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Synthetic Access to All Four Stereoisomers of Oxetin

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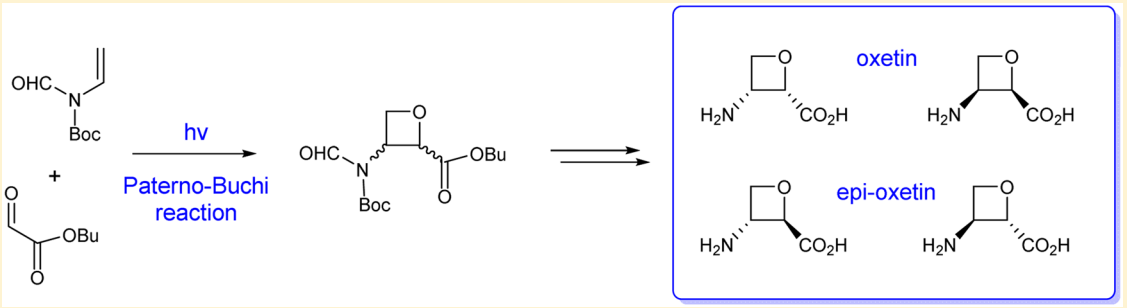
Supporting Information



ABSTRACT: A short synthesis of all four stereoisomers of 3-amino-2-oxetanecarboxylic acid (oxetin) is described. The oxetane core is built using a Paternò–Büchi photochemical [2 + 2] cycloaddition; from the key intermediates, complementary resolution protocols provide access to enantiomerically pure oxetin and *epi*-oxetin on gram-scale.

The β-amino acid (2*R*,3*S*)-*cis*-3-amino-2-oxetanecarboxylic acid, named oxetin, was first isolated by Ōmura et al. in 1984 from the soil bacterium *Streptomyces sp.* OM-2317 (Figure 1). It showed herbicidal activity through inhibition of plant

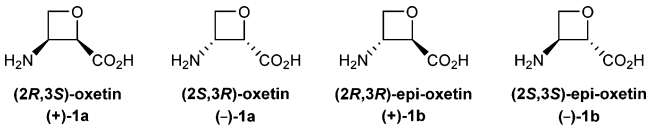
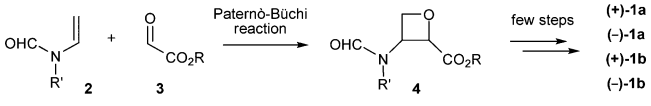


Figure 1. Four stereoisomers of oxetin.

glutamine synthetase and exhibited antibacterial activity against *Bacillus subtilis, Piriculaia oryzae,* and other microorganisms.[1] The same authors described the synthesis of (2*R*,3*S*)-oxetin from D-glucose, which also provided the three other stereoisomers in more than 10 steps for each stereoisomer and a combined overall yield of 7%.[2] In 1997, Bach and Schröder applied the Paternò–Büchi [2 + 2] photocycloaddition reaction to the synthesis of oxetin; this synthesis required only four steps and provided oxetin in 14% overall yield, but only the racemic cis stereoisomer was obtained.[3] More recently, Blauvelt and Howell investigated an approach to oxetin starting from L-serine; the unexpected diastereoselectivity observed during the reduction of a spiroepoxide intermediate led to a single enantiomer of the trans diastereoisomer, *epi*-oxetin, in 10 steps and 1.5% overall yield.[4]

Functionalized oxetanes are important building blocks for the synthesis of complex molecules and drug discovery,[5] and as a cyclic β-amino acid, oxetin has further potential for inclusion in biologically active peptides.[6−8] These observations, alongside the initial reports of biological activity for natural (2*R*,3*S*)-oxetin, warrant further development of a short, reliable access to all stereoisomers on an exploitable scale. A comparison of the three previous studies suggested to us that the Paternò–Büchi reaction was the most promising strategy;[9−11] we describe herein its successful application, employing *N*-formyl enamine **2**[12] and glyoxylate ester **3**[13] to provide to core oxetane skeleton **4**, from which the requisite targets are obtained as single enantiomers on gram-scale (Scheme 1).

Scheme 1



We began by investigating the influence of the alkyl moiety of the glyoxylate ester on the course of the Paternò–Büchi reaction. To this end, we prepared the *n*-butyl, methyl, and *t*-butyl esters (**3a–c**): the former two were obtained by periodate-mediated oxidative cleavage of the corresponding dialkyl tartrates[14] and the latter by ozonolysis of *tert*-butyl acrylate.[15] These compounds had to be freshly distilled from P_2O_5 immediately before use; even so, their marked propensity for hydrate or hemiacetal formation imposed the use of a dry

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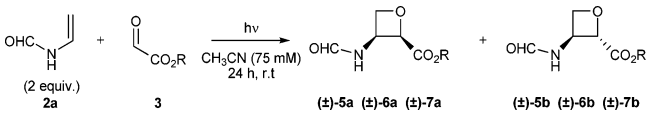
aprotic solvent in the photochemical reaction. Our first choice of enamine partner was *N*-vinylformamide **2a**, a stable, commercially available material.

Freshly distilled glyoxylates **3a**−**c** in anhydrous acetonitrile (75 mM) were each engaged in a [2 + 2] photocycloaddition reaction with two equivalents of **2a** in a Pyrex reaction vessel (200 mL) using a 400 W Hg-vapor lamp for 24 h to furnish oxetanes **5**−**7** in 34−37% yields (Table 1). In each case,

Table 1. Influence of the Nature of the Glyoxylate Ester



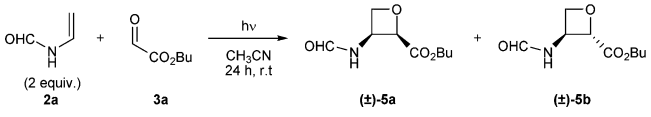
entry	R	glyoxylate	ratio **a**/**b**[a]	yield (%)[b]
1	*n*-Bu	**3a**	**5a**/**5b** 51:49	37
2	Me	**3b**	**6a**/**6b** 50:50	37
3	*t*-Bu	**3c**	**7a**/**7b** 54:46[c]	34

[a]Ratio determined from crude ^{1}H NMR spectra. [b]Isolated yield of inseparable diastereoisomeric mixture. [c]Diastereoisomers were not unambiguously assigned.

complete regioselectivity was observed while the cis/trans ratio was close to 1:1; in no case could the **a**/**b** diastereoisomers be separated on a preparative scale. The moderate efficiency is typical of Paternò−Büchi reactions where the carbonyl reagent is not an aromatic aldehyde and is quite acceptable given the intrinsic low stability of glyoxylates and their sensitivity to photodecomposition.[16] The high regioselectivity and poor diastereoselectivity are in agreement with mechanistic arguments of the Paternò−Büchi reaction.[17] Most literature precedents featuring a glyoxylate in Paternò−Büchi reactions employ the *n*-butyl ester **3a**;[13] we likewise retained it for subsequent studies.

The influence of concentration and scale were investigated next (Table 2). Whereas concentration had no effect on the

Table 2. Scaling of the Reaction between 2a and 3a



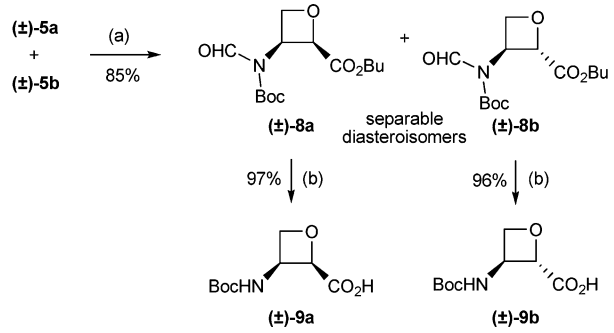
entry	concn	scale	Ratio **5a**/**5b**[a]	yield (%)[b]
1	75 mM	200 mL	51:49	37
2	20 mM	200 mL	47:53	33
3	150 mM	200 mL	51:49	34
4	75 mM	1000 mL	50:50	43
5	100 mM	1000 mL	50:50	46
6[c]	75 mM	100 mL	48:52	19

[a]Ratio determined from crude ^{1}H NMR spectra. [b]Isolated yield of diastereoisomeric mixture. [c]Performed using Rayonet apparatus RPR-200.

efficiency (entries 1−3), working on a larger scale was perceptibly beneficial (entries 4 and 5). The best result was obtained by employing **3a** (100 mM) and two equivalents of **2a** in acetonitrile in a large Pyrex reaction vessel (1 L) using a 400 W Hg-vapor lamp, which gave the photoadducts **5a**/**5b** in 46% yield on multigram-scale (9.3 g, 46 mmol). The same reaction was also examined using a Rayonet apparatus, but the efficiency was significantly lower (entry 6).

Four-membered ring *β*-amino acids are susceptible to ring opening when the amine function is not deactivated by a protecting group.[18] To facilitate subsequent manipulations, we decided to introduce a carbamate protecting group onto **5a**/**5b** in place of the formyl group. The **5a**/**5b** mixture was treated with Boc_2O to provide the corresponding derivatives **8a** and **8b** in 85% yield up to 10 g scale; significantly, these two diastereoisomers could be conveniently separated by column chromatography (Scheme 2). Thus, starting from *N*-vinyl-

Scheme 2

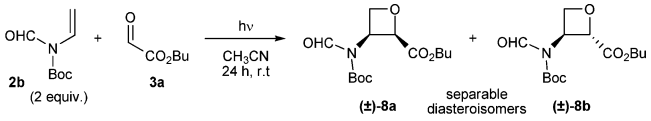


Conditions: (a) Boc_2O, DMAP, THF, 24 h, rt; (b) K_2CO_3, MeOH, then H_2O, 3 h, rt.

formamide **2a** and glyoxylate **3a**, the two-step protocol provided both **8a** and **8b** as single diastereoisomers in 39% combined overall yield. Each derivative was engaged in a one-pot selective deprotection sequence employing K_2CO_3 in methanol to give racemic Boc-protected (±)-oxetin **9a** and (±)-*epi*-oxetin **9b** in 97 and 96% yields, respectively (Scheme 2).

Here, it became evident that we should consider an alternative pathway to **8a** and **8b** using *N*-Boc-*N*-vinylformamide **2b** as a Paternò−Büchi partner; this substrate was prepared in 93% yield from *N*-vinylformamide **2a** upon treatment with Boc_2O and was evaluated in the photochemical reaction with **3a** (Table 3). The first experiment, conducted at

Table 3. Scaling of the Reaction between 2b and 3a



entry	concn	scale	ratio **8a**/**8b**[a]	yield (%)[b]
1	75 mM	200 mL	48:52	13
2	40 mM	200 mL	44:56	18
3	20 mM	200 mL	43:57	45
4	20 mM	1000 mL	48:52	45
5[c]	75 mM	200 mL	50:50	53

[a]Ratio determined from crude ^{1}H NMR spectra. [b]Combined yield of isolated diastereoisomers. [c]Reaction performed using 5 equiv of **2b**.

75 mM, gave only 13% combined yield of adducts **8a**/**8b** (entry 1). Further investigation (entries 2 and 3) revealed that a high **2b** concentration was deleterious to the efficiency of the reaction and that the best yield was obtained when the concentration of **3a** was 20 mM (entry 3). This result could be reproduced on a larger scale (1 L; entry 4). On the premise that photochemical degradation of reagent **2b** might be occurring

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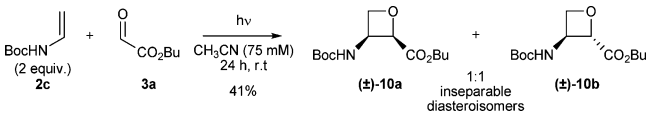
during the reaction time,[19] an experiment was conducted in which the concentration of **2b** (75 mM) represented a 5-fold excess with respect to **3a** (entry 5); in this case, the reaction was indeed more efficient and **8a**/**8b** was obtained in 53% yield. In the course of these investigations, the cis/trans ratio remained close to 1:1. The best result, obtained at 20 mM on large scale (1 L) gave both **8a** and **8b** as single diastereoisomers in 45% yield. This approach represents a valid alternative for access to **8a** and **8b**; starting from *N*-vinylformamide **2a**, the two-step protocol is slightly more efficient than the first route (42% combined overall yield) but requires higher dilution for the photochemical step.

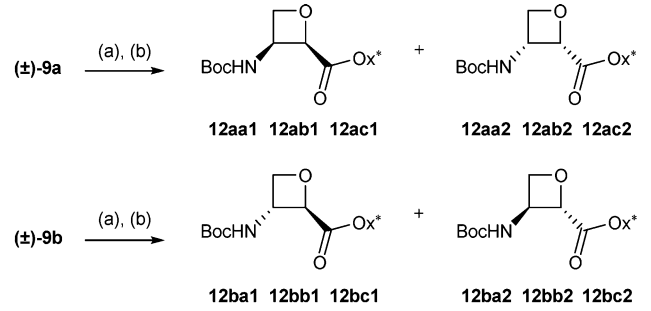
For completeness, we examined a third enamine substrate, *N*-vinyl *tert*-butyl carbamate **2c**, obtained in 98% yield by selective deformylation of **2b** using NaOH in THF. The Paternò–Büchi reaction of **2c** in acetonitrile (75 mM, 200 mL scale) with two equivalents of **3a** gave **10a** and **10b** in 41% yield as an inseparable 1:1 diastereoisomeric mixture (Scheme 3). Because this route offered no advantage with respect to the previous series, it was not pursued.

Scheme 3



We turned our attention to the matter of resolution. Noting previous successes with chiral nonracemic oxazolidinones as resolving agents for cyclic β-amino acids,[20] we screened three such auxiliaries for the chiral derivatization of **9a** and **9b** (Table 4). Standard peptide coupling reagents were unproductive, so we applied more stringent conditions: the acid function of **9a** or **9b** was activated using pivaloyl chloride and then treated with the lithium salt of the oxazolidinone **11a**–**c**; highest yields were obtained using an excess of both of these reagents.

Table 4. Chiral Resolution



entry	sub. 9	LiOx• 11	product	separation[a]	yield (%)[b]
1	**9a**	**11a**	**12aa1/2**	poor	45 (52)
2		**11b**	**12ab1/2**	good	51c (57)
3		**11c**	**12ac1/2**	excellent	69 (81)
4	**9b**	**11a**	**12ba1/2**	good	66 (86)
5		**11b**	**12bb1/2**	fair	34 (44)
6		**11c**	**12bc1/2**	poor	48 (55)

[a]Ease of preparative chromatographic separation of diastereoisomers **12** and unreacted **11**. [b]Combined yield of diastereoisomers; in parentheses, yields based on recovered **9**.

After optimization, (±)-*N*-Boc-oxetin **9a** and oxazolidinone **11a** gave diastereoisomers **12aa1** and **12aa2** in 45% combined yield, which equated to 52% yield taking recovered starting material **9a** into account (entry 1). The modest yield was compounded by the impracticality of the separation of the two diastereoisomers and unreacted **11a**. With oxazolidinone **11b**, the yield and ease of separation improved slightly (entry 2). Oxazolidinone **11c** gave better results: diastereoisomers **12ac1** and **12ac2** were obtained in 69% combined yield (81% based on recovered **9a**) and were easily separated by chromatography (entry 3).

With (±)-*N*-Boc-*epi*-oxetin **9b**, oxazolidinone **11a** provided diastereoisomers **12ba1** and **12ba2** in 66% combined yield (86% yield based on recovered **9b**), and separation by chromatography was satisfactory (entry 4). This turned out to be the most practical system, for the corresponding derivatizations using oxazolidinones **11b** and **11c** gave lower yields and poorer separations (entries 5 and 6).

An important spin-off from the above endeavors was the isolation of crystals of derivatives **12ab2** and **12bb2**, which were suitable for X-ray diffraction analysis, thus confirming the molecular structures and revealing the absolute configurations of the oxetane stereogenic centers (Figure 2).

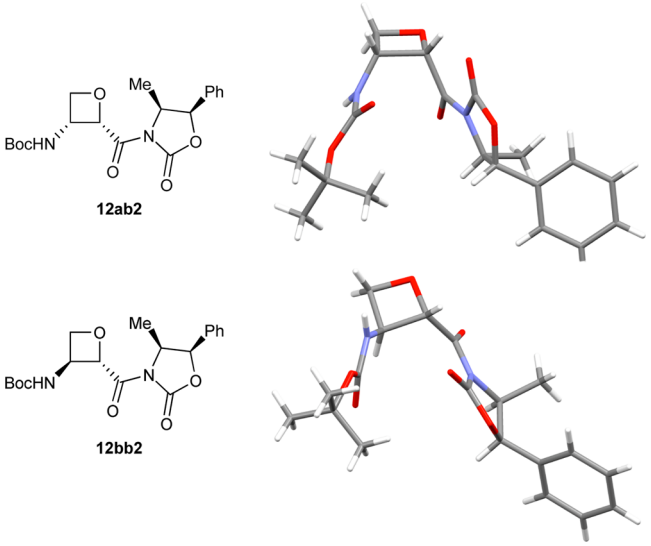


Figure 2. X-ray structures of **12ab2** and **12bb2**.

Enantiomerically pure *N*-Boc-oxetins (2*R*,3*S*)-**9a** and (2*S*,3*R*)-**9a** were obtained in high yields by $LiOH/H_2O_2$ hydrolysis of derivatives **12ac1** and **12ac2**, respectively, in a procedure that allowed recovery and recycling of oxazolidinone **11c**. Similarly, derivatives **12ba1** and **12ba2** provided *N*-Boc-*epi*-oxetins (2*R*,3*R*)-**9b** and (2*S*,3*S*)-**9b** as well as recovered oxazolidinone **11a**. The absolute configurations of these compounds were deduced by conducting analogous hydrolyses on **12ab2**, which gave (+)-(2*S*,3*R*)-**9a**, and **12bb2**, which gave (−)-(2*S*,3*S*)-**9b**. Each *N*-Boc-β-amino acid was deprotected in excellent yield using TFA to complete the stated objectives and provide all four oxetin and *epi*-oxetin stereoisomers: (+)-**1a**, (−)-**1a**, (+)-**1b**, and (−)-**1b** (Scheme 4). Spectroscopic and

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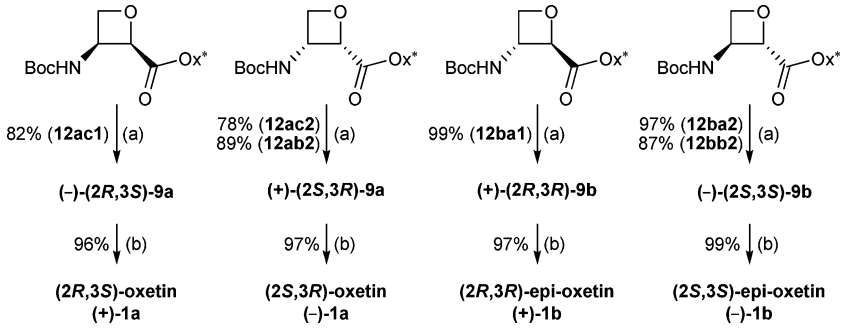
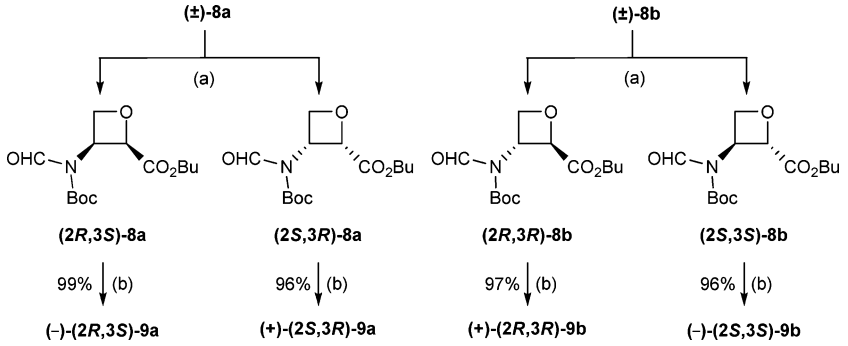
Scheme 4



Conditions: (a) LiOH, H_2O_2 THF/H_2O (4:1), 2 h, 0 °C; (b) TFA, CH_2Cl_2, 3 h, rt, then Dowex, NH_4OH.

Scheme 5



Conditions: (a) chiral HPLC separation; (b) K_2CO_3, MeOH, then H_2O, 3 h, rt.

optical rotation data were in full agreement with the literature.[2,4]

Chiral derivatization may not always be a favored option, so we considered an alternative access to single oxetin stereoisomers using chiral HPLC. Racemates (±)-**9a** and (±)-**9b** (Scheme 2) were extensively degraded regardless of the nature of the stationary phase. Pleasingly, however, each racemate, (±)-**8a** and (±)-**8b** (Table 3), was separated on a lux cellulose column with good selectivity (α = 1.63 for **8a** and α = 1.25 for **8b**) providing ∼1 g of each enantiomer (>99% ee by chiral HPLC analysis) in 12 h using an automatic injection sequence. We verified that the one-pot selective deprotection protocol proceeded without incident and obtained the expected single enantiomers of *N*-Boc-oxetin **9a** and *N*-Boc-*epi*-oxetin **9b** in high yields on gram-scale (Scheme 5).

In summary, an expedient access to all stereoisomers of oxetin on gram-scale has thus been established via a Paternò–Büchi synthetic strategy starting from **2b** and **3a**. For any individual oxetin target, the protocol requires five synthetic steps and two chromatographic separations if a resolving agent is employed or just three steps plus one chromatographic separation and one chiral HPLC operation if this latter technique is preferred. The overall yield for a single isomer is ∼8% in the former case and ∼11% in the latter.

EXPERIMENTAL SECTION

General Experimental Information. All reagents and solvents were of commercial grade and used without further purification with the exception of MeCN, which was distilled from P_2O_5, *n*-BuOH, which was distilled from $MgSO_4$, CH_2Cl_2, which was dried over activated alumina, and THF, which was distilled from sodium/benzophenone. Flash chromatography was performed on columns of silica gel (35–70 μm). Analytical thin-layer chromatography was carried out on commercial 0.25 mm silica gel plates, which were visualized by UV fluorescence at 254 nm and then revealed using a phosphomolybdic acid solution (10% in EtOH) or a ninhydrin solution (0.3% in *n*-BuOH). Retention factors (R_f) are given for such TLC analyses. Melting points were obtained in open capillary tubes and are uncorrected. Optical rotations were measured using a 10 cm quartz cell; values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature T using solutions of concentration (c) in units of g/100 mL. Fourier-transform infrared (IR) spectra were recorded for neat samples using an ATR diamond accessory; maximum absorbances (ν) are given in cm^{-1}. Nuclear magnetic resonance (NMR) data were acquired on a spectrometer operating at 400/360/300/250 MHz for ^1H and at 90/75/63 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm with respect to tetramethylsilane (δ = 0 ppm). Splitting patterns for ^1H and ^{13}C NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), broad singlet (br s), or m (multiplet). Coupling constants (J) are reported in Hz. High-resolution mass spectrometry (HRMS) data were recorded using a spectrometer equipped with an electrospray ionization source in either positive or negative mode as appropriate with a tandem Q-TOF analyzer. Preparative HPLC purification of the two enantiomers of the compounds **8a** and **8b** was carried out on a commercial apparatus equipped with a semipreparative autosampler and collector accessories. All solvents were HPLC grade and were filtered through a 0.45 μm PTFE membrane. Injected solutions were filtered through a 0.22 μm PTFE membrane. Methyl glyoxylate **3b**,[14] *tert*-butyl glyoxylate **3c**,[14] oxazolidin-2-one **11a**,[21a] and oxazolidin-2-one **11b**[21b] were prepared according to literature procedures.

General Procedure A for the Paternò–Büchi Reaction. A solution of glyoxylate **3** (1 equiv) and enamine derivative **2** (2 equiv) in MeCN was placed in a cylindrical immersion photochemical reactor and degassed with an argon stream for 30 min. The solution was irradiated for 24 h with a 400 W medium-pressure Hg lamp fitted with a Pyrex filter and a water-cooling jacket. The solution was then

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evaporated under reduced pressure to give the crude product, which was purified by flash chromatography to afford the requisite product.

General Procedure B for the Deformylation/Saponification Sequence. To an ice-cold solution of compound **8** (1 equiv) in MeOH (13 mL/mmol) was added K_2CO_3 (3 equiv). The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. Water (6 mL/mmol) was added, and the reaction mixture was further stirred at room temperature for 1 h. MeOH was evaporated under reduced pressure, and the remaining aqueous solution was washed with EtOAc (3 × 6 mL/mmol). The aqueous phase was then acidified with $KHSO_4$ and extracted with EtOAc (4 × 6 mL/mmol). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give product **9**.

General Procedure C for Oxazolidinone Coupling. To a cold (−78 °C) solution of racemic compound **9** (1 equiv) and triethylamine (1.2 equiv) in THF (10 mL/mmol) was added pivaloyl chloride (1.5 equiv) dropwise. The mixture was stirred at 0 °C for 1 h to form the mixed anhydride and then cooled to −78 °C. In a separate flask, a cold (−40 °C) solution of oxazolidinone **11** (1.6 equiv) in THF (5 mL/mmol) was treated with a hexane solution of *n*-BuLi (1.6 equiv) and stirred for 25 min. The resulting solution was cooled to −78 °C and added by rapid cannulation to the cooled (−78 °C) solution of the mixed anhydride. Residual metalated oxazolidinone was taken up by rinsing with dry THF and added to the cooled reaction mixture. After 2 h, the reaction mixture was quenched at −78 °C by addition of a saturated aqueous solution of $NaHCO_3$ and then allowed to warm to room temperature. THF was removed under reduced pressure, and the remaining aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL/mmol). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL/mmol) then brine (15 mL/mmol), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography to afford the two diastereoisomers **12**. Unreacted **9** was recovered from the basic aqueous phase by acidification and then extraction with CH_2Cl_2.

General Procedure D for Oxazolidinone Cleavage. To an ice-cold solution of the indicated compound **12** (1 equiv) in a 1:4 mixture of water and THF (25 mL/mmol) was added a 35% w/w solution of H_2O_2 (2 equiv). The resulting mixture was stirred at 0 °C for 5 min, and then a solution of $LiOH·H_2O$ (2 equiv) in water (6 mL/mmol) was added. The mixture was stirred at 0 °C for 2 h, and then saturated aqueous solutions of Na_2SO_3 (14 mL/mmol) and $NaHCO_3$ (14 mL/mmol) were added successively. THF was removed under reduced pressure, and the residual aqueous solution was washed with CH_2Cl_2 to remove and recycle the chiral auxiliary. The aqueous solution was then acidified to pH 1 with an aqueous solution of $KHSO_4$ (1 M) and extracted with CH_2Cl_2 (3 × 10 mL/mmol). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give nonracemic product **9**.

General Procedure E for Boc Group Removal. To a solution of the indicated compound **9** (1 equiv) in CH_2Cl_2 (15 mL/mmol) under argon was added trifluoroacetic acid (15 equiv). The solution was stirred for 3 h, then the reaction mixture was concentrated under reduced pressure. The residue was applied to a column of Dowex 50W-X8 cation exchange resin (200 mesh) and eluted using 1 M NH_4OH to give the target amino acid.

Di-n-butyl Tartrate. To a mixture of tartaric acid (118 g, 0.78 mol, 1 equiv) and *n*-BuOH (350 mL, 3.93 mol, 5 equiv) was added TMSCl (200 mL, 1.56 mol, 2 equiv). The reaction mixture was refluxed for 6 h and then cooled to room temperature. Excess *n*-BuOH and TMSCl were removed under reduced pressure, and the oily residue was distilled under reduced pressure (0.45 mmHg) at 130 °C to give the expected product as a colorless oil (121 g, 59%). R_f (25:75 EtOAc/petroleum ether) = 0.60; IR ν 3487, 2961, 2935, 2875, 1738, 1243, 1124, 1086; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.48 (s, 2H), 4.18 (t, J = 6.6 Hz, 4H), 3.53 (s, 2H), 1.67−1.53 (m, 4H), 1.41−1.25 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H);[14a] ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6 (2C), 72.2 (2CH), 66.0 ($2CH_2$), 30.5 ($2CH_2$), 18.9 ($2CH_2$), 13.5 ($2CH_3$);[14a] HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{12}H_{22}O_6Na$ 285.1314, found 285.1302.

n-Butyl Glyoxylate ***3a***. To a solution of di-*n*-butyl tartrate (31.5 g, 120 mmol, 1 equiv) in Et_2O (1 L) at 0 °C under argon was added periodic acid dihydrate (27.3 g, 120 mmol, 1 equiv) in portions (3 × 9.1 g) over a period of 1 h. The reaction mixture was stirred further for 5 h at room temperature. The resulting mixture was then filtered through a pad of Celite/Na_2SO_4, and the filtrate was concentrated under reduced pressure. The residue was distilled from P_2O_5 under reduced pressure (18 mmHg) at 70 °C to give product **3a** as a colorless oil (27 g, 86%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.40 (s, 1H), 4.32 (t, J = 6.7 Hz, 2H), 1.81−1.63 (m, 2H), 1.51−1.34 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H);[14d] ^{13}C NMR (63 MHz, $CDCl_3$) δ 184.0 (CH), 159.6 (C), 66.4 (CH_2), 30.3 (CH_2), 18.9 (CH_2), 13.5 (CH_3); HRMS (ESI-TOF) not stable.

tert-Butyl Formyl(vinyl)carbamate ***2b***. To a solution of *N*-vinylformamide **2a** (4.18 mL, 60 mmol, 1 equiv) in THF (200 mL) were added Boc_2O (15.7 g, 72 mmol, 1.2 equiv) and 4-dimethylaminopyridine (73 mg, 0.6 mmol, 0.01 equiv). The reaction mixture was stirred for 22 h under argon at room temperature, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (20:80 EtOAc/petroleum ether) to give product **2b** as a colorless liquid (9.55 g, 93%). R_f (5:95 EtOAc/petroleum ether) = 0.46; IR ν 2982, 1740, 1709, 1349, 1297, 1249, 1140, 1053; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.23 (s, 1H), 6.57 (dd, J = 16.2, 9.7 Hz, 1H), 5.65 (dd, J = 16.2, 1.2 Hz, 1H), 5.01 (d, J = 9.7 Hz, 1H), 1.54 (s, 9H);[22] ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.1 (CH), 151.3 (C), 126.1 (CH), 107.8 (CH_2), 84.8 (C), 27.8 ($3CH_3$); HRMS (ESI-TOF) not stable.

tert-Butyl Vinylcarbamate ***2c***. To a solution of *tert*-butyl formyl(vinyl)carbamate **2b** (7.16 g, 41.9 mmol, 1 equiv) in THF (25 mL) at 0 °C was added carefully over a 20 min period a 2 M aqueous solution of NaOH (25 mL, 50 mmol, 1.2 equiv). The reaction mixture was left at 0 °C for a further 10 min and then stirred at room temperature for 2.5 h. The reaction mixture was diluted with water (20 mL) and extracted with ^{t}BuOMe (4 × 20 mL). The combined organic phases were then washed with water and then brine. The resulting organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was then recrystallized at −20 °C overnight in pentane to give product **2c** as a white solid (5.87 g, 98%). R_f (50:50 EtOAc/petroleum ether) = 0.33; mp 65−67 °C (lit.[22] mp 67−68 °C); IR ν 3324, 2986, 2974, 1690, 1646, 1369, 1250, 1152, 1083, 977; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.75−6.58 (m, 1H), 6.29 (br s, 1H), 4.40 (d, J = 15.7 Hz, 1H), 4.21 (d, J = 8.2 Hz, 1H), 1.47 (s, 9H);[22] ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.9 (C), 130.2 (CH), 92.0 (CH_2), 80.4 (C), 28.3 ($3CH_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_7H_{14}NO_2$ 144.1019, found 144.1021.

n-Butyl 3-Formamidooxetane-2-carboxylate ***5a/b***. General procedure A was applied for the photochemical reaction between *n*-butyl glyoxylate **3a** (13.0 g, 100 mmol) and *N*-vinylformamide **2a** (14.2 g, 13.9 mL, 200 mmol) in MeCN (1 L). Flash chromatography (70:30 EtOAc/petroleum ether) gave a mixture of two inseparable diastereoisomers **5a** and **5b** (50/50 dr) as a colorless oil (9.17 g, 46%). R_f (70:30 EtOAc/petroleum ether) = 0.32; IR ν 3675, 3309, 2964, 2901, 1735, 1669, 1394, 1212, 1042; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_9H_{15}NO_4Na$ 224.0899, found 224.0891. From the mixture, the following NMR data was deduced. For **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.83−6.73 (m, 1H), 5.56−5.41 (m, 1H), 5.29 (d, J = 7.8 Hz, 1H), 4.97 (dd, J = 7.6, 6.9 Hz, 1H), 4.66 (t, J = 6.6 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 1.71−1.55 (m, 2H), 1.44−1.29 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.1 (C), 161.0 (CH), 83.2 (CH), 76.7 (CH_2), 65.4 (CH_2), 44.1 (CH), 30.5 (CH_2), 18.9 (CH_2), 13.5 (CH_3). For **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.71−6.62 (m, 1H), 5.14- 5.01 (m, 2H), 4.84 (t, J = 6.9 Hz, 1H), 4.56 (t, J = 6.3 Hz, 1H), 4.19 (t, J = 6.6 Hz, 2H), 1.69−1.55 (m, 2H), 1.42−1.28 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.3 (C), 161.2 (CH), 83.9 (CH), 75.6 (CH_2), 65.5 (CH_2), 46.5 (CH), 30.4 (CH_2), 18.9 (CH_2), 13.6 (CH_3).

Methyl 3-Formamidooxetane-2-carboxylate ***6a/b***. General procedure A was applied for the photochemical reaction between methyl glyoxylate **3b** (924 mg, 10.5 mmol) and *N*-vinylformamide **2a** (1.49 g,

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1.46 mL, 21 mmol) in MeCN (200 mL). Flash chromatography (90:10 EtOAc/petroleum ether) gave a mixture of two inseparable diastereoisomers **6** (50/50 dr) as a white solid (622 mg, 37%). R_f (90:10 EtOAc/petroleum ether) = 0.21; IR ν 3676, 3299, 2987, 2971, 2961, 2901, 1735, 1670, 1522, 1388, 1230, 1178, 1042, 993; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_6H_9NO_4Na$ 182.0424, found 182.042. From the mixture, the following NMR data was deduced. For **6a**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 5.36−5.25 (m, 1H), 5.21 (d, J = 7.8 Hz, 1H), 4.81 (t, J = 7.2 Hz, 1H), 4.55 (t, J = 6.6 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.1 (C), 161.3 (CH), 83.1 (CH), 76.2 (CH_2), 52.0 (CH_3), 44.0 (CH). For **6b**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H), 5.02−4.93 (m, 2H), 4.69 (t, J = 6.8 Hz, 1H), 4.48 (t, J = 6.2 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.6 (C), 161.4 (CH), 83.5 (CH), 75.4 (CH_2), 52.3 (CH_3), 46.2 (CH).

tert-Butyl 3-Formamidooxetane-2-carboxylate ***7a/b***. General procedure A was applied for the photochemical reaction between *tert*-butyl glyoxylate **3c** (1.06 g, 8.18 mmol) and *N*-vinylformamide **2a** (1.16 g, 1.14 mL, 16.4 mmol) in MeCN (200 mL). Flash chromatography (85:15 EtOAc/petroleum ether) gave a mixture of two inseparable and indistinguishable diastereoisomers (54/46 dr) as a colorless oil (557 mg, 34%). R_f (90:10 EtOAc/petroleum ether) = 0.31; IR ν 3311, 2977, 2932, 2899, 2854, 1731, 1684, 1369, 1248, 1154, 1027; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.11 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 5.41−5.30 (m, 1H), 5.15 (d, J = 7.6 Hz, 1H), 5.07−4.95 (m, 1H), 4.93−4.85 (m, 2H), 4.75 (t, J = 7.0 Hz, 1H), 4.58 (t, J = 6.4 Hz, 1H), 4.49 (t, J = 6.5 Hz, 1H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.5 (C), 169.2 (C), 161.1 (CH), 161.0 (CH), 84.3 (CH), 83.2 (CH), 83.0 (C), 82.7 (C), 76.4 (CH_2), 75.4 (CH_2), 46.5 (CH), 44.3 (CH), 28.1 ($3CH_3$), 27.9 ($3CH_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_9H_{15}NO_4Na$ 224.0893, found 224.0889.

Butyl 3-(N-(tert-Butoxycarbonyl)formamido)oxetane-2-carboxylate ***8a*** *and* ***8b***. General procedure A was applied for the photochemical reaction between *n*-butyl glyoxylate **3a** (2.44 g, 18.8 mmol) and enecarbamate **2b** (6.42 g, 37.5 mmol) in MeCN (1 L). Flash chromatography (70:20:10 petroleum ether/CH_2Cl_2/EtOAc) of the crude mixture of diastereoisomers **8** (48/52 dr by NMR analysis) gave cis diastereoisomer **8a** (1.00 g, 18%) and trans diastereoisomer **8b** (1.53 g, 27%) as colorless oils (2.53 g, 45%). For **8a**: R_f (70:20:10 petroleum ether/CH_2Cl_2/EtOAc) = 0.22; IR ν 2963, 2936, 1739, 1696, 1348, 1299, 1147, 1078, 1024; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.06 (s, 1H), 5.46 (dd, J = 16.3, 8.3 Hz, 1H), 5.22 (dd, J = 7.7, 6.2 Hz, 1H), 5.17 (d, J = 8.6 Hz, 1H), 4.81 (dd, J = 8.4, 6.2 Hz, 1H), 4.12 (t, J = 6.8 Hz, 2H), 1.66−1.57 (m, 2H), 1.52 (s, 9H), 1.40−1.29 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.3 (C), 163.0 (CH), 151.5 (C), 85.6 (C), 81.4 (CH), 74.3 (CH_2), 65.2 (CH_2), 47.1 (CH), 30.5 (CH_2), 28.0 ($3CH_3$), 19.1 (CH_2), 13.7 (CH_3); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{23}NO_6Na$ 324.1418, found 324.1433. For **8b**: R_f (70:20:10 petroleum ether/CH_2Cl_2/EtOAc) = 0.35; IR ν 2963, 2936, 1740, 1698, 1369, 1248, 1218, 1148, 1049; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.13 (s, 1H), 5.43 (d, J = 7.1 Hz, 1H), 5.34 (dd, J = 15.2, 7.2 Hz, 1H), 4.93 (t, J = 6.7 Hz, 1H), 4.73 (dd, J = 8.1, 6.2 Hz, 1H), 4.21 (q, J = 6.6 Hz, 2H), 1.72−1.59 (m, 2H), 1.57 (s, 9H), 1.47−1.31 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.0 (C), 162.9 (CH), 151.4 (C), 85.7 (C), 81.5 (CH), 73.0 (CH_2), 65.4 (CH_2), 48.4 (CH), 30.6 (CH_2), 28.1 ($3CH_3$), 19.0 (CH_2), 13.7 (CH_3); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{23}NO_6Na$ 324.1418, found 324.1423.

To a solution of Boc_2O (17.1 g, 78.5 mmol, 1.5 equiv) and *n*-butyl 3-formamidooxetane-2-carboxylate **5a/b** (50/50 dr; 10.5 g, 52.3 mmol, 1 equiv) in THF (400 mL) was added 4-dimethylaminopyridine (64 mg, 0.52 mmol, 0.01 equiv). The reaction mixture was stirred under argon at room temperature for 24 h. The solvent was removed under reduced pressure. Flash chromatography of the residue (70:20:10 petroleum ether/CH_2Cl_2/EtOAc) gave cis diastereoisomer **8a** (5.75 g, 37%) and trans diastereoisomer **8b** (7.61 g, 48%) as colorless oils. Spectral data of **8a** and **8b** were identical to those described above.

Butyl 3-(tert-Butoxycarbonylamino)oxetane-2-carboxylate ***10a/b***. General procedure A was applied for the photochemical reaction between *n*-butyl glyoxylate **3a** (2.10 g, 16.1 mmol) and enecarbamate **2c** (4.61 g, 32.3 mmol) in MeCN (200 mL). Flash chromatography (20:80 EtOAc/petroleum ether) gave the mixture of two inseparable and indistinguishable diastereoisomers **10** (50/50 dr) as a colorless oil (1.79 g, 41%). R_f (10:90 EtOAc/petroleum ether) = 0.33; IR ν 3350, 2965, 1696, 1367, 1249, 1161, 1062; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.58−5.05 (m, 4H), 4.99−4.45 (m, 6H), 4.22−4.04 (m, 4H), 1.66−1.50 (m, 4H), 1.44−1.27 (m, 22H), 0.92−0.83 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.3 (C), 170.3 (C), 154.5 (2C), 84.9 (CH), 84.2 (CH), 80.3 (2C), 78.3 (CH_2), 76.5 (CH_2), 65.3 (CH_2), 65.1 (CH_2), 49.4 (CH), 46.7 (CH), 30.7 (CH_2), 30.6 (CH_2), 28.4 ($3CH_3$), 28.3 ($3CH_3$), 19.1 (CH_2), 19.0 (CH_2), 13.7 ($2CH_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{23}NO_5Na$ 296.1468, found 296.1462.

cis-3-(tert-Butoxycarbonylamino)oxetane-2-carboxylic Acid ***9a***. General procedure B was applied on compound **8a** (1.01 g, 3.36 mmol) using K_2CO_3 (1.39 g, 10.1 mmol) in MeOH (45 mL) to give product **9a** as a white solid (703 mg, 97%). Mp 153−155 °C; IR ν 3285, 2977, 1749, 1654, 1568, 1288, 1202, 1165, 1066; ^{1}H NMR (250 MHz, CD_3OD) δ 5.17 (d, J = 7.8 Hz, 1H), 5.06−4.94 (m, 1H), 4.83−4.77 (m, 1H), 4.58 (t, J = 6.6 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (63 MHz, CD_3OD) δ 173.1 (C), 157.2 (C), 85.5 (CH), 80.7 (C), 77.0 (CH_2), 48.3 (CH), 28.6 ($3CH_3$); HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_9H_{14}NO_5$ 216.0877, found 216.0882.

trans-3-(tert-Butoxycarbonylamino)oxetane-2-carboxylic Acid ***9b***. General procedure B was applied on compound **8b** (1.00 g, 3.33 mmol) using K_2CO_3 (1.38 g, 10.0 mmol) in MeOH (45 mL) to give product **9b** as a white solid (687 mg, 96%). Mp 124−125 °C; IR ν 3363, 2981, 1724, 1693, 1533, 1169, 1055; ^{1}H NMR (300 MHz, CD_3OD) δ 4.96 (d, J = 4.8 Hz, 1H), 4.72−4.60 (m, 2H), 4.53−4.46 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (90 MHz, CD_3OD) δ 173.9 (C), 157.0 (C), 85.6 (CH), 80.9 (C), 76.9 (CH_2), 50.7 (CH), 28.6 ($3CH_3$); HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_9H_{14}NO_5$ 216.0877, found 216.0872.

tert-Butyl (2R,3S)-2-[(R)-2-Oxo-4-phenyloxazolidine-3-carbonyl]-oxetan-3-yl carbamate ***12ac1*** *and tert-Butyl (2S,3R)-2-[(R)-2-Oxo-4-phenyloxazolidine-3-carbonyl]oxetan-3-yl carbamate* ***12ac2***. General procedure C was applied using racemic Boc-oxetin **9a** (1.30 g, 5.99 mmol) and triethylamine (1.0 mL, 7.19 mmol) in THF (60 mL), pivaloyl chloride (1.10 mL, 8.98 mmol), (*R*)-4-phenyloxazolidin-2-one **11c** (1.56 g, 9.58 mmol) in THF (29 mL), and *n*-BuLi (1.51 M solution in hexane; 6.35 mL, 9.58 mmol). Flash chromatography (80:20 Et_2O/petroleum ether then 75:25 Et_2O/EtOAc) gave diastereoisomers **12ac1** (764 mg, 35%) and **12ac2** (731 mg, 34%) as white powders. In addition, unreacted **9a** was recovered (190 mg, 15%). For **12ac1**: R_f (80:20 Et_2O/petroleum ether) = 0.20; mp 84−85 °C; $[\alpha]_D^{27}$ −76 (c 0.5, $CHCl_3$); IR ν 3316, 2977, 1777, 1704, 1383, 1251, 1161, 989; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44−7.27 (m, 5H), 6.22 (d, J = 7.0 Hz, 1H), 5.47 (dd, J = 8.6, 3.5 Hz, 1H), 5.34−5.13 (m, 2H), 4.90 (t, J = 7.0 Hz, 1H), 4.69 (t, J = 8.8 Hz, 1H), 4.47 (t, J = 5.7 Hz, 1H), 4.35 (dd, J = 8.8, 3.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.4 (C), 154.3 (C), 153.0 (C), 138.3 (C), 129.3 (2CH), 129.1 (CH), 126.3 (2CH), 85.0 (CH), 80.4 (C), 77.4 (CH_2), 71.1 (CH_2), 57.3 (CH), 48.6 (CH), 28.3 ($3CH_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{22}N_2O_6Na$ 385.1370, found 385.1354. For **12ac2**: R_f (80:20 Et_2O/petroleum ether) = 0.09; mp 146−148 °C; $[\alpha]_D^{27}$ +11 (c 0.5, $CHCl_3$); IR ν 3308, 2976, 1793, 1697, 1383, 1206, 1160, 1001; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.46−7.28 (m, 5H), 6.03 (d, J = 7.7 Hz, 1H), 5.40 (dd, J = 8.7, 3.5 Hz, 1H), 5.36 (br s, 1H), 4.85−4.71 (m, 3H), 4.37 (t, J = 6.8 Hz, 1H), 4.30 (dd, J = 8.9, 3.5 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.6 (C), 154.0 (C), 153.1 (C), 139.0 (C), 129.5 (2CH), 129.0 (CH), 126.2 (2CH), 84.8 (CH), 80.5 (C), 78.1 (CH_2), 71.4 (CH_2), 57.6 (CH), 48.2 (CH), 28.4 ($3CH_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{22}N_2O_6Na$ 385.1370, found 385.1352.

tert-Butyl (2R,3S)-2-[(4S,5R)-4-Methyl-2-oxo-5-phenyloxazolidine-3-carbonyl]oxetan-3-yl Carbamate ***12ab1*** *and tert-Butyl (2S,3R)-2-[(4S,5R)-4-Methyl-2-oxo-5-phenyloxazolidine-3-*

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carbonyl]oxetan-3-yl Carbamate ***12ab2***. General procedure C was applied using racemic Boc-oxetin **9a** (400 mg, 1.84 mmol) and triethylamine (0.31 mL, 2.21 mmol) in THF (18 mL), pivaloyl chloride (0.34 mL, 2.76 mmol), (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one **11b** (523 mg, 2.95 mmol) in THF (9 mL), and *n*-BuLi (1.37 M solution in hexane; 2.15 mL, 2.95 mmol). Flash chromatography (80:20 Et_2O/petroleum ether) gave diastereoisomers **12ab1** (170 mg, 25%) and **12ab2** (182 mg, 26%) as white powders. Each compound was purified by precipitation from Et_2O solution by slow addition of petroleum ether. In addition, unreacted **9a** was recovered (45 mg, 11%). For **12ab1**: R_f (90:10 Et_2O/petroleum ether) = 0.16; mp 190−192 °C; $[\alpha]_D^{27}$ −30 (*c* 0.5, $CHCl_3$); IR ν 3349, 2981, 1770, 1706, 1356, 1206, 1151, 978; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48−7.27 (m, 5H), 6.23 (d, *J* = 7.6 Hz, 1H), 5.77 (d, *J* = 7.2 Hz, 1H), 5.44−5.24 (m, 1H), 5.20−5.05 (m, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 4.90−4.77 (m, 1H), 4.58 (t, *J* = 6.6 Hz, 1H), 1.41 (s, 9H), 0.96 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.8 (C), 153.9 (C), 152.2 (C), 133.0 (C), 129.0 (CH), 128.8 (2CH), 125.6 (2CH), 84.9 (CH), 80.8 (C), 80.1 (CH), 77.6 (CH_2), 54.5 (CH), 48.5 (CH), 28.3 ($3CH_3$), 14.5 (CH_3); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{24}N_2O_6Na$ 399.1527, found 399.1510. For **12ab2**: R_f (90:10, Et_2O/petroleum ether) = 0.22; mp 183−184 °C; $[\alpha]_D^{24}$ +15 (*c* 0.25, $CHCl_3$); IR ν 3356, 2984, 2973, 1770, 1711, 1364, 1249, 1216, 1147, 979; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48−7.27 (m, 5H), 6.28 (d, *J* = 7.5 Hz, 1H), 5.68 (d, *J* = 7.1 Hz, 1H), 5.49 (br s, 1H), 5.32−5.14 (m, 1H), 4.95 (t, *J* = 7.1 Hz, 1H), 4.90−4.75 (m, 1H), 4.55 (t, *J* = 6.6 Hz, 1H), 1.42 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.5 (C), 154.4 (C), 152.4 (C), 133.0 (C), 129.0 (CH), 128.8 (2CH), 125.7 (2CH), 85.2 (CH), 80.5 (C), 80.3 (CH), 77.2 (CH_2), 54.7 (CH), 48.8 (CH), 28.3 ($3CH_3$), 14.7 (CH_3); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{24}N_2O_6Na$ 399.1527, found 399.1533.

tert-Butyl (2R,3R)-2-[(S)-4-Benzyloxymethyl-2-oxooxazolidine-3-carbonyl]oxetan-3-yl Carbamate ***12ba1*** *and tert-Butyl (2S,3S)-2-[(S)-4-Benzyloxymethyl-2-oxooxazolidine-3-carbonyl]oxetan-3-yl Carbamate* ***12ba2***. General procedure C was applied using racemic Boc-*epi*-oxetin **9b** (250 mg, 1.15 mmol) and triethylamine (0.19 mL, 1.38 mmol) in THF (12 mL), pivaloyl chloride (0.21 mL, 1.73 mmol), (*S*)-4-(benzyloxymethyl)oxazolidin-2-one **11a** (382 mg, 1.84 mmol) in THF (6 mL), and *n*-BuLi (1.55 M solution in hexane; 1.19 mL, 1.84 mmol). Flash chromatography (50:50 then 60:40 EtOAc/petroleum ether) gave the diastereoisomers **12ba1** as a colorless oil (130 mg, 28%) and **12ba2** as a white solid (177 mg, 38%). The latter compound was purified by precipitation from Et_2O solution by slow addition of petroleum ether. In addition, unreacted **9b** was recovered (60 mg, 24%). For **12ba1**: R_f (55:45 EtOAc/petroleum ether) = 0.42; $[\alpha]_D^{26}$ +46 (*c* 0.5, $CHCl_3$); IR ν 3349, 2967, 1779, 1702, 1365, 1260, 1160, 1092, 1014; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5H), 5.84 (d, *J* = 5.5 Hz, 1H), 5.67 (br s, 1H), 4.86−4.75 (m, 1H), 4.67−4.51 (m, 5H), 4.49−4.43 (m, 2H), 3.83 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.64 (dd, *J* = 9.8, 1.8 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.6 (C), 155.2 (C), 153.9 (C), 137.3 (C), 128.7 (2CH), 128.2 (CH), 127.9 (2CH), 83.2 (CH), 80.2 (C), 76.1 (CH_2), 73.6 (CH_2), 67.5 (CH_2), 67.0 (CH_2), 53.6 (CH), 50.3 (CH), 28.4 ($3CH_3$); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2O_7Na$ 429.1632, found 429.1631. For **12ba2**: R_f (55:45 EtOAc/petroleum ether) = 0.35; mp 124−126 °C; $[\alpha]_D^{26}$ +41 (*c* 0.5, $CHCl_3$); IR ν 3351, 2980, 2884, 1775, 1710, 1691, 1384, 1247, 1204, 1165, 986; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39−7.22 (m, 5H), 5.97 (d, *J* = 5.8 Hz, 1H), 5.75 (br s, 1H), 4.84−4.66 (m, 2H), 4.62−4.36 (m, 6H), 3.79 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.59 (d, *J* = 9.9 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.7 (C), 155.1 (C), 153.7 (C), 137.3 (C), 128.5 (2CH), 128.0 (CH), 127.6 (2CH), 84.2 (CH), 80.2 (C), 75.4 (CH_2), 73.3 (CH_2), 67.5 (CH_2), 66.5 (CH_2), 53.7 (CH), 50.1 (CH), 28.3 ($3CH_3$); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2O_7Na$ 429.1632, found 429.1611.

tert-Butyl (2R,3R)-2-[(4S,5R)-4-Methyl-2-oxo-5-phenyloxazolidine-3-carbonyl]oxetan-3-yl Carbamate ***12bb1*** *and tert-Butyl (2S,3S)-2-[(4S,5R)-4-Methyl-2-oxo-5-phenyloxazolidine-3-carbonyl]-oxetan-3-yl Carbamate* ***12bb2***. General procedure C was applied using racemic Boc-*epi*-oxetin **9b** (150 mg, 0.69 mmol) and triethylamine (0.12 mL, 0.83 mmol) in THF (7 mL), pivaloyl chloride (0.13 mL, 1.04 mmol), (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one **11b** (196 mg, 1.11 mmol) in THF (3.5 mL), and *n*-BuLi (1.52 M solution in hexane; 0.73 mL, 1.11 mmol). Flash chromatography (80:20 Et_2O/petroleum ether) gave the single diastereoisomer **12bb2** as a white solid (45 mg, 17%) and a mixture of diasteroisomers **12bb1** and **12bb2** as a white solid (44 mg, 17%). In addition, unreacted **9b** was recovered (34 mg, 23%). For **12bb2**: R_f (80:20 Et_2O/petroleum ether) = 0.26; mp 147−148 °C; $[\alpha]_D^{27}$ −50 (*c* 0.38, $CHCl_3$); IR ν 3380, 2990, 2886, 1795, 1713, 1346, 1256, 1247, 1197, 1161, 989; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.46−7.28 (m, 5H), 6.10 (d, *J* = 3.8 Hz, 1H), 5.81 (d, *J* = 7.1 Hz, 1H), 5.66 (d, *J* = 5.8 Hz, 1H), 4.89−4.74 (m, 3H), 4.64−4.55 (m, 1H), 1.44 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.6 (C), 155.3 (C), 153.1 (C), 133.0 (C), 129.0 (CH), 128.8 (2CH), 125.7 (2CH), 84.8 (CH), 80.5 (C), 80.2 (CH), 75.3 (CH_2), 55.0 (CH), 50.3 (CH), 28.3 ($3CH_3$), 14.6 (CH_3); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{24}N_2O_6Na$ 399.1527, found 399.1511. From the diastereoisomeric mixture, the following NMR data was deduced. For **12bb1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.28 (m, 5H), 5.94 (d, *J* = 5.4 Hz, 1H), 5.76 (d, *J* = 7.5 Hz, 1H), 5.63 (d, *J* = 3.5 Hz, 1H), 4.89−4.75 (m, 2H), 4.73−4.64 (m, 1H), 4.64−4.55 (m, 1H), 1.47 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.3 (C), 154.9 (C), 152.5 (C), 132.8 (C), 128.4 (CH), 128.3 (2CH), 125.4 (2CH), 84.1 (CH), 79.7 (CH), 79.4 (C), 74.9 (CH_2), 54.0 (CH), 49.7 (CH), 27.9 ($3CH_3$), 14.0 (s, CH_3).

(2R,3S)-3-(tert-Butoxycarbonylamino)oxetane-2-carboxylic Acid (−)-9a. General procedure D was applied on compound **12ac1** (78 mg, 0.22 mmol) in a 1:4 mixture of water and THF (5 mL) with a 35% w/w solution of H_2O_2 (0.037 mL, 0.43 mmol) and LiOH·H_2O (18 mg, 0.43 mmol) in water (0.8 mL) to give (−)-**9a** (38 mg, 82%). $[\alpha]_D^{27}$ −31 (*c* 0.5, $CHCl_3$). Spectral data were identical to those obtained for racemic material described above.

General procedure B was applied on compound (**2*R*,3*S*)-8a** (1.51 g, 5.0 mmol) using K_2CO_3 (2.07 g, 15.0 mmol) in MeOH (65 mL) to give (−)-**9a** (1.08 g, 99%). $[\alpha]_D^{26}$ −32 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above.

(2S,3R)-3-(tert-Butoxycarbonylamino)oxetane-2-carboxylic Acid (+)-9a. General procedure D was applied on compound **12ac2** (62 mg, 0.17 mmol) in a 1:4 mixture of water and THF (4 mL) with a 35% w/w solution of H_2O_2 (0.030 mL, 0.34 mmol) and LiOH·H_2O (14 mg, 0.34 mmol) in water (0.5 mL) to give (+)-**9a** (29 mg, 78%). $[\alpha]_D^{27}$ +32 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above for racemic material.

General procedure D was applied on compound **12ab2** (39 mg, 0.10 mmol) in a 1:4 mixture of water and THF (2.5 mL) with a 35% w/w solution of H_2O_2 (0.018 mL, 0.21 mmol) and LiOH·H_2O (9 mg, 0.21 mmol) in water (0.4 mL) to give (+)-**9a** (20 mg, 89%). $[\alpha]_D^{27}$ +30 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above.

General procedure B was applied on compound (**2*S*,3*R*)-8a** (1.01 g, 3.35 mmol) using K_2CO_3 (1.39 g, 10.1 mmol) in MeOH (45 mL) to give (+)-**9a** (698 mg, 96%). $[\alpha]_D^{25}$ +33 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above.

(2R,3R)-3-(tert-Butoxycarbonylamino)oxetane-2-carboxylic Acid (+)-9b. General procedure D was applied on compound **12ba1** (140 mg, 0.35 mmol) in a 1:4 mixture of water and THF (10 mL) with a 35% w/w solution of H_2O_2 (0.060 mL, 0.69 mmol) and LiOH·H_2O (29 mg, 0.69 mmol) in water (2 mL) to give (+)-**9b** (75 mg, 99%). $[\alpha]_D^{24}$ +35 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above for racemic material.

General procedure B was applied on compound (**2*R*,3*R*)-8b** (1.28 g, 4.25 mmol) using K_2CO_3 (1.76 g, 12.8 mmol) in MeOH (55 mL) to give (+)-**9b** (890 mg, 97%). $[\alpha]_D^{26}$ +31 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above.

(2S,3S)-3-(tert-Butoxycarbonylamino)oxetane-2-carboxylic Acid (−)-9b. General procedure D was applied on compound **12ba2** (59 mg, 0.15 mmol) in a 1:4 mixture of water and THF (3 mL) with a 35% w/w solution of H_2O_2 (0.025 mL, 0.29 mmol) and LiOH·H_2O (12 mg, 0.29 mmol) in water (0.5 mL) to give (−)-**9b** (31 mg, 97%).

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$[\alpha]_D^{26}$ −36 (*c* 0.5, $CHCl_3$) {lit.[4] $[\alpha]_D^{25}$ −61.2 (*c* 0.5, $CDCl_3$)}. Spectral data were identical to those described above for racemic material and in the literature.[4]

General procedure D was applied on compound **12bb2** (76 mg, 0.20 mmol) in a 1:4 mixture of water and THF (5 mL) with a 35% w/w solution of H_2O_2 (0.035 mL, 0.40 mmol) and $LiOH{\cdot}H_2O$ (17 mg, 0.40 mmol) in water (1 mL) to give (−)-**9b** (38 mg, 87%). $[\alpha]_D^{22}$ −33 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above.

General procedure B was applied on compound (2*S*,3*S*)-**8b** (1.02 g, 3.40 mmol) and K_2CO_3 (1.41 g, 10.2 mmol) in MeOH (45 mL) to give (−)-**9b** (710 mg, 96%). $[\alpha]_D^{25}$ −32 (*c* 0.5, $CHCl_3$). Spectral data were identical to those described above.

(2R,3S)-3-Aminooxetane-2-carboxylic Acid (+)-1a. General procedure E was applied on (2*R*,3*S*)-Boc-oxetin (87 mg, 0.40 mmol) in CH_2Cl_2 (6 mL) with trifluoroacetic acid (0.460 mL, 6.02 mmol) to give (2*R*,3*S*)-oxetin (+)-**1a** (45 mg, 96%). Mp 199−201 °C (lit.[2] mp 185−190 °C); $[\alpha]_D^{26}$ +54 (*c* 0.18, H_2O) {lit.[2] $[\alpha]_D^{25}$ +56.4 (*c* 1.0, H_2O)}; IR ν 3117, 2986, 2895, 1636, 1618, 1555, 1410, 1378 1297, 1007, 952; ^{1}H NMR (360 MHz, D_2O) δ 5.13 (d, *J* = 6.9 Hz, 1H), 4.88−4.81 (m, 1H), 4.46−4.35 (m, 2H);[2] ^{13}C NMR (90 MHz, D_2O) δ 175.2 (C), 81.1 (CH), 72.9 (CH_2), 47.4 (CH);[2] HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_4H_8NO_3$ 118.0499, found 118.0501.

(2S,3R)-3-Aminooxetane-2-carboxylic Acid (−)-1a. General procedure E was applied on (2*S*,3*R*)-Boc-oxetin (+)-**9a** (128 mg, 0.59 mmol) in CH_2Cl_2 (9 mL) with trifluoroacetic acid (0.677 mL, 8.85 mmol) to give (2*S*,3*R*)-oxetin (−)-**1a** (67 mg, 97%). Mp 199−201 °C (lit.[2] mp 185−190 °C); $[\alpha]_D^{27}$ −54 (*c* 0.2, H_2O) {lit.[2] $[\alpha]_D^{21}$ −56.0 (*c* 1, H_2O)}; IR ν 3117, 2986, 2895, 1636, 1618, 1555, 1410, 1378 1297, 1007, 952; ^{1}H NMR (360 MHz, D_2O) δ 5.13 (d, *J* = 6.9 Hz, 1H), 4.88−4.81 (m, 1H), 4.46−4.35 (m, 2H);[2] ^{13}C NMR (90 MHz, D_2O) δ 174.9 (C), 80.3 (CH), 72.2 (CH_2), 47.3 (CH);[2] HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_4H_8NO_3$ 118.0499, found 118.0498.

(2R,3R)-3-Aminooxetane-2-carboxylic Acid (+)-1b. General procedure E was applied on (2*R*,3*R*)-Boc-*epi*-oxetin (+)-**9b** (130 mg, 0.60 mmol) in CH_2Cl_2 (9 mL) with trifluoroacetic acid (0.688 mL, 8.99 mmol) to give (2*R*,3*R*)-*epi*-oxetin (+)-**1b** (68 mg, 97%). Mp 182−183 °C; $[\alpha]_D^{27}$ +13 (*c* 0.5, H_2O) {lit.[2] $[\alpha]_D^{21}$ +13.7 (*c* 1, H_2O)}; IR ν 3663, 2971, 2903, 1565, 1392, 1297, 946, 928; ^{1}H NMR (250 MHz, D_2O) δ 4.91 (t, *J* = 5.2 Hz, 1H), 4.72−4.60 (m, 1H), 4.56−4.45 (m, 1H), 4.26−4.14 (m, 1H);[2] ^{13}C NMR (90 MHz, D_2O) δ 176.8 (C), 83.1 (CH), 72.0 (CH_2), 49.7 (CH);[2] HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_4H_7NO_3Na$ 140.0318, found 140.0321.

(2S,3S)-3-Aminooxetane-2-carboxylic Acid (−)-1b. General procedure E was applied on (2*S*,3*S*)-Boc-*epi*-oxetin (−)-**9b** (108 mg, 0.5 mmol in CH_2Cl_2 (7.5 mL) with trifluoroacetic acid (0.57 mL, 7.46 mmol) to give (2*S*,3*S*)-*epi*-oxetin (−)-**1b** (58 mg, 99%). Mp 182−183 °C; $[\alpha]_D^{26}$ −12 (*c* 0.5, H_2O) {lit.[2] $[\alpha]_D^{15}$ −12 (*c* 1, H_2O); lit.[4] $[\alpha]_D^{25}$ −13.6 (*c* 1, H_2O)}; IR ν 3663, 2971, 2903, 1565, 1392, 1297, 946, 928; ^{1}H NMR (250 MHz, D_2O) δ 4.91 (virt. t, *J* = 5.2 Hz, 1H), 4.72−4.60 (m, 1H), 4.56−4.45 (m, 1H), 4.26−4.14 (m, 1H);[2,4] ^{13}C NMR (90 MHz, D_2O) δ 176.8 (C), 83.1 (CH), 72.0 (CH_2), 49.7 (CH);[2,4] HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_4H_7NO_3Na$ 140.0318, found 140.0320.

Enantiomeric Separation of 8a. Separation was performed using a Lux cellulose-1 column (250 mm × 10 mm; particle size 5 μm). The HPLC system was operated with 80:20 hexane/2-propanol as mobile phase flowing at a rate of 5 mL min^{-1}. The mobile phase and the column were thermostated at 20 ± 2 °C. Detection was performed at 210 nm with a 15 min run time. Sample solutions were in 2-propanol (500 mg mL^{-1}), and the injection volume was 100 μL. For (2*R*,3*S*)-**8a**: retention time = 10.0 min; $[\alpha]_D^{26}$ −20 (*c* 0.5, $CHCl_3$); spectral data were identical to those reported above. For (2*S*,3*R*)-**8a**: retention time = 7.0 min; $[\alpha]_D^{26}$ +21 (*c* 0.5, $CHCl_3$). Spectral data were identical to those reported for racemic material above.

Enantiomeric Separation of 8b. Separation was performed using a Lux Cellulose-2 column (250 mm × 10 mm; particle size 5 μm). The HPLC system was operated with 80:20 hexane/ethanol as mobile phase flowing at a rate of 5 mL min^{-1}. The mobile phase and the column were thermostated at 20 ± 2 °C. Detection was performed at 210 nm with a 15 min run time. Sample solutions were in ethanol (500 mg mL^{-1}), and the injection volume was 75 μL. For (2*R*,3*R*)-**8b**: retention time = 11.9 min; $[\alpha]_D^{25}$ −3 (*c* 1.5, $CHCl_3$); spectral data were identical to those reported above. For (2*S*,3*S*)-**8b**: retention time = 10.0 min; $[\alpha]_D^{25}$ +3 (*c* 1.5, $CHCl_3$); spectral data were identical to those reported for racemic material above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01795.

Copies of ^{1}H and ^{13}C NMR spectra and chiral HPLC chromatograms (PDF)

Crystallographic data for compound **12ab2** (CCDC 1491706) (CIF)

Crystallographic data for compound **12bb2** (CCDC 1491705) (CIF)

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Notes

The authors declare no competing financial interest.

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