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Brief Communication

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Substrate-Controlled Diastereoselectivity Reversal in NHC-Catalyzed Cross-Benzoin Reactions Using *N*-Boc-*N*-Bn-Protected α-Amino Aldehydes

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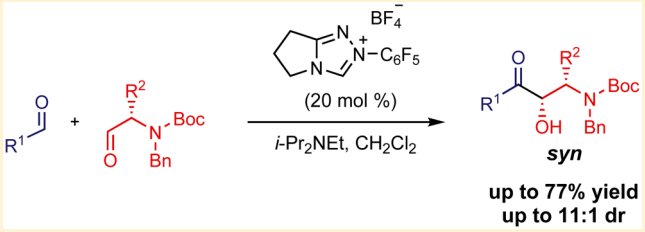
Supporting Information

ABSTRACT: The effectiveness of utilizing *N*-Bn-*N*-Boc-α-amino aldehydes in cross-benzoin reactions with heteroaromatic aldehydes is demonstrated. The reaction is both chemoselective and *syn*-selective, making it complementary to the *anti*-selective cross-benzoin reaction of *N*HBoc-α-amino aldehydes. Good diastereoselectivity is obtained for a variety of amino aldehydes, including nonhindered ones. A Felkin−Anh model can be used to rationalize the observed diastereoselectivity.

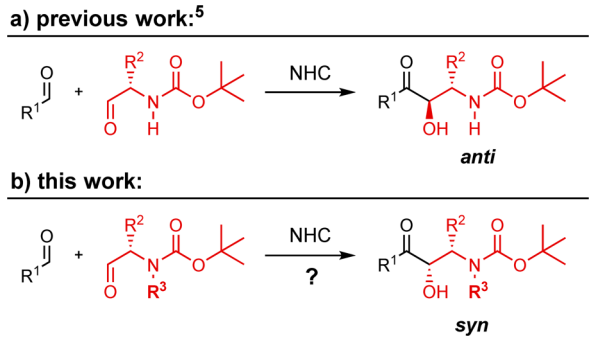


The N-heterocyclic carbene (NHC)-catalyzed cross-benzoin reaction serves as a convenient method for accessing α-hydroxy ketones.[1] Despite renewed interest directed in this reaction, the variant in which two different aldehydes are directly coupled via the *umpolung* of one partner remains limited in scope. The main reason for this limitation is the difficulty in controlling the product distribution.[1g] In order for a cross-benzoin reaction to be of practical synthetic value, chemoselective formation of one of the four possible benzoin products must be accomplished. The chemoselectivity problem has generally been addressed by tuning the electronic and steric environments of one of the aldehydes. For example, the NHC-catalyzed cross-benzoin reaction between *ortho*-substituted aromatic aldehydes and aliphatic or electron-poor aromatic aldehydes has been reported.[2] Alternatively, we have demonstrated that increasing the steric hindrance on the NHC allows for the chemoselective coupling between a wide range of aromatic and aliphatic aldehydes.[3] Despite these successes, the chemoselective cross-benzoin reaction between aldehydes remains in its infancy, particularly when issues of diastereo- and enantioselectivity are also taken into account.[2c,e,3a,4]

In recent work, we demonstrated that *N*-Boc-α-amino aldehydes, with their synergistic balance between electronic activation and steric hindrance imposed by the α-substituent, provide a route to chemo- and diastereoselective cross-benzoin reactions (Scheme 1a).[5] Furthermore, facile access to enantioenriched α-amino aldehydes[6] allows formation of enantioenriched α-hydroxy-β-amino ketone products. These building blocks provide a useful entry point to the synthesis of many natural products and biologically relevant molecules.[7]

Prompted by the synthetic utility of the α-hydroxy-β-amino ketone products, we became interested in expanding the scope of this reaction. In this regard, it was intriguing to examine whether modifications to the protocol could be used to preferentially obtain the opposite *syn* diastereomer (Scheme 1b). The realization of this objective is described herein.

Scheme 1



It has been shown that the nature of the protecting groups can alter the facial selectivity of the attack on α-amino aldehydes.[6a,8] We hypothesized that modifying the amino moiety from *N*-monoprotected (as used in our prior method) to a doubly protected amino aldehyde might alter the conformation of this reaction partner in the transition state and favor the *syn* diastereomer of the cross-benzoin product. To this effect, a variety of protecting groups were examined including *N*-Tosyl-*N*-Bn, *N*-Boc-*N*-Alkyl, *N*-Boc-*N*-Bn, and *N*-phtalamide. Of these, it was found that only *N*-Boc-*N*-Bn- and *N*-Tosyl-*N*-Bn-derived-L-alaninal afforded any significant amount of cross-benzoin product in a reaction with 2-furaldehyde (Scheme 2). Despite the competence of the *N*-Tosyl-*N*-Bn-derived substrate, we were reluctant to use this derivative as its use may facilitate racemization of the α-amino aldehyde under the basic reaction conditions. In any event, the

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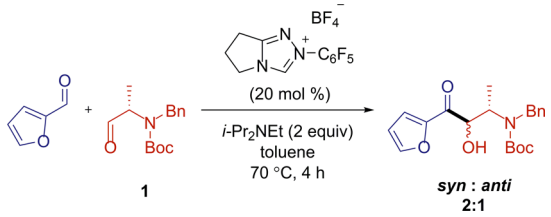
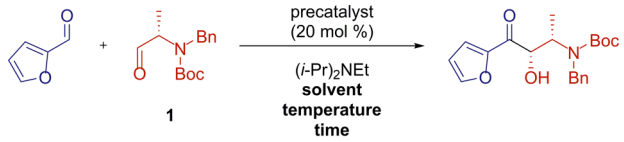
Scheme 2. Cross-Benzoin Reaction between Amino Aldehyde 1 and 2-Furaldehyde

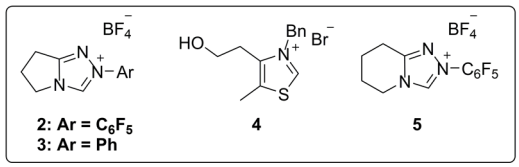


desired product was obtained in a modest 2:1 diastereomeric ratio, and it appeared that the facial selectivity had been reversed relative to that observed when using −NHBoc-protected substrates. The major diastereomer was isolated, recrystallized, and subjected to X-ray diffraction crystallography. The *syn* relationship between the methyl and hydroxyl substituents was clearly established in this manner (see the Supporting Information).

A brief optimization was performed in order to improve the diastereoselectivity of this process (Table 1). Screening of

Table 1. Optimization of the Reaction Conditions[a]





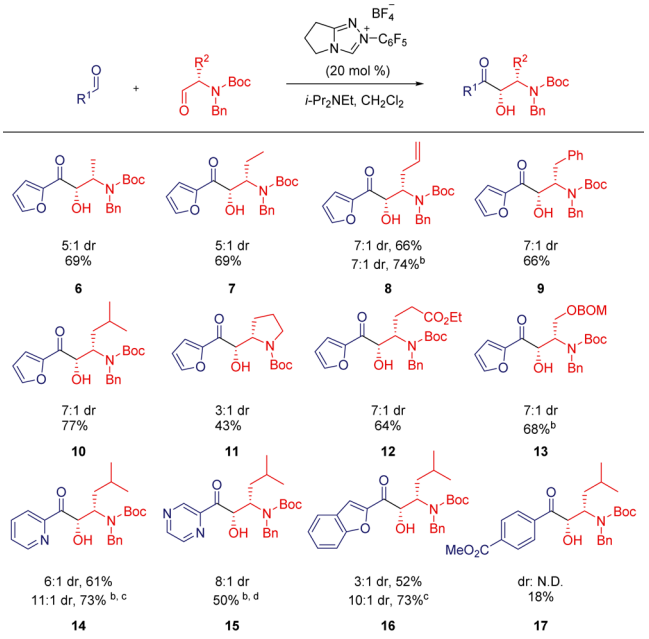
entry	precatalyst	solvent	T (°C)	time (h)	NMR yield[b] (%)	dr (syn/anti)
1	**2**	toluene	70	4	34	2:1
2	**2**	MeOH	70	4	43	3:1
3	**2**	THF	70	4	63	4:1
4	**2**	CH_2Cl_2	70	4	93	4:1
5	**3**	CH_2Cl_2	70	4	<5	N/A
6	**4**	CH_2Cl_2	70	4	85	2:1
7	**5**	CH_2Cl_2	70	4	30	2:1
8	**2**	CH_2Cl_2	40	4	91	5:1
9	**2**	CH_2Cl_2	40	1	81	6:1

[a]Reaction conditions: 1 equiv of *N*-Boc-*N*-Bn-amino aldehyde, 1.3 equiv of hetereoaromatic aldehyde, 1 equiv of Hünig's base, CH_2Cl_2 (0.5 M). [b]Combined yield of both diastereomers of the cross-benzoin product as determined by ^{1}H NMR spectroscopy (DMSO-d_6 at 80 °C) using dimethylterephthalate as an internal standard.

various solvents showed that the reaction is best performed in dichloromethane (entries 1−4). Reactions utilizing a number of known azolium salts showed that triazolium **2** was the superior choice (entries 4−7). It is noteworthy that thiazolium **4** also provides efficient access to the cross-benzoin product, albeit in lower diastereomeric ratio. Notably, the desired cross-benzoin products are obtained in high yield using only a slight excess of the partner heteroaromatic aldehyde (1.5 equiv). We sought to improve the diastereoselectivity with the hope of simplifying the purification of the products. Gratifyingly, we found that by decreasing the reaction time and temperature an improvement in diastereoselectivity was accompanied by only a mild decrease in yield (entries 8 and 9).

Having established optimal reaction conditions, we set out to investigate the scope of this reaction using a variety of heteroaromatic aldehydes and *N*-Boc-*N*-Bn-amino aldehydes (Table 2).

Table 2. Scope of the *Syn*-Selective Cross-Benzoin Reaction[a]



[a]Reaction conditions: 1 equiv of *N*-Boc-*N*-Bn-amino aldehyde, 1.5 equiv of hetereoaromatic aldehyde, 1 equiv of Hünig's base, CH_2Cl_2 (0.5 M), 40 °C, 1 h. Reported yield is that of the isolated major diastereomer. [b]3 equiv of hetereoaromatic aldehyde was used. [c]Modifications to reaction conditions: CH_2Cl_2 (0.15 M), 0 °C, 30 min. [d]Modifications to reaction conditions: CH_2Cl_2 (0.15 M), −15 °C, 15 min.

Unlike our previously reported *anti*-selective method, good diastereoselectivities are obtained regardless of the steric bulk of the amino aldehyde substituent (**6**−**10**). Still, there appears to be a trend toward greater diastereoselectivity with increasing substituent size. However, the use of cyclic substrates such as *N*-Boc-prolinal results in a lower diastereomeric ratio (Table 2, entry 11). The reaction displays good functional group tolerance as demonstrated by application of a glutamic acid-derived amino aldehyde (**12**) and *N*-Boc-*N*-Bn-*O*-BOM-L-serinal (**13**). With the exception of **8**, all products in Table 2 are obtained from enantiomerically enriched amino aldehydes. Importantly, comparison of HPLC chromatograms of **10** to those of a racemic sample showed no erosion of enantiomeric ratio during the course of the reaction (see the Experimental Section). Benzofuran-2-carboxaldehyde affords moderate yields and diastereomeric ratios under these reaction conditions (**16**). A survey of the reaction conditions revealed that successful application of highly reactive hetereoaromatic aldehydes necessitates the use of lower temperatures and shorter reaction times (**14**−**16**).[9] The use of pyrazine-2-carboxaldehyde necessitated even lower temperatures and shorter reaction times to obtain acceptable yields of the cross-benzoin products (Table 2, entry 15). In addition to an increase in yield, the modified conditions also improve the diastereomeric ratio for

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these substrates.[10] These observations can be rationalized by considering the faster rates in both the forward and reverse direction using these more reactive aldehydes. Lowering the temperature thus minimizes the thermodynamic equilibration between the two energetically similar diastereomers.[11]

Although the yields obtained using 1.5 equiv of heteroaromatic aldehyde are generally good, it was found that they could be increased by using a larger excess (**8** and **13**–**15**). Unfortunately, the use of aromatic (entry 17) or aliphatic (not shown) aldehydes results in poor yields.[12] Despite this limitation, we believe this method to be of particular synthetic value given the continued interest of heteroaromatic building blocks in medicinal chemistry as well as the underutilized synthetic potential of the furan moiety in particular.[13]

In our previous work, the presence of a hydrogen bond was postulated to explain the *anti* diastereoselectivity in cross-benzoin reactions using NHBoc amino aldehydes.[5] In the current study, the diastereoselectivity observed when using *N*-Bn-*N*-Boc-amino aldehydes can be predicted using a polar Felkin–Anh transition-state model (Figure 1). Indeed, replacing the −NHBoc moiety with −NBnBoc prevents formation of an intramolecular hydrogen bond, effectively acting as a Cram chelate.

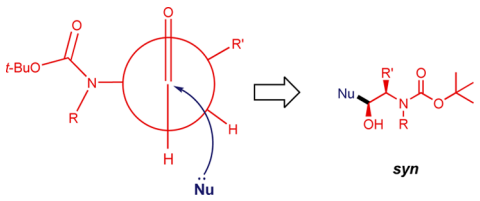

Figure 1. Proposed transition-state models to rationalize the observed diastereoselectivity.

In summary, we have developed a complementary approach for the chemo- and *syn*-selective cross-benzoin reaction between α-amino and heteroaromatic aldehydes. Combined with the accessibility of both *R* and *S* α-amino aldehydes, all stereoisomers for the cross-benzoin products of these aldehydes are now directly available. Application of these methods to the total synthesis of natural products is underway.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded in $CDCl_3$ solution at 500 MHz for ^1H and 125 MHz for ^{13}C. The residual solvent protons (^1H, 7.26 ppm) or the solvent carbons (^{13}C, 77.16) were used as internal standards for chemical shifts. High-resolution mass spectra (HRMS) were obtained on a double-focusing high-resolution spectrometer. Infrared spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. All samples were prepared as a film on a KBr disk for IR analysis. Melting points were measured on a melting point apparatus and are uncorrected. Anhydrous solvents were dried using a Braun solvent purification system and were stored under nitrogen over activated 3 Å molecular sieves for at least 48 h prior to use. Moisture content was analyzed by a Karl Fischer coulometer 20D and at no time exceeded 15 ppm prior to use. Commercially available aldehydes that are solids at room temperature were used directly with no further purification; aldehydes that are liquids at room temperature were distilled immediately prior to use. All reactions were carried out under an inert atmosphere of argon. *N*-Boc-prolinol, 2-furaldehyde, benzofuran-2-carboxaldehyde, 2-pyridinecarboxaldehyde, and methyl 4-formylbenzoate were purchased from commercial sources. Pyrazine-2-carboxaldehyde was prepared according to the reported literature procedure.[14]

Synthesis of *N*-Boc-*N*-Bn-amino Aldehydes. *General Procedure A. A(I): N-Benzyl Protection.* Following a modified procedure,[15] to a solution of the corresponding α-amino alcohol (1 equiv) in dry MeOH (0.25 M) was added freshly distilled benzaldehyde (1 equiv) at room temperature. The resulting solution was stirred for 2 h before being cooled to 0 °C using an ice bath. $NaBH_4$ (5 equiv) was slowly added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for 1 h. The suspension was once again cooled to 0 °C and quenched with the addition of satd $NH_4Cl_{(aq.)}$ The reaction mixture was extracted with EtOAc (×3), and the combined organic layers were dried over $MgSO_4$. The crude mixture was reduced in vacuo and carried to the next step without further purification.

A(II): N-Boc Protection.[16] To a solution of *N*-Bn-amino alcohol (1.0 equiv) in THF (0.3 M) was added triethylamine (1 equiv) at room temperature. To this solution was added di-*tert*-butyl dicarbonate (Boc_2O) (1.1 equiv) following by stirring at ambient temperature for 16 h. The reaction was quenched by addition of HCl (1 M) and extracted with Et_2O (×3). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography.

A(III): Oxidation.[5] IBX (1.5 equiv) was added to a solution of *N*-Boc-*N*-Bn-amino alcohol (1.0 equiv) in acetonitrile (0.2 M) and heated to reflux. The reaction was monitored for complete consumption of starting material (typical reaction time = 30 min). After completion, the contents were cooled to room temperature, filtered through a pad of Celite, and washed with EtOAc (×3). The resulting mixture was concentrated and purified by column chromatography.

General Procedure B. B(I): N-Benzyl Protection. Following a modified procedure,[17] to a solution of amino ester HCl salt (1 equiv) in dry MeOH (0.7 M) were added triethylamine (1 equiv) followed by freshly distilled benzaldehyde (1.5 equiv) at room temperature. The resulting solution was stirred for 1.5 h before being cooled to 0 °C using an ice bath. $NaBH_4$ (2 equiv) was slowly added to the mixture in three portions. The resulting suspension was warmed to rt and stirred for 2 h. The volatiles were removed under reduced pressure, and the crude reaction mixture was partitioned between H_2O and EtOAc. The layers were separated, and the aqueous layer was further extracted with EtOAc (×2). The organic layers were combined and dried over $MgSO_4$, and volatiles were removed under reduced pressure. The crude product was purified by column chromatography.

B(II): N-Boc Protection.[16] To a solution of *N*-benzylamino ester (1.0 equiv) in THF (0.3 M) was added triethylamine (1 equiv) at room temperature. To this solution was added di-*tert*-butyl dicarbonate (Boc_2O) (1.1 equiv) and stirred at ambient temperature for 16 h. The reaction was quenched with addition of HCl (1 M) and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography.

B(III): $LiAlH_4$ Reduction.[5] To a suspension of $LiAlH_4$ (3 equiv) in THF (0.2 M) was added the crude ester from the previous step (1 equiv) in dry THF (0.2 M) at 0 °C. After the reaction was completed (as judged by TLC analysis) an aqueous solution of Rochelle's salt (0.5 M) was slowly added to the mixture at 0 °C. The reaction was vigorously stirred at room temperature for 2 h. The reaction mixture was diluted in EtOAc, and the layers were separated. The aqueous phase was extracted using EtOAc (×2), and the combined organic layers were dried over $MgSO_4$. The resulting mixture was concentrated in vacuo and purified by column chromatography.

B(IV): Oxidation:[5] IBX (1.5 equiv) was added to a solution of *N*-Boc-*N*-benzylamino alcohol (1.0 equiv) in acetonitrile (0.2 M) and heated to reflux. The reaction was monitored for complete consumption of starting material (typical reaction time = 30 min). After completion, the contents were cooled to room temperature, filtered through a pad of Celite, and washed with EtOAc (×3). The resulting mixture was concentrated and purified by column chromatography.

*tert-Butyl (S)-Benzyl(1-oxopropan-2-yl)carbamate (**1**).* Prepared According to General Procedure A. A(I): (*S*)-2-(Benzylamino)propan-

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1-ol (**S1**) was isolated as a mixture of product and benzyl alcohol. This mixture was carried to the next step without further purification.

A(II): *tert*-Butyl (*S*)-benzyl(1-hydroxypropan-2-yl)carbamate[18] (**S2**) was isolated by column chromatography (9:1 hexanes/EtOAc) as a clear colorless oil (9.56 g, 90% over two steps): R_f = 0.21 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 4H), 7.26−7.22 (m, 1H), 4.39 (br s, 2H), 4.05−3.90 (m, 1H), 3.73−2.85 (m, 1H), 2.93 (br s, 1H), 1.43 (s, 9H), 1.14 (br d, J = 4.9 Hz, 3H).

A(III): *tert*-Butyl (I)-benzyl(1-oxopropan-2-yl)carbamate[18] (**1**) was isolated by column chromatography (6:1 hexane/Et_2O, R_f = 0.26 (11% EtOAc in hexane)) as a clear colorless oil (0.455 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 9.49 (s, 0.4H), 9.43 (s, 0.6 H), 7.38−7.26 (m, 5H), 4.85 (d, J = 15.0 Hz, 0.6H), 3.79−3.68 (m, 0.4H), 3.51−3.40 (m, 0.6H), 1.46 (s, 9H), 1.34−1.23 (m, 3H).

*tert-Butyl (S)-Benzyl(1-oxobutan-2-yl)carbamate (**S6**).* Prepared According to General Procedure B. B(I): Methyl (*S*)-2-(benzylamino)butanoate (**S3**) was isolated a mixture of product benzyl alcohol. This mixture was carried to the next step without further purification.

B(II): Methyl (*S*)-2-(benzyl(*tert*-butoxycarbonyl)amino)butanoate (**S4**) and small amounts of an unknown impurity were isolated by column chromatography (9:1 hexanes/EtOAc). R_f = 0.15 (10% EtOAc in hexanes). This mixture was carried to the next step without further purification.

B(III): *tert*-Butyl (*S*)-benzyl(1-hydroxybutan-2-yl)carbamate (**S5**) was isolated by column chromatography (3:1 hexane/EtOAc). as a clear colorless oil (0.550 g, 38% over three steps): R_f = 0.17 (25% EtOAc in hexane); $[\alpha]_D^{26}$ = −33 (*c* 1.1, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3445, 2972, 2877, 1690, 1496, 1454, 1366, 1251, 1048; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.40−7.26 (m, 4H), 7.26−7.22 (m, 1H), 4.76−4.51 (m, 0.3H), 4.51−4.11 (m, 1.7H), 3.87−3.70 (m, 3H), 3.16−2.91 (m, 1H), 1.74−1.59 (m, 1H), 1.50 (br s, 2.8H), 1.42 (br s, 9H), 0.96−0.78 (m, 3H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 157.2, 139.3, 128.6, 127.7*, 127.2, 127.2, 80.4, 64.3, 61.6, 50.0, 48.2*, 28.5, 22.6*, 21.8, 11.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{25}NO_3Na$ 302.1727, found 302.1722.

B(IV): *tert*-Butyl (*S*)-benzyl(1-oxobutan-2-yl)carbamate (**S6**) was isolated by column chromatography (8:1 hexanes/EtOAc) as a clear colorless oil (0.360 g, 91%): R_f = 0.17 (11% EtOAc in hexanes); $[\alpha]_D^{27}$ = −161 (*c* 2.0, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}): 3369, 2976, 2934, 1695, 1497, 1455, 1367, 1250, 1166, 1049, 897, 742, 701; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 9.46 (s, 0.4H), 9.35 (s, 0.6H), 7.40−7.26 (m, 5H), 5.02 (d, J = 15.0 Hz, 0.6H), 4.71 (d, J = 15.6 Hz, 0.4H), 4.22 (d, J = 15.8 Hz, 0.4H), 4.13 (d, J = 15.0 Hz, 0.6H), 3.75−3.60 (m, 0.4H), 3.35 (dd, J = 7.2, 5.0 Hz, 0.6H), 2.01 (ddq, J = 13.9, 7.3, 7.3 Hz, 1H), 1.85−1.63 (m, 1H), 1.45 (s, 9H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 199.7, 155.7*, 155.3, 138.3*, 137.8, 128.9, 128.8*, 128.5, 127.9*, 127.7, 81.7, 81.2*, 67.4*, 67.3, 52.3, 51.7*, 28.4*, 28.3, 21.6, 20.5*, 11.1, 11.0*; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{23}NO_3Na$ 300.1570, found 300.1552.

*tert-Butyl Benzyl(1-oxopent-4-en-2-yl)carbamate (**S11**). Benzyl Glycinate (**S7**).* To a solution of ethyl glycinate·HCl salt (21.5 mmol, 3.0 g) in dry MeOH (33 mL (0.7 M) was added triethylamine (21.49 mmol, 3.0 mL) followed by freshly distilled benzaldehyde (32.2 mmol, 3.3 mL) at room temperature. The resulting solution was stirred for 1.5 h before being cooled to 0 °C using an ice bath. Sodium borohydride (43.0 mmol, 1.63 g) was added slowly to the mixture in three portions. The resulting suspension was warmed to rt and stirred for additional 2 h. The volatiles were removed under reduced pressure, and the crude reaction mixture was partitioned between H_2O (ca. 75 mL) and CH_2Cl_2 (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined and dried over $MgSO_4$, and volatiles were removed under reduced pressure. Crude ethyl benzylglycinate (**S7**) was carried to the next step without further purification.

*tert-Butyl Ethyl N-Benzyl-N-(tert-butoxycarbonyl)glycinate[19] (**S8**).* To a solution of crude **S7** (21.5 mmol) in THF (72 mL (0.3 M)) was added triethylamine (21.5 mmol, 3.0 mL) at room temperature. To this solution was added di-*tert*-butyl dicarbonate (Boc_2O) (23.6 mmol, 5.15 g), and the reaction was stirred at ambient temperature for 16 h. The reaction was quenched with addition of HCl (1 M) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was concentrated in vacuo and purified by column chromatography (7:1 hexanes/EtOAc). The corresponding *tert*-butyl ethyl *N*-benzyl-*N*-(tert-butoxycarbonyl)glycinate[19] (**S8**) was obtained as a clear, colorless oil (4.37g, 85% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.36−7.29 (m, 1H), 7.29−7.19 (m, 4H), 4.55 (s, 1H), 4.51 (s, 1H), 4.16 (q, J = 4.8, 1H), 4.15 (q, J = 7.0, 1H), 3.92 (s, 1H), 1.47 (s, 4.1H), 1.47 (s, 4.9H), 1.24 (t, J = 1.5 Hz, 3H).

*Ethyl 2-(Benzyl(tert-butoxycarbonyl)amino)pent-4-enoate (**S9**).* According to literature precedent,[20] to a flame-dried flask was added diisopropylamine (1.05 mmol, 0.150 mL) followed by THF (1.4 mL) under inert atmosphere. This solution was cooled to 0 °C using an ice bath, and *n*-BuLi (2.5 M) in THF (0.962 mmol, 0.385 mL) was added dropwise. The reaction mixture was stirred at this temperature for an additional 15 min. The reaction was cooled to −78 °C, and a solution of **S8** (0.837 mmol, 0.200 g) in THF (2.8 mL) was added dropwise to this solution. Stirring was continued for an additional 40 min, and allyl bromide (1.26 mmol, 0.110 mL) was added to the reaction mixture. The reaction was stirred at −78 °C for additional 3.5 h and then allowed to warm to 0 °C. The reaction was quenched with the addition of satd NH_4Cl_{aq} and extracted with Et_2O (3 × 3 mL). The organic layers were combined, washed with HCl (1 M) (1 × 3 mL), and dried over sodium sulfate. The crude product was concentrated in vacuo and purified by column chromatography (9:1 hexanes/Et_2O). Ethyl 2-(benzyl(*tert*-butoxycarbonyl)amino)pent-4-enoate[20] (**S9**) was isolated along with small amounts of an unknown impurity. This mixture was taken to the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.36−7.27 (m, 4H), 7.26−7.20 (m, 1H), 5.80−5.56 (m, 1H), 5.08−5.00 (m, 1H), 5.08−4.95 (m, 2H), 4.68 (d, J = 15.5 HZ, 0.5H), 4.52 (J = 15.8 Hz, 0.5H), 4.44−4.36 (m, 0.5H), 4.35−4.27 (m, 1H), 4.12−3.94 (m, 2H), 3.90−3.80 (m, 0.5H), 2.71 (dt, J = 14.4, 6.3 Hz, 1H), 2.62−2.41 (m, 1H), 1.47 (s, 5H), 1.39 (s, 4H), 1.19 (t, J = 7.1 Hz, 3H).

*Ethyl Benzyl(1-hydroxypent-4-en-2-yl)carbamate (**S10**).* To a suspension of $LiAlH_4$ (4.66 mmol, 0.177g) in THF (7 mL) was added the crude (**S9**) (1.55 mmol) in dry THF (10.5 mL) at 0 °C. After the reaction was complete (judged by TLC analysis), an aqueous solution of Rochelle's salt (0.5 M) (ca. 20 mL) was slowly added to the mixture at 0 °C. The reaction was vigorously stirred at room temperature for an additional 2 h. The reaction mixture was diluted in EtOAc (30 mL), and the layers were separated. The aqueous phase was extracted using EtOAc (2 × 30 mL), and the combined organic layers were dried over $MgSO_4$. The crude product was concentrated in vacuo and purified by column chromatography (4:1 hexanes/EtOAc), and ethyl benzyl(1-hydroxypent-4-en-2-yl)carbamate (**S10**) was obtained as a clear colorless oil (0.350, 36% over two steps): R_f = 0.10 (25% EtOAc in hexane; FTIR (KBr film) ν_{max} (cm^{-1}) 3442, 3066, 1683, 1496, 1367, 1167, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.37−7.22 (m, 5H), 5.73 (br s, 1H), 5.16−4.93 (m, 2H), 3.96−3.46 (m, 3H), 3.36 (br s, 0.6H), 2.54−2.20 (m, 2H), 1.86−1.32 (m, 9H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk) δ 156.9, 139.2, 150.3, 135.0, 128.6, 127.7*, 127.2, 117.3, 80.5, 64.2, 63.8*, 60.0, 59.6*, 50.8, 48.9*, 34.5*, 33.4, 28.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{25}NO_3Na$ 314.1727, found 314.1737.

*Ethyl Benzyl(1-hydroxypent-4-en-2-yl)carbamate (**S11**).* IBX (2.30 mmol, 0.642 g) was added to a solution of **S10** (1.15 mmol, 0.350g) in acetonitrile (5.8 mL (0.2 M)) and heated to reflux. The reaction was monitored for complete consumption of starting material. After 40 min, the contents were cooled to room temperature, filtered through a pad of Celite, and washed with EtOAc (3 × 5 mL). The resulting solution was concentrated and purified by chromatography

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(5:1 hexanes/Et_2O). *tert*-Butyl benzyl(1-oxopent-4-en-2-yl)carbamate (**S11**) was obtained as a clear colorless oil (0.298, 86%): R_f = 0.21 (16% Et_2O in hexane; FTIR (KBr film) ν_{max} (cm^{-1}) 2979, 2816, 1738, 1703, 1454, 1422, 1250, 1165; ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 9.45 (s, 0.4H), 9.35 (s, 0.6H), 7.39−7.27 (m, 5H), 5.89−5.68 (m, 1H), 5.16−5.06 (m, 1H), 5.05 (d, J = 15.2 Hz, 0.4H), 4.77 (d, J = 15.9 Hz, 0.6H), 4.16 (d, J = 14.7 Hz, 0.4H), 4.07 (d, J = 15.0 Hz, 0.6H), 3.67 (dd, J = 9.2, 5.2 Hz, 0.4H), 3.46 (dd, J = 8.9, 5.2 Hz, 0.6H), 2.81−2.68 (m, 1H), 2.56 (ddd, J = 14.0, 7.1, 7.1 Hz 0.4H), 2.44 (ddd, J = 14.0, 7.1, 7.1 Hz, 0.4H), 1.47 (s, 9H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 198.9*, 198.8, 155.6*, 155.0, 138.0*, 137.7, 134.5*, 134.2, 128.9, 128.8*, 128.5, 127.9*, 127.8, 118.3, 118.1*, 81.9, 81.3*, 65.7*, 65.5, 52.3, 52.2*, 32.9, 31.9*, 28.4*, 28.3; HRMS (FD-TOF) m/z [M] Calcd for $C_{17}H_{23}NO_3$ 289.1678, found 396.1683.

*tert-Butyl (S)-Benzyl(1-oxo-3-phenylpropan-2-yl)carbamate (**S14**).* Prepared According to General Procedure A. A(I): (*S*)-2-(Benzylamino)-3-phenylpropan-1-ol (**S12**) and benzyl alcohol were obtained as a mixture. This mixture was carried to the next step without further purification.

A(II): *tert*-Butyl (*S*)-benzyl(1-hydroxy-3-phenylpropan-2-yl)-carbamate (**S13**) and small amounts of an unknown impurity were isolated by column chromatography (3:1 hexanes/acetone). This mixture was carried to the next step without further purification: ^1H NMR (600 MHz, $CDCl_3$) δ 7.34−7.26 (m, 3H), 7.26−7.18 (m, 2H), 4.49−4.29 (m, 1H), 3.86 (d, J = 14.5 Hz, 0.5H), 3.78−3.59 (m, 2.5H), 3.10−2.88 (m, 1H), 1.44 (s, 7.5H), 1.29−1.24 (m, 1.5H).

A(III): *tert*-butyl (*S*)-benzyl(1-oxo-3-phenylpropan-2-yl)-carbamate[18] (**S14**) was isolated by column chromatography (8:1 hexane/EtOAc, R_f = 0.28 (11% EtOAc in hexane)) as a light yellow oil (0.756 g, 22% over three steps): ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 9.46 (s, 0.4H), 9.36 (s, 0.6H), 7.37−7.27 (m, 4H), 7.26−7.22 (m, 2.2H), 7.17 (d, J = 7.3 Hz, 0.8H), 7.14 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 7 Hz, 2H), 4.89 (d, J = 15.0 Hz, 0.6H), 4.40 (d, J = 15.5 Hz, 0.4H), 3.61 (dd, J = 10.1, 4.5 Hz, 0.4H), 3.53 (dd, J = 10.0, 4.3 Hz, 0.6H), 3.33 (t, J = 6.3 Hz, 0.4H), 3.31 (t, J = 4.5 Hz, 0.6H), 3.22 (d, J = 15.6 Hz, 0.4H), 3.12 (dd, J = 13.9, 10.2 Hz, 0.4H), 3.05 (d, J = 15.1 Hz, 0.6H), 2.96 (dd, J = 13.9, 10.0 Hz, 0.6H), 1.51 (s, 5H), 1.50 (s, 4H).

*tert-Butyl (S)-Benzyl(4-methyl-1-oxopentan-2-yl)carbamate (**S17**).* Prepared According to General Procedure A. A(I): (*S*)-2-(Benzylamino)-4-methylpentan-1-ol (**S15**) and benzyl alcohol were obtained as a mixture. This mixture was carried to the next step without further purification.

A(II): *tert*-Butyl (*S*)-benzyl(1-hydroxy-4-methylpentan-2-yl)-carbamate[18] (**S16**) was isolated by column chromatography (6:1 hexanes/acetone) as a clear colorless oil (2.37g, 90% over two steps): R_f = 0.11 (24% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.35−7.20 (m, 10H), 4.69−4.47 (m, 0.4H), 4.47−4.35 (m, 0.6H), 4.35−4.18 (m, 1H), 4.12−3.97 (m, 0.4H), 3.96−3.78 (m, 0.6H), 3.69−3.35 (m, 2H), 2.97−2.81 (m, 1H), 1.54−1.32 (m, 11H), 1.30−1.07 (m, 1H), 0.89 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H).

A(III): *tert*-butyl (*S*)-benzyl(4-methyl-1-oxopentan-2-yl)-carbamate[18] (**S17**) was isolated by column chromatography (9:1 hexane/EtOAc): R_f = 0.26 (10% EtOAc in hexane) as a clear colorless oil (0.451 g, 91%); ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.44 (s, 0.4H), 9.34 (s, 0.6H), 7.37−7.27 (m, 5H), 5.01 (d, J = 14.8 Hz, 0.6H), 4.71 (d, J = 15.5 Hz, 0.4H), 4.19 (d, J = 15.5 Hz, 0.4H), 4.10 (d, J = 15.0 Hz, 0.6H), 3.94−3.85 (m, 0.4H), 4.54 (dd, J = 7.0, 5.0 Hz, 0.6H), 1.90−1.76 (m, 1H), 1.67−1.55 (m, 2H), 1.46 (s, 9H), 0.94−0.88 (m, 3H), 0.86 (d, J = 6.6 Hz, 3H).

*tert-Butyl Benzyl(4-methyl-1-oxopentan-2-yl)carbamate (**S20**).* Prepared According to General Procedure B. B(I): Methyl benzylleucinate (**S18**) and benzyl alcohol were obtained as a mixture. This mixture was carried to the next step without further purification.

B(II): Methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)leucinate[18] (**S19**) was isolated by column chromatography (9:1 hexanes/EtOAc) as a clear colorless oil (2.17 g, 59% over two steps): R_f = 0.23 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$): mixture of rotamers; δ 7.41−7.26 (m, 3.6H), 7.26−7.20 (m, 1.4H), 4.79−4.65 (m, 0.5H), 4.59 (d. J = 14.9 Hz, 0.5H), 4.52 (d, J = 16.5 Hz, 0.5H), 4.39 (d, J = 14.8 Hz, 0.5H), 4.30 (d, J = 14.9 Hz, 0.5H), 4.22−4.04 (m, 0.5H), 3.58 (s, 3H), 1.81−1.69 (m, 1H), 1.64−1.57 (m, 1H), 1.48 (s, 5H), 1.43−1.32 (m, 5H).

B(III): *tert*-Butyl benzyl(1-hydroxy-4-methylpentan-2-yl)-carbamate[18] (**S20**) was isolated by column chromatography (3:1 hexane/EtOAc) as a clear colorless oil (0.858 g, 93%): R_f = 0.20 (25% EtOAc in hexane); ^1H NMR spectrum was identical to that of **S16**.

B(IV): *tert*-Butyl benzyl(4-methyl-1-oxopentan-2-yl)carbamate[18] (**S21**) was isolated by column chromatography (9:1 hexanes/EtOAc) as a clear colorless oil (0.455 g, quantitative): R_f = 0.26 (10% EtOAc in hexanes); ^1H NMR spectrum was identical to tha tof **S17**.

*Ethyl (S)-4-(Benzyl(tert-butoxycarbonyl)amino)-5-oxopentanoate (**S25**). (S)-2-(Benzylamino)-5-ethoxy-5-oxopentanoic Acid (**S22**).*[21] To a solution of (*S*)-2-amino-5-ethoxy-5-oxopentanoic acid (11.4 mmol, 2.00 g) in dry MeOH (23 mL (0.5 M)) was added triethylamine (22.8 mmol, 3.2 mL) followed by freshly distilled benzaldehyde (17.13 mmol, 1.8 mL) at room temperature. The resulting solution was stirred for 1 h before being cooled to 0 °C using an ice bath. Sodium borohydride (34.3 mmol, 1.30 g) was added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for an additional 2 h. The volatiles were removed under reduced pressure, and the crude reaction mixture was partitioned between H_2O (ca. 75 mL) and EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The organic layers were combined and dried over $MgSO_4$, and volatiles were removed under reduced pressure to afford the title compound and benzyl alcohol as white crystals. The crude reaction mixture was carried to the next step without further purification.

*(S)-2-(Benzyl(tert-butoxycarbonyl)amino)-5-ethoxy-5-oxopentanoic Acid[22] (**S23**).* To a solution of crude **S22** (3.78 mmol) in (1:1 v/v) dioxane/H_2O (13 mL (0.3 M)) was added triethylamine (11.4 mmol, 1.6 mL) at room temperature. To this solution was added di-*tert*-butyl dicarbonate (Boc_2O) (3.79 mmol, 0.826 g) following by stirring at ambient temperature for 16 h. The reaction was quenched with addition of HCl (1 M) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was concentrated in vacuo and purified by column chromatography (1:1 hexane/EtOAc). N^2-Benzyl-N^2-(*tert*-butoxycarbonyl)-*N*-ethyl-L-glutamine and benzyl alcohol were obtained as a mixture which was carried to the next step without further purification: ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.36−7.26 (m, 5H), 4.70−4.61 (m, 0.4H), 4.61−4.48 (m, 0.6H), 4.35 (d, J = 15.6 Hz, 1H), 4.28−4.14 (m, 0.6H), 4.12−4.01 (m, 1.8H), 4.00−3.88 (m, 0.6H), 2.40−2.15 (m, 3H), 2.15−1.97 (m, 1H), 1.46 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H).

*Ethyl (S)-4-(Benzyl(tert-butoxycarbonyl)amino)-5-hydroxypentanoate (**S24**).* Crude **S23** (1.01 mmol, 0.369 g) was dissolved in THF (5.1 mL (0.2 M)) and cooled to −10 °C. To this solution was added 4-methylmorpholine (NMM) (2.03 mmol, 0.22 mL) followed by ethyl chloroformate (1.52 mmol, 0.14 mL). The mixture was stirred at this temperature for 1 h, and then $NaBH_4$ (3.04 mmol, 0.115g) was added in one portion followed by addition of MeOH (10.2 mL). The mixture was stirred for an additional 30 min, and the crude product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The resulting solution was concentrated in vacuo and purified by column chromatography (1:1 hexane/EtOAc) to obtain **S24** as a clear colorless oil (0.239 g, 27% over three steps): R_f = 0.18 (50% EtOAc in hexane; $[\alpha]_D^{27}$ = −122 (*c* 1.1, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3458, 2978, 1735, 1690, 1496, 1392, 1366, 1249, 1165; ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.36−7.27 (m, 4H), 7.26−7.23 (m, 1H), 4.56−4.39 (m, 1H), 4.39−4.21 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.77−3.50 (m, 3H), 3.23−3.15 (m, 1H), 2.47−2.18 (m, 2H), 2.08−1.83 (m, 2H), 1.44 (br s, 9H), 1.24 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 173.3, 156.9, 139.1, 128.7, 127.4, 127.4, 80.8, 64.4, 60.6, 59.4, 59.1,

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50.8, 48.4, 31.0, 28.5, 25.6*, 23.6, 14.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{29}NO_5Na$ 374.1937, found 374.1945.

Ethyl (*S*)-4-(benzyl(*tert*-butoxycarbonyl)amino)-5-oxopentanoate (**S25**): IBX (2.30 mmol, 0.642 g) was added to a solution of **S24** (0.595 mmol, 0.209 g) in acetonitrile (6 mL (0.1 M)) and heated to reflux. The reaction was monitored for complete consumption of starting material. After 1 h, the contents were cooled to room temperature, filtered through a pad of Celite, and washed with EtOAc (3 × 5 mL). The resulting solution was concentrated and purified by chromatography (7:1 hexane/EtOAc). **S25** was obtained as a clear colorless oil (0.179, 86%): R_f = 0.16 (13% EtOAc in hexane); $[\alpha]_D^{27}$ = −120 (*c* 3.2, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3389, 2993, 1738, 1703, 1497, 1250, 1163, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.38 (s, 0.4H), 9.27 (s, 0.6H), 7.36−7.26 (m, 5H), 5.04 (d, *J* = 14.9 Hz, 0.6H), 4.77 (d, *J* = 15.5 Hz, 0.4H), 4.18 (d, *J* = 15.5 Hz, 0.6H), 4.15−4.08 (m, 2H), 4.06 (d, *J* = 14.9 Hz, 0.6H), 3.77−3.67 (m, 0.4H), 3.56 (app t, *J* = 6.3 Hz, 0.6H), 2.45−2.25 (m, 3H), 2.08−1.90 (m, 1H), 1.47 (s, 3H), 1.44 (s, 6H), 1.24, (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 199.0, 190.0*, 173.1*, 173.0, 155.5*, 155.1, 138.0*, 137.7, 128.9, 128.6, 128.0*, 127.8, 82.0, 81.4*, 64.8*, 64.5, 60.6, 60.6*, 51.9, 51.8*, 30.5, 28.4*, 28.2, 23.6, 22.6*, 14.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{27}NO_5Na$ 372.1781, found 372.1795.

*tert-Butyl (S)-Benzyl(1-((benzyloxy)methoxy)-3-oxopropan-2-yl)-carbamate (**S30**).* Prepared According to General Procedure B. B(I): Methyl benzyl-L-serinate (**S26**) and benzyl alcohol were isolated as a mixture. This mixture was carried to the next step without further purification.

B(II): Methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-L-serinate[23] (**S27**) was isolated by column chromatography (9:1 hexane/EtOAc) as a clear colorless oil (2.11 g, 53% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.37−7.27 (m, 5H), 4.58−4.51 (m, 1.5H), 4.47−4.39 (m, 0.5H), 4.15−4.02 (m, 1.5H), 3.87−3.73 (m, 1H), 3.70 (s, 3H), 3.52−3.43 (m, 0.5H), 3.13−3.04 (m, 0.5H), 2.43−2.34 (m, 0.5H), 1.45 (s, 9H).

*Methyl N-Benzyl-O-((benzyloxy)methyl)-N-(tert-butoxycarbonyl)-L-serinate[23] (**S28**).* To a solution of **S27** (1.90 g, 6.15 mmol) in dry DMF (6.2 mL (1 M)) was added *i*-Pr_2NEt (3.4 mL, 19.7 mmol) at room temperature under argon. This was followed by the addition of BOMCl (70% purity w/w) (4.11 g, 18.4 mmol). After 24 h, the reaction mixture was diluted in EtOAc (150 mL) and washed sequentially with satd NH_4Cl_{aq} (150 mL), distilled water (150 mL), and brine (150 mL). The organic layer was dried over $MgSO_4$ and concentrated. The volatiles were removed in vacuo, and the reaction mixture was purified by chromatography (7:1 hexane/EtOAc) to afford methyl **S28** as light yellow oil (2.00 g, 76%): R_f = 0.17 (13% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): mixture of rotamers; δ 7.38−7.26 (m, 8.8H), 7.26−7.20 (m, 1.2H), 4.77 (d, *J* = 15.3 Hz, 0.5H), 4.72−4.66 (m, 1H), 4.66−4.63 (m, 0.5H), 4.61−4.55 (m, 1.5H), 4.52−4.39 (m, 3H), 4.11−4.04 (m, 1H), 4.03−3.95 (m, 1H), 3.84 (app t, 9.4 Hz, 0.5H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 1.44 (s, 4.5H), 1.39 (s, 4.5H).

B(III): *tert*-Butyl (*R*)-benzyl(1-((benzyloxy)methoxy)-3-hydroxypropan-2-yl)carbamate[23] (**S29**) was isolated by column chromatography (2:1 hexane/EtOAc) as a clear colorless oil (0.346 g, 74%): R_f = 0.22 (33% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.39−7.26 (m, 8.2H), 7.26−7.22 (m, 1.8H), 4.74−4.64 (m, 2H), 4.64−4.58 (m, 0.7H), 4.54 (dd, *J* = 12.1, 2.5 Hz, 2.3H), 4.43−4.30 (m, 1H),3.96−3.62 (m, 5H), 3.40 (br s, 1H), 1.54−1.37 (m, 9H).

B(IV): *tert*-Butyl (*S*)-benzyl(1-((benzyloxy)methoxy)-3-oxopropan-2-yl)carbamate[23] (**S30**) was isolated by column chromatography (5:1 hexanes/acetone) as a clear colorless oil (0.271 g, 79%): R_f = 0.20 (17% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.44 (s, 0.4H), 9.33 (s, 0.6H), 7.39−7.27 (m, 10H), 5.11 (d, *J* = 15.0 Hz, 0.6H), 4.88 (d, *J* = 15.5 Hz, 0.4 Hz), 4.74 (app t, *J* = 6.9 Hz, 0.8H), 4.71 (app t, *J* = 6.0 Hz, 1.2H), 4.60−4.52 (m, 2H), 4.29 (d, *J* = 15.6 Hz, 0.4H), 4.22 (d, *J* = 15 Hz, 0.6H), 4.18−4.09 (m, 1H), 3.98 (app t, 7.8 Hz, 0.4H), 3.91−3.79 (m, 1H), 3.69 (app t, *J* = 6.9 Hz, 0.6H), 1.46 (s, 4H), 1.43 (s, 5H).

*tert-Butyl (S)-2-Formylpyrrolidine-1-carboxylate (N-Boc-prolinal) (**S31**).*[24] IBX (3.74 mmol, 1.05 g) was added to a solution of *N*-Boc-prolinol (2.49 mmol, 0.500 g) in acetonitrile (12.5 mL (0.2 M)) and heated to reflux. The reaction was monitored for complete consumption of starting material. After 30 min, the contents were cooled to room temperature, filtered through a pad of Celite, and washed with EtOAc (3 × 10 mL). The resulting mixture was concentrated and purified by column chromatography. **S31** was isolated by column chromatography (8:1 hexane/EtOAc, R_f = 0.10 (11% EtOAc in hexane)) as clear colorless oil (0.413 g, 83%): ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 9.56 (s, 0.4H), 9.46 (d, *J* = 2.8 Hz, 0.6H), 4.25−4.14 (m, 0.4H), 410−3.99 (m, 0.6H), 3.61−3.52 (m, 0.gH), 3.52−3.39 (m, 1.4H), 2.17−2.09 (m, 0.6H), 2.08−2.01 (m, 0.4H), 2.01−1.91 (m, 1H), 1.91−1.82 (m, 2H), 1.48 (s, 3H), 1.43 (s, 6H).

General Procedures for the Cross-Benzoin Reaction. *General Procedure C.* The corresponding *N*-Boc-*N*-Bn-amino aldehyde (0.152 mmol, 1.0 equiv) and triazolium salt **1** (0.0304 mmol, 0.2 equiv) were added to an oven-dried test tube with a Schlenk take-off and fitted with a septum. The vessel was placed under vacuum and refilled with argon three times to ensure inert atmosphere. The hetereoaromatic aldehyde (0.228 mmol, 1.5 equiv) and CH_2Cl_2 (0.3 mL (0.5 M)) were added sequentially. Lastly, *i*-Pr_2NEt (0.152 mmol, 1 equiv) was added, and the septum was then quickly exchanged for a coldfinger. Once the inert atmosphere was re-established, the flask was sealed and heated to 40 °C for 1 h. (WARNING: when performed on a larger scale, it is advised to use a water condenser instead of a coldfinger to avoid the small pressure buildup.) The crude reaction mixture was cooled to room temperature and quenched by addition of HCl (2 mL (1 M)). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography followed by preparative thin-layer chromatography to afford the corresponding cross-benzoin product.

General Procedure D. The corresponding *N*-Boc-*N*-Bn-amino aldehyde (0.152 mmol, 1.0 equiv) and triazolium salt **1** (0.0304 mmol, 0.2 equiv) were added to an oven-dried test tube with a Schlenk take-off and fitted with a septum. The vessel was placed under vacuum and refilled with argon three times to ensure inert atmosphere. The hetereoaromatic aldehyde (0.228 mmol, 1.5 equiv) and CH_2Cl_2 (1.0 mL, 0.15 M) were added sequentially. The reaction was cooled to 0 °C, and *i*-Pr_2NEt (0.152 mmol, 1 equiv) was added. After 30 min, the reaction mixture was warmed to room temperature and quenched by addition of 1 M HCl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography followed by preparative thin-layer chromatography to afford the corresponding cross−benzoin product.

*tert-Butyl Benzyl((2S,3S)-4-(furan-2-yl)-3-hydroxy-4-oxobutan-2-yl)carbamate (**6**).* Prepared according to general procedure C. Column chromatography (5:1 hexane/acetone) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as white solids (38 mg, 69%): R_f = 0.22 (17% acetone in hexanes); mp = 121.1 °C, $[\alpha]_D^{26}$ = −30 (*c* 1.9, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3457, 3123, 2978, 1678, 1466, 1392, 1367, 1166, 1034, 921, 769, 733, 700; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.89 (br s, 1H), 7.70 (s, 1H), 7.33−7.27 (m, 2H), 7.24−7.17 (m, 3H), 6.62 (dd, *J* = 3.7, 1.7 Hz, 1H), 5.09 (app d, *J* = 3.7 Hz, 1H), 4.73−4.60 (m, 2H), 4.49 (d, *J* = 16.8 Hz, 1H), 4.05 (d, *J* = 5.3 Hz, 0.8H), 3.58 (br s, 0.2H), 1.57 (s, 1.5H), 1.38 (s, 7.5H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 187.5, 156.4, 148.2, 147.7*, 140.5, 128.3, 126.8, 126.4, 122.08, 120.0*, 112.8, 80.5, 77.4, 76.7*, 55.4, 54.9*, 48.7, 28.7*, 28.4, 13.5*, 11.5*; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{25}NO_5Na$ 382.1625, found 382.1620.

*tert-Butyl Benzyl((2S,3S)-1-(furan-2-yl)-2-hydroxy-1-oxopentan-3-yl)carbamate (**7**).* Prepared according to general procedure C. Column chromatography (7:1 hexane/acetone) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a clear colorless oil (39 mg, 69%): R_f = 0.18 (13% acetone in hexanes); $[\alpha]_D^{26}$ = +31 (*c* 1.3, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3452, 2934, 1679, 1568, 1496, 1367, 1297, 1250, 1165; ^{1}H NMR (500 MHz, $CDCl_3$) mixture

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of rotamers δ 7.81 (br s, 1H), 7.67 (s, 1H), 7.39−7.28 (m, 4H), 7.25−7.17 (m, 1H), 6.60 (s, 1H), 5.00 (dd, *J* = 5.2, 2.2 Hz, 1H), 4.62 (d, *J* = 15.8 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 4.35 (br s, 1H), 3.49 (br s, 0.2H), 1.84−1.67 (m, 1H), 1.56−1.45 (m, 2H), 1.39 (s, 8H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 187.9, 157.0, 149.9, 147.9, 139.9, 128.3, 127.9*, 127.2, 126.9, 121.8, 120.1*, 112.8, 80.6, 78.2, 62.6, 50.0*, 28.7*, 28.4, 19.3, 11.2, 10.8*; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{27}NO_5Na$ 396.1781, found 396.1789.

*tert-Butyl (1-(Benzofuran-2-yl)-2-hydroxy-1-oxohex-5-en-3-yl) (Benzyl)carbamate (**8**).* Prepared according to general procedure C. Column chromatography (4:1 hexane/EtOAc) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a clear colorless oil (1.5 equiv of 2-furaldehyde: 40 mg, 66%; 3 equiv of 2-furaldehyde: 45 mg, 74%): R_f = 0.45 (13% EtOAc in toluene); FTIR (KBr film) ν_{max} (cm^{-1}) 3444, 2978, 1679, 1568, 1465, 1367, 1165, 1033, 914; ^{1}H NMR (600 MHz, $CDCl_3$) mixture of rotamers δ 7.70 (br s, 1H), 7.66 (s, 1H), 7.33−7.26 (m, 3H), 7.26−7.20 (m, 2H), 6.58 (br s, 1H), 5.48 (dddd, *J* = 16.0, 7.4, 7.4, 7.4 Hz, 0.8H), 5.44−5.33 (m, 0.2H), 4.99 (s, 1H), 4.94 (d, *J* = 17.0 Hz, 0.7H), 4.90 (d, *J* = 10.2 Hz, 1 H), 4.87−4.81 (m, 0.3H), 4.61 (d, *J* = 16.0 Hz, 1.7 H), 4.43 (br s, 1H), 4.35 (d, *J* = 16.1 Hz, 1H), 3.53 (br s, 0.2H), 2.62−2.50 (m, 0.9H), 2.50−2.39 (m, 0.1H), 2.18 (ddd, *J* = 14.4, 6.9, 6.9 Hz, 1H), 1.52 (s, 2H), 1.39 (s, 7H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 187.6, 156.9, 150.1, 147.9, 139.4, 134.5, 128.3, 127.9*, 127.3, 127.0, 121.7, 120.1*, 118.0, 117.7*, 112.7, 80.7, 77.9, 70.0, 50.9, 30.9, 28.6*, 28.39; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{27}NO_5Na$ 408.1781, found 408.1798.

*tert-Butyl Benzyl((2S,3S)-4-(furan-2-yl)-3-hydroxy-4-oxo-1-phenylbutan-2-yl)carbamate (**9**).* Prepared according to general procedure C. Column chromatography (4:1 hexane/acetone) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a light yellow oil (43 mg, 66%): R_f = 0.25 (20% acetone in hexanes); $[\alpha]_D^{26}$ = −34 (*c* 2.2, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3446, 3029, 1679, 1569, 1496, 1367, 1249, 1165; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.69−7.51 (m, 2H), 7.37−7.26 (m, 0.7H), 7.26−7.09 (m, 6H), 7.09−6.98 (m, 3H), 6.90−6.82 (m, 0.3H), 6.58 (s, 0.2H), 6.52 (s, 0.8H), 5.08−4.91 (m, 1.3H), 4.71−4.43 (m, 0.7H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.04−3.76 (m, 0.7H), 3.76−3.60 (m, 0.3 H), 3.28−3.04 (m, 0.8H), 2.99−2.87 (m, 0.2H), 2.79 (dd, *J* = 14.2, 4.9 Hz, 0.9H), 2.73−2.58 (m, 0.1H), 1.45−1.28 (m, 9H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 187.3, 157.0, 150.2, 147.6, 146.9, 138.9, 138.0, 129.5*, 129.4, 128.6, 128.5*, 128.3, 127.3, 126.9, 126.5, 121.4, 119.8*, 112.8*, 112.6, 80.9, 78.0, 63.3, 52.1*, 32.6, 31.7*, 28.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{29}NO_5Na$ 458.1938, found 458.1927.

*tert-Butyl Benzyl((2S,3S)-1-(furan-2-yl)-2-hydroxy-5-methyl-1-oxohexan-3-yl)carbamate (**10**).* Prepared according to general procedure C. Column chromatography (5:1 hexane/acetone) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a clear colorless oil (49 mg, 77%): R_f = 0.25 (20% acetone in hexanes); $[\alpha]_D^{26}$ = +5.9 (*c* 1.6, $CHCl_3$); HPLC analysis Chiralcel IC column, 2% in hexanes, 0.1 mL/min, major, 20.0 min; minor, 33.0 min; FTIR (KBr film) ν_{max} (cm^{-1}) 3452, 2958, 1679, 1496, 1390, 1366, 1165, 991; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.84 (br s, 1H), 7.68 (s, 1H), 7.41−7.26 (m, 4H), 7.24−7.16 (m, 1H), 6.61 (s, 1H), 5.03 (s, 1H), 4.81−4.54 (m, 2H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.14 (br s, 0.8H), 3.57 (br s, 0.2H), 1.76−1.57 (m, 1H), 1.31−1.22 (m, 1H), 1.52 (s, 2.2H), 1.38 (s, 6.8H), 1.00−0.77 (m, 1H), 0.69−0.41 (m, 6H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 187.7, 156.9, 149.7, 148.1, 147.7*, 140.2, 128.3, 127.6*, 127.0, 126.8, 121.8, 120.0*, 112.9, 111.1*, 80.5, 78.5, 58.2, 49.2*, 34.9, 28.6*, 28.4, 24.8, 24.2*, 23.14, 21.7, 21.4*; HRMS (ESI-TOF) *m*/*z* $[M + 1]^+$ calcd for $C_{23}H_{32}NO_5$ 402.2275, found 402.2271.

*rac-tert-Butyl Benzyl-(furan-2-yl)-2-hydroxy-5-methyl-1-oxohexan-3-yl)carbamate (rac-**10**).* Prepared according to general procedure C. Column chromatography (5:1 hexane/EtOAc) afforded the major diastereomer as a clear colorless oil (48 mg, 77%): R_f = 0.21 (16% EtOAc in hexanes); HPLC analysis Chiralcel IC column, 2% 2-propanol in hexanes, 0.1 mL/min, major, 20.0 min; minor, 32.9 min; ^{1}H NMR spectrum was identical to that of **10**.

*tert-Butyl (S)-2-((S)-2-(Furan-2-yl)-1-hydroxy-2-oxoethyl)-pyrrolidine-1-carboxylate (**11**).* Prepared according to general procedure C. Column chromatography (3:1 hexane/acetone) followed by (7:1 toluene/EtOAc) afforded the product along with small amounts of impurities. This mixture was recrystallized in hexanes to afford the major diastereomer as white solids (38 mg, 43%): R_f = 0.28 (25% acetone in hexanes); mp = 91.0 °C; $[\alpha]_D^{26}$ = +120 (*c* 1.9, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3460, 2976, 1683, 1466, 1394, 1168, 1084, 771; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 7.81 (d, *J* = 3.4 Hz, 0.7H), 7.70 (s, 0.7H), 7.67 (s, 0.3H), 7.35 (br s, 0.3H), 6.64−6.56 (m, 1H), 5.37 (dd, *J* = 6.4, 1.7 Hz, 0.7H), 5.20−5.10 (m, 0.3H), 4.30−4.21 (m, 0.7H), 4.21−4.12 (m, 0.3H), 3.82 (d, *J* = 6.4 Hz, 0.7H), 3.59−3.55 (m, 0.3H), 3.55−3.50 (m, 0.2H), 3.47−3.32 (m, 1.8H), 2.08−1.96 (m, 1H), 1.82−1.62(m, 3H), 1.48 (s, 9H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 188.4*, 188.2, 155.1, 154.1*, 150.6*, 149.8, 148.11, 147.6*, 122.0, 119.9*, 112.8*, 112.8, 80.2*, 79.7, 74.9*, 74.7, 61.5, 60.4*, 47.3, 47.1*, 28.6, 26.3*, 24.8, 24.8, 23.7; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{21}NO_5Na$ 318.1312, found 318.1318.

*Ethyl (4S,5S)-4-(Benzyl(tert-butoxycarbonyl)amino)-6-(furan-2-yl)-5-hydroxy-6-oxohexanoate (**12**).* Prepared according to general procedure A. Column chromatography (4:1 hexanes/acetone) followed by PTLC (7:3 toluene/EtOAc) afforded the major product as a light yellow oil (43 mg, 64%): R_f = 0.18 (20% acetone in hexane); $[\alpha]_D^{27}$ = +17 (*c* 2.2, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3451, 2979, 1733, 1683, 1496, 1392, 1251, 1164; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.71 (br s, 1H), 7.66 (d, *J* = 1.1 Hz, 1H), 7.40−7.27 (m, 4H), 7.25−7.17 (m, 1H), 6.59 (s, 1H), 5.00 (dd, *J* = 5.1, 2.2 Hz, 1H), 4.63 (d, *J* = 16.0 Hz, 1H), 4.43 (d, *J* = 15.7 Hz, 1H), 4.34 (br s, 0.7H), 3.97 (q, *J* = 7 Hz, 2H), 3.59 (br s, 0.2H), 2.14−1.85 (m, 3H), 1.71−1.59 (m, 1H), 1.50 (s, 2H), 1.40 (s, 7H), 1.13 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk) δ 187.4, 172.7, 156.8, 149.9, 147.8, 139.5, 128.4, 127.9*, 127.3, 127.0, 121.8, 120.0*, 112.8, 80.9, 77.8, 60.4, 60.0, 50.0*, 31.0, 30.5*, 28.4, 22.5*, 21.7, 14.2; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{31}NO_7Na$ 468.1993, found 468.2005.

*tert-Butyl Benzyl((2S,3S)-1-((benzyloxy)methoxy)-4-(furan-2-yl)-3-hydroxy-4-oxobutan-2-yl)carbamate (**13**).* Prepared according to general procedure D with the following modifications: in place of 1.5 equiv of heteroaromatic aldehyde, 3 equiv of that reagent was used.

Column chromatography (4:1 hexane/acetone) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a light yellow wax (51 mg, 68%): R_f = 0.24 (20% acetone in hexane); $[\alpha]_D^{27}$ = +3.1 (*c* 2.0, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3442, 2976, 1681, 1497, 1391, 1250, 1165, 1047; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.71 (br s, 1H), 7.65 (d, *J* = 0.9 Hz, 1H), 7.38−7.27 (m, 5.5H), 7.26−7.16 (m, 4.5H), 6.58 (s, 1H), 5.03 (br s, 1H), 4.72 (m, 2H), 4.52−4.40 (m, 3H), 4.37 (s, 2H), 3.82−3.72 (m, 1H), 3.72−3.63 (m, 0.8H), 3.63−3.54 (m, 0.2 H), 1.54 (s, 2H), 1.39 (s, 7H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk) δ 187.0, 156.6, 150.1, 147.5, 139.6, 137.8, 128.5, 128.4, 128.0, 127.8, 126.9, 126.8, 120.9, 112.6, 94.5, 80.9, 76.4, 69.4, 64.5, 60.1, 50.6*, 28.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{33}NO_7Na$ 518.2149, found 518.2159.

*tert-Butyl Benzyl((2S,3S)-2-hydroxy-5-methyl-1-oxo-1-(pyridin-2-yl)hexan-3-yl)carbamate (**14**).* Prepared according to general procedure D. Column chromatography (7:1 hexane/acetone) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a clear colorless oil (1.5 equiv of 2-pyridinecarboxaldehyde: 38 mg, 61%; 3 equiv of 2-pyridinecarboxaldehyde: 44 mg, 71%): R_f = 0.17 (17% EtOAc in hexane); $[\alpha]_D^{27}$ = −22 (*c* 1.2, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3470, 2958, 1690, 1584, 1496, 1347, 1244, 1166; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 8.68 (d, *J* = 3.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.52 (s, 1H), 7.40−7.26 (m, 3H), 7.26−7.06 (m, 1H), 5.41−5.09 (m, 2H), 4.79−4.49 (m, 2H), 4.49−4.37 (m, 1H), 1.67−1.53 (m, 1H), 1.40−1.32 (m, 4H), 1.29 (s,

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6H), 1.19−0.98 (m, 0.7H), 0.95−0.85 (m, 0.3H), 0.71−0.43 (m, 6H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 199.7*, 199.3, 156.3, 152.3, 152.0, 148.7, 140.2, 137.7, 137.5, 128.2, 127.8, 127.2, 126.7, 123.4, 123.3, 80.0, 79.0, 78.6, 57.8, 49.5*, 36.5, 28.3, 28.2*, 24.8, 24.2*, 23.2, 21.8, 21.4*; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{32}N_2O_4Na$ 435.2254, found 435.2267.

*tert-Butyl Benzyl((2S,3S)-2-hydroxy-5-methyl-1-oxo-1-(pyrazin-2-yl)hexan-3-yl)carbamate (**15**).* Prepared according to general procedure D with the following modifications: in place of 1.5 equiv of heteroaromatic aldehyde, 3 equiv of that reagent was used, and in place of an ice bath, a brine ice bath (ca. −15 °C) was used. The reaction was quenched at 15 min.

Column chromatography (3:1 hexane/EtOAc) followed by PTLC (3:1 toluene/acetone) afforded a mixture. The mixture was washed with cold hexanes, and the filtrate was concentrated in vacuo to afford the major diastereomer as a light yellow oil (37 mg, 50%): R_f = 0.24 (25% acetone in hexane); $[\alpha]_D^{27}$ = +11 (c 0.9, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3439, 2958, 1690, 1407,1497, 1166, 1052, 1018; ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.29 (s, 0.1H), 9.22 (s, 0.9H), 8.86−8.76 (m, 0.9H), 8.74 (s, 0.1H), 8.70 (s, 0.1H), 8.64 (s, 0.9H), 7.41−7.28 (m, 3.1H), 7.25−7.02 (m, 1.9H), 5.47−5.41 (m, 0.1H), 5.38 (dd, J = 9.9, 4.8 Hz, 0.9H), 4.75−4.34 (m, 3.7H), 3.74 (br s, 0.3H), 1.69−1.60 (m, 1H), 1.42 (s, 3H), 1.33 (s, 6H), 0.71−0.46 (m, 6H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 200.1*, 199.4, 156.4, 148.6*, 148.3, 146.7, 144.8, 143.3, 139.8, 128.3, 127.7*, 127.3, 126.9, 80.5*, 78.1, 58.1, 50.3*, 36.5, 28.4*, 28.3, 28.2, 24.8, 24.2*, 23.1, 22.7*, 21.9, 21.5*; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{31}N_3O_4Na$ 436.2207, found 436.2226.

*tert-Butyl ((2R,3R)-1-(Benzofuran-2-yl)-2-hydroxy-5-methyl-1-oxohexan-3-yl)(benzyl)carbamate (**16**).* Prepared according to general procedure D. Column chromatography (5:1 hexane/Et_2O) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a clear colorless oil (50 mg, 73%): R_f = 0.18 (25% Et_2O in hexanes); $[\alpha]_D^{27}$ = −30 (c 2.5, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3455, 2958, 1678, 1550, 1496, 1367, 1165, 1030; ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 8.13 (br s, 1H), 7.79 (d, J = 7.4 Hz, 0.8H), 7.76−7.71 (m, 0.2H), 7.60 (d, J = 8.2 Hz, 1H), 7.55−7.46 (m, 1H), 7.41−7.28 (m, 5H), 7.26−7.19 (m, 1H), 5.16 (s, 1H), 4.72 (d, J = 16.0 Hz, 1H), 6.63 (br s, 0.9H), 4.45 (d, J = 16.0 Hz, 1H), 3.59 (br s, 0.1H), 1.85−1.62 (m, 1H), 1.51 (s, 2H), 1.41 (s, 7H), 1.36−1.24 (s, 1H), 1.10−0.98 (s, 1H), 0.68−0.48 (m, 6H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 189.9, 157.00, 156.0, 149.7, 139.9, 129.2, 128.37, 127.7*, 127.1, 124.2, 124.2, 123.6*, 117.5, 115.9*, 112.7, 80.7, 79.0, 77.9*, 59.0, 50.1*, 35.07. 28.6*, 28.4, 24.8, 24.1*, 23.14, 21.9, 21.5*; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{27}H_{33}NO_5Na$ 474.2262, found 474.2260.

*Methyl 4-((2S,3S)-3-(Benzyl(tert-butoxycarbonyl)amino)-2-hydroxy-5-methylhexanoyl)benzoate (**17**).* Prepared according to general procedure C. Column chromatography (9:1 hexanes/EtOAc) followed by PTLC (4:1 hexane/acetone) afforded the major product as a clear colorless oil (13 mg, 18%): R_f = 0.20 (10% EtOAc in hexanes); $[\alpha]_D^{27}$ = −28 (c 1.3, $CHCl_3$); FTIR (KBr film) ν_{max} (cm^{-1}) 3461, 2957, 1730, 1683, 1496, 1367, 1281, 1164; ^1H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 8.26−8.12 (m, 3.4H), 8.07−7.96 (m, 0.6H), 7.39−7.27 (m, 4H), 7.24−7.17 (m, 1H), 5.34 (s, 0.7H), 5.29 (s, 0.3H), 7.72 (d, J = 16.1 Hz, 1H), 4.65 (br s, 1H), 4.46 (d, J = 15.8 Hz, 1H), 4.12 (br s, 0.6H), 2.96 (s, 3H), 3.72 (br s, 0.2H), 1.70−1.58 (m, 1H), 1.48 (s, 3H), 1.38 (s, 6H), 1.23−1.12 (m, 1H), 0.83−0.71 (m, 0.7H), 0.69−0.61 (m, 0.3H), 0.57−0.42 (m, 6H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 200.1, 166.2, 256.8, 140.3, 136.8, 134.8, 130.2, 129.2, 128.8*, 128.3, 127.5*, 126.9, 126.7, 80.5, 78.6, 78.1*, 56.8, 52.7*, 48.9, 39.9, 28.7,*, 28.4, 24.7, 24.0*, 23.1, 21.7, 21.3*; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{27}H_{35}NO_6Na$ 492.2357, found 492.2351.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02568.

Crystallographic data for compound **6** (CIF)

^1H NMR and $^{13}C\{^1H\}$NMR spectra of all new compounds, and HPLC chromatograms for compounds **10** and *rac*-**10** (PDF)

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Notes

The authors declare no competing financial interest.

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