d** and many impurities. [c]Confirmed many impurities and no remaining **9d**. [d]Not isolated. [e]Confirmed by ^{1}H NMR spectroscopy. [f]HPLC assay yield (isolated yield after recrystallization). [g]Confirmed by HPLC.

In the final synthesis of **1a**, the use of $SnCl_2$ and MeOH under reflux afforded **1a** in 70% yield with a conventional method.[2b-e] Our investigation revealed that Fe powder (ϕ = 45 μm) with AcOH/MeOH (1:1) reduced the nitro group, followed by an intramolecular cyclization to provide **1a** in 96% yield (Scheme 4).[10]



Scheme 4. Nitro reduction and successive cyclization of **8e**

Optimization of the total synthetic procedure was investigated to further improve the synthesis of **1a**. Products **9d** and **9e** were found to be an amorphous solid and liquid, respectively. They were thus difficult to purify by simple methods such as recrystallization (Scheme 5). When the alkylation step was complete, the reaction solvent was substituted with MeOH and H_2SO_4 was added, allowing for a subsequent esterification. Upon completion, water soluble salts and impurities were removed by extraction. The organic layer was substituted with TFA, and nitration was performed by the addition of $NaNO_3$ without the isolation of **9e**. The reaction mixture was then extracted, the organic layer was substituted for 2-PrOH, and **8e** was recrystallized in 29% yield from **4b**[11] and 99.0% HPLC purity. This was then reduced and cyclized with Fe, which was then removed by filtration and extracted with aqueous HCl using a reduction-cyclization step. Finally, the precipitated solid was washed with n-hexane/AcOEt (5:1) to afford **1a** in 93% yield with over 99.9% HPLC purity.



Scheme 5. Optimization of synthetic procedure toward new route

In the previous synthesis, the total yield of **1a** was 12% with six steps. It required six isolation steps and purification by four silica gel columns. With this improved procedure, **1a** was produced in 27% yield with no need for purification by silica gel column chromatography and with only two isolation steps (Table 5).

Table 5. Comparison of previous and new routes

	number of steps	number of isolation steps	number of silica gel columns	total yield (%)
previous route	6	6	4	12
new route	4	2	0	27

CONCLUSION

A practical, efficient four-step process for the synthesis of **1a** was developed. This novel procedure afforded **1a** in high purity and an improved overall yield of 27% compared with the previous yield of 12%. Alkylation with hindered electrophiles **2b** and **4b** afforded **9d** in high yield when a combination of Et_3N and 2-PrOH was used. Nitration with $NaNO_3$ in TFA preferentially afforded **8e** at the desired position with good purity following recrystallization in 2-PrOH. Final product **1a** was synthesized using Fe in the nitro reduction of **8e** and cyclization, resulting in high yield and purity. Optimization of this synthetic procedure resulted in reducing the isolation steps from six to two, and did not require purification by column chromatography.

EXPERIMENTAL

GENERAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *J*EOL GSX400 or *J*EOL ECP500 or *J*EOL JNM-ECS400 spectrometer at ambient temperature. Chemical shifts are reported as ppm downfield from tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and the number of protons. HPLC analyses were conducted on a Waters alliance series. In process method for preparations of **9d**, **9c** and **9e**; C8 column (3.5 μm; 4.6 mm I.D. × 150 mm) (X Bridge^{TM}), Mobile phase A: 0.05% TFA in water, Mobile phase B: 0.05% TFA in MeCN, Gradient condition: 0 min 95% A, 5 min 95% A, 25 min 10% A, 30 min 10% A, column temperature 40 °C, 1.0 mL/min flow rate, UV detector at 225 nm. Retention times: **4b** (6.3 min), **9d** (13.6 min), **9c** (16.5 min), **9e** (19.0 min). In process method for preparations of **8e** and **1a**; C8 column (3.5 μm; 4.6 mm I.D. × 150 mm) (X Bridge^{TM}), isocratic elution with 10 mM $CH_3CO_2NH_4$ aq/MeCN (60:40), column temperature 40 °C, 1.0 mL/min flow rate, UV detector at 225 nm. Retention times: **1a** (4.9 min), **9e** (9.8 min), **8e** (13.7 min), **11e** (16.8 min), **12e** (18.9 min).

2-Bromo-5-(1-carboxy-1-methylethylamino)benzoic acid (9d). To a mixture of

5-amino-2-bromobenzoic acid **4b** (10.0 g, 46.3 mmol), 2-bromoisobutyric acid **2b** (11.6 g, 69.5 mmol) and anhydrous 2-PrOH (100 mL) was added Et_3N (26.0 ml, 0.187 mol), and the mixture was stirred for 20 h at 50 °C. When the reaction was completed, the reaction mixture was evaporated under vacuum pressure. Water (300 mL) and 6M HCl (20 mL) were added and extracted with AcOEt (150 mL×2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum pressure to achieve the **9d** as a pale yellow solid (12.3 g, 88%). HPLC purity: 95.8%, which was used in the next reaction without any purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.42 (s, 6H), 6.51 (dd, J = 8.8, 2.9 Hz, 1H), 6.87 (d, J = 2.9 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 12.86 (br s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 25.52, 55.99, 104.57, 115.15, 117.11, 133.40, 133.66, 145.96, 167.67, 176.80; IR (KBr) cm^{-1}: 1035, 1157, 1218, 1257, 1473, 1601, 1717, 2510, 2769, 2987, 3387; Mp 105 °C; HRMS (EI): calcd for $C_{11}H_{12}BrNO_4$ [M^+]: 300.9950. Found; 300.9952.

Methyl 2-Bromo-5-(1-carboxy-1-methylethylamino)benzoate (9c). To a mixture of methyl 5-amino-2-bromobenzoate **4a** (0.436 g, 1.90 mmol), 2-bromoisobutyric acid **2b** (0.479 g, 2.87 mmol) and anhydrous 2-PrOH (4.5 mL) was added Et_3N (1.07 mL, 7.68 mmol), and the mixture was stirred for 19 h at 50 °C. When the reaction was completed, the reaction mixture was evaporated under vacuum pressure. Water (30 mL) and 1M HCl (5 mL) were added and extracted with AcOEt (15 mL×2). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the organic solution was concentrated to dryness under reduced pressure. The residue was was purified by column chromatography to afford **9c** as a pale yellow solution (0.407 g, 68%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.42 (s, 6H), 3.81 (s, 3H), 6.54 (dd, J = 8.8, 3.3 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 12.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 25.52, 52.36, 56.04, 104.54, 115.26, 117.54, 132.11, 133.83, 146.09, 166.57, 176.74; IR (KBr) cm^{-1}: 1032, 1154, 1254, 1334, 1437, 1474, 1601, 1725, 2949, 2991, 3388; HRMS (EI): calcd for $C_{12}H_{14}BrNO_4$ [M^+]: 315.0106. Found; 315.0090.

Methyl 2-Bromo-5-(1-methoxycarbonyl-1-methylethylamino)benzoate (9e). To a mixture of 2-bromo-5-(1-carboxy-1-methylethylamino)benzoic acid **9d** (10.8 g, 35.8 mmol) and anhydrous MeOH (150 mL) was added 12% HCl (15 mL), and the mixture was stirred for 22 h at 70 °C. When the reaction was completed, the reaction mixture was evaporated under vacuum pressure. Water (200 mL) was added and extracted with AcOEt (120 mL×2). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the organic solution was concentrated to dryness under reduced pressure. The residue was purified by chromatography to afford **9e** as a colorless solution (9.44 g, 80%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.45 (s, 6H), 3.61 (s, 3H), 3.81 (s, 3H), 6.46 (dd, J = 8.7, 2.7 Hz, 1H), 6.51 (s, 1H), 6.85 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 25.55,

52.25, 52.37, 56.31, 104.87, 115.51, 117.19, 132.10, 133.99, 145.78, 166.41, 175.64; IR (KBr) cm^{-1}: 1031, 1147, 1247, 1335, 1386, 1436, 1475, 1516, 1601, 1733, 2953, 2994, 3398; HRMS (EI): calcd for $C_{13}H_{16}BrNO_4$ [M^+]: 329.0263. Found; 329.0260.

Methyl 6-Bromo-3-(1-methoxycarbonyl-1-methylethylamino)-2-nitrobenzoate. (8e). To a mixture of methyl 2-bromo-5-(1-methoxycarbonyl-1-methylethylamino)benzoate **9e** (0.861g, 2.61 mmol) and TFA (4.30 mL) was added $NaNO_3$ (0.224g, 2.63 mmol) at 50 °C, and the mixture was stirred for 5 h at 50 °C. When the reaction was completed, the reaction mixture was evaporated under vacuum. Water (10 mL) and 4M NaOH aq (4.0 mL) were added and extracted with AcOEt (15 mL×2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum pressure. 2-PrOH was added and the mixture was stirred for 20 h, and the precipitated solid was filtered. The filtered cake was further washed with 2-PrOH (0.5 mL) and dried in vacuo at 50 °C to afford compound **8e** as an orange solid (0.368 g, 38%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.61 (s, 6H), 3.70 (s, 3H), 3.86 (s, 3H), 6.70 (d, J = 9.3 Hz, 1H), 7.76 (d, J = 9.3 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 25.41, 52.98, 53.23, 57.44, 105.20, 118.35, 130.68, 132.59, 138.86, 141.78, 165.24, 174.15; IR (KBr) cm^{-1}: 1031, 1088, 1151, 1217, 1262, 1358, 1387, 1444, 1498, 1605, 1734, 2958, 3004, 3377, 3455; Mp 119 °C; HRMS (EI): calcd for $C_{13}H_{15}BrN_2O_6$ [M^+]: 374.0113. Found; 374.0113.

7-Bromo-8-methoxycarbonyl-3,3-dimethyl-3,4-dihydro-1*H*-quinoxalin-2-one (1a). To a mixture of methyl 6-bromo-3-(1-methoxycarbonyl-1-methylethylamino)-2-nitrobenzoate **8e** (0.500 g, 1.33 mmol), MeOH (3.75 mL) and AcOH (3.75 mL) was added Fe (ϕ=45 μm) (0.224 g, 4.01 mmol) at ice cooling, and the mixture was stirred for 12 h at rt. When the reaction was completed, the MeOH and AcOH were evaporated under vacuum pressure. AcOEt (20 mL) was added and the mixture was sttired for 20 min at 60 °C. The mixture was filtered by celite® and the filtrate was added H_2O (20 mL) and extracted. The organic layer was evaporated under vacuum pressure to achieve a pale gray solid (0.400 g, 96%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.22 (s, 6H), 3.84 (s, 3H), 6.46 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 24.68, 52.79, 53.71, 105.98, 116.25, 120.96, 124.53, 126.28, 134.01, 165.51, 170.29; IR (KBr) cm^{-1}: 1027, 1160, 1265, 1286, 1311, 1358, 1387, 1436, 1469, 1591, 1691, 1716, 1855, 2969, 3060, 3113, 3206, 3325; Mp 156 °C; HRMS (EI): calcd for $C_{12}H_{13}BrN_2O_3$ [M^+]: 312.0110. Found; 312.0098.

Optimaized process for **1a**. To a mixture of 5-amino-2-bromobenzoic acid **4b** (500 g, 2.32 mol), 2-bromoisobutyric acid **2b** (580 g, 3.47 mol) and 2-PrOH (5.00 L) was added Et_3N (1.29 L, 9.26 mol), and the mixture was stirred for 7 h at 50 °C. When the reaction was completed as indicated by HPLC

(conv. >92%), the reaction mixture was filtered and the filtrate was evaporated under vacuum pressure and azeotroped with MeOH (2.5 L×2). Dry MeOH (10 L) and 12% HCl (500 mL) were added to the mixture and the mixture was stirred for 19 h at 70 °C. When the reaction was completed as indicated by HPLC (conv. >90%), the reaction mixture was evaporated under vacuum pressure and water (5.00 L) was added and extracted with AcOEt (5.00 L×2). The combined organic layer was evaporated under vacuum pressure to achieve an oil (641 g). TFA (4.80 L) was added to the oil and stirred at 20 °C. $NaNO_3$ (164.9 g, 1.94 mol) was added to the mixture and stirred for 5 h at 50 °C. When the reaction was completed as indicated by HPLC (conv. >98%), the reaction mixture was evaporated under vacuum pressure and neutralized by 4 M NaOH aq (1.44 L). Water (3.6 L) was added to the mixture and extracted with AcOEt (5.00 L). The organic layer was evaporated under vacuum pressure to achieve an oil. 2-PrOH (1.80 L) was added to the oil and stirred for 12 h at rt. The precipitated solid was filtered and the filtered cake was further washed with 2-PrOH (500 mL) and dried in vacuo to a constant weight at 50 °C to afford compound **8e** as an orange solid (247 g, 29% yield from **4b**, HPLC purity: 99.0%). To a mixture of methyl 6-bromo-3-(1-methoxycarbonyl-1-methylethylamino)-2-nitrobenzoate **8e** (247 g, 0.658 mol), MeOH (1.73 L) and AcOH (1.73 L) was added Fe (ϕ=45 μm) (110 g, 1.98 mol) at ice cooling, and the mixture was stirred for 23 h at rt. When the reaction was completed as indicated by HPLC (conv. >99%), the reaction mixture was filtered by celite® and the filtrate was evaporated under vacuum pressure. To the mixture was added 1M HCl (3.75 L) and extracted with AcOEt (3.75 L). The organic layer was washed by H_2O (3.75 L), filtered and evaporated under vacuum pressure to give a solid. The solid was washed with *n*-hexane:AcOEt (5:1), (250 mL) and dried in vacuo to a constant weight at 50 °C to afford compound **1a** as a pale gray solid (191 g, 93%). HPLC purity: >99.9%.

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3. Examples of alkylation of **2** and **4** homologs were reported before, but the reported yields were not stable for every substrate, see: F. Hoffmann, et al. WO2011/128251 A1.; K. Tachibana, et al. EP1790640 A1.; S. D. Clarke, J. C. Metcalfe, and G. A. Smith, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 1187.
4. Compounds **9b** and **A** were assumed by ^{1}H NMR. **9b**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.09 (t, J = 7.0 Hz, 3H), 1.44 (s, 6H), 4.08 (q, J = 7.0 Hz, 2H), 6.42 (s, 1H), 6.46 (dd, J = 8.7, 3.2 Hz, 1H), 6.84 (d, J = 3.2 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 13.10 (br s, 1H). **A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.20 (t, J = 7.0 Hz, 3H), 1.59 (s, 6H), 4.14 (q, J = 7.0 Hz, 2H), 5.59 (s, 2H), 6.64 (dd, J = 8.4, 2.9 Hz, 1H), 6.92 (d, J = 2.9 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H).
5. Sample preparation of ^{1}H NMR analysis: sampling of small amount from reaction mixture and controlling mild acid by HCl aq and H_2O. The mixture was extracted with AcOEt and the organic layer was concentrated to dryness.
6. An addition product of H_2O or low steric alcohol was not isolated and not observed by ^{1}H NMR and HPLC analysis.
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8. Compounds **11e** and **12e** were assumed by ^{1}H NMR. **11e**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.63 (s, 6H), 3.74 (s, 3H), 3.88 (s, 3H), 6.97 (s, 1H), 8.18 (s, 1H), 8.34 (s, 1H). **12e**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.60 (s, 6H), 3.76 (s, 3H), 3.93 (s, 3H), 8.32 (s, 1H), 8.68 (s, 1H).
9. Although the causes of regioselectivity are unknown, it is assumed to be comprehensive affection of substituents on the aromatic and vicinal effect in methyl carbonyl function.
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11. Although **4b** can be procured at an appropriate cost, the detailed information is not disclosable. **4b** was synthesized from 3-aminobenzoic acid with NBS in 78% in laboratory scale, see: K. Kudou, N. Yamamoto, M. Ban, and A. Ohno, WO 2012/108455 A1.