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Chelation controlled reduction of *N*-protected β-amino ketones toward the synthesis of HPA-12 and analogues

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ABSTRACT

Diastereoselective reduction of *N*-protected β-amino ketones does not proceed effectively under the conditions used for chelation controlled reductions of *N*-alkyl β-amino ketones. A thorough analysis of various conditions required for the stereoselective reduction of γ-aryl-γ-oxo-β-amino alcohols is reported. The products of the *syn*-selective reduction are used for the preparation of a ceramide trafficking inhibitor HPA-12 and analogues.

1. Introduction

Amino alcohols and amino diols are structural units of various bioactive molecules, natural products, chiral ligands, and chiral auxiliaries.[1] Various methods are available for the synthesis of amino alcohols, which include organocatalysis, Mannich type reactions, rearrangement of isoxazolidines, Corey–Link reactions, and crystallization induced asymmetric transformations.[2] 1,3-Amino alcohols are most commonly synthesized by the reduction of β-amino ketones. Various reagents are available for the chelation controlled reduction of such compounds, which include $LiAlH_4/TiCl_4$, DIBAL-H/$ZnCl_2$,[3] and $NaBH_4$/AcOH.[4] It has been shown that SmI_2 can be used for the directed reduction of β-amino ketones to *syn*- or *anti*-1,3-amino alcohol derivatives.[5] *N*-Sulfinyl β-amino ketones can be selectively reduced to either *syn*- or *anti*-1,3-amino alcohols using Li(*t*-BuO)$_3$AlH and $LiEt_3BH$, respectively.[6] L-Selectrides can also be used for the stereoselective reduction of various β-amino ketones to the corresponding 1,3-amino alcohols.[7] The chelation controlled stereoselective reduction of *N*-alkyl β-amino ketones using catalytic amounts of metal salts and equivalent amounts of $NaBH_4$ is a reliable route for the synthesis of *syn*-γ-amino alcohols.[8] The reduction proceeds through a tight transition state, where the metal atoms are coordinated to the carbonyl oxygen and the amino group. The ability of the amino group to coordinate tightly with the metal ions is critical to the selectivity achieved in such reductions. β-Amino ketones are not necessarily obtained as the *N*-alkyl or free amino derivatives in a synthesis and are quite often protected as a carbamate or an amide. Such compounds with reduced nucleophilicity on the nitrogen atom do not undergo chelation controlled reduction under conditions which can be employed for the reduction of *N*-alkyl β-amino ketones. Herein we report the results of our studies on the diastereoselective reduction of *N*-Boc derivatives of γ-aryl-γ-oxo-β-amino alcohols. The diamino diol derivatives synthesized are used for the synthesis of a ceramide trafficking inhibitor HPA-12 and its analogues.

The transport of ceramide, a component of sphingomyelin, from endoplasmic reticulum to the Golgi apparatus is mediated by a 68 kDa cytosolic protein CERT. The effective transport of ceramide leading to the synthesis of sphingolipids is vital, since misregulation of this process could lead to a variety of diseases. As one of the mediators for sphingolipid homeostasis, CERT possibly has a role in many of the resulting disease states.[9] (1*R*,3*R*)-*N*-(3-Hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecamide (HPA-12) was found to be an inhibitor of CERT dependent ceramide trafficking and is the first specific inhibitor of sphingomyelin biosynthesis in mammalian cells. However, in a recent report on the synthesis of HPA-12 by Berkeš et al., the potent molecule was shown to have a (1*R*,3*S*)-configuration, which is contrary to the initial reports.[10] The revised structure was confirmed using X-ray crystallographic analysis by Kobayashi et al.[11] Thus the revised structure of HPA-12 has a *syn*-orientation of the amino and hydroxyl groups and hence methodologies for its synthesis should rely on *syn*-stereoselective reduction of the corresponding oxo-amino compounds. Recent reports on the synthesis of the (1*R*,3*S*) derivative of HPA-12 include a tandem approach using (*S*)-Wynberg lactone by Snowden et al.,[12] Ru-catalyzed asymmetric rearrangement of isoxazolidines reported by Kang et al.,[13] and the synthesis of HPA-12 and its analogues from serinol by Arenz et al.[14] Very recently, Delgado et al. reported a straightforward synthesis of HPA-12 from D-aspartic acid,[15] while Genisson et al. have used crystallization induced

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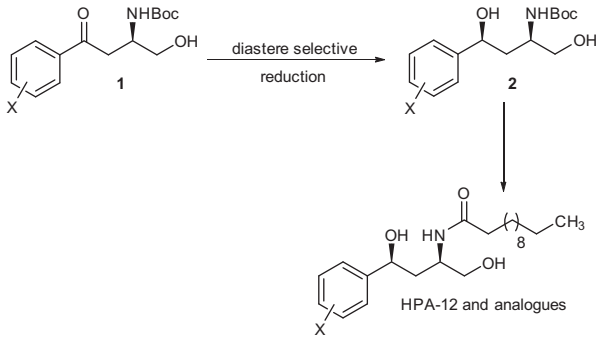
asymmetric transformation technology for the multi-gram scale synthesis of HPA 12 and its isomers.[16]

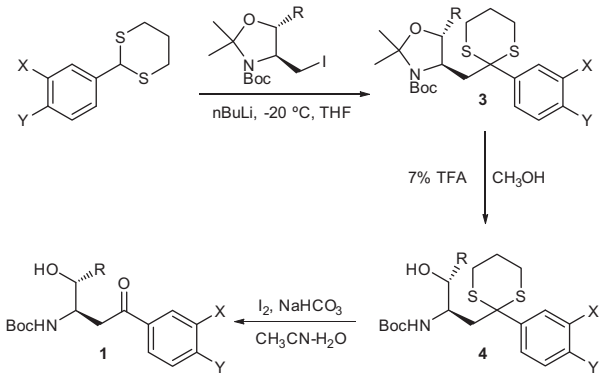
2. Results and discussion

We have reported an effective synthesis of enantiopure γ-aryl-γ-oxo-α-amino acids starting from serine and aromatic dithianes.[17] One of the key intermediates of the synthesis is γ-aryl-γ-oxo-β-amino alcohols **1**, which upon reduction provide 1-aryl-3-amino-1,4-diols. A *syn*-selective reduction of **1** would provide intermediates **2**, which could be used for the synthesis of HPA-12 and its analogues (Scheme 1).



Scheme 1. Strategy for the synthesis of HPA-12 and its analogues.

To begin with, we synthesized γ-aryl-γ-oxo-β-amino alcohols starting from an iodide derivative of L-serine and aromatic dithianes in excellent overall yields, following a strategy that we had developed (Scheme 2).[17] The iodide derivative was coupled with aryl dithianes using *n*-BuLi (THF, −20 °C) and the resulting dithiane derivatives **3** were treated with trifluoroacetic acid (7% in CH_3OH) to give the amino alcohol derivatives **4**. Hydrolysis of the dithiane group in **4** (I_2, $NaHCO_3$) yielded the required γ-aryl-γ-oxo-β-amino alcohols **1**. We have already shown that these transformations proceed without a loss of enantiopurity and that the amino alcohols **1** retain the configuration of the serine derivative used.[17] We also



R = H, X = H, Y = H: **3a** (85%), **4a** (93%), **1a** (84%)
R = H, X = H, Y = CH_3: **3b** (83%), **4b** (94%), **1b** (85%)
R = H, X = H, Y = $CH(CH_3)_2$: **3c** (85%), **4c** (89%), **1c** (79%)
R = H, X = H, Y = OCH_3: **3d** (85%), **4d** (89%), **1d** (80%)
R = H, X = OCH_3, Y = OCH_3: **3e** (87%), **4e** (94%), **1e** (84%)
R = H, X = H, Y = F: **3f** (80%), **4f** (93%), **1f** (88%)
R = H, X = Cl, Y = H: **3g** (86%), **4g** (89%), **1g** (84%)
R = CH_3, X= H, Y = H: **3h** (76%), **4h** (85%), **1h** (94%)
R = CH_3, X= H, Y = OCH_3: **3i** (81%), **4i** (89%), **1i** (95%)
R = CH_3, X= OCH_3, Y = OCH_3: **3j** (80%), **4j** (86%), **1j** (96%)

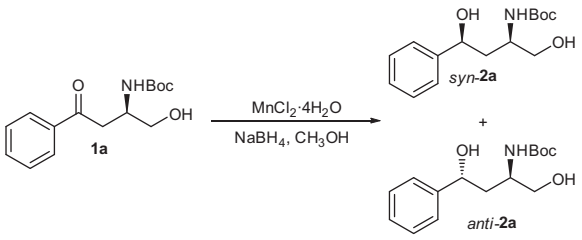
Scheme 2. Synthesis of γ-aryl-γ-oxo-β-amino alcohols **1**.

synthesized three analogous derivatives **3h–j** from L-threonine using the same method (Scheme 2).

With access to the required β-amino ketones as the *N*-Boc derivatives in hand, we looked at available procedures for the stereoselective reduction of such compounds. Various conditions are available in the literature to achieve either *syn*- or *anti*-selective reduction of β-amino ketones. However, all of the reported procedures are only effective with *N*-alkyl derivatives, which would allow chelation of the amino group to a metal ion effectively. Berkeš et al. have reported the diastereoselective reduction of γ-oxo-γ-aryl-α-amino acids, which are structurally very similar to **1**, using $NaBH_4$ in the presence of $MnCl_2{\cdot}4H_2O$.[8c] We hoped that compound **1**, would undergo selective *syn*-reduction under such conditions that would provide the amino diols **2** required for the preparation of HPA-12 and related compounds. The reduction of **1a** using $NaBH_4$ (2 equiv) in the presence of a catalytic amount of $MnCl_2{\cdot}4H_2O$ (20 mol %), at room temperature, as reported, did not generate any diastereoselectivity. As explained by Berkeš et al., the key criterion for achieving a *syn*-selective reduction under such conditions is the preferential reduction of the chelated amino ketone to the reduction of non-complexed amino ketone by $NaBH_4$. It is not surprising that the *N*-benzyl derivatives of the amino ketones used by Berkeš et al., coordinated better with Mn^{2+} and provided a tighter transition state required for the chelation controlled reduction than the Boc protected amino group in **1a**. We assumed that using stoichiometric or more amounts of the metal salt and the addition of $NaBH_4$ only after complexation of **1a** with the Mn^{2+} could increase the selectivity. However the selectivity was only 11:9 in favor of the *syn*-isomer **2a** when the reaction was carried out at 30 °C (2 equiv $MnCl_2{\cdot}4H_2O$ and 2 equiv of $NaBH_4$, added after 20 min). Decreasing the temperature to −5 °C had a positive impact on selectivity for the formation of **2a**. We achieved a selectivity of 16:4; carrying out the reaction at −50 °C or −80 °C and in the presence of 2 equiv of $MnCl_2{\cdot}4H_2O$, did not improve the selectivity. It was obvious from our observations that an improved selectivity could only be achieved at lower temperatures and in the presence of excess amount of the metal salt (Table 1).

It is also known in the literature that various other metal salts such as Zn^{2+} coordinates with β-amino ketones to give *syn*-selective reductions. Since the results obtained using $MnCl_2{\cdot}H_2O$ were not satisfactory, we decided to carry out a thorough analysis of the reduction of **1a** to **2a** in the presence of various Lewis acids.

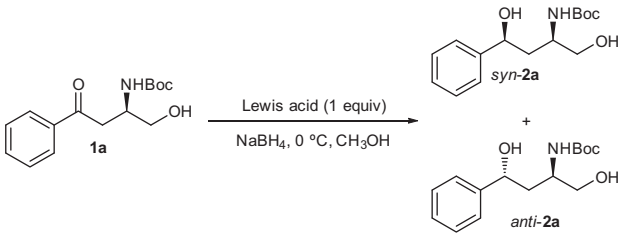
Table 1
Diastereoselective reduction of **1a** with $MnCl_2{\cdot}4H_2O$ and $NaBH_4$



Entry	Equiv of $MnCl_2{\cdot}4H_2O$	Temperature (°C)	*syn*/*anti*[a]	Yield[b] (%)
1	0	30	50:50	97
2	0.20	30	50:50	96
3	1	30	50:50	98
4	2	30	55:45	94
5	2	0	60:40	96
7	2	−50	80:20	95
8	2	−80	80:20	94

[a] As determined from ^1H NMR spectra.
[b] Isolated yields of the mixture of diastereomers.

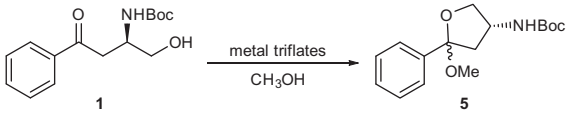
Table 2
Diastereoselective reduction of **1a** with various Lewis acids



Entry	Lewis acid	*syn*/*anti*[a]	Yield[b] (%)
1	None	50:50	97
2	$MnCl_2{\cdot}4H_2O$	60:40	96
3	$BF_3{\cdot}Et_2O$	60:40[c]	60
4	$ZnCl_2$	No reaction	—
5	CuI	No reaction	—
6	$CeCl_3$	85:15	98
7	$CeCl_3{\cdot}7H_2O$	75:25	97
8	Metal triflates[d]	No reaction[e]	—

[a] As determined from ^{1}H NMR spectra.
[b] Isolated yields of the mixture of diastereomers.
[c] CH_2Cl_2 is the solvent used.
[d] Triflates used are $Sm(OTf)_3$, $Bi(OTf)_3$, $Fe(OTf)_3$, $Sc(OTf)_3$, $Sn(OTf)_3$, $Yb(OTf)_3$, $Ag(OTf)_3$, $In(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_3$, $Cu(OTf)_2$.
[e] Cyclic ketal **5** was formed as the product.

The results of our attempts on the stereoselective reduction of **1a** with different Lewis acids (1 equiv) and $NaBH_4$ (2 equiv) are given in Table 2. The best results were obtained with $CeCl_3$ and the *syn*-selectivity achieved in this case was better than those achieved using $MnCl_2{\cdot}4H_2O$ and $BF_3{\cdot}Et_2O$ (carried out in CH_2Cl_2). It was interesting to note that the reduction did not happen in the presence of $ZnCl_2$ and CuI. It was found that in the presence of $ZnCl_2$ and CuI, even a non-selective reduction of **1a** could not be achieved with excess of $NaBH_4$ (4 equiv). Use of a number of metal triflates for these reduction reactions led to the formation of a cyclic ketal **5**, which did not undergo reduction. The formation of **5** from **1a** was observed upon the addition of metal triflates even in the absence of $NaBH_4$ (Scheme 3).



Scheme 3. Formation of cyclic ketal **5** from **1a** in the presence of metal triflates.

Having established that $CeCl_3$ was the best Lewis acid to catalyze the *syn*-selective reduction of **1a**, we attempted to increase the selectivity by varying the temperature and equivalents of $CeCl_3$ used. However, we did not find any noticeable increment in selectivity for the reduction of **1a** at lower temperatures and on using up to 2 equiv of $CeCl_3$. It is to be assumed that 1 equiv of $CeCl_3$ at 30 °C quantitatively forms a chelate with **1a** and the reduction proceeds with a preference for the formation of the *syn*-isomer through a transition state similar to the one proposed by Berkeš et al. (Fig. 1).[8c] The preference for the major isomer results from the preferred orientation of the hydroxymethyl group to an equatorial position. The structure of the major diastereomer was confirmed to be that of **2a** by matching NMR spectra of the diastereomers with those reported.

Having found suitable conditions for the diastereoselective reduction of 3-(*tert*-butyloxycarbonylamino)-4-hydroxy-1-phenyl butan-1-one **1a** to (1*S*,3*R*)-3-(*tert*-butyloxycarbonylamino)-1-phenylbutane-1,4-diol **2a**, we reduced the remaining β-amino

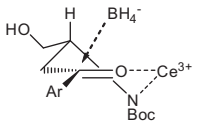
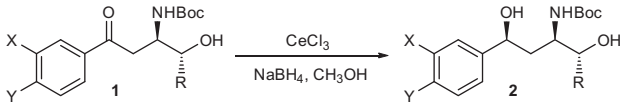


Figure 1. Proposed transition state for the chelation controlled reduction of **1a**.

ketones **1b–j** under the same conditions (1 equiv $CeCl_3$, 2 equiv $NaBH_4$, 30 °C, CH_3OH). The diastereoselectivity was high and the *syn*-isomers were formed preferentially (Table 3). The best selectivity was achieved for the reduction of **1e** to **2e**, which proceeded with 100% selectivity while the *anti*-diastereomer was not detected (entry 5). Both isomers, when formed could be isolated and characterized. All of the major isomers had similar ^{1}H NMR patterns and their *syn*-structure was confirmed unambiguously by the single crystal X-ray structure analysis of a hydrochloride salt of the amine derived from **2f**, formed by the deprotection of the *N*-Boc using HCl in ethyl acetate (Fig. 2).[18] The amino ketones **1h** and **1i** (entries 8 and 9), derived from L-threonine underwent more selective reduction than **1a** and **1d** (their analogues were derived from L-serine, entries 1 and 4). The diastereoselectivity in the reduction of **1j** (entry 10) was very high, although it was not 100% as with **1e** (entry 5). The high diastereoselective reduction of derivatives formed from

Table 3
syn-Selective reduction of **1**–**2**



Entry	**1**(X, Y, R)	Yield of **2**[a] (%)	*syn*/*anti* ratio for **2**	
			Crude[b]	Isolated
1	**1a** (X = H, Y = H, R = H)	92	85:15	87:13
2	**1b** (X = H, Y = CH_3, R = H)	95	85:15	86:14
3	**1c** (X = H, Y = $(CH_3)_2CH$, R = H)	94	85:15	87:13
4	**1d** (X = H, Y = OCH_3, R = H)	93	80:20	84:16
5	**1e** (X = OCH_3, Y = OCH_3, R = H)	91	>99:1	100:0
6	**1f** (X = H, Y = F, R = H)	90	85:15	85:15
7	**1g** (X = Cl, Y = H, R = H)	93	80:20	82:18
8	**1h** (X = H, Y = H, R = CH_3)	94	90:10	87:13
9	**1i** (X = H, Y = OCH_3 R = CH_3)	94	95:05	92:08
10	**1j** (X = OCH_3, Y = OCH_3 R = CH_3)	92	95:05	95:05

[a] Combined yield for both the diastereomers.
[b] As determined from ^{1}H NMR spectra.

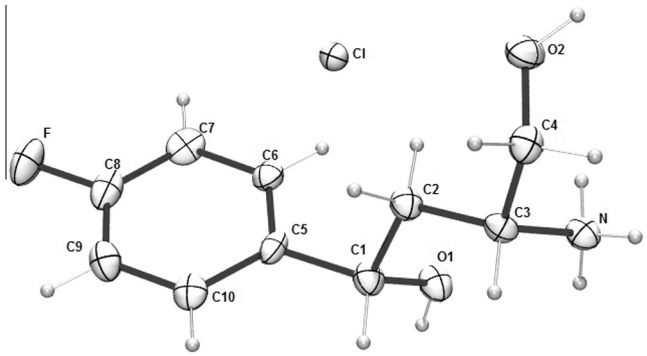
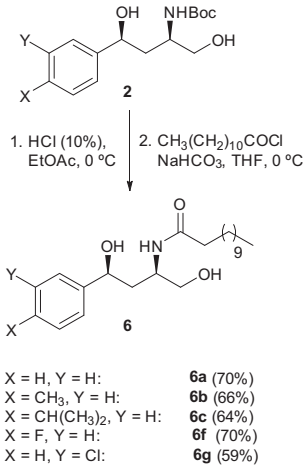


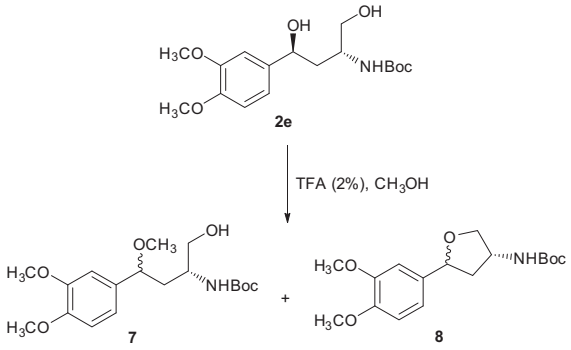
Figure 2. ORTEP diagram of the hydrochloride salt derived from **2f** (displacement ellipsoids are shown at 50% probability level), confirming the *syn*-orientation of amino and hydroxyl groups for the major diastereomer formed by the reduction of **1f**.[13]



Scheme 4. Synthesis of HPA-12 **6a** and its analogues from **2**.

L-threonine could be attributed to the increased preference of the hydroxyethyl group (compared to the hydroxymethyl group of those derived from L-serine) to be at the equatorial position in the transition state shown in Figure 1.

The structures of **2a** and **2b** were confirmed by comparing the specific rotations and ^{13}C NMR with reported compounds.[19] The amino diol **2a** was converted into HPA-12 **6a** in two steps. The *N*-Boc groups were removed by treating **2a** with HCl (10%) in ethyl acetate and the crude hydrochloride salt was acylated using lauryl chloride ($NaHCO_3$, THF, 0 °C) to give **6a** in 70% overall yield (Scheme 4) and the structure was confirmed by comparing the spectroscopic data with those reported in the literature.[10,12] This provides an easy and effective route for the synthesis of HPA-12 starting from benzaldehyde and L-serine. The other amino alcohols **2b**–**g** were also treated similarly to give analogues of **6a** (Scheme 4). However, amino diols **2d** and **2e** yielded a complex reaction mixture when treated with HCl to remove the Boc group. It is interesting to note that both these substrates decomposed in commercial $CDCl_3$ upon standing overnight. The electron rich aromatic rings in the above compounds could lead to the elimination of the hydroxyl group even in the presence of mild acids, making the selective deprotection of the Boc group difficult. Our efforts to use different acids at varying strengths to deprotect the Boc group in **2d** and **2e** selectively were unsuccessful. As an effort to understand this unexpected reactivity, we treated **2e** with 2% TFA in methanol. Even under such mild acidic conditions, **2e** underwent S_N1 reactions to give the solvolysis product **7** and an intramolecular substitution product **8** as mixtures of diastereomers (Scheme 5).



Scheme 5. Acid sensitivity of the electron rich amino diol **2e**.

3. Conclusion

We have developed a very effective method for the diastereoselective reduction of *N*-Boc derivatives γ-aryl-γ-oxo-β-amino alcohols to give the corresponding *syn*-3-amino-1-arylbutane-1,4-diols using $CeCl_3$ and $NaBH_4$ (Luche reagent) in CH_3OH. The reported methods for the chelation controlled reduction of such compounds do not work with the *N*-protected derivatives. The use of 1 equiv of $CeCl_3$ allowed for chelation controlled reduction even when the amino group is rendered electron deficient through Boc protection; the diastereoselectivity achieved was generally high and almost complete in at least one of the examples studied. Together with a methodology we have developed for the synthesis of γ-aryl-γ-oxo-β-amino alcohols, we were able to obtain the CERT dependent ceramide trafficking inhibitor HPA-12 and a number of its analogues in good yields using very simple synthetic transformations.

4. Experimental

4.1. General information

All chemicals were purchased from commercial sources and were used without further purification. ^1H and ^{13}C NMR spectra were recorded either on a 400 MHz (100 MHz for ^{13}C) or on a 500 MHz (125 MHz for ^{13}C) JEOL-Lambda NMR spectrometer at 25 °C. The ^{19}F NMR spectra were recorded on a 470 MHz machine at 25 °C. The ^1H NMR signals are referenced to TMS (δ = 0.00 ppm) and the ^{13}C NMR peaks are referenced to residual $CHCl_3$ signal (δ = 77.0 ppm). Chemical shifts are reported in parts per million and coupling constants in Hz. The multiplicities are assigned as s (singlet), d (doublet), t (triplet), br s (broad singlet), dd (double doublet) and m (multiplet). High-resolution mass spectra were obtained using a Waters Q/Tof Premier Micromass HAB213 spectrometer with an ESI source. IR spectra were recorded on Bruker Vector 22 FTIR instrument, optical rotations were recorded at 25 °C on a Rudolph Research Analytical Autopol—IV digital polarimeter and melting points were recorded on a DBK automatic programmable digital instrument. Column chromatography was done using 100–200 mesh silica gel and appropriate mixtures of petroleum ether and ethyl acetate were used as eluent.

4.2. Synthesis of γ-aryl-γ-oxo-β-amino alcohols

The γ-aryl-γ-oxo-β-amino alcohols were prepared according to the previously reported methodology,[12] where the characterization data for the β-amino ketones **1**–**g** along with those for the intermediates **3a**–**g** and **4a**–**g** are available.

4.2.1. (4*R*,5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2,5-trimethyl-4-((2-phenyl-1,3-dithian-2-yl)methyl)oxazolidine 3h

Column chromatography (95:5 petroleum ether/EtOAc); clear oil (0.955 g, 76%); $[\alpha]_D^{25}$ = +4.2 (*c* 0.700, $CHCl_3$); IR (thin film): 2977, 2932, 1697, 1384, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): mixture of rotamers: δ = 7.95–7.94 (m, 2H), 7.39–7.36 (m, 2H), 7.26–7.24 (m, 1H), 4.00–3.82 (m, 1H), 3.41–3.25 (m, 1H), 2.72–2.57 (m, 4H), 2.49–2.16 (m, 2H), 1.92–1.89 (m, 2H), 1.50, 1.37 (s, 15H), 0.98–0.91 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.7, 151.6, 141.4, 141.3, 129.0, 128.9, 127.3, 93.6, 92.8, 80.5, 80.1, 60.1, 59.9, 57.9, 57.5, 49.5, 48.6, 29.0, 28.8, 28.5, 28.4, 28.2, 27.6, 27.5, 27.3, 24.9, 21.6 ppm; HRMS (ES): *m*/*z* calcd for $C_{22}H_{33}NO_3S_2$ [M+Na^+]: 446.1800, found: 446.1809.

4.2.2. (4*R*,5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2,5-trimethyl-4-((2-(4-methoxyphenyl)-1,3-dithian-2-yl)methyl)oxazolidine 3i

Column chromatography (93:7 petroleum ether/EtOAc); clear oil (1.100 g, 81%); $[\alpha]_D^{25}$ = −12.9 (*c* 0.610, $CHCl_3$); IR (thin film):

2977, 2931, 1697, 1504, 1385, 1251, 1167, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): mixture of rotamers: δ = 7.85–7.79 (m, 2H), 6.90–6.87 (m, 2H), 4.40–4.38 (m, 1H), 3.80 (s, 3H), 3.59–3.42 (m, 1H), 2.75–2.62 (m, 4H), 2.35–2.26 (m, 2H), 1.94–1.89 (m, 2H), 1.44, 1.37 (s, 15H), 1.01 (d, J = 6.65 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 158.7, 15.5, 133.2, 130.4, 130.2, 129.9, 114.0, 79.3, 57.1, 55.4, 55.3, 52.7, 46.7, 31.0, 29.7, 29.4, 28.8, 28.4, 28.3, 27.7, 27.5, 25.0, 21.7, 19.9 ppm; HRMS (ES): m/z calcd for $C_{23}H_{35}NO_4S_2$ [M+Na^+]: 476.1905, found: 476.1905.

4.2.3. (4*R*,5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2,5-trimethyl-4-((2-(3,4-dimethoxyphenyl)-1,3-dithian-2-yl)methyl)oxazolidine 3j

Column chromatography (90:10 petroleum ether/EtOAc); solid (1.159 g, 80%); $[\alpha]_D^{25}$ = −8.1 (c 0.610, $CHCl_3$); IR (KBr): 2976, 2932, 1696, 1508, 1385, 1256, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): mixture of rotamers: δ = 7.56–7.42 (m, 2H), 6.85–6.84 (m, 1H), 3.97–3.91 (m, 1H), 3.88, 3.87 (s, 6H), 3.46–3.35 (m, 1H), 2.72–2.47 (m, 4H), 2.25–2.16 (m, 2H), 1.91–1.88 (m, 2H), 1.53–1.39 (s, 15H), 1.02–0.96 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.6, 149.0, 148.1, 133.6, 121.7, 121.5, 112.1, 112.0, 111.2, 111.0, 93.6, 92.8, 80.4, 80.1, 60.2, 59.9, 57.8, 57.3, 56.0, 55.9, 49.5, 48.5, 29.8, 28.8, 28.5, 28.2, 27.7, 27.5, 27.3, 25.0, 21.8 ppm; HRMS (ES): m/z calcd for $C_{24}H_{37}NO_5S_2$ [M+Na^+]: 506.2011, found: 506.2014.

4.2.4. (2*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-4-(2-phenyl-1,3-dithian-2-yl)butan-2-ol 4h

Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.651 g, 85%); $[\alpha]_D^{25}$ = +7.0 (c 0.283, $CHCl_3$); IR (thin film): 3414, 2929, 2973, 1691, 1507, 1365, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (d, J = 7.30 Hz, 2H), 7.37 (t, J = 7.35 Hz, 2H,), 7.26–7.23 (m, 1H), 4.38 (bm, 1H), 3.56–3.45 (m, 2H), 2.71–2.67 (m, 4H), 2.37–2.28 (m, 2H), 1.95–1.90 (m, 2H), 1.37 (s, 9H), 1.01 (d, J = 6.10 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.9, 141.5, 128.8, 128.6, 127.2, 79.4, 70.2, 57.5, 52.7, 46.7, 28.4, 27.7, 27.6, 24.9, 19.8 ppm; HRMS (ES): m/z calcd for $C_{19}H_{29}NO_3S_2$ [M+Na^+]: 406.1487, found: 406.1487.

4.2.5. (2*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-4-(2-(4-methoxyphenyl)-1,3-dithian-2-yl)butan-2-ol 4i

Column chromatography (65:35 petroleum ether/EtOAc); clear oil (0.735 g, 89%); $[\alpha]_D^{25}$ = +12.5 (c 0.400, $CHCl_3$); IR (thin film): 3384, 2971, 2922, 1691, 1504, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.79 (d, J = 8.55 Hz, 2H), 6.88 (d, J = 8.55 Hz, 2H), 4.40 (bm, 1H), 3.80 (s, 3H), 3.58–3.54 (m, 1H), 3.46–3.41 (m, 1H), 2.75–2.66 (m, 4H), 2.39–2.25 (m, 2H), 1.93–1.90 (m, 2H), 1.36 (s, 9H), 1.00 (d, J = 6.45 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 158.5, 155.9, 133.2, 129.9, 114.0, 79.3, 70.3, 51.1, 55.3, 52.7, 46.7, 28.4, 27.7, 27.5, 25.0, 19.8 ppm; HRMS (ES): m/z calcd for $C_{20}H_{31}NO_4S_2$ [M+Na^+]: 436.1592, found: 436.1596.

4.2.6. (2*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-4-(2-(3,4-dimethoxyphenyl)-1,3-dithian-2-yl)butan-2-ol 4j

Column chromatography (65:35 petroleum ether/EtOAc); clear oil (0.761 g, 86%); $[\alpha]_D^{25}$ = +7.1 (c 0.700, $CHCl_3$); IR (thin film): 3383, 2932, 2972, 2834, 1693, 1509, 1257, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.46–7.44 (m, 2H), 6.85–6.83 (m, 1H), 4.39 (bm, 1H), 3.88, 3.87 (2s, 6H), 3.59–3.54 (m, 1H), 3.48–3.45 (m, 1H), 2.76–2.67 (m, 4H), 2.33–2.24 (m, 2H), 1.94–1.89 (m, 2H), 1.35 (s, 9H), 1.01 (d, J = 6.30 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.9, 148.9, 148.0, 133.7, 121.1, 111.9, 110.9, 79.3, 70.3, 57.5, 56.0, 55.8, 52.6, 46.8, 28.3, 27.8, 27.6, 25.0, 19.8 ppm; HRMS (ES): m/z calcd for $C_{21}H_{33}NO_5S_2$ [M+Na^+]: 466.1698, found: 466.1693.

4.2.7. (3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-hydroxy-1-phenylpentan-1-one 1h

Column chromatography (65:35 petroleum ether/EtOAc); solid (0.550 g, 94%); mp: 64–66 °C; $[\alpha]_D$ = −2.2 (c 0.900, $CHCl_3$); IR (KBr): 3380, 2975, 2931, 1686, 1502, 1366, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): compound is in equilibrium with the cyclic hemiketal: δ = 7.96–7.95 (m, 2H), 7.56–7.42 (m, 3H), 5.24 (bm, 1H), 3.98–3.93 (m, 1H), 3.36–3.30 (m, 3H), 1.39 (s, 9H), 1.20 (d, J = 6.75 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 199.5, 156.4, 136.8, 133.5, 128.7, 128.3, 79.7, 68.6, 52.9, 40.9, 28.3, 20.5 ppm; HRMS (ES): m/z calcd for $C_{16}H_{23}NO_4$ [M+Na^+]: 316.1525, found: 316.1521.

4.2.8. (3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-hydroxy-1-(4-methoxyphenyl)pentan-1-one 1i

Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.613 g, 95%); $[\alpha]_D^{25}$ = −6.4 (c 0.466, $CHCl_3$); IR (thin film): 3481, 3391, 3366, 2978, 2935, 1705, 1611, 1524, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): compound is in equilibrium with the cyclic hemiketal: δ = 7.97–7.92 (m, 2H), 7.54–7.53 (m, 0.5H), 6.93–6.87 (m, 2H), 6.38–6.37 (m, 0.2H), 6.01–5.99 (m, 0.2H), 3.97–3.90 (m, 1.5H), 3.86 (s, 3H), 3.81–3.80 (m, 1H), 3.31–3.27 (m, 1.5H), 2.34–2.33 (m, 0.7H), 1.44, 1.40 (s, 9H), 1.24–1.20 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.2, 197.0, 164.2, 163.9, 158.6, 156.4, 152.3, 151.2, 130.8, 124.8, 114.1, 114.0, 113.9, 107.5, 104.2, 79.8, 68.6, 67.4, 55.6, 55.3, 53.1, 52.4, 40.7, 39.6, 28.4, 28.3, 20.6, 20.5 ppm; HRMS (ES): m/z calcd for $C_{17}H_{25}NO_5$ [M+Na^+]: 346.1630, found: 346.1630.

4.2.9. (3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3,4-dimethoxyphenyl)-4-hydroxypentan-1-one 1j

Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.677 g, 96%); $[\alpha]_D^{25}$ = +1.9 (c 1.050, $CHCl_3$); IR (thin film): 3376, 2974, 2930, 1690, 1515, 1272, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): compound is in equilibrium with the cyclic hemiketal: δ = 7.64–7.62 (m, 1H), 7.51 (m, 1H), 6.86 (d, J = 6.30 Hz, 1H), 5.23 (bm, 1H), 3.94–3.93 (m, 1H), 3.91, 3.90 (s, 6H), 3.45 (m, 1H), 3.31–3.21 (m, 2H), 1.38 (s, 9H), 1.19 (d, J = 6.10 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.1, 156.4, 153.7, 149.1, 129.9, 123.5, 110.2, 110.1, 79.7, 68.4, 56.1, 56.0, 53.2, 40.6, 28.4, 20.5 ppm; HRMS (ES): m/z calcd for $C_{18}H_{27}NO_6$ [M+Na^+]: 376.1736, found: 376.1731.

4.3. Diastereoselective reduction of β-amino ketones, 1a–j

To a solution of the β-amino ketone (2 mmol) in methanol (5 mL) at rt (30 °C), $CeCl_3$ (0.492 g, 2 mmol) was added and stirred for 5 min. To the solution $NaBH_4$ (0.150 g, 4 mmol) was added in portions using a solid addition funnel. After the complete disappearance of the starting material (cc 20 min), the reaction was quenched with saturated $NaHCO_3$ (10 mL), extracted with dichloromethane (2 × 30 mL) and dried over anhydrous Na_2SO_4, and concentrated under vacuum. The diastereomeric ratio was determined from the ^1H NMR spectra of the crude mixture and the desired amino diols **2a–j** were purified by column chromatography.

4.3.1. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-phenylbutane-1,4-diol 2a

Column chromatography (petroleum ether/EtOAc, 70:30); white solid (0.449 g, 80%); mp 112–114 °C; $[\alpha]_D^{25}$ = +32.5 (c 0.191, $CHCl_3$); lit.[19a] $[\alpha]_D$ = +33.8 (c 0.8, $CHCl_3$); IR (KBr): 3354, 3030, 2976, 1684, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.29–7.20 (m, 5H), 5.27 (bm, 1H), 4.73–4.71 (m, 1H), 3.91 (bm, 1H), 3.56–3.55 (d, J = 3.7 Hz, 2H), 1.96–1.82 (m, 2H), 1.40 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.4, 144.4, 128.5, 127.6, 125.8,

79.8, 71.3, 65.1, 50.4, 41.2, 28.4 ppm; lit.;[19a] HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}NO_4$ [M+Na$^+$]: 304.1525; found 304.1520.

4.3.2. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-phenylbutane-1,4-diol *anti*-2a

Column chromatography (75:25 petroleum ether/EtOAc); clear oil (0.067 g, 12%); $[\alpha]_D^{25} = -6.4$ (*c* 0.333, $CHCl_3$); lit.[19a] $[\alpha]_D = -7.5$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.36–7.22$ (m, 5H), 4.75 (m, 1H), 3.96–3.94 (m, 1H), 3.74–3.62 (m, 2H), 1.87–1.75 (m, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 157.3$, 144.0, 128.4, 127.4, 125.6, 80.3, 70.5, 65.5, 49.8, 42.3, 28.4 ppm lit.[19a,b]

4.3.3. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-*p*-tolylbutane-1,4-diol 2b

Column chromatography (petroleum ether/EtOAc, 70:30); white solid (0.483 g, 82%); mp 92–94 °C; $[\alpha]_D^{25} = +21.2$ (*c* 0.103, $CHCl_3$); IR (KBr): 3353, 2925, 1685, 1169, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.22–7.20$ (m, 2H), 7.13–7.12 (m, 2H), 5.25 (bm, 1H), 4.77–4.75 (m, 1H), 3.73 (m, 1H), 3.63 (d, $J = 3.9$ Hz, 2H), 2.31 (s, 3H), 2.00–1.86 (m, 2H), 1.43 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 156.4$, 141.3, 137.4, 129.3, 125.7, 79.8, 71.5, 65.6, 50.8, 41.1, 28.4, 21.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{25}NO_4$ [M+Na$^+$]: 318.1681, found: 318.1683.

4.3.4. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-*p*-tolylbutane-1,4-diol *anti*-2b

Column chromatography (75:25 petroleum ether/EtOAc); clear oil (0.076 g, 13%); $[\alpha]_D^{25} = +3.4$ (*c* 0.910, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.24–7.22$ (m, 2H), 7.13–7.11 (m, 2H), 5.13 (bm, 1H), 4.71–4.68 (m, 1H), 3.96–3.60 (m, 3H), 2.31 (s, 3H), 1.81–1.77 (m, 2H), 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 157.3$, 141.1, 137.0, 129.1, 125.5, 80.2, 70.4, 65.5, 49.9, 42.1, 28.4, 21.1 ppm.

4.3.5. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-isopropylphenyl)butane-1,4-diol 2c

Column chromatography (petroleum ether/EtOAc, 70:30); white solid (0.529 g, 82%); mp 79–80 °C; $[\alpha]_D^{25} = -17.9$ (*c* 0.111, $CHCl_3$); IR (KBr): 3352, 2961, 1686, 1170, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.25–7.23$ (d, $J = 7.95$ Hz, 2H), 7.18–7.17 (d, $J = 7.95$ Hz, 2H), 5.29 (bm, 1H), 4.78–4.75 (m, 1H), 3.74 (m, 1H), 3.62 (d, $J = 3.4$ Hz, 2H), 2.90–2.84 (s, 1H), 2.03–1.86 (m, 2H), 1.42 (s, 9H), 1.22 (d, $J = 6.75$ Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 156.4$, 148.4, 141.7, 126.8, 125.7, 79.7, 71.4, 65.5, 50.8, 41.0, 33.8, 28.4, 24.0 ppm; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{29}NO_4$ [M+Na$^+$]: 346.1994, found: 346.1995.

4.3.6. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-isopropylphenyl)butane-1,4-diol *anti*-2c

Column chromatography (75:25 petroleum ether/EtOAc); clear oil (0.077 g, 12%); $[\alpha]_D^{25} = +1.3$ (*c* 0.716, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.26–7.24$ (m, 2H), 7.17–7.15 (m, 2H), 5.17 (bm, 1H), 4.71–4.68 (m, 1H), 4.00–3.96 (m, 1H), 3.69–3.58 (m, 2H), 2.92–2.81 (s, 1H), 1.84–1.76 (m, 2H), 1.43 (s, 9H), 1.21 (d, $J = 7.12$ Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 157.3$, 141.1, 137.0, 129.1, 125.5, 80.2, 70.4, 65.5, 49.9, 42.1, 33.8, 28.4, 21.1 ppm.

4.3.7. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-methoxyphenyl)butane-1,4-diol 2d

Column chromatography (petroleum ether/EtOAc, 60:40); colorless oil (0.485 g, 78%); $[\alpha]_D^{25} = +12.0$ (*c* 0.083, $CHCl_3$); IR (thin film): 3359, 2975, 2931, 1685, 1611, 1513, 1247, 1172, 1033 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz): $\delta = 7.86$ (m, 1H), 7.28 (m, 2H), 6.85 (m, 2H), 4.64 (m, 1H), 3.74 (s, 3H), 3.46–3.28 (m, 3H), 1.92 (m, 2H), 1.43 (br s, 9H) ppm; ^{13}C NMR (CD_3OD, 125 MHz): $\delta = 159.1$, 156.6, 136.4, 127.2, 113.4, 78.7, 70.9, 63.8, 54.3, 49.7, 40.2, 27.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{25}NO_5$ [M+Na$^+$]: 334.1630, found: 334.1628.

4.3.8. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-methoxyphenyl)butane-1,4-diol *anti*-2d

Column chromatography (40:60 petroleum ether/EtOAc); clear oil (0.093 g, 15%); $[\alpha]_D^{25} = +25.0$ (*c* 0.950, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 7.13–7.11$ (m, 2H), 6.73–6.70 (m, 2H), 4.54–4.46 (m, 1H), 3.61 (s, 3H), 3.06–3.01 (m, 3H), 1.86–1.51 (m, 2H), 1.29 (s, 9H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 157.4$, 155.6, 135.5, 125.1, 111.7, 77.2, 68.5, 62.7, 52.7, 48.2, 39.1, 25.8 ppm.

4.3.9. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3,4-dimethoxyphenyl)butane-1,4-diol 2e

Column chromatography (petroleum ether/EtOAc, 55:45); colorless oil (0.629 g, 91%); $[\alpha]_D^{25} = +4.2$ (*c* 0.70, $CHCl_3$); IR (thin film): 3367, 2925, 1684, 1596, 1515, 1260, 1163, 1027 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz): $\delta = 7.95–7.90$ (m, 1H), 6.95–6.88 (m, 2H), 4.68–4.64 (m, 1H), 3.84 (s, 6H), 3.46–3.37 (m, 3H), 1.94–1.91 (m, 2H), 1.42 (br s, 9H) ppm; ^{13}C NMR (CD_3OD, 125 MHz): $\delta = 156.6$, 148.9, 148.3, 137.4, 118.4, 111.4, 109.8, 78.6, 71.1, 63.9, 55.2, 55.0, 48.0, 40.3, 27.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{27}NO_6$ [M+Na$^+$]: 369.1736, found: 369.1733.

4.3.10. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3,4-dimethoxyphenyl)butane-1,4-diol *anti*-2e

Column chromatography (40:60 petroleum ether/EtOAc); clear oil (This isomer was prepared by a non-selective reduction of **1e**, for characterization). $[\alpha]_D^{25} = -2.5$ (*c* 0.400, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 6.85–6.75$ (m, 3H), 4.55–4.46 (m, 1H), 3.69, 3.66 (s, 6H), 3.04–2.97 (m, 3H), 1.78–1.55 (m, 2H), 1.30 (s, 9H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 155.5$, 147.4, 146.6, 136.5, 116.4, 109.8, 107.8, 77.2, 68.7, 62.7, 53.6, 53.4, 48.2, 39.1, 25.8 ppm.

4.3.11. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-fluorophenyl)butane-1,4-diol 2f

Column chromatography (petroleum ether/EtOAc, 70:30); pale yellow oil (0.460 g, 77%); $[\alpha]_D^{25} = -14.2$ (*c* 0.266, $CHCl_3$); IR (thin film): 3346, 2978, 2930, 1685, 1510, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.26–7.24$ (m, 2H), 6.98–6.95 (m, 2H) 5.28 (bm, 1H), 4.74 (bm, 1H), 3.94 (m, 1H), 3.67–3.59 (m, 2H), 1.99–1.90 (m, 2H), 1.39 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 163.0$, 161.0, 156.2, 139.9, 127.4, 115.2, 79.9, 70.8, 65.1, 50.4, 41.4, 28.2 ppm; ^{19}F NMR ($CDCl_3$, 470 MHz): −114.7 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{22}FNO_4$ [M+Na$^+$]: 322.1431, found: 322.1433.

4.3.12. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-fluorophenyl)butane-1,4-diol *anti*-2f

Column chromatography (50:50 petroleum ether/EtOAc); clear oil (0.080 g, 13%); $[\alpha]_D^{25} = +4.1$ (*c* 1.216, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.31–7.27$ (m, 2H), 6.99–6.95 (m, 2H), 5.17 (m, 1H), 4.68 (m, 1H), 3.91 (m, 1H), 3.69–3.57 (m, 2H), 1.81–1.72 (m, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 163.2$, 160.8, 157.4, 139.9, 127.2, 115.2, 80.3, 69.8, 65.3, 49.7, 42.4, 28.4 ppm; ^{19}F NMR ($CDCl_3$, 470 MHz): −115.4 ppm.

4.3.13. (1*S*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3-chlorophenyl)butane-1,4-diol 2g

Column chromatography (petroleum ether/EtOAc, 70:30); pale yellow oil (0.435 g, 76%); $[\alpha]_D^{25} = -43.8$ (*c* 0.086, $CHCl_3$); IR (thin film): = 3348, 2977, 1685, 1169, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.29–7.14$ (m, 4H), 5.34 (bm, 1H), 4.71–4.70 (m, 1H), 3.89 (m, 1H), 3.59 (m, 2H), 1.90–1.80 (m, 2H), 1.38 (s, 9H)

ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.4, 146.5, 134.3, 129.8, 127.5, 125.8, 123.9, 80.0, 70.6, 64.8, 50.1, 41.1, 28.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{22}ClNO_4$ [M+H$^+$]: 316.1316, found: 316.1316.

4.3.14. (1*R*,3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3-chlorophenyl)butane-1,4-diol *anti*-2g

Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.109 g, 17%); $[\alpha]_D^{25}$ = +2.0 (*c* 0.500, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.34 (m, 1H), 7.23–7.17 (m, 3H), 5.18 (bm, 1H), 4.69–4.66 (m, 1H), 3.96–3.90 (m, 1H), 3.72–3.68 (m, 1H), 3.62–3.58 (m, 1H), 1.84–1.68 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.5, 146.3, 134.3, 129.7, 127.3, 125.9, 123.7, 80.4, 69.8, 65.3, 49.5, 42.4, 28.4 ppm.

4.3.15. (1*S*,3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-1-phenylpentane-1,4-diol 2h

Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.482 g, 82%); $[\alpha]_D^{25}$ = −19.4 (*c* 1.233, $CHCl_3$); IR (thin film): 3405, 2975, 1686, 1506, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30–7.23 (m, 5H), 5.20 (m, 1H), 4.74–4.73 (m, 1H), 3.95–3.85 (m, 2H), 3.56–3.50 (m, 1H), 2.04–2.00 (m, 1H), 1.90–1.84 (m, 1H), 1.42 (s, 9H), 1.12 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.5, 144.4, 128.5, 127.5, 125.8, 79.6, 71.2, 69.2, 53.4, 42.2, 28.4, 20.1 ppm; HRMS (ES): *m*/*z* calcd for $C_{16}H_{25}NO_4$ [M+Na$^+$]: 318.1681, found: 318.1683.

4.3.16. (1*R*,3*R*,4*R*)-3-(*tert*-Butylcarbonylamino)-1-phenylpentane-1, 4-diol *anti*-2h

Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.072 g, 12%); $[\alpha]_D^{25}$ = +5.6 (*c* 1.066, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.34–7.20 (m, 5H), 5.13 (bm, 1H), 4.68–4.66 (m, 1H), 4.36 (m, 1H), 3.81–3.72 (m, 1H), 1.87–1.71 (m, 2H), 1.44 (s, 9H), 1.19 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.9, 144.3, 128.4, 127.2, 125.6, 80.1, 70.3, 69.4, 53.0, 43.7, 28.4, 20.6 ppm.

4.3.17. (1*S*,3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-methoxyphenyl)pentane-1,4-diol 2i

Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.568 g, 87%); $[\alpha]_D^{25}$ = −21.0 (*c* 0.616, $CHCl_3$); IR (thin film): 3396, 2930, 2975, 1682, 1513, 1249, 1173, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.28–7.23 (m, 2H), 6.85 (d, *J* = 8.85 Hz, 2H), 5.06 (m, 1H), 4.66–4.64 (m, 1H), 4.11–4.01 (m, 1H), 3.85–3.83 (m, 1H), 3.77 (s, 3H), 1.86–1.73 (m, 2H), 1.45 (s, 9H), 1.21 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 159.1, 156.5, 136.5, 127.1, 113.9, 79.5, 70.9, 69.4, 55.3, 53.5, 42.2, 28.4, 20.2 ppm; HRMS (ES): *m*/*z* calcd for $C_{17}H_{27}NO_5$ [M+Na$^+$]: 348.1787, found: 348.1794.

4.3.18. (1*R*,3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(4-methoxyphenyl)pentane-1,4-diol *anti*-2i

Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.042 g, 7%); $[\alpha]_D^{25}$ = −4.2 (*c* 0.466, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.23 (d, *J* = 8.55 Hz, 2H), 6.83 (d, *J* = 8.55 Hz, 2H), 5.16 (bm, 1H), 4.74–4.71 (m, 1H), 3.85–3.84 (m, 1H), 3.76 (s, 3H), 3.54–3.36 (m, 1H), 2.03–1.86 (m, 2H), 1.42 (s, 9H), 1.13 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 158.8, 157.8, 136.4, 126.8, 113.8, 80.1, 69.9, 69.6, 55.3, 53.2, 43.7, 28.4, 20.7 ppm.

4.3.19. (1*S*,3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3,4-dimethoxyphenyl)pentane-1,4-diol 2j

Column chromatography (55:45 petroleum ether/EtOAc); clear oil (0.627 g, 88%); $[\alpha]_D^{25}$ = −14.6 (*c* 0.883, $CHCl_3$); IR (thin film): 3385, 2972, 2927, 1686, 1516, 1263, 1162, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.87–6.77 (m, 3H), 5.15 (m, 1H), 4.74–4.71 (m, 1H), 3.84, 3.82 (s, 6H), 3.55 (m, 2H), 2.04–1.87 (m, 2H), 1.42 (s, 9H), 1.14 (d, *J* = 5.7 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.5, 149.0, 148.4, 137.1, 118.0, 111.1, 109.1, 79.6, 71.2, 69.4, 55.9, 55.9, 53.5, 42.3, 28.4, 20.2 ppm; HRMS (ES): *m*/*z* calcd for $C_{18}H_{29}NO_6$ [M+Na$^+$]: 378.1893, found: 378.1891.

4.3.20. (1*R*,3*R*,4*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(3,4-dimethoxyphenyl)pentane-1,4-diol 2j-*anti*

Column chromatography (55:45 petroleum ether/EtOAc); clear oil (0.026 g, 4%); $[\alpha]_D^{25}$ = −5.5 (*c* 0.716, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.93–6.78 (m, 3H), 5.07 (m, 1H), 4.65 (m, 1H), 4.21 (m, 1H), 3.87, 3.84 (s, 6H), 3.78–3.74 (m, 1H), 1.88–1.73 (m, 2H), 1.45 (s, 9H), 1.23–1.21 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.8, 149.0, 148.1, 137.0, 117.7, 111.0, 108.9, 80.2, 70.1, 69.5, 56.0, 55.9, 52.9, 43.8, 28.4, 20.7 ppm.

4.3.21. (3*R*)-3-(*tert*-Butyloxycarbonylamino)-5-methoxy-5-phenyltetrahydrofuran 5

To a solution of the β-amino ketone **1a** (1 mmol) in methanol (5 mL) at rt (30 °C), triflates (10 mol %) was added and stirred well for 5 min. To this solution, $NaBH_4$ (0.150 g, 4 mmol) was added in portions using a solid addition funnel. After the complete disappearance of starting material, reaction was quenched with saturated $NaHCO_3$ (10 mL) and extracted with dichloromethane (2 × 30 mL). Organic layer dried over anhydrous Na_2SO_4 and concentrated under vacuum and crude diastereomers were purified through column chromatography. Diastereomer 1 Column chromatography (95:5 petroleum ether/EtOAc); clear oil (0.131 g, 45%); IR (thin film): 3345, 3061, 2977, 1715, 1511, 1170, 1042 cm^{-1}; 1H NMR ($CDCl_3$, 500 MHz): δ = 7.45–7.25 (m, 5H), 5.60–5.58 (bm, 1H), 4.48–4.42 (m, 2H), 3.88–3.87 (m, 1H), 3.04 (s, 3H), 2.24–2.22 (m, 1H), 2.10–2.06 (m, 1H), 1.46 (s, 9H) ppm; 13C NMR (CDCl3, 125 MHz): δ = 155.4, 139.4, 128.3, 128.2, 126.2, 109.4, 79.5, 75.8, 50.4, 49.4, 47.2, 28.5 ppm; HRMS (ES): *m*/*z* calcd for $C_{16}H_{23}NO_4$ [M+Na+]: 316.1500, found: 316.1508

Diastereomer 2; Column chromatography (95:5 petroleum ether/EtOAc); clear oil (0.161 g, 55%); IR (thin film): 3345, 3061, 2977, 1715, 1511, 1170, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.48–7.25 (m, 5H), 4.62–4.60 (bm, 1H), 4.51–4.44 (m, 1H), 4.23–4.20 (m, 1H), 3.91–3.89 (m, 1H), 2.98 (s, 3H), 2.75–2.71 (m, 1H), 1.79–1.75 (m, 1H), 1.40 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.3, 140.2, 128.4, 128.1, 126.1, 108.8, 79.7, 73.3, 51.4, 49.6, 48.0, 28.4 ppm; HRMS (ES): *m*/*z* calcd for $C_{16}H_{23}NO_4$ [M+Na$^+$]: 316.1500, found: 316.1508.

4.4. Synthesis of HPA-12 and its analogues 6

N-Boc protected amino diol **2** (1 mmol) was dissolved in methanol (1 mL) and cooled to 0 °C. Ethyl acetate saturated with HCl (3 mL) was added with stirring and the reaction mixture was allowed to attain rt. Upon the complete disappearance of **2** on TLC, the solvents were removed under reduced pressure and the residue was dissolved in anhydrous THF (5 mL). This solution was cooled to 0 °C, after which solid $NaHCO_3$ (1 g) was added and the mixture was vigorously stirred. Lauroyl chloride (0.231 mL, 0.219 g, 1 mmol, 1 equiv) was added to this mixture dropwise and stirring was continued at 0 °C for 1 h and then at rt for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and filtered, the residue was washed with dichloromethane (20 mL) and the filtrate and washings were combined. The crude solution of the 5 in dichloromethane was washed with water (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography.

4.4.1. *N*-((2*R*,4*S*)-1,4-Dihydroxy-4-phenylbutan-2-yl)dodecanamide 6a

Column chromatography (petroleum ether/EtOAc, 50:50); white solid (0.254 g, 70%); mp 86–88 °C; lit.;[12] mp 90–91 °C; lit.[10] mp 81–82 °C; $[\alpha]_D^{25} = -30.7$ (*c* 0.533, $CHCl_3$); lit.[12] $[\alpha]_D = -34.8$ (*c* 1.0, $CHCl_3$); lit.[10] $[\alpha]_D = -34.7$ (*c* 0.36, $CHCl_3$) IR (KBr): 3293, 2920, 1642, 1551, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.30–7.22$ (m, 5H), 6.52 (b, 1H), 4.75 (m, 1H), 4.01 (m, 1H), 3.64–3.58 (m, 2H), 2.12–2.09 (t, $J = 7.7$ Hz, 2H), 2.01–1.85 (m, 2H), 1.56–1.54 (m, 2H), 1.24 (m, 16H), 0.86 (t, $J = 6.7$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 174.4$, 144.4, 128.6, 127.6, 125.6, 71.7, 65.4, 50.3, 40.8, 36.8, 32.0, 29.73, 27.71, 29.6, 29.4, 29.3, 25.8, 22.7, 14.2 ppm; lit.[10] (^{13}C NMR); lit.[12] (^{13}C NMR); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}NO_3$ [M+Na^+]: 386.2671, found: 386.2679.

4.4.2. *N*-((2*R*,4*S*)-1,4-Dihydroxy-4-*p*-tolylbutan-2-yl)dodecanamide 6b

Column chromatography (petroleum ether/EtOAc, 50:50); white solid (0.248 g, 66%); mp 103–104 °C; $[\alpha]_D^{25} = -12.0$ (*c* 0.250, $CHCl_3$); IR (KBr): 3297, 2919, 1643, 1549, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.20–7.19$ (d, $J = 7.95$ Hz, 2H), 7.12–7.11 (d, $J = 7.6$ Hz, 2H), 6.46 (b, 1H), 4.74 (m, 1H), 4.01 (m, 1H), 3.62 (m, 2H), 2.31 (s, 3H), 2.13 (t, $J = 7.65$ Hz, 2H), 2.00–1.88 (m, 2H), 1.56 (m, 2H), 1.26–1.24 (m, 16H), 0.87 (t, $J = 6.75$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 174.4$, 141.3, 137.4, 129.3, 125.5, 71.8, 65.7, 50.6, 40.73, 36.8, 32.0, 29.7, 29.6, 29.46, 29.43, 29.39, 25.8, 22.7, 21.1, 14.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{39}NO_3$ [M+Na^+]: 400.2828, found: 400.2828.

4.4.3. *N*-((2*R*,4*S*)-1,4-Dihydroxy-4-(4-isopropylphenyl)butan-2-yl)dodecanamide 6c

Column chromatography (petroleum ether/EtOAc, 50:50); white solid (0.259 g, 64%); mp 96–98 °C; $[\alpha]_D^{25} = -10.0$ (*c* 0.300, $CHCl_3$); IR (KBr): 3298, 2920, 1643, 1549, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.25–7.23$ (d, $J = 8.00$ Hz, 2H), 7.19–7.17 (d, $J = 7.80$ Hz, 2H), 6.46 (b, 1H), 4.76 (m, 1H), 4.04 (m, 1H), 3.66–3.60 (m, 2H), 2.87 (s, 1H), 2.14 (t, $J = 7.45$ Hz, 2H), 2.03–1.88 (m, 2H), 1.58 (m, 2H), 1.27–1.21 (m, 22H), 0.86 (t, $J = 6.30$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 174.2$, 148.5, 141.6, 126.7, 125.6, 71.98, 65.9, 56.7, 40.5, 36.9, 33.8, 31.9, 29.76, 29.7, 29.61, 29.45, 29.43, 25.8, 24.0, 22.7, 14.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{43}NO_3$ [M+Na^+]: 428.3141, found: 428.3149.

4.4.4. *N*-((2*R*,4*S*)-4-(4-Fluorophenyl)-1,4-dihydroxybutan-2-yl) dodecanamide 6f

Column chromatography (petroleum ether/EtOAc, 60:40); white solid (0.267 g, 70%); mp 78–79 °C; $[\alpha]_D^{25} = -21.0$ (*c* 0.666, $CHCl_3$); IR (KBr): 3290, 2920, 1642, 1552, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.30–7.27$ (m, 2H), 7.01–6.98 (m, 2H), 6.38–6.37 (b, 1H), 4.78–4.76 (m, 1H), 4.03 (m, 1H), 3.68–3.62 (m, 2H), 2.15 (t, $J = 7.9$ Hz, 2H), 2.02–1.85 (m, 2H), 1.59–1.55 (m, 2H), 1.24 (m, 16H), 0.86 (t, $J = 7.05$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 173.5$, 162.3, 160.3, 139.2, 126.4, 114.6, 114.4, 70.4, 64.6, 49.4, 40.2, 36.0, 31.1, 28.9, 28.8, 28.7, 28.5, 28.5, 28.4, 24.9, 21.8, 13.3 ppm; ^{19}F NMR ($CDCl_3$, 470 MHz): −114.6 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{36}FNO_3$ [M+H^+]: 382.2750, found: 382.2757.

4.4.5. *N*-((2*R*,4*S*)-4-(3-Chlorophenyl)-1,4-dihydroxybutan-2-yl) dodecanamide 6g

Column chromatography (petroleum ether/EtOAc, 55:45); white solid (0.235 g, 59%); mp 58–60 °C; $[\alpha]_D^{25} = -13.8$ (*c* 0.650, $CHCl_3$); IR (KBr): 3297, 2920, 1641, 1551, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.32–7.16$ (m, 4H), 6.44 (bm, 1H), 4.75–4.73 (m, 1H), 4.04 (m, 1H), 3.68–3.62 (m, 2H), 2.12 (t, $J = 7.65$ Hz, 2H), 2.02–1.83 (m, 2H), 1.55 (m, 2H), 1.24 (m, 16H), 0.86 (t, $J = 7.05$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 174.5$, 146.6, 134.4, 129.8, 127.6, 125.8, 123.8, 71.1, 65.1, 50.0, 41.0, 36.8, 31.9, 29.77, 29.72, 29.61, 29.44, 29.43, 29.4, 25.78, 22.7, 14.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{36}ClNO_3$ [M+H^+]: 398.2464, found: 398.2462.

4.5. Acid sensitivity of the electron rich amino diol 2e

Amino diol **2e** (0.341 g, 1 mmol) was dissolved in a solution of TFA (2%) in CH_3OH (8 mL) at 0 °C and stirred until **2e** disappeared in TLC (2 h). The reaction mixture was then neutralized with $NaHCO_3$ (1 g), filtered, and the filtrate was removed under vacuum and the products were isolated by column chromatography. The solvolysis product **7** and the intramolecular S_N1 product **8** were isolated in equimolar amounts, as mixtures of diastereomers.

4.5.1. 2-(*tert*-Butyloxycarbonylamino)-4-(3,4-dimethoxyphenyl)-4-methoxybutan-1-ol 7

Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.177 g, 50%); IR (thin film): 3364, 2926, 2854, 1692, 1515, 1261, 1169, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): mixture of diastereomers: $\delta = 6.81–6.77$ (m, 3H), 5.19–5.15 (m, 1H), 4.16–4.14 (m, 1H), 3.85, 3.84 (s, 6H), 3.69–3.56 (m, 3H), 3.17–3.15 (s, 3H), 1.95–1.75 (m, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 156.2$, 149.3, 148.6, 134.2, 133.9, 118.9, 111.0, 109.2, 109.0, 81.1, 79.5, 65.5, 56.5, 56.3, 55.9, 51.1, 50.7, 40.0, 28.4 ppm; HRMS (ES): *m*/*z* calcd for $C_{18}H_{29}NO_6$ [M+Na^+]: 378.1893, found: 378.1897.

4.5.2. 5-(3,4-Dimethoxyphenyl)tetrahydrofuran-3-(*tert*-butyloxy carbonylamine) 8

Column chromatography (petroleum ether/EtOAc 85:15); clear oil (0.161 g, 50%); IR (thin film): 3355, 2973, 2928, 1709, 1516, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): mixture of diastereomers: $\delta = 6.88–6.78$ (m, 3H), 4.96–4.71 (m, 1H), 4.34–4.22 (m, 1H), 4.00–3.96 (m, 0.5H), 3.86–3.81 (m, 6H), 3.70–3.69 (m, 0.5H), 2.69–2.62 (m, 0.5H), 2.18–2.04 (m, 0.5H), 1.76–1.64 (m, 1H), 1.43–1.40 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 155.4$, 149.1, 148.5, 134.5, 117.9, 111.1, 108.8, 80.0, 79.4, 74.0, 56.0, 55.9, 52.0, 51.8, 41.8, 41.6, 28.4 ppm; HRMS (ES): *m*/*z* calcd for $C_{17}H_{25}NO_5$ [M+Na^+]: 346.1630, found: 346.1631.

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