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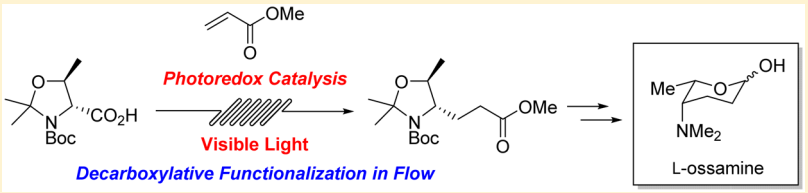
Formal Total Synthesis of L-Ossamine via Decarboxylative Functionalization Using Visible-Light-Mediated Photoredox Catalysis in a Flow System

Shinsuke Inuki,[†] Keisuke Sato,[†] Takahide Fukuyama,[‡] Ilhyong Ryu,[‡] and Yukari Fujimoto*[,†]

[†]Graduate School of Science and Technology, Keio University, Yokohama, Kanagawa 223-8522, Japan

[‡]Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Supporting Information



ABSTRACT: A formal total synthesis of L-ossamine was achieved. The key feature of the synthesis was the decarboxylative functionalization of a threonine derivative using visible-light-mediated photoredox catalysis. This reaction was implemented in a flow reactor, allowing for the efficient conversion to the desired product.

Deoxyaminosugar motifs occur in a number of biologically active natural products and pharmaceuticals, including aminoglycosides, macrolides, or anthracyclines, which play fundamental roles in regulating numerous biological processes.[1] The development of efficient methods for synthesizing deoxyaminosugars is an important issue in the field of organic synthesis.[2] A deoxyaminosugar, ossamine,[3] is contained in ossamycin[4] derived from the bacterial species *Streptomyces hygroscopicus* (Figure 1), which inhibits oxidative phosphorylation by targeting the mitochondrial FOF1 ATP synthase.[5] Ossamine and its analogues have been the target of synthetic studies,[6] and some groups have accomplished the total synthesis of ossamine.[3,7] Several groups have also reported the total synthesis of *epi*-ossamine (forosamine).[8]

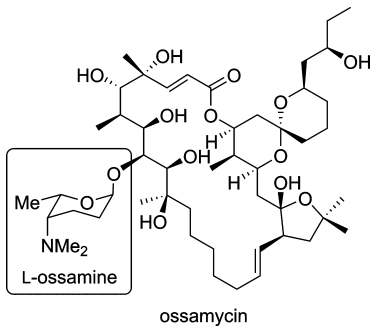


Figure 1. Structures of ossamycin and ossamine.

Visible-light-mediated photoredox reactions employing transition-metal complexes have received considerable attention in recent years.[9] These types of reactions enable mild and efficient transformations using a commercially available household light bulb. Visible-light-mediated decarboxylative functionalizations of carboxylic acids and their derivatives present a promising approach to new carbon−carbon or carbon−heteroatom bond formation.[10] Oda and co-workers developed the photosensitized decarboxylative Michael addition of *N*-(acyloxy)phthalimides using $Ru(bpy)_3Cl_2$.[11] MacMillan et al. reported a number of decarboxylative functionalization reactions of carboxylic acids using photoredox catalysis.[12] Recently, we developed a decarboxylative benzoyloxylation of *β*-hydroxy amino acids in the presence of $Ru(bpy)_3Cl_2$ and benzoylperoxide $(BzO)_2$.[13] We focused on the visible-light-mediated decarboxylative Michael addition of carboxylic acids[12c] and expected that this type of transformation reaction of threonine derivatives could provide ready access to the deoxyaminosugar, ossamine. Furthermore, in order to enhance the visible-light-mediated photoredox catalysis, we planned to implement a continuous flow reactor.[14] Recently, several groups reported implementing the photoredox reactions in a flow system,[14b,15] which enabled efficient conversions mainly by improving irradiation of the reaction mixture as compared to batch processing.

The synthetic strategy for achieving L-ossamine is illustrated in Scheme 1. The visible-light-mediated photoredox reaction of the threonine derivative **1** and acrylic acid ester derivative **2** was expected to enable carbon homologation and provide the functionalized 1,2-amino alcohol **3** for the synthesis of ossamine. This reaction proceeded through an *α*-amino radical intermediate **A**, which could be generated from the threonine derivative **1** via visible-light-mediated decarboxylation. The

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Scheme 1. Synthetic Strategy toward L-Ossamine via Decarboxylative Functionalization Using Visible-Light-Mediated Photoredox Catalysis in a Flow System

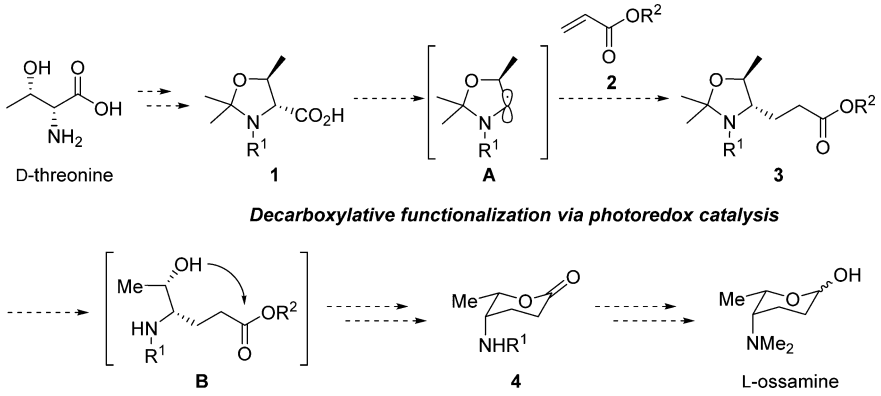
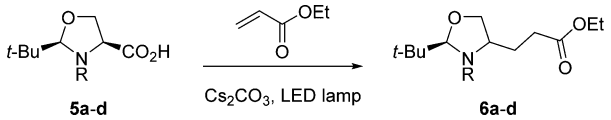


Table 1. Initial Studies and Reaction Optimization



entry[a]	sub	R	photoredox catalyst (mol %)	additive	solvent	yield[b,c] (%)	dr[d]
1	**5a**	Boc	$Ru(bpy)_3Cl_2·6H_2O$ (1)		DMF	ND	
2	**5a**	Boc	$Ir(ppy)_3$ (1)		DMF	ND	
3	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (1)		DMF	50 (41)	81:19
4	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (1)		EtOH	ND	
5	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (1)		MeCN	21	
6	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (1)		dioxane	22	73:27
7	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2)		DMF	73 (62)	77:23
8	**5b**	CO_2Me	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2)		DMF	47	79:21
9	**5c**	Z	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2)		DMF	(27)	85:15
10	**5d**	Troc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2)		DMF	39 (12)	72:28
11	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2)	H_2O (10 equiv)	DMF	85 (79)	78:22
12[e]	**5a**	Boc	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2)	H_2O (10 equiv)	DMF	62 (50)	78:22

[a]Reaction conditions: 0.1 mmol of substrate, 2.0 equiv of ethyl acrylate, 1.5 equiv of base, 1 or 2 mol % of photoredox catalyst at room temperature with irradiation from a 6.5 W LED light bulb. [b]Yields were determined by ^1H NMR analysis. Yields of the isolated products are given in parentheses. [c]ND = not detected. [d]Determined by ^1H NMR analysis. [e]K_2HPO_4 was used instead of Cs_2CO_3. bpy = 2,2′-bipyridine; ppy = 2-phenylpyridine; $dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

intermediate **A** could react with acrylic acid derivatives **2** to give the desired 1,2-amino alcohol **3**, which could be converted to L-ossamine through lactonization, reduction, and dimethylation. It should be noted that in previous synthetic studies of ossamine the threonine-derived carboxylic acid **1** was converted to compound **3** in at least four steps (esterification of the carboxylic acid **1**, reduction to aldehyde, homologation, and reduction of the resulting olefin),[6] but this synthetic route enables the direct introduction of C3 units at a 1,2 amino alcohol under mild conditions.

Initially, we investigated model studies of a visible light-mediated photoredox reaction of the *β*-hydroxy amino acid derivatives **5a–d** (Table 1). Treatment of **5a**[16] and ethyl acrylate with 1 mol % $Ru(bpy)_3Cl_2·6H_2O$ or $Ir(ppy)_3$ as a photoredox catalyst, along with Cs_2CO_3 in DMF under irradiation with visible light, did not afford the desired product. Next, referring to MacMillan's report,[12c] we used $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ as a photoredox catalyst to give the desired product **6a** in 50% yield as a 81:19 diastereomixture (entry 3). Changing the solvent from DMF to EtOH, MeCN, or dioxane did not enhance the yield of the desired product. Increased loading of the photoredox catalyst (2 mol %) improved the yield to 73% (entry 7). The use of *N*-CO_2Me,[17] Z, and Troc derivatives (**5b–d**) decreased the yields of the desired products (entries 8–10). The addition of H_2O produced the desired product in 85% yield (entry 11). Recently, Overman et al. reported that the presence of H_2O improved the photoredox reaction of oxalate salts.[18] The use of K_2HPO_4 as a base (optimal conditions, as reported by MacMillan et al.) was not effective (entry 12).[12c]

With optimized conditions in hand (Table 1, entries 7 and 11), we next examined decarboxylative functionalizations of threonine derivatives **7**[19] and **8**,[20] which were easily prepared from D-threonine (Table 2). The reaction of oxazolizinone derivative **7a** under the optimized conditions (Table 1, entry 7) gave a trace amount of the desired product (entry 1). Introduction of a Boc group to the nitrogen atom provided the desired product in low yield (entry 2). Next, the treatment of Z-protected derivative **8a** under the same conditions gave the desired products **10a** in low yields (entry 3). Changing from the Z to the Boc group enhanced the yield of desired product **10b** (70%) as a 65:35 diastereomixture (entry 4). The NMR spectral data of major diastereomer were in agreement with those reported by Pak et al.,[21] which indicated that the major

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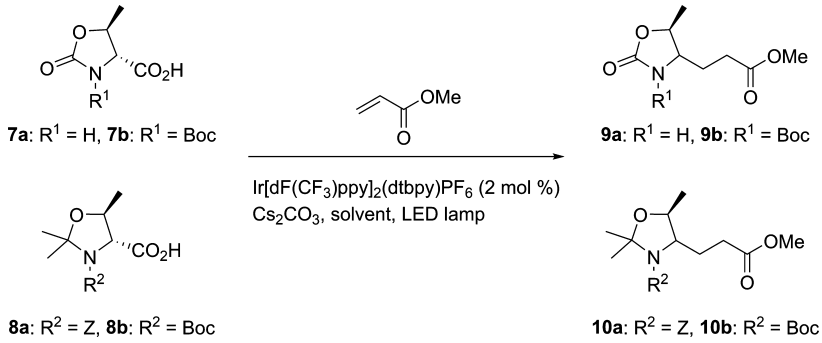
Table 2. Decarboxylative Functionalization of Threonine Derivatives

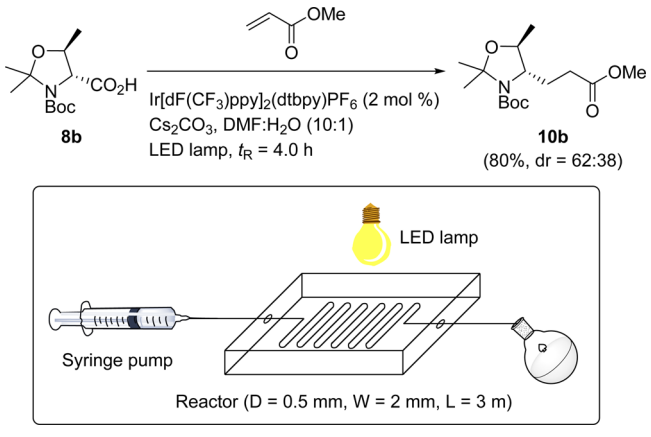


entry[a]	sub	R^1	R^2	solvent	time (h)	products	yield[b] (%)	dr[c]
1	**7a**	H		DMF	42	**9a**	trace	
2	**7b**	Boc		DMF	48	**9b**	20	
3	**8a**		Z	DMF	43	**10a**	14	60:40
4	**8b**		Boc	DMF	45	**10b**	70	65:35
5	**8b**		Boc	DMF/H_2O (10:1)	47	**10b**	50	61:39

[a]Reaction conditions: 0.1 mmol of substrate, 2.0 equiv of methyl acrylate, 1.5 equiv of base, 2 mol % of photoredox catalyst at room temperature with irradiation from a 6.5 W LED light bulb. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis. dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

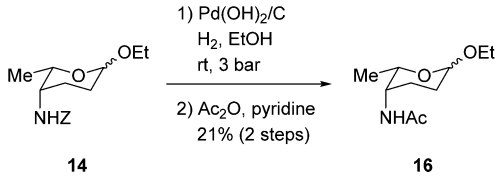
diastereomer had the *trans*-configuration. In order to increase the efficiency of the reaction and conduct it on a larger scale, we planned to apply this reaction to continuous flow chemistry. The optimized conditions described above (Table 1, entries 7 and 11) were heterogeneous, which is unsuitable for the flow reactor. Therefore, the reaction conditions were modified to homogenize the reaction mixture. When DMF/H_2O (10:1) was used as a solvent, the reaction mixture was dissolved, and the desired product **10b** was obtained in 50% yield (entry 5). Next, we performed the reaction using continuous flow reactor as shown in Scheme 2 and Figure 2. The flow reaction in 4 h

Scheme 2. Continuous Flow Decarboxylative Functionalization of Threonine Derivatives



residence time under irradiation of a 48 W LED lamp using a 3 mL reactor provided full conversion of the starting material to the desired product **10b** in 80% yield (50% yield in 47 h in batch, Table 2, entry 5). Using the photo flow reactor could allow the enhancement of irradiation per unit volume to have significant effects on the photoredox reaction course.

With the requisite carbon framework **10b** in hand, we next examined the conversion to L-ossamine (Scheme 3). Removal of the isopropylidene group with the simultaneous lactonization under acidic conditions gave the diastereomixture of the lactone **11**[6b] (63% yield), which was difficult to separate. Removal of the isopropylidene group, separation of the resulting 1,2-amino alcohol, and lactonization thus afforded the desired lactone **11**. The lactone **11** was converted into the corresponding Z-protected lactone **12** by treatment with TFA, followed by ZCl and Et_3N. Reduction of the lactone with DIBAL-H and the formation of ethyl acetal provided **14**. Finally, removal of the Z group using $Pd(OH)_2$ and hydrogen led to the amine **15**, the enantiomer of which, *ent*-**15**, has been described by Voelter et al. where the conversion from *ent*-**15** to D-ossamine was reported.[7b] The conversion of **14** to an acetyl amide derivative **16** was carried out for spectral analysis (eq 1). The NMR spectral data agreed well with the data reported for *ent*-**16**.[7b]



(1)

In conclusion, we accomplished the formal total synthesis of the deoxyaminosugar L-ossamine starting from threonine. This synthetic route features the visible-light-mediated decarboxylative functionalization of β-hydroxy amino acids, which allowed direct access to the core structure of the deoxyaminosugar from the threonine derivative. Implementation of this reaction in the continuous flow reactor improved the efficiency of the photoredox catalysis reaction.

EXPERIMENTAL SECTION

General Methods. All moisture-sensitive reactions were performed using syringe−septum cap techniques under an argon atmosphere, and all glassware was dried in an oven at 80 °C for 2 h prior to use. Reactions at −78 °C employed a CO_2−MeOH bath. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (0.25 mm thickness). For flash chromatography, silica gel 60 N [spherical neutral (40−50 μm)] was employed. Melting points were measured by a hot-stage melting point apparatus

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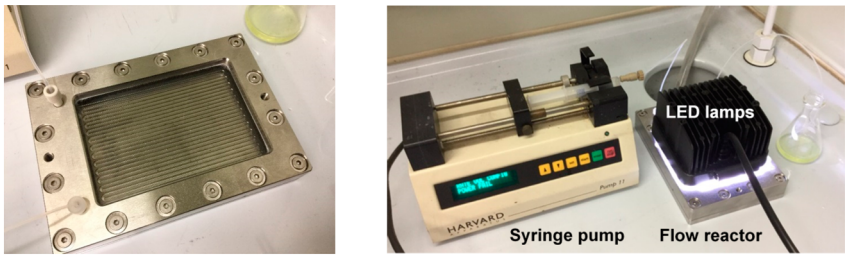
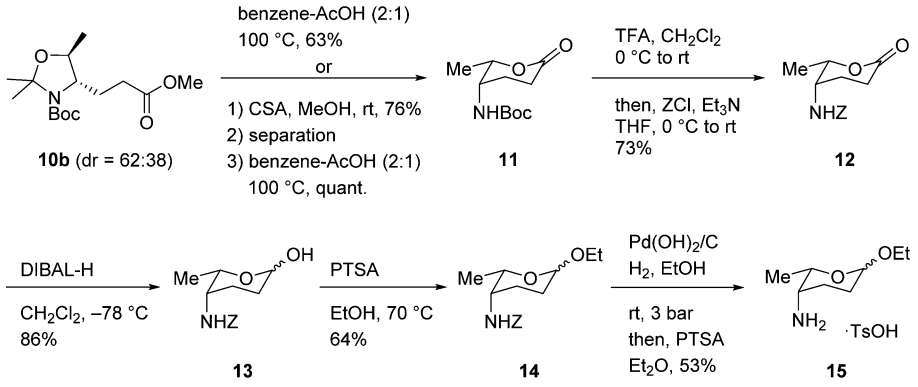


(a) (b)

Figure 2. (a) Flow reactor for photoreactions (2 mm width, 0.5 mm depth, 3 m length, MiChS Co., Ltd.). (b) Flow reactor setup for the visible-light-mediated decarboxylative functionalization.

Scheme 3. Formal Total Synthesis of L-Ossamine



(uncorrected). Optical rotations were measured with a polarimeter. All NMR spectral data were recorded on an NMR spectrometer for ^{1}H (400 MHz) and ^{13}C (100 MHz). Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR). ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Exact mass (HRMS) spectra were recorded on an electronspray ionization quadrupole time-of-flight (ESI-QTOF) mass spectrometer. Microflow photoredox reactions were carried out by using a photoreactor, MiChS L (2 mm width, 0.5 mm depth, 3 m length, MiChS Co., Ltd.).

General Procedure for Visible-Light-Mediated Decarboxylative Functionalization: *tert*-Butyl (2*R*)-2-*tert*-Butyl-4-(3-ethoxy-3-oxopropyl)oxazolidine-3-carboxylate (6a). *Decarboxylative Functionalization Reaction (Table 1, Entry 7).* To a dried Pyrex tube equipped with a stir bar were added **5a** (27.3 mg, 0.10 mmol), $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2.24 mg, 2.0 μmol), and Cs_2CO_3 (48.9 mg, 0.15 mmol). After the vial was sealed, evacuated, and backfilled with argon, DMF (3.3 mL) and ethyl acrylate (21.8 μmol, 0.20 mmol) were added to the vial. The reaction was stirred and irradiated with two 6.5 W LED bulbs until complete consumption of carboxylic acid **5a**. The mixture was diluted with saturated $NaHCO_3$ aq. The whole was extracted twice with Et_2O. The extract was washed with saturated $NaHCO_3$ aq and H_2O and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (6:1) to give **6a** as a colorless oil (20.3 mg, 62% yield, dr = 77:23). The ratio of the diastereomer were determined by ^{1}H NMR analysis.

Decarboxylative Functionalization Reaction in the Presence of H_2O (Table 1, Entry 11). To a dried Pyrex tube equipped with a stir bar were added **5a** (27.3 mg, 0.10 mmol), $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2.24 mg, 2.0 μmol), and Cs_2CO_3 (48.9 mg, 0.15 mmol). After the vial was sealed, evacuated, and backfilled with argon, DMF (3.3 mL), H_2O (18 μL), and ethyl acrylate (21.8 μmol, 0.20 mmol) were added to the vial. The reaction was stirred and irradiated with two 6.5 W LED bulbs until complete consumption of carboxylic acid **5a**. The mixture was diluted with saturated $NaHCO_3$ aq. The whole was extracted twice with Et_2O. The extract was washed with saturated $NaHCO_3$ aq., H_2O and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (6:1) to give **6a** as a colorless oil (25.9 mg, 79% yield, dr = 78:22). The ratio of the diastereomer were determined by ^{1}H NMR analysis. **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.20 (dd, J = 8.3, 6.3 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.92−3.87 (m, 1H), 3.74 (dd, J = 8.3, 2.4 Hz, 1H), 2.24−2.14 (m, 2H), 2.22−2.05 (m, 2H), 1.48 (s, 9H), 1.24 (t, J = 7.2 Hz, 3H), 0.93 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.3, 151.9, 93.7, 79.8, 74.7, 62.5, 51.4, 29.7, 28.1 (3C), 28.0, 27.0, 26.5 (3C), 20.0; HRMS (ESI) (m/z) calcd for $C_{17}H_{31}NNaO_5$ $[M + Na]^+$ 352.2094, found 352.2103.

Benzyl (5S)-4-(3-Methoxy-3-oxopropyl)-2,2,5-trimethyloxazolidine-3-carboxylate (10a). By a procedure identical with that described for synthesis of **6a** from **5a** (Table 1, entry 7), the carboxylic acid **8a** (27.9 mg, 0.10 mmol) and methyl acrylate (17.9 μmol, 0.20 mmol) were converted into **10a** as a colorless oil (4.7 mg, 14% yield, dr = 60:40). The ratio of the diastereomer was determined by ^{1}H NMR analysis: ^{1}H NMR of major isomer (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 5.14 (s, 2H), 4.00−3.93 (m, 1H), 3.72−3.60 (m, 1H), 3.57 (s, 3H), 2.49−2.20 (m, 2H), 2.16−1.89 (m, 2H), 1.68−1.45 (m, 6H), 1.31 (d, J = 6.3 Hz, 3H); ^{1}H NMR of minor isomer (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 5.19 (d, J = 12.6 Hz, 1H), 5.01 (d, J = 12.6 Hz, 1H), 4.25−4.18 (m, 1H), 4.00−3.88 (m, 1H), 3.67 (s, 3H), 2.49−2.20 (m, 2H), 2.16−1.89 (m, 2H), 1.68−1.45 (m, 6H), 1.27 (d, J = 6.3 Hz, 3H); ^{13}C NMR of major isomer (400 MHz, $CDCl_3$) δ 173.5, 152.4, 136.3, 128.5 (2C), 128.1(2C), 128.0, 93.2, 75.3, 66.7, 62.4, 51.4, 30.7, 27.0, 24.8, 23.5, 20.3; HRMS (ESI) (m/z) calcd for $C_{18}H_{25}NNaO_5$ $[M + Na]^+$ 358.1625, found 358.1620.

tert-Butyl (5S)-4-(3-Methoxy-3-oxopropyl)-2,2,5-trimethyloxazolidine-3-carboxylate (10b). By a procedure identical with that described for the synthesis of **6a** from **5a** (Table 1, entry 7), the carboxylic acid **8b** (25.9 mg, 0.10 mmol) and methyl acrylate (17.9 μmol, 0.20 mmol) were converted into **10b** as a colorless oil (21.1 mg, 70% yield, dr = 65:35). The ratio of the diastereomers was determined by ^{1}H NMR analysis: ^{1}H NMR of major isomer (400 MHz, $CDCl_3$) δ 3.98−3.90 (m, 1H), 3.68 (s, 3H), 3.58−3.42 (m, 1H), 2.39−2.28 (m, 2H), 2.12−1.97 (m, 2H), 1.60 (s, 3H), 1.53−1.44 (m, 12H), 1.31 (d, J

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= 6.3 Hz, 3H); ^{1}H NMR of minor isomer: (400 MHz, $CDCl_3$) δ 4.24−4.15 (m, 1H), 3.71−3.41 (m, 4H), 2.39−2.28 (m, 2H), 2.12−1.97 (m, 2H), 1.59−1.44 (m, 15H), 1.25 (d, J = 6.3 Hz, 3H); ^{13}C NMR of major isomer (400 MHz, $CDCl_3$) δ 173.3, 151.9, 93.7, 79.8, 74.7, 62.5, 51.4, 29.7, 28.1 (3C), 28.0, 27.0, 26.5, 20.0; HRMS (ESI) (m/z) calcd for $C_{15}H_{27}NNaO_5$ [M + Na]$^+$ 324.1781, found 324.1775. All spectral data were in agreement with those reported for *ent*-**10b** by Pak et al.[21]

General Procedure for Visible-Light-Mediated Decarboxylative Functionalization Using a Flow System. To a dried round-bottom flask equipped with a stir bar were added **8b** (117 mg, 0.45 mmol), $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (10.2 mg, 9.0 μmol), and Cs_2CO_3 (222 mg, 0.68 mmol). After the flask was sealed, evacuated, and backfilled with argon, DMF (13.6 mL), H_2O (1.36 mL), and methyl acrylate (81.4 μmol, 0.90 mmol) were added to the flask. The mixture was pumped into a flow reactor (2 mm width, 0.5 mm depth, 3 m length, MiChS Co., Ltd.) at room temperature by a syringe pump at a flow rate of 0.75 mL/h (residence time: 4.0 h) and irradiated with a 48 W LED bulb. The product stream was collected into an Erlenmeyer flask. The mixture was collected for 6 mL in total, and diluted with saturated $NaHCO_3$ aq. The whole was extracted twice with Et_2O. The extract was washed with saturated $NaHCO_3$ aq and H_2O and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (6:1) to give **10b** as colorless oil. The ratio of the diastereomers was determined by ^{1}H NMR analysis.

*tert-Butyl [(2S,3S)-2-Methyl-6-oxotetrahydro-2H-pyran-3-yl] Carbamate (**11**). One-Step Process.* To a stirred solution of **10b** (42.7 mg, 0.14 mmol) in benzene (1.0 mL) was added acetic acid (0.50 mL) at 100 °C. After being stirred for 24.0 h at the same temperature, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give **11** as a colorless oil (20.3 mg, 63% yield, 62:38 diastereomixture). All spectral data were in agreement with those reported by Nishiyama et al.[6b]

Two-Step Process. To a stirred solution of **10b** (37.5 mg, 0.12 mmol) in MeOH was added CSA (2.9 mg, 12 μmol) at room temperature. After being stirred for 2.0 h at the same temperature, the mixture was quenched with H_2O. The whole was extracted twice with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ aq and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give the 1,2-amino alcohol as a colorless oil (24.6 mg, 76% yield, diasteromixture). The pure diastereomer of amino alcohol was isolated by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1). To a stirred solution of the above pure diastereomer of amino alcohol (71.0 mg, 0.27 mmol) in benzene (2.0 mL) was added acetic acid (1.0 mL) at 100 °C. After being stirred for 16.5 h at the same temperature, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:2) to give **11** as a colorless oil (66.7 mg, quant.).

*Benzyl [(2S,3S)-2-Methyl-6-oxotetrahydro-2H-pyran-3-yl] Carbamate (**12**).* To a stirred solution of **11** (48.8 mg, 0.213 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C was added trifluoroacetic acid (0.40 mL), and the mixture was stirred for 2.0 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was dissolved in THF (2 mL). To the solution at 0 °C were added ZCl (33.8 μL, 0.234 mmol) and dropwise Et_3N (75.7 μL, 0.533 mmol). After being stirred for 13.0 h at room temperature, the mixture was quenched with saturated $NaHCO_3$ aq. The whole was extracted twice with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ aq and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:1) to give **12** as colorless oil (40.9 mg, 73% yield): $[\alpha]^{28}_D$ −32.1 (*c* 1.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 5.88 (d, J = 8.8 Hz, 1H), 5.10 (s, 2H), 4.51−4.43 (m, 1H), 4.07 (m, 1H), 2.57−2.44 (m, 2H), 2.21−2.08 (m, 1H), 1.97−1.87 (m,1H), 1.30 (d, J = 6.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.5, 156.3, 136.2, 128.3 (2C), 128.0, 127.7 (2C), 77.2, 66.7, 47.0, 25.8, 25.3, 16.8; HRMS (ESI) (m/z) calcd for $C_{14}H_{17}NNaO_4$ [M + Na]$^+$ 286.1050, found 286.1052.

*Benzyl [(2S,3S)-6-Hydroxy-2-methyltetrahydro-2H-pyran-3-yl] Carbamate (**13**).* To a stirred solution of **12** (40.9 mg, 0.155 mmol) in CH_2Cl_2 (2 mL) was added DIBAL-H in *n*-hexane (1.03 M; 202 μL, 0.208 mmol) at −78 °C. After being stirred for 1.0 h at this temperature, the mixture was quenched with MeOH and saturated Rochelle salt aq. After being stirred for 5.5 h at room temperature, the whole was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the filtrated was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (1:1) to give **13** as a colorless oil (35.4 mg, 86% yield, 62:38 anomeric mixture): $[\alpha]^{28}_D$ −7.58 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) of major anomer δ 7.39−7.29 (m, 5H), 5.53 (d, J = 9.3 Hz, 1H), 5.11 (s, 2H), 4.82−4.74 (m, 1H), 3.77−3.71 (m, 2H), 2.13−1.95 (m, 2H), 1.85−1.67 (m, 2H), 1.19 (d, J = 6.3 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) of minor anomer: δ 7.39−7.25 (m, 5H), 5.32 (d, J = 9.3 Hz, 1H), 5.23−5.12 (m, 1H), 5.11 (s, 2H), 4.37−4.31 (m, 1H), 3.70−3.63 (m, 1H), 1.84−1.66 (m, 2H), 1.52−1.39 (m, 2H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) of major anomer δ 156.2, 136.5, 128.5 (2C), 128.0 (2C), 127.9, 96.3, 73.2, 66.6, 47.8, 27.9, 23.3, 17.6; ^{13}C NMR (400 MHz, $CDCl_3$) of minor anomer: δ 156.2, 136.4, 128.5 (2C), 128.1 (2C), 127.9, 91.5, 66.7, 65.3, 48.7, 27.3, 24.2, 17.5; HRMS (ESI) (m/z) calcd for $C_{14}H_{19}NNaO_4$ [M + Na]$^+$ 288.1206, found 288.1207.

*Benzyl [(2S,3S)-6-Ethoxy-2-methyltetrahydro-2H-pyran-3-yl] Carbamate (**14**).* To a stirred solution of **13** (42.09 mg, 0.159 mmol) in EtOH (2.6 mL) was added *p*-toluenesulfonic acid monohydrate (3.02 mg, 15.9 μmol) at room temperature. After being stirred for 3.0 h at 70 °C, the mixture was quenched with H_2O. The whole was extracted twice with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ aq and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give **14** as colorless oil (30.0 mg, 64% yield, 65:35 anomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) of major anomer δ 7.39−7.25 (m, 5H), 5.26 (d, J = 9.3 Hz, 1H), 5.11 (s, 2H), 4.79−4.73 (m, 1H), 4.12−4.05 (m, 1H), 3.72−3.63 (m, 2H), 3.48−3.40 (m, 1H), 2.09−1.91 (m, 2H), 1.79−1.65 (m, 2H), 1.27−1.14 (m, 3H), 1.10 (d, J = 6.3 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) of minor anomer δ 7.39−7.25 (m, 5H), 5.33 (d, J = 9.3 Hz, 1H), 5.10 (s, 2H), 4.46−4.41 (m, 1H), 3.98−3.90 (m, 1H), 3.72−3.65 (m, 2H), 3.55−3.47 (m, 1H), 1.79−1.66 (m, 2H), 1.62−1.46 (m, 2H), 1.27−1.15 (m, 3H), 1.20−1.15 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) of major anomer δ 156.2, 136.5, 128.5 (2C), 128.0 (2C), 127.7, 96.8, 66.7, 65.0, 62.6, 48.8, 28.1, 24.1, 17.5, 15.1; ^{13}C NMR (400 MHz, $CDCl_3$) of minor anomer δ 156.2, 136.6, 128.4 (2C), 128.1 (2C), 127.9, 101.9, 72,9, 66.5, 64.3, 48.1, 26.1, 24.3, 17.5, 15.1; HRMS (ESI) (m/z) calcd for $C_{16}H_{23}NNaO_4$ [M + Na]$^+$ 316.1519, found 316.1522.

*(2S,3S)-6-Ethoxy-2-methyltetrahydro-2H-pyran-3-amine−Hydrogen p-Toluenesulfonate (**15**).* To a stirred solution of **14** (30.0 mg, 0.102 mmol) in EtOH (1 mL) was added $Pd(OH)_2/C$ (20% on charcoal, 6.00 mg, 8.55 μmol) at room temperature. After being stirred for 14.0 h under a H_2 atmosphere (3 bar) at the same temperature, the mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was taken up in Et_2O and treated with an ethereal solution of *p*-toluenesulfonic acid, and the mixture was filtered to give **15** as a white amorphous solid (17.96 mg, 53% yield, 63:37 anomeric mixture): mp 125−126 °C [lit.[7b] mp 145−146 °C (the anomeric ratio was not shown in the literature)]; ^{1}H NMR (400 MHz, $CDCl_3$) of major anomer δ 7.75 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 4.67−4.63 (m, 1H), 4.02−3.95 (m, 1H), 3.66−3.56 (m, 1H), 3.43−3.33 (m, 1H), 3.26 (m, 1H), 2.35 (s, 3H), 2.07−1.87 (m, 2H), 1.45−1.37 (m, 2H), 1.21−1.12 (m, 6H); ^{1}H NMR (400 MHz, $CDCl_3$) of minor anomer δ 7.75 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 4.43−4.38 (m, 1H), 3.91−3.82 (m, 1H), 3.71−3.61 (m,

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1H), 3.52−3.43 (m, 2H), 3.29 (m, 1H), 2.35 (s, 3H), 1.79−1.64 (m, 2H), 1.63−1.54 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.21−1.12 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) of major anomer: δ 141.6, 140.2, 128.8 (2C), 126.1 (2C), 96.4, 63.2, 62.6, 49.4, 22.9, 22.1, 21.3, 17.2, 15.2; ^{13}C NMR (400 MHz, $CDCl_3$) of minor anomer δ 141.6, 140.2, 128.8 (2C), 126.1 (2C), 101.6, 71.3, 63.7, 48.6, 25.8, 25.0, 21.3, 17.2, 15.0; HRMS (ESI) (m/z) calcd for $C_8H_{17}NNaO_2$ $[M + Na]^+$ 182.1151, found 182.1150.

*N-[(2S,3S)-6-Ethoxy-2-methyltetrahydro-2H-pyran-3-yl]-acetamide (**16**).* To a stirred solution of **14** (25.6 mg, 87.3 μmol) in EtOH (1 mL) was added $Pd(OH)_2/C$ (20% on charcoal, 5.10 mg, 7.27 μmol) at room temperature. After being stirred for 18.0 h under a H_2 atmosphere (3 bar) at the same temperature, the mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to give a crude amine, which was used without further purification. To a stirred solution of the above amine in pyridine (0.40 mL) was added acetic anhydride (0.20 mL) at room temperature. After being stirred for 20.0 h at the same temperature, the mixture was diluted with CH_2Cl_2, washed with 1 M HCl, H_2O, saturated $NaHCO_3$ aq, and brine, and dried over Na_2SO_4. The filtrate was concentrated in vacuo to give **16** as a white amorphous solid (5.25 mg, 21% yield, 58:42 anomeric mixture): mp 113−114 °C [lit.[7b] mp 150−151 °C (the anomeric ratio was not shown in the literature)]; ^{1}H NMR (400 MHz, $CDCl_3$) of major anomer δ 4.83−4.76 (m, 1H), 4.14−4.06 (m, 1H), 3.96−3.91 (m, 1H), 3.73−3.64 (m, 1H), 3.48−3.41 (m, 1H), 2.04 (s, 3H), 1.79−1.56 (m, 4H), 1.28−1.18 (m, 3H), 1.08 (d, J = 6.3 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) of minor anomer δ 4.48−4.42 (m, 1H), 4.00−3.94 (m, 1H), 3.93−3.88 (m, 1H), 3.72−3.66 (m, 1H), 3.60−3.51 (m, 1H), 2.01(s, 3H), 1.79−1.56 (m, 4H), 1.28−1.18 (m, 3H), 1.17 (d, J = 6.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) of major anomer δ 169.8, 96.8, 65.0, 64.5, 46.9, 24.5, 23.8, 23.5, 17.6, 15.1; ^{13}C NMR (400 MHz, $CDCl_3$) of minor anomer δ 169.8, 102.7, 72.9, 62.7, 46.3, 27.8, 26.3, 23.4, 17.6, 15.1; HRMS (ESI) (m/z) calcd for $C_{10}H_{19}NNaO_3$ $[M + Na]^+$ 224.1257, found 224.1254.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02531.

NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fujimotoy@chem.keio.ac.jp.

ORCID

Yukari Fujimoto: 0000-0001-5320-3192

Notes

The authors declare no competing financial interest.

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