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Truncated diastereoselective Passerini reaction, a rapid construction of polysubstituted oxazole and peptides having an α-hydroxy-β-amino acid component

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Abstract—The reaction of aldehydes and ketones, including aliphatic and aromatic ones, with amides of α-isocyano-β-phenylpropionic acid in toluene in the presence of lithium bromide gives 2,4,5-trisubstituted oxazoles in good to excellent yield. Protected chiral α-amino aldehydes participate in this reaction to give, after hydrolysis of the oxazoles, norstatine-containing peptides in good overall yield. The nucleophilic addition of isonitriles to *N*,*N*-dibenzylphenylalanal is investigated for the first time and is found to be stereoselective leading predominantly to the *anti*-adduct (dr=9/1). On the other hand, the reaction between the *N*-Boc phenylalanal and isonitrile is non-stereoselective.

1. Introduction

The reaction of an isonitrile, an aldehyde and a carboxylic acid to provide an α-acyloxy amide was discovered by Passerini about 80 years ago.[1] Together with the Ugi reaction, it is among the most powerful multicomponent reactions and have found wide applications in the synthesis of large arrays of chemical species.[2] Recently, a sequence involving Passerini reaction followed by an intramolecular *O* to *N*-acyl migration has been developed by the group of Banfi[3] and Semple,[4] respectively, for the rapid atom-economy synthesis of enzyme inhibitors.[5] Lewis acid-mediated two-component variants leading to α-hydroxycarboxylic amides has been described by Seebach[6] and more recently, an enantioselective version has been uncovered by Denmark and Fan.[7] Being interested in the development of novel multicomponent synthesis of heterocycles, we have described a three-component synthesis of 5-aminooxazoles by condensation of aldehydes, amines and α-isocyano amides[8] and its subsequent transformation to a variety of polyheterocycles[9,10] and macrocycles.[11] Ganem and co-workers subsequently reported a Lewis acid promoted condensation between aldehydes and α-isocyano amides for the synthesis of polysubstituted 5-aminooxazoles.[12] As a continuation of our work in this field, we report herein a synthesis of 2,4,5-trisubstituted oxazoles (**1**) by a truncated Passerini reaction between aldehydes and α-alkyl-α-isocyano amides under mild conditions[13] and its application in the synthesis of peptides having a β-amino-α-hydroxy acid fragment (Fig. 1). The β-amino-α-hydroxy acid (norstatine) is the essential moiety of a large number of well-known natural or synthetic compounds that are endowed with powerful biological activities. Anticancer drugs such as paclitaxel and

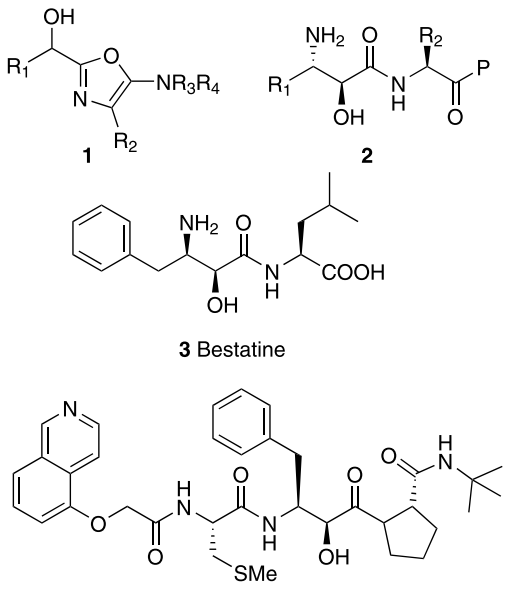

Figure 1.

Keywords: Diastereoselectivity; *N*,*N*-Dibenzyl aminoaldehyde; α-Hydroxy-β-amino acid; Multicomponent reaction; Oxazole; Passerini reaction.

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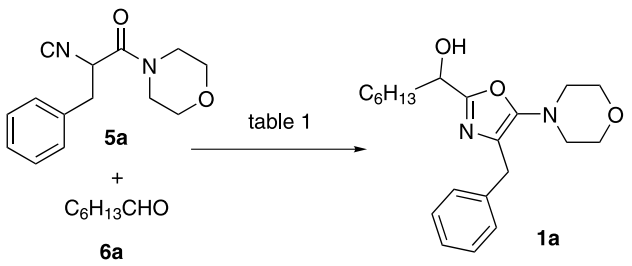
taxotère,[14] the potent aminopeptidase B inhibitor bestatine (**3**)[15] and potent HIV protease inhibitor (**4**)[16] are notable examples.

The reaction between α-isocyano β-phenyl propionamide (**5**) and heptanal (**6**) was investigated under different set of conditions following our previous work (Scheme 1). Table 1 summarized the results of reaction optimization under different conditions varying the solvent, the temperature and additives (weak Brønsted acids and weak Lewis acid). As can be seen, no reaction occurred in MeOH (entry 1) and toluene (entry 4) in the absence of promoters. However, lithium bromide (LiBr),[17] ammonium chloride (NH_4Cl)[18] and camphorsulphonic acid (CSA),[19] were all able to assist this transformation leading to the oxazole in good to excellent yields. Interestingly, in the presence of these promoters the condensation reaction took place in both polar protic solvent (MeOH) and non-polar aprotic solvent (toluene). The optimum conditions consist of heating the isocyanide (**5a**) and heptanal (**6a**) in toluene (70 °C) in the presence of 1 equiv. of LiBr. Under these conditions, the desired oxazole **1a** was isolated in 89% yield (entry 5). It is worthy noting that LiBr and NH_4Cl are sparsely soluble in toluene, so the reaction is in fact catalytic in nature.



Scheme 1.

Table 1. Screening of reaction conditions for the synthesis of **1a**

Entry	Solvent	Additive	Temperature (°C)	Yield (%)[a]
1	MeOH	—	55	0
2	MeOH	LiBr[b]	55	86
3	MeOH	NH_4Cl[b]	55	30
4	Toluene	—	70	0
5	Toluene	LiBr[b]	70	89
6	Toluene	NH_4Cl[b]	70	68
7	Toluene	CSA[c]	70	50

[a] Isolated yield.
[b] 1 equiv.
[c] CSA=camphorsulphonic acid, 0.1 equiv.

The generality of this transformation was demonstrated by applying the procedure to various aldehydes and α-alkyl α-isocyanoacetamides. Figure 2 lists 2-hydroxyalkyl-5-amino oxazoles synthesized by this new protocol. Aliphatic carbonyl compounds, including linear (heptanal), α-branched aldehydes (isobutyraldehyde) and activated aldehydes or ketones such as ethyl glyoxylate and keto malonate participate in this transformation to give the corresponding adducts. Aromatic aldehydes with electron withdrawing group or moderate electron donating group react smoothly leading to the oxazoles (**1g** to **1k**). However, 4-methoxybenzaldehyde failed to produce the corresponding oxazole, presumably because of its lower electrophilicity and/or the low stability of the resulting benzyl alcohol. The amine part of the α-isocyano-β-phenyl-propionamide influenced the reaction efficiency as well as the stability of adducts. Thus, piperidine-containing oxazoles are less stable than the morpholine derivatives (**1a** vs. **1b**, and **1h** vs. **1i**). In fact, it is rather difficult to obtain analytically pure **1b** and **1i** due to their low stability that partly explained the decreased yield of oxazoles **1b** and **1i**.

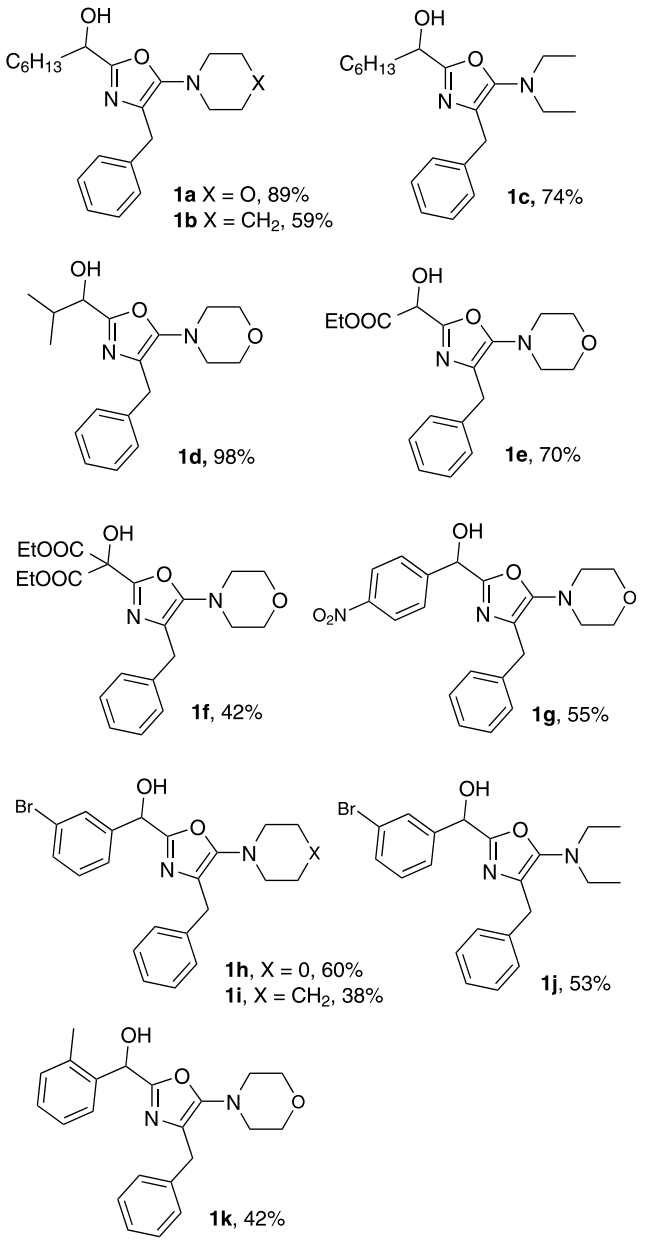
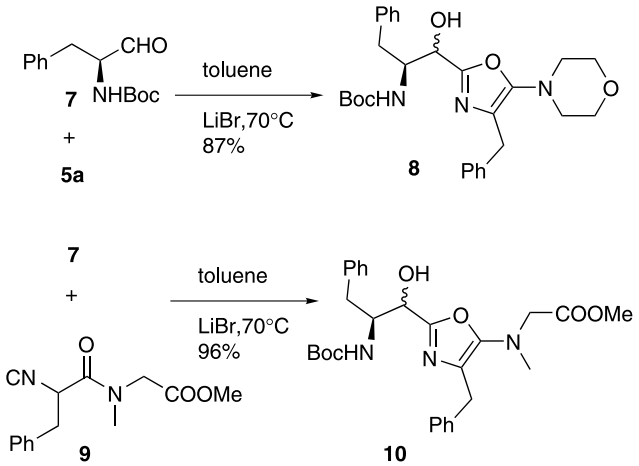


Figure 2.

It is important to note that it is essential to use the α-alkyl α-isocyanoacetamide since the reaction of heptanal and isocyanoacetate under identical conditions provided a complex reaction mixture.

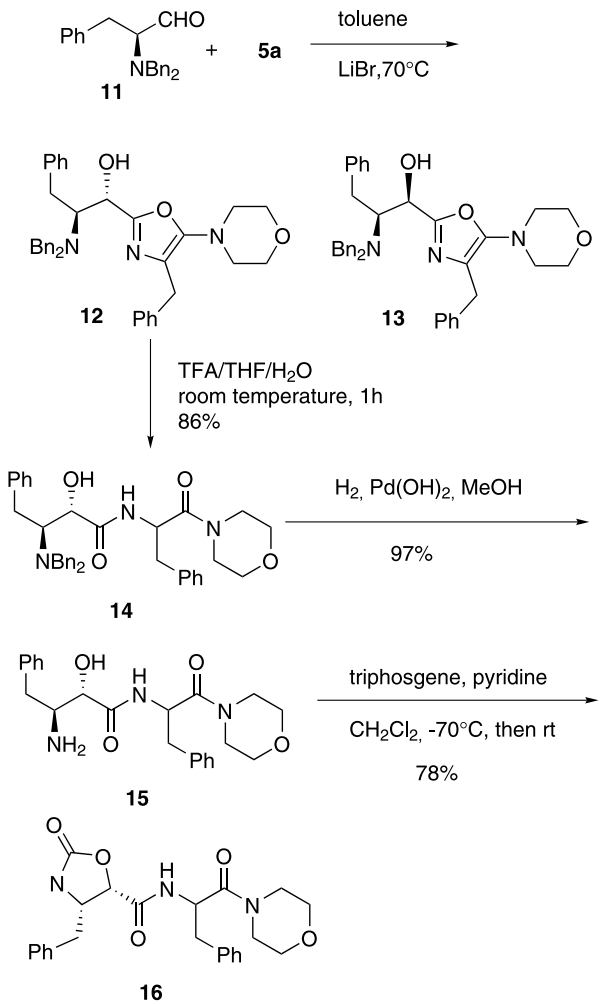
Synthesis of non-proteinogenic β-amino-α-hydroxy acids (norstatines),[20] followed by peptide coupling is the conventional way to prepare the peptide of general structure

2 (Fig. 1). Since 5-aminooxazole can be hydrolyzed to the acetamido amide under mild acidic conditions,[21] a two-step synthesis of norstatine-containing peptides can thus be envisaged starting from chiral non-racemic amino aldehydes. Indeed, the reaction of L-*N*-Boc-phenylalanal **7** with **5a** and dipeptidic isocyanide **9**[22] provided the corresponding oxazoles **8** and **10** in 87 and 96% yields, respectively. Unfortunately, the diastereoselectivity of this transformation was unacceptably low (dr=3/2). The chirality of α-isocyano amide (**5a**) has no influence on the diastereoselectivity since both (L) and racemic form provided similar results (Scheme 2).



Scheme 2.

The low selectivity in the formation of compounds **8** and **10** was not unexpected since the Passerini reaction involving chiral carbonyl compounds produce generally low to moderate diastereoselectivity, due to the low steric requirement of isocyano group. Recent elegant work from Marcaccini, Torroba[23] and Lamberth[24] nevertheless illustrated that excellent diastereoselectivity could be achieved if appropriate chiral starting materials were used. In light of Reetz's original contributions[25] and our own experiences on the diastereoselective transformation of *N*,*N*-dibenzylamino aldehyde,[26] the *N*,*N*-dibenzyl phenylalanal **11** was next examined. To our delight, the reaction of **5a** and **11** is much more stereoselective leading to the formation of two diastereomeric amino alcohols in a ratio of 9:1 (determined from the ^{1}H NMR spectra of the crude reaction mixture) and the major stereomer **12** was isolated in 64% yield. Hydrolysis of **12** under acidic conditions (THF–H_2O, TFA, room temperature) proceeded smoothly to provide the dipeptide **14** in 86% yield. The protonation of the C-4 carbon was non-stereoselective leading to the formation of dipeptide as a mixture of two separable diastereomers. Both diastereomers (**14a** and **14b**) were transformed to the corresponding oxazolidinone (**16**) in order to determine the relative stereochemistry of the amino alcohol (Scheme 3). Thus, hydrogenolysis of **14** under standard conditions [$Pd(OH)_2$, H_2, 1 atm, MeOH] provided the corresponding amino alcohol **15** which was reacted with triphosgene in the presence of pyridine to provide the oxazolidinone in 78% yield. The coupling constant (J_{Ha-Hb}=8.5 Hz) indicated a *cis* relation for these two protons and hence the *anti* stereochemistry of the amino alcohol in compound **12**. Nucleophilic addition to *N*,*N*-



Scheme 3.

dibenzylamino aldehydes leading to *anti*-adducts is well-known[25] and can be explained by the usual Felkin–Anh model (Fig. 3).[27]

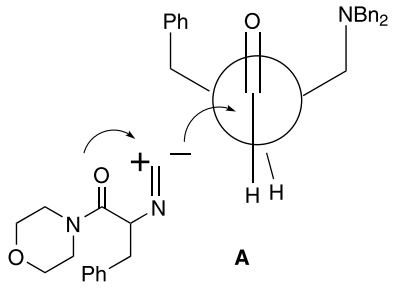


Figure 3.

In summary, we have developed a new synthesis of 2,4,5-trisubstituted oxazole by reaction of aldehyde with peptidic isocyanide. Using *N*,*N*-dibenzylamino phenylalanal, a highly diastereoselective Passerini reaction occurred to provide, after acidic hydrolysis of oxazole, the phenylnorstatine-containing dipeptide. To the best of our knowledge, this is the first example in which *N*,*N*-dibenzylamino aldehyde was used as chiral carbonyl input in the Passerini reaction. We expect the further application of the readily

available *N*,*N*-dibenzylamino aldehydes in the Passerini as well as in the Ugi type multicomponent reactions.

2. Experimental

2.1. Preparation of isonitrile 5a and 9

These two isonitriles were obtained by dehydration of the corresponding *N*-formyl derivatives.[22] Typical procedure: A stirred solution of morpholinyl amide of *N*-formyl phenylalanine (10 mmol) and triethylamine (50 mmol) in 50 mL of dry dichloromethane was cooled to −20 to −30°C. Phosphorus oxychloride (15 mmol) was added dropwise and the reaction mixture was stirred for 2 h at −20 to −30°C. An aqueous solution of sodium bicarbonate was introduced dropwise so that the temperature of mixture was maintained at −20 to −30°C. The mixture was stirred for 0.5 h and raised to room temperature. The aqueous layer was separated and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel to provide the isocyanide **5a**.

2.1.1. Compound 5a. Yield: 95%; eluant: Hept/EtOAc=2/1; white solid, mp 79–81°C; IR ($CHCl_3$) ν 2928, 2863, 2142, 1668, 1496, 1456, 1116 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 3.13–3.78 (m, 10H), 4.55 (t, 1H, J=7.3 Hz), 7.22–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 39.1, 42.9, 46.2, 55.0, 65.9, 66.4, 127.7, 128.8 (2CH), 129.4 (2CH), 135.0, 159.8, 163.5; MS (EI): *m*/*z* 244.

2.1.2. Compound 9. Yield 98% (eluant: EtOAc/Hept=1/5); IR ($CHCl_3$, cm^{-1}) ν 3009, 2142, 1751, 1677, 1497, 1456, 1439, 1407, 1366, 1238, 1183, 1121, 1080, 1032; $[\alpha]_D$=−8.3 (c=0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, ppm), two rotamers (4/1 ratios) δ 3.08 (3.02) (s, 3H), 3.15 (dd, J=8.7, 14.0 Hz, 1H), 3.28 (dd, J=5.3, 14.0 Hz, 1H), 3.76 (s, 3H), 4.02 (3.90) [d, J=17.3 (17.2) Hz, 1H], 4.26 (4.09) (d, J=17.3 (17.2) Hz, 1H), 4.62 (4.39) [d, J=5.5 (5.5), 8.7 (8.8) Hz, 1H], 7.20–7.36 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$, ppm), two rotamers (4/1 ratios) δ 35.90, 36.75, 38.68, 39.03, 50.14, 51.22, 52.39, 55.80, 127.7, 128.8, 129.5, 135.2, 160.0, 165.8, 168.9; MS (EI) *m*/*z* 260, 233, 201, 174. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.62; H, 6.15; N, 10.77. Found: C, 64.77; H, 6.07; N, 10.74.

2.2. Typical procedure for the truncated Passerini reaction, synthesis of compound 1a

To a solution of heptanal (**6a**, 0.20 mmol, 26.9 μL) and α-isocyano β-phenyl propionamide (**5a**) (0.15 mmol, 37.6 mg) in dry toluene (0.30 mL) was added lithium bromide (0.15 mmol, 13.4 mg.). The reaction mixture is stirred at 60 °C for 4 h. After the disappearance of isonitrile, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatograph (AcOEt/Hept 1/2) to give the corresponding oxazole **1a** (49.3 mg, 89% yield). R_f=0.39 (eluant: AcOEt/Hept=2/3); IR ($CHCl_3$) ν 3416, 2929, 2860, 1737, 1665, 1454, 1376, 1264, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.87 (m, 3H), 1.25 (m, 8H), 1.73–1.86 (m, 2H), 2.94 (m, 4H), 3.70 (m, 4H), 3.80 (s, 2H), 4.61 (br t, 1H, J=6.2 Hz), 7.18–7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.1, 28.9, 31.4, 31.7, 51.1, 66.9, 71.9, 124.7, 128.3–128.4, 139.3, 151.9, 160.7; MS (ESI) *m*/*z* 359 (M+H), 381 (M+Na); HRMS (ESI) *m*/*z* calculated for $C_{21}H_{30}N_2O_3$+Na: 381.21333, found 381.2132.

Compounds **1b**–**1k**, **8**, **10** and **12** were prepared under identical conditions.

2.2.1. Compound 1b. R_f=0.68 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3411, 2930, 2860, 1723, 1631, 1496, 1453, 1269, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.87 (m, 3H), 1.27 (m, 8H), 1.52 (m, 2H), 1.61 (m, 4H), 1.83 (m, 2H), 2.94 (m, 4H), 3.78 (s, 2H), 4.60 (br t, 1H, J=5.8 Hz), 7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5, 22.6, 23.9, 25.9, 28.9, 31.4, 31.7, 52.2, 71.7, 123.4, 128.5, 139.7, 153.5, 159.9; MS (ESI) *m*/*z* 357 (M+H), 379 (M+Na).

2.2.2. Compound 1c. R_f=0.70 (eluant: AcOEt/Hept=1/1); ^1H NMR (250 MHz, $CDCl_3$, 293 K) δ 0.87 (m, 3H), 0.98 (t, 6H, J=7.3 Hz), 1.26 (m, 8H), 1.83 (m, 2H), 2.71 (d, 1H, J=5.5 Hz, OH), 2.95 (q, 4H, J=7.3 Hz), 3.77 (s, 2H), 4.62 (m, 1H), 7.25 (m, 5H); MS (ESI) *m*/*z* 367 (M+Na), 383 (M+K).

2.2.3. Compound 1d. R_f=0.43 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3411, 2964, 2927, 2856, 1638, 1454, 1262, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.92 (d, 3H, J=6.7 Hz), 0.96 (d, 3H, J=6.7 Hz), 2.11 (m, 1H), 2.95 (m, 4H), 3.72 (m, 4H), 3.82 (s, 2H), 4.39 (d, 1H, J=6.7 Hz), 7.19–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.4, 31.8, 33.5, 51.2, 66.9, 73.05, 124.7, 126.3, 128.5, 139.4, 152.1, 160.1; MS (ESI) *m*/*z* 317 (M+H), 339 (M+Na).; HRMS (ESI) *m*/*z* calculated for $C_{18}H_{24}N_2O_3$+Na: 339.1664, found 339.1665.

2.2.4. Compound 1e. R_f=0.50 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3519, 2862, 2142, 1743, 1664, 1453, 1265, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.26 (t, 3H, J=7.3 Hz), 2.97 (m, 4H), 3.72 (m, 4H), 3.82 (s, 2H), 4.31 (m, 2H), 5.16 (s, 1H), 7.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 31.6, 50.7, 62.6, 66.6, 67.1, 125.1, 127.6, 128.3, 129.3, 139.1, 154.2, 163.4, 169.9; MS (ESI) *m*/*z* 347 (M+H), 369 (M+Na), 385 (M+K); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{22}N_2O_5$+Na: 369.1426, found 369.1381.

2.2.5. Compound 1f. R_f=0.49 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3494, 2987, 1747, 1660, 1453, 1264, 1115 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 293 K) δ 1.29 (t, 6H, J=7.0 Hz), 2.95 (m, 4H), 3.71 (m, 4H), 3.83 (s, 2H), 4.36 (m, 4H), 7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 31.8, 50.8, 63.5, 66.7, 125.1, 126.2, 128.3, 128.5, 139.2, 152.3, 153.0, 166.8; MS (ESI) *m*/*z* 419 (M+H), 441 (M+Na), 457 (M+K), 859 (2M+Na); HRMS (ESI) *m*/*z* calculated for $C_{21}H_{26}N_2O_7$+Na: 441.1638, found 441.1599.

2.2.6. Compound 1g. R_f=0.34 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3400, 2925, 2860, 1666, 1529, 1454, 1349, 1264, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.92 (m, 4H), 3.71 (m, 4H), 3.80 (s, 2H), 5.76 (s, 1H), 7.21 (m, 5H), 7.65 (d, 2H, J=8.8 Hz), 8.22 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7, 50.9, 66.8, 69.0, 123.8, 124.6, 126.5, 127.4, 127.8, 128.5, 128.6, 128.9, 129.5, 139.0, 146.3, 147.8, 152.9, 157.9; MS (ESI) m/z 396 (M+H), 418 (M+Na); HRMS (ESI) m/z calculated for $C_{21}H_{21}N_3O_5$+Na: 418.1379, found 418.1398.

2.2.7. Compound 1h. R_f=0.45 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3391, 2968, 2921, 2861, 1664, 1453, 1263, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.92 (m, 4H), 3.69 (m, 4H), 3.80 (s, 2H), 5.63 (s, 1H), 7.23 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 51.0, 66.7, 69.2, 122.6, 124.4, 125.4, 126.3, 128.5, 129.4, 129.7, 131.3, 139.3, 141.7, 152.6, 158.6; MS (ESI) m/z 429, 431 (M+H), 451, 453 (M+Na), 467, 469 (M+K); HRMS (ESI) m/z calculated for $C_{21}H_{21}N_2O_3Br$+Na: 451.0633 and 453.0613, found 451.0662 and 453.0630.

2.2.8. Compound 1i. IR ($CHCl_3$) ν 3403, 2942, 2858, 1631, 1453, 1271, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.50–1.60 (m, 6H), 2.90 (m, 4H), 3.77 (s, 2H), 5.60 (s, 1H), 7.19–7.29 (m, 6H), 7.32 (d, 1H, J=7.4 Hz), 7.41 (d, 1H, J=8.0 Hz), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.9, 31.7, 52.0, 69.3, 122.6, 122.9, 125.2, 126.2, 128.5, 129.4, 129.7, 131.2, 139.5, 141.8, 154.2, 157.8; MS (ESI) m/z 427, 429 (M+H); 449, 451 (M+Na); HRMS (ESI) m/z calculated for $C_{22}H_{23}N_2O_2Br$+Na: 449.0796 and 451.0775, found 449.0802 and 451.0791.

2.2.9. Compound 1j. R_f=0.67 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3417, 2932, 1728, 1633, 1455, 1383, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.94 (t, 6H, J=7.3 Hz), 2.92 (q, 4H, J=7.3 Hz), 3.77 (s, 2H), 5.63 (br s, 1H), 7.19–7.27 (m, 6H), 7.32 (d, 1H, J=7.3 Hz), 7.42 (dd, 1H, J=1.7, 7.3 Hz), 7.58 (d, 1H, J=1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 31.4, 47.8, 69.5, 122.6, 125.2, 126.1, 127.9, 128.3, 128.5, 128.6, 129.7, 129.9, 130.1, 131.3, 139.3, 141.9, 151.7, 159.0; MS (IE) m/z 414, 416 (M)+; HRMS (ESI) m/z calculated for $C_{21}H_{23}N_2O_2Br$+Na: 437.0841 and 439.0820, found 437.0864 and 439.0850.

2.2.10. Compound 1k. R_f=0.41 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3404, 2967, 2922, 2861, 1636, 1495, 1453, 1263, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.39 (s, 3H), 2.89 (m, 4H), 3.69 (m, 4H), 3.81 (s, 2H), 5.90 (s, 1H), 7.19–7.27 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 31.6, 51.0, 66.8, 67.5, 124.5, 126.2, 126.6, 128.4, 128.5, 129.1, 130.6, 130.8, 136.0, 137.7, 139.3, 146.3, 152.3, 159.1; MS (ESI) m/z 365 (M+H), 387 (M+Na), 403 (M+K); HRMS (ESI) m/z calculated for $C_{22}H_{24}N_2O_3$+Na: 387.1685, found 387.1664.

2.2.11. Compound 8a. R_f=0.41 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−1 ($CHCl_3$, c 1.9); IR ($CHCl_3$) ν 3439, 2927, 2862, 1705, 1495, 1454, 1368, 1162, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.38 (s, 9H), 2.76 (dd, 1H, J_1=6.3 and J_2=13.9 Hz), 2.78 (dd, 1H, J=6.3, 13.9 Hz), 2.93 (m, 4H), 3.72 (m, 4H), 3.79 (s, 2H), 4.32 (m, 1H), 4.67 (d, 1H, J=2.9 Hz), 5.07 (br d, 1H, J=9.0 Hz), 7.11–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 29.4, 29.7, 31.7, 50.9, 53.8, 66.8, 79.7, 126.4, 128.4, 129.0, 137.5, 139.3, 152.3, 157.5; MS (ESI) m/z 516 (M+Na).

2.2.12. Compound 8b. R_f=0.45 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−6 ($CHCl_3$, c 1.4); IR ($CHCl_3$) ν 3439, 2927, 2862, 1705, 1495, 1454, 1368, 1162, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.30 (s, 9H), 2.92 (m, 6H), 3.69 (m, 4H), 3.74 (d, 1H, J=15.4 Hz), 3.76 (d, 1H, J=15.4 Hz), 4.23 (m, 1H), 4.50 (d, 1H, J=2.9 Hz), 4.91 (br d, 1H, J=10.3 Hz), 7.14–7.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 29.4, 29.7, 31.7, 50.9, 53.8, 66.8, 79.7, 126.4, 128.4, 129.0, 137.5, 139.3, 152.3, 157.5; MS (ESI) m/z 494 (M+H), 516 (M+Na); HRMS (ESI) m/z calculated for $C_{28}H_{35}N_3O_5$+Na: 516.2430, found 516.2429.

2.2.13. Compound 10a. R_f=0.45 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−3 ($CHCl_3$, c 0.9); IR ($CHCl_3$) ν 3434, 2931, 1710, 1497, 1368, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.30 (s, 9H), 2.83 (s, 3H), 2.91 (d, 2H, J=8.1 Hz), 3.67 (s, 3H), 3.68 (s, 2H), 3.72 (d, 1H, J=15.4 Hz), 3.80 (d, 1H, J=15.4 Hz), 4.20 (m, 1H), 4.47 (d, 1H, J=2.9 Hz), 4.93 (br d, 1H, J=9.6 Hz), 7.16–7.27 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 29.7, 31.4, 37.7, 40.9, 51.8, 55.7, 68.1, 79.2, 126.1, 126.5, 128.4, 128.5, 129.4, 137.9, 139.4, 152.3, 157.7, 170.6; MS (ESI) m/z 510 (M+H), 532 (M+Na), 548 (M+K).

2.2.14. Compound 10b. R_f=0.42, (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−7 ($CHCl_3$, c 0.8); IR ($CHCl_3$) ν 3434, 2931, 1710, 1497, 1368, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.37 (s, 9H), 2.70 (dd, 1H, J=6.4, 13.8 Hz), 2.76 (dd, 1H, J=6.4, 13.8 Hz), 2.86 (s, 3H), 3.69 (s, 7H), 3.82 (s, 2H), 4.30 (m, 1H), 4.64 (d, 1H, J=2.9 Hz), 5.12 (br d, 1H, J=9.6 Hz), 7.14–7.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 29.7, 31.4, 37.7, 40.9, 51.8, 55.7, 68.1, 79.2, 126.1, 126.5, 128.4, 128.5, 129.4, 137.9, 139.4, 152.3, 157.7, 170.6; MS (IE) m/z 509 $(M)^+$.

2.2.15. Compound 12. R_f=0.65 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−13 ($CHCl_3$, c 0.7); IR ($CHCl_3$) ν 3400, 2927, 1495, 1454, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.75 (m, 4H), 2.86–2.93 (dd, 1H, J=7.7, 13.7 Hz), 2.98–3.05 (dd, 1H, J=6.0, 13.7 Hz), 3.37–3.43 (m, 1H), 3.53 (d, 2H, J=13.7 Hz), 3.59 (d, 2H, J=13.7 Hz), 3.64 (m, 4H), 3.69 (d, 1H, J=15.4 Hz), 3.75 (d, 1H, J=15.4 Hz), 4.71 (br d, 1H, J=3.8 Hz), 7.15–7.26 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 31.7, 51.0, 54.7, 63.4, 66.8, 125.2, 126.0, 126.1, 127.1, 127.4, 128.3, 128.33, 128.5, 128.6, 128.9, 129.1, 129.13, 129.4, 139.3, 151.9, 158.9. MS (ESI) m/z 596 (M+Na); HRMS (ESI) m/z calculated for $C_{37}H_{39}N_3O_3$+Na: 596.2889, found 596.2871.

2.2.16. Compound 13. R_f=0.67 (eluant: AcOEt/Hept 1:1) $[\alpha]_D$=+11 ($CHCl_3$, c 0.2); IR ($CHCl_3$) ν 3401, 2925, 1497, 1454, 1115 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.56 (dd, 1H, J=7.1, 14.3 Hz), 2.66 (m, 4H), 3.08 (dd, 1H, J=5.5, 14.3 Hz), 3.42–3.48 (m, 1H), 3.47 (d, 2H, J=13.2 Hz), 3.59 (m, 4H), 3.68 (s, 2H), 3.93 (d, 2H, J=13.2 Hz), 4.57 (d, 1H, J=9.3 Hz), 6.98–7.34 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 31.7, 51.0, 54.7, 63.4, 66.8, 125.2, 126.0, 126.1, 127.1, 127.4, 128.3, 128.33,

128.5, 128.6, 128.9, 129.1, 129.13, 129.4, 139.3, 151.9, 158.9; MS (ESI) *m/z* 574 (M+H), 596 (M+Na); HRMS (ESI) *m/z* calculated for $C_{37}H_{39}N_3O_3$ $(M+H)^+$ 574.3070, found 574.3074.

2.2.17. Compound 14. To the solution of oxazole **12** (72 mg, 0.13 mmol) in THF (0.3 mL) and water (0.3 mL), was added trifluoroacetic acid (0.3 mL). After being stirred at room temperature for 30 min, the reaction mixture was diluted with CH_2Cl_2, and washed with a saturated solution of $NaHCO_3$. The aqueous portion is extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was then purified on preparative TLC (eluant: AcOEt/methanol 10:0.1) to give **14** as a mixture of two separable diastereomers (1/1) in 86% yield.

*Diastereomer **14a***. R_f=0.17 (eluant: AcOEt/Hept 2/1); $[\alpha]_D$=−3 ($CHCl_3$, *c* 0.3); IR ($CHCl_3$) ν 3400, 2963, 1638, 1496, 1455, 1262, 1113, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.60–2.76 (m, 4H), 3.10–3.22 (m, 4H), 3.28–3.39 (m, 4H), 3.52 (m, 1H), 3.59 (d, 2H, *J*=13.7 Hz), 3.76 (d, 2H, *J*=13.7 Hz), 3.97 (br d, 1H, *J*=3.6 Hz), 4.97–5.05 (m, 1H), 7.07–7.10 (m, 1H), 7.19–7.34 (m, 20H), 7.74 (br d, 1H, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.4, 40.2, 41.9, 45.7, 48.9, 53.4, 54.9, 63.7, 65.8, 66.1, 68.4, 126.2, 127.1, 127.5, 128.4, 128.5, 128.6, 128.7, 128.9, 129.1, 129.5, 129.6, 136.2, 138.2, 138.9, 139.5, 169.1, 172.7; MS (ESI) *m/z* 592 (M+H), 614 (M+Na), 630 (M+K); HRMS (ESI) *m/z* calculated for $C_{37}H_{41}N_3O_4$+H: 592.3175, found 592.3207.

*Diastereomer **14b***. R_f=0.42 (eluant: AcOEt/Hept 2/1); $[\alpha]_D$=−14 ($CHCl_3$, *c* 0.5); IR ($CHCl_3$) ν 3400, 2963, 1638, 1496, 1455, 1262, 1113, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.59–3.44 (m, 13H), 3.48 (d, 2H, *J*=13.8 Hz), 3.72 (d, 2H, *J*=13.8 Hz), 3.90 (d, 1H, *J*=3.6 Hz), 4.99 (td, 1H, *J*=5.0, 8.9 Hz), 7.16–7.34 (m, 20H), 7.76 (d, 1H, *J*=8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 40.2, 41.9, 45.7, 48.9, 54.9, 63.8, 65.8, 66.1, 68.4, 126.2, 127.1, 127.5, 128.4, 128.6, 128.7, 128.9, 129.5, 129.6, 136.2, 138.9, 139.5, 169.1, 172.7; MS (ESI) *m/z* 592 (M+H), 614 (M+Na); HRMS (ESI) *m/z* calculated for $C_{37}H_{41}N_3O_4$+H: 592.3175, found 592.3212.

2.2.18. Compound 15. A solution of diastereomerically pure compound **14** (diastereomer **14a**, 191 mg, 0.32 mmol) in MeOH was stirred in the presence of palladium hydroxide under hydrogen pressure for 3 h. The reaction mixture was filtered through a Celite pad and washed with methanol. The resulting filtrate is evaporated under reduced pressure to give the desired free amino alcohol **15a** (140 mg, 97% yield): R_f=0.10 (eluant: AcOEt/Hept 4:1); $[\alpha]_D$=−1 ($CHCl_3$, *c* 0.6); IR ($CHCl_3$) ν 3392, 2928, 1638, 1518, 1445, 1268, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 293 K) δ 2.49 (dd, 1H, *J*=4.8, 14.4 Hz), 2.64 (dd, 1H, *J*=9.7, 14.4 Hz), 2.94 (dd, 1H, *J*=7.8, 13.3 Hz), 2.98 (dd, 1H, *J*=7.8, 13.3 Hz), 3.44–3.58 (m, 8H), 3.70 (m, 1H), 4.29 (br d, 1H, *J*=2.4 Hz), 5.04 (t, 1H, *J*=7.8 Hz), 7.18–7.36 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD) δ 34.3, 39.3, 43.7, 47.5, 51.0, 56.3, 67.3, 67.4, 71.9, 128.3, 128.5, 129.7, 130.0, 130.5, 130.7, 136.9, 137.5, 171.5, 172.3. MS (ESI) *m/z* 412 (M+H); HRMS (ESI) *m/z* calculated for $C_{23}H_{29}N_3O_4$+Na: 434.2056, found 434.2048.

The diastereomer **15b** was prepared from **14b** following the identical procedure.

Compound **15b**. R_f=0.14 (eluant: AcOEt/Hept 9:1); $[\alpha]_D$=−2 ($CHCl_3$, *c* 0.3); IR ($CHCl_3$) ν 3392, 2928, 1638, 1518, 1445, 1268, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 293 K) δ 2.78 (dd, 1H, *J*=8.5, 14.6 Hz), 2.94–3.08 (m, 5H), 3.17–3.23 (m, 2H), 3.43–3.61 (m, 4H), 3.78–3.80 (m, 1H), 4.31 (br d, 1H, *J*=2.4 Hz), 4.95 (m, 1H), 7.25–7.32 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD) δ 34.6, 39.4, 43.7, 47.4, 51.3, 56.8, 67.2, 67.4, 71.6, 128.3, 128.4, 129.8, 129.9, 130.1, 130.5, 130.7, 136.9, 137.4, 171.4, 172.2; MS (ESI) *m/z* 412 (M+H); HRMS (ESI) *m/z* calculated for $C_{23}H_{29}N_3O_4$+H: 412.2236, found 412.2248.

2.2.19. Compound 16. A solution of trisphosgene (19.7 mg, 0.07 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to a solution of pyridine (65 μL, 0.79 mmol) and the amino alcohol **15a** (54.6 mg, 0.13 mmol) in CH_2Cl_2 (0.45 mL) cooled to −70 °C. Once addition was completed, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The resultant homogenous solution was quenched with saturated ammonium chloride and the aqueous portion was separated and extracted with CH_2Cl_2. The organic extract were washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified on preparative TLC (eluant: AcOEt/methanol 10:1) to give the desired oxazolidinone **16a** (45 mg, 78% yield): R_f=0.60 (eluant: AcOEt/methanol 10/1); $[\alpha]_D$=−100 ($CHCl_3$, *c* 0.8); IR ($CHCl_3$) ν 3399, 2927, 1777, 1678, 1643, 1521, 1445, 1267, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.11 (dd, 1H, *J*=12.7, 12.8 Hz), 2.81 (dd, 1H, *J*=12.8, 2.8 Hz), 2.97–3.34 (m, 6H), 3.37–3.63 (m, 4H), 4.11 (ddd, 1H, *J*=2.8, 8.4, 12.7 Hz), 5.02 (d, 1H, *J*=8.4 Hz), 5.20–5.26 (m, 1H), 7.08–7.35 (m, 10H), 7.56 (d, 1H, *J*=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 36.5, 39.8, 42.4, 46.0, 49.2, 55.5, 66.1, 66.5, 127.2, 127.4, 128.3, 128.7, 128.8, 129.1, 129.3, 129.5, 129.6, 135.7, 136.1, 165.8, 169.1; MS (ESI) *m/z* 460 (M+Na). The diastereomer **16b** was prepared from **15b** following the identical procedure.

Compound **16b**. R_f=0.61 (eluant: AcOEt/methanol 10/1); $[\alpha]_D$=−123 ($CHCl_3$, *c* 0.6); IR ($CHCl_3$) ν 3399, 2927, 1777, 1678, 1643, 1521, 1445, 1267, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.40 (dd, 1H, *J*=11.8, 13.2 Hz), 2.91–3.08 (m, 7H), 3.33–3.55 (m, 4H), 4.24 (ddd, 1H, *J*=2.9, 8.5, 11.8 Hz), 5.05 (d, 1H, *J*=8.5 Hz), 5.13 (q, 1H, *J*=8.0 Hz), 7.18–7.32 (m, 10H), 7.70 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 39.3, 42.4, 46.1, 49.5, 55.7, 66.1, 66.5, 127.3, 127.5, 128.8, 129.1, 129.5, 135.7, 136.2, 156.6, 166.1, 169.3; MS (ESI) *m/z* 460 (M+Na); HRMS (ESI) *m/z* calculated for $C_{24}H_{27}N_3O_5$+Na: 460.1848, found 460.1848.

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