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Scalable Enantioselective Synthesis of Fmoc-β²-Serine and Fmoc-β²-Threonine by an Organocatalytic Mannich Reaction

Daniel Meyer,[a] Roger Marti,*[a] and Dieter Seebach[b]

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The diastereoselective Mannich reaction of functionalized aldehydes, using a phenethylamine-derived iminium precursor, by activation with prolines and prolinol derivatives have been studied. Optimized reaction conditions have been developed, allowing for scale-up and preparation of γ-amino alcohol derivatives on multi-gram scale from β-hydroxypropanal and -butanal, with diastereoselectivites of typically >73:27 and yields of >60 %. After chromatographic diastereoisomer separation, hydrogenolytic debenzylation, enantiomerically pure Fmoc-β²-Ser(*t*Bu)-OH and Fmoc-β²-Thr(*t*Bu)-OH were thus prepared on multi-gram scale in 6 steps and with overall yields of 24 % and 10 %, respectively, starting from commercially available starting compounds.

Introduction

Since the discovery in 1996[1] that peptides containing homologated proteinogenic amino acids form more stable secondary structures than the natural counterpart, the chemistry of β-peptides was investigated intensively.[2] In addition to this variety of structures, β-peptides (and mixed β/α-peptides) are generally proteolytically and metabolically stable in vitro and in vivo, and they can mimic biological activities of natural peptides, which makes them interesting for biomedical research.[3] The synthesis of β²-amino acids is still a big challenge and only a few of them are commercially available. In contrast to β³-amino acids, the β²-isomers cannot be obtained simply by enantiospecific homologation of the α-amino acids, but have to be prepared by multistep enantioselective reactions.[4] β²-Amino acids with functionalized side chains, such as β²-serine and β²-threonine require up to 9[5] respectively 13[6] steps from commercially available starting materials.

One possible way to synthesize β²-amino acid is the enantioselective aminomethylation of aldehydes via organocatalytic Mannich reactions (Figure 1).[7] As formaldehyde does not form stable imines, the iminium source has to be generated in situ from N,O-acetals to provide the electrophile in the Mannich process.[8] First, Gellman et al. and Córdova et al. examined L-proline and chiral pyrrolidine derivatives as catalysts for nucleophilic activation of aldehyde reactants using dibenzyl-N,O-acetal as iminium ion sources.[7a,7d] This process was further modified by the use of N,O-acetal **1** to yield diastereomeric products, which can be readily separated via column chromatography or crystallization of the HCl salts.[7b] So far, this process has been mostly applied to non-functionalized aldehydes and to a milligram scale.

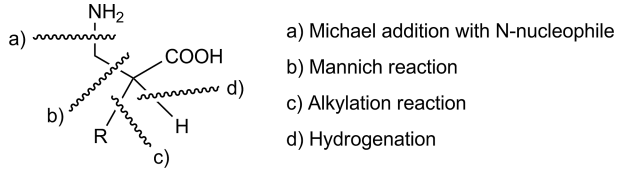

Figure 1. Synthesis of β²-amino acids.

Herein, we report the process optimization of an organocatalytic overall enantioselective α-amino-methylation and preparation of β²-amino acids from β-heterosubstituted aldehydes on multi-gram scale. Fmoc-β²-Serine and Fmoc-β²-threonine were thus synthesized in 6 steps starting from commercially available starting materials.

Results and Discussion

Optimization of Condition for the Organocatalytic Step, Using 3-Methylbutanal

N,O-Acetals **1** and **2** were prepared by reaction of benzyl-phenethylamine with paraformaldehyde in anhydrous MeOH or *i*PrOH in yields of 79 % and 59 %, respectively.[9]

[a] HES-SO Haute école spécialisée de Suisse occidentale, Haute école d'ingénierie et d'architecture Fribourg, Institute ChemTech, Bd. de Pérolles 80, 1700 Fribourg, Switzerland
E-mail: roger.marti@hefr.ch
http://chemtech.heia-fr.ch
[b] Laboratorium für Organische Chemie, Departement für Chemie und Angewandte Biowissenschaften, ETH-Zürich, Hönggerberg HCI, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland
E-mail: seebach@org.chem.ethz.ch
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Since both enantiomers of the chiral amine are commercially available, both enantiomers of **1** and **2** are thus accessible.

In initial experiments, we screened different reaction conditions – reaction temperature, equivalents and type of additives – using isovaleraldehyde and iminium sources **1** and **2** in the diastereoselective Mannich reaction by activation with diphenylprolinol TMS-ether **C9** (Table 1). The two iminium sources (*S*)-**1** and (*R*)-**1** gave the same diastereomeric ratio (*dr* = 92:8) of the product, indicating that the chirality center of the iminium ion has no influence on enantioface selectivity of the prolinol-derived enamine in the Mannich reaction (Table 1, entries 1 and 2). Under similar conditions Gellman et al. had obtained a *dr* of 95:5.[7b] Decreasing the reaction temperature from –25 °C to –35 °C had no influence on the selectivity (Table 1, entries 4 and 5), whereas at higher reaction temperature the diastereoselectivity decreased from 92:8 to 86:14 (Table 1, entry 6). The addition of acetic acid increases the reaction rate but has no influence on the selectivity (Table 1, entries 1, 8 and 9). Replacement of acetic acid by the more acidic monochloroacetic acid (MCA, pK_a 2.87) and dichloroacetic acid (DCA, pK_a = 1.25)[10] lowered the selectivity of the reaction to 77:23 and 68:32, respectively (Table 1, entries 10 and 11). Addition of higher quantities of LiBr (1 equiv. instead of 0.4 equiv.) had no influence on the reaction selectivity but made the reaction mixture more viscous and less practical to handle (Table 1, entry 7).

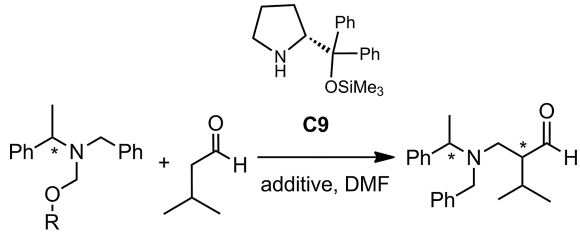
Next, we used N,O-acetal (*S*)-**1** and isovaleraldehyde for a catalysts screening of proline and diarylprolinol derivatives (**C1**–**C16**) at –25 °C. The results are summarized in Table 2. The additives LiBr and AcOH were only used with the diarylprolinol derivatives **C5**–**C16** as catalysts.[7a,7b,7d] In proline-catalyzed reactions these additives lowered in general the selectivity and were therefore not used.

Generally, reactions catalyzed with diarylprolinol ethers showed higher conversion rates compared with these catalyzed by proline. With L-proline **C2**, the *dr* was 82:18 while with D-proline **C3** the product was formed with a diastereoselectivity of 74:26 (Table 2, entries 2 and 3). This difference of stereoselectivity is a case of so-called matched/mismatched relationship between the source of chirality of the imminium ion and that of the proline-derived enamine in the transition state.

Interestingly, such an effect was not observed in the diarylprolinol ether activation. Replacement in the diphenylprolinol of the methyl ether (**C5** and **C8**, Table 2, entries 5 and 8) by a TMS ether (**C6** and **C9**) has no influence on the diastereoselectivity (Table 2, entries 6 and 9). The substitution with a TBDMS ether slightly enhance the diastereoselectivity from 92:8 to 94:6 (Table 2, entries 7 and 10). With 3,5-disubstituted diarylprolinol catalysts **C11**–**C16** the diastereoslectivities and conversion rate decreased (Table 2, entries 11–16).

Based on this optimization work the best conditions for further scale-up of the organocatalytic Mannich approach is the reaction of 1 equiv. iminium source (*S*)-**1** or (*R*)-**1** with 2 equiv. of the corresponding aldehyde by activation with 0.2 equiv. organocatalyst at –25 °C in DMF. Using pyrrolidines **C5**–**C16** as catalysts 0.4 equiv. LiBr and 0.2 equiv. AcOH should be added to enhance the selectivity and the reaction rate. Taking into account the price for the

Table 1. Diastereoselective Mannich reaction using isovaleraldehyde and the Hayashi catalyst **C9**. **C9**, LiBr (1 mmol) and the acid were stirred in DMF (5 mL) at room temperature for 5 min. Next, isovaleraldehyde (5 mmol) and the N,O-acetal (2.5 mmol) were added at –25 °C. Conversion and *dr* were determined by ^{1}H-NMR of the reaction mixture after 2 h.



(*S*)-**1**, R = Me
(*R*)-**1**, R = Me
(*S*)-**2**, R = *i*Pr

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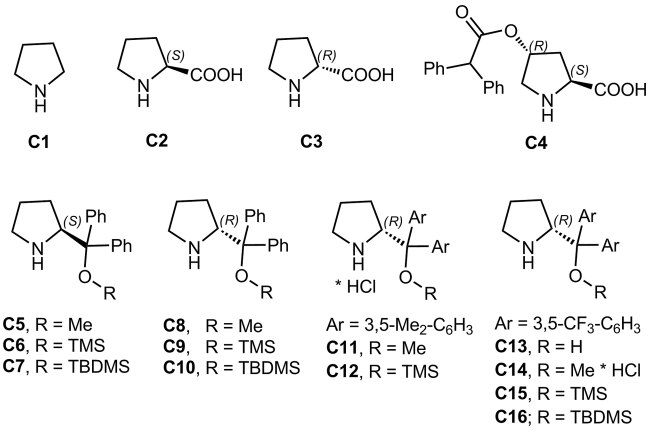
Entry	N,O-Acetal	Acid	**C9** [equiv.]	Conversion [%]	*dr* (*S*,*S*):(*R*,*S*)
1	(*S*)-**1**	0.2 equiv. AcOH	0.2	>95	92:8
2	(*R*)-**1**	0.2 equiv. AcOH	0.2	>95	92:8[a]
3	(*S*)-**2**	0.2 equiv. AcOH	0.2	>95	92:8
4	(*S*)-**1**	0.1 equiv. AcOH	0.1	50	92:8
5[b]	(*S*)-**1**	0.1 equiv. AcOH	0.1	40	92:8
6[c]	(*S*)-**1**	0.1 equiv. AcOH	0.1	70	86:14
7[d]	(*S*)-**1**	0.2 equiv. AcOH	0.2	>95	91:9
8	(*S*)-**1**	–	0.2	80	92:8
9	(*S*)-**1**	0.5 equiv. AcOH	0.2	>95	92:8
10	(*S*)-**1**	0.1 equiv. MCA	0.1	90	77:23
11	(*S*)-**1**	0.1 equiv. DCA	0.1	20	68:32

[a] *dr* (*S*,*R*):(*R*,*R*). [b] –35 °C reaction temperature. [c] –15 °C reaction temperature. [d] 2.5 mmol (1 equiv.) LiBr was added.

Table 2. Screening of various catalysts **C1**–**C16** at –25 °C. The catalysts (0.2 mmol), LiBr (0.4 mmol) and AcOH (0.2 mmol) were stirred in DMF (4 mL) at room temperature for 5 min. Next, isovaleraldehyde (2 mmol) and N,O-acetal (*S*)-**1** (1 mmol) were added at –25 °C. Conversion and *dr* were determined by ^{1}H-NMR of the reaction the mixture after 2 h.



Entry	Cat.	Conversion [%][b]	*dr* (*S*,*S*):(*R*,*S*)
1	**C1**	60	53:47
2[a]	**C2**	20	82:18
3[a]	**C3**	20	26:74
4[b]	**C4**	> 95 (r.t.)	69:31
5	**C5**	90	8:92
6	**C6**	80	8:92
7	**C7**	70	6:94
8	**C8**	90	92:8
9	**C9**	80	92:8
10	**C10**	70	94:6
11	**C11**	20	85:15
12	**C12**	20	89:11
13	**C13**	2	73:27
14	**C14**	20	85:15
15	**C15**	20	90:10
16	**C16**	20	91:9

[a] No LiBr and AcOH added. [b] Reaction control after 24 h at room temp.

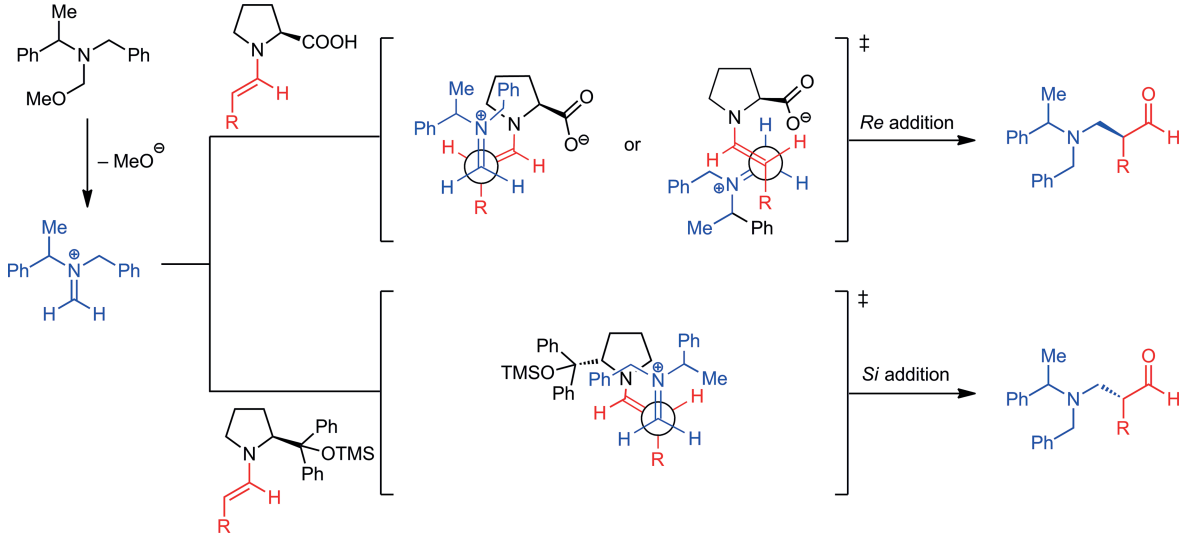
catalysts, the proline catalysts **C2** and **C3** are preferred to the diarylpyrolinol ethers **C5**–**C16**.

Mechanistic Considerations

As expected, catalysis by L-proline[11] and by (*S*)-diarylprolinol ethers[12] provide enantiomeric products, see the trajectories in Scheme 1 and an extensive discussion in a review article.[13] For the prolinol ether catalyzed Mannich reaction Córdova et al. have also considerated an S_N2-type substitution of the OR group in the formaldehyde N,O-acetal by the enamine nucleophile, i.e. a mechanism without formation of an iminium ion.[7d] We have observed exactly the same selectivity with the N,O-acetals carrying an MeO and an *i*PrO group, see (*S*)-**1** and (*S*)-**2** (Table 1, entries 1 and 3). We would have expected that the two different leaving groups in an S_N2-type reaction would give detectably different results. Therefore we do not include this alternative mechanism in Scheme 1.

Application of the Mannich Reaction with β-Hydroxy Aldehyde Derivatives

For the preparation of β²-serine and β²-threonine we chose 3-*tert*-butoxy-propanal and 3-*tert*-butoxybutanal as aldehyde components. Both contain a potential leaving group in the β-position of the carbonyl group. Compounds of this type are known to undergo β-elimination under basic and acidic conditions. For the purpose of our synthesis the *t*BuO group would have to "survive" the organocatalysis step and the condition of subsequent transformations ($NaBH_4$ reduction, TEMPO/NaOCl or $Na_2Cr_2O_7$ oxidation, see below). Furthermore, the 3-*tert*-butoxybutanal **9** is a chiral derivative, the stereogenic center of which could influence the stereochemical course of the reaction. Finally,



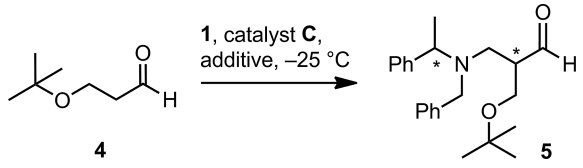
Scheme 1. Transition states of the proline and prolinol-catalyzed Mannich reaction.

the scale-up from 2 mmol of the N,O-acetal **1** by a factor up to 100 is accompanied by a change of addition-time periods.

Preparation of Fmoc-(*S*)-β²-Ser(*t*Bu)-OH and Fmoc-(*R*)-β²-Ser(*t*Bu)-OH

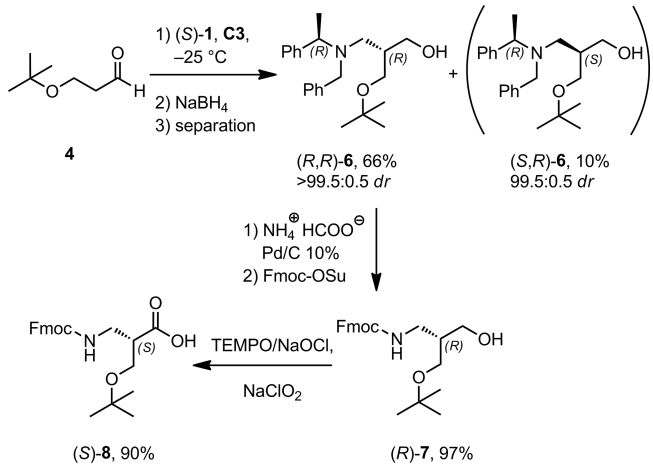
For the preparation of β²-serine, we first prepared the 3-*tert*-butoxypropanal **4** in two steps starting from commercially available acrolein ethylene acetal by addition of *tert*-butanol followed by aqueous acidic cleavage of the acetal group in an overall yield of 42%.[14] Aldehyde **4** was then used for the Mannich reaction with the above described optimized condition, using proline **C2** and **C3** as well as the prolinol ethers **C9** and **C10** as catalysts (Table 3). The Hayashi-type catalysts **C9** and **C10** gave a slightly lower selectivity as compared to the reaction of isovaleraldehyde (cf. Table 3, entries 4 and 5 with Table 2, entries 9 and 10). On the other hand, the activation with D-proline gave a slightly better *dr* of 84:16, compared to L-proline with a *dr* of 80:20 with the N,O-acetal (*S*)-**1** (Table 3, entries 1 and 2).

Table 3. Diastereoselective Mannich reaction of aldehyde **4**. The catalysts (0.5 mmol), LiBr (1 mmol) and AcOH (0.5 mmol) were stirred in DMF (5 mL) at room temperature for 5 min. Next, aldehyde **4** (5 mmol) and the N,O-acetals (2.5 mmol) were added at –25 °C. Conversion and *dr* were determined by ^{1}H-NMR of the reaction mixture after 2 h.



Entry	N,O-Acetal	Cat.	Conv. [%]	*dr*	Favored diastereomer
1	(*S*)-**1**	**C2**	20	80:20	(*R*,*S*)
2	(*S*)-**1**	**C3**	20	84:16	(*S*,*S*)
3	(*R*)-**1**	**C3**	20	80:20	(*S*,*R*)
4	(*S*)-**1**	**C9**	>95	89:11	(*R*,*S*)
5	(*S*)-**1**	**C10**	>95	84:16	(*R*,*S*)

As outlined in Scheme 2, we synthesized alcohol **6** in a multi-gram scale [51 g of N,O-acetal (*R*)-**1**] by the diastereoselective Mannich reaction followed by reduction with $NaBH_4$. To obtain the (*S*)-β²-Ser(*t*Bu)-OH precursor (*R*,*R*)-**6** as major diastereoisomer, D-proline **C3** was used as catalyst. Compared to the small scale experiments, the scale-up by a factor of 100 improved the diastereomeric ratio of the crude product slightly to 87:13. The two diastereoisomers could be easily separated by column chromatography to give the diastereomerically pure (*dr* >99.5:0.5) alcohol (*R*,*R*)-**6** in 66% yield together with 10% of alcohol (*S*,*R*)-**6** (*dr* 99.5:0.5). For the scale-up procedure, a slurry of D-proline in DMF had to be stirred overnight before carrying out the reaction. Otherwise the yield dropped dramatically (< 20%). This may be caused by the slow dissolution of the catalysts or by forming finer partials (i.e. larger surface) by grinding with the magnetic stirring bar.



Scheme 2. Enantioselective synthesis of Fmoc-(*S*)-β²-Ser(*t*Bu)-OH (*S*)-**8** and Fmoc-(*R*)-β²-Ser(*t*Bu)-OH (*R*)-**8**. The minor diastereomer of the Mannich reaction (*R*,*S*)-**6** (10% yield) was converted in the same manner to give (*S*)-**7** and (*R*)-**8** in yields of 95% and 88%, respectively.

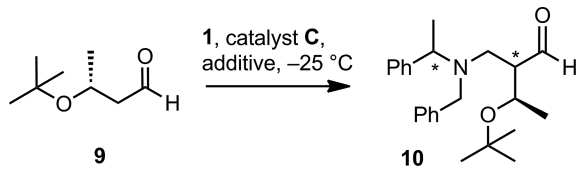
Catalytic hydrogenolytic removal of the benzyl and the phenethyl group, followed by Fmoc-protection of the resulting primary amino group gave the Fmoc-amino alcohols (*R*)-**7** and (*S*)-**7** in yields of 97% and 95%, respectively. By optimization the process, we reduced the quantity of Pd/C 10% from 100 wt.-% to 10 wt.-% and the ammonium formate as hydrogen source from 10 equiv. to 5 equiv. making the process less expensive.[7a,7b,7d] Subsequent oxidation provided Fmoc-(*S*)-β²-Ser(*t*Bu)-OH (*S*)-**8** and Fmoc-(*R*)-β²-Ser(*t*Bu)-OH (*R*)-**8** in yields of 90% and 88%, respectively. For the scale-up run [49 g of (*R*)-**7**], we replaced the originally employed Jones oxidation[7a,7b] and $RuCl_3/NaIO_4$[7d] in CCl_4 by the "greener" TEMPO/NaOCl/$NaClO_2$[15] system. The optical rotation $[\alpha]_D^{20}$ of (*S*)-**8** was +7.3 (c 2.0, $CHCl_3$) – identically with the value reported in the literature[5b] {$[\alpha]_D^{20}$ = +7.32 (c 0.68, $CHCl_3$)}. The enantiopurity was also determined by HPLC on a CHIRALPAK IA-3 column indicated the high enantiomeric purity of (*S*)-**8** and (*R*)-**8** of 99.8:0.2 and 99.6:0.4, respectively.

Preparation of Fmoc-(*S*,*R*)-β²-Thr(*t*Bu)-OH

The required aldehyde **9** was prepared from ethyl (*R*)-3-hydroxybutyrate[16] in two steps: by etherification with *tert*-butyl 2,2,2-trichloroacetimidate (66% yield),[17] followed by DIBAL reduction of the ester group (57% yield).[18] The diastereselective Mannich reaction of aldehyde **9** was in general less selective than with the aldehyde **4** and activation with D-proline **C3** gave product **10** of higher *dr* than with prolinol silyl ethers **C9** and **C10**, see Table 4.

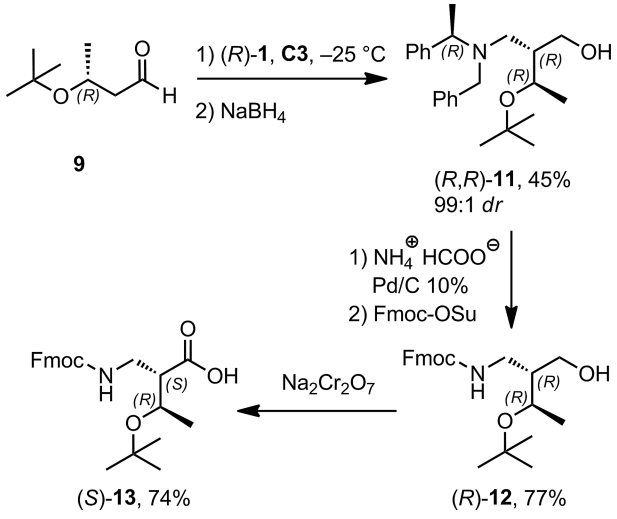
The corresponding in situ sequence of Mannich reaction [**9** + (*R*)-**1**/cat. **C3**], followed by reduction with $NaBH_4$ yielded the amino alcohol derivative (*R*,*R*)-**11** with a *dr* of 73:27 (Scheme 3). Separation by column chromatography afforded (*R*,*R*)-**11** in a yield of 45% with a *dr* of 99:1.

Table 4. Diastereoslective Mannich reaction of aldehyde **9**. The catalysts (0.5 mmol), LiBr (1 mmol) and AcOH (0.5 mmol) were stirred in DMF (5 mL) at room temperature for 5 min. Next, aldehyde **9** (5 mmol) and the N,O-acetals (2.5 mmol) were added at –25 °C. Conversion and *dr* were determined by ^{1}H-NMR of the reaction mixture after 2 h.



Entry	N,O-Acetal	Cat.	Conv. [%]	*dr*	Favored diastereomer
1	(*S*)-**1**	**C3**	20	76:24	(*S*,*S*)
2	(*R*)-**1**	**C3**	20	73:27	(*S*,*R*)
3	(*S*)-**1**	**C9**	40	71:29	(*R*,*S*)
4	(*S*)-**1**	**C10**	20	59:41	(*R*,*S*)

Hydrogenolytic deprotection followed by Fmoc-protection and Jones oxidation gave Fmoc-(*S*,*R*)-β²-Thr(*t*Bu)-OH (*S*)-**13** in a yield of 57%.



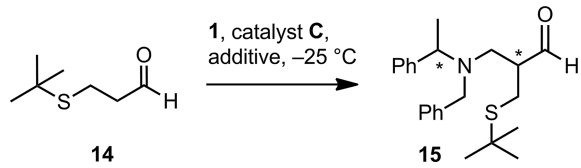
Scheme 3. Enantioselective synthesis of Fmoc-(*S*)-β²-Thr(*t*Bu)-OH (*S*)-**13**.

Attempted Preparation of β²-Cysteine Derivative

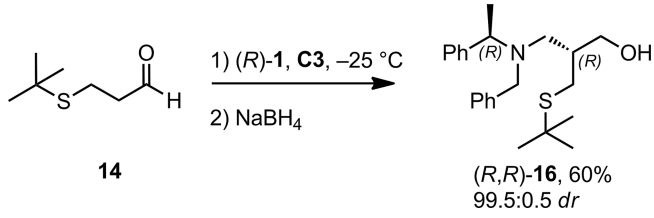
We also tried to prepare a β²-cysteine derivative from 3-*tert*-butylthiopropanal (**14**) and the Mannich reagent **1**. The aldehyde **14** was obtained in 86% yield from acrolein and *tert*-butyl-mercaptan.[19] This aldehyde and its derivatives will be even more prone to undergo β-elimination than the oxygen analogs **4** and **9**.

The diastereoselective Mannich reaction with aldehyde **14** gave actually the desired product **15** even with higher *dr* of 83:17 compared to aldehydes **4** and **9** (Table 5) and, after $NaBH_4$ reduction and separation by column chromatography, in approximately the same yield as with aldehyde **4**: 60% with *dr* >99.5:0.5 (Scheme 4). As was to be expected a subsequent hydrogenolytic removal of the benzylic groups was not successful, due to of the well-known sulfur poisoning of the Pd/C.[20]

Table 5. Diastereoselective Mannich reaction of aldehyde **14**. The catalysts (0.5 mmol), LiBr (1 mmol) and AcOH (0.5 mmol) were stirred in DMF (5 mL) at room temperature for 5 min. Next, aldehyde **14** (5 mmol) and the N,O-acetals (2.5 mmol) were added at –25 °C. Conversion and *dr* were determined by ^{1}H-NMR of reaction mixture after 2 h.



Entry	N,O-Acetal	Cat.	Conv. [%]	*dr*	Favored diastereomer
1	(*S*)-**1**	**C3**	70	88:12	(*R*,*S*)
2	(*R*)-**1**	**C3**	70	83:17	(*R*,*R*)
3	(*S*)-**1**	**C9**	50	85:15	(*S*,*S*)
4	(*S*)-**1**	**C10**	40	80:20	(*S*,*S*)



Scheme 4. Synthesis of (*R*)-*N*-benzyl-*N*-α-methylbenzyl-(*R*)-β²-cysteine(*t*Bu) alcohol (*R*,*R*)-**16**.

Conclusions

In summary, we optimized and tested several proline and prolinol catalysts for direct catalytic asymmetric α-aminomethylation of isovaleraldehyde using chiral N,O-acetals derived from benzylphenethylamine. The simple reactions are highly chemo- and diastereoelective with a *dr* up to 94:6. We applied the diastereoselective Mannich reaction to β-hetero-substituted aldehydes to get the precursor γ-amino alcohol derivatives of Fmoc-β²-Ser(*t*Bu)-OH, Fmoc-β²-Thr(*t*Bu)-OH and Fmoc-β²-Cys(*t*Bu)-OH with a diastereoselectivity of >73:27 in the crude product and of ≥99:1 after chromatographic separation of the diastereoisomers. The Fmoc-β²-amino acids can be synthesized by hydrogenolytic removal of the benzylic groups followed by Fmoc-protection and oxidation with TEMPO/NaOCl/$NaClO_2$. Our scalable catalytic diastereoselective method provides a facile and practical access to – so far hard to synthesize – enantiopure Fmoc-β²-Ser(*t*Bu)-OH and Fmoc-β²-Thr(*t*Bu)-OH in 6 steps starting from commercially available starting materials on multi-gram scale.

Experimental Section

General Remarks: D-Proline was purchased from Bachem AG. All other starting materials were provided from Sigma–Aldrich. All reactions involving oxygen- or moisture-sensitive compound were carried out under a dry argon atmosphere. Reaction temperatures refer to external bath temperatures. Column chromatography was performed with Macherey–Nagel Silica gel 60 M (pore size 60 Å, 230–400 mesh particle size) packed in glass columns. Reactions were monitored by thin-layer chromatography (TLC) using aluminum Merck 60 UV_{254} silica gel plates (0.2 mm thickness). Visualization was performed by ultraviolet light or by $KMnO_4$ stain, followed by gentle heating. NMR spectra were recorded at 300 MHz (for ^1H NMR) or 75 MHz (for ^{13}C NMR) in $CDCl_3$. Chemical shifts are reported as δ (ppm) downfield from tetramethylsilane (δ = 0.00 ppm) using residual solvent signal as an internal standard: δ singlet 7.26 (^1H), triplet 77.0 (^{13}C). Enantiomer purity was determined by HPLC on a CHIRALPAK IA-3 column (250 mm, 4.6 mm, 3 μm) using hexane/*i*PrOH/TFA, 80:20:0.1 as a mobile phase (flow rate 1 mL/min, λ = 264 nm). IR spectra were obtained on neat samples (ATR spectroscopy). High-resolution mass spectra were recorded on an ESI-TOF MS spectrometer. Optical rotations were obtained at a wavelength of 589 nm using a 1.0 dm cell.

(*R*)-*N*-Benzyl-*N*-(methoxymethyl)-1-phenylethan-1-amine [(*R*)-1]: Paraformaldehyde (16.0 g, 532 mmol) was added to a mixture of (*R*)-*N*-benzyl-1-phenylethan-1-amine (102.1 g, 483 mmol) and potassium carbonate (1.34 g, 9.67 mmol) in MeOH (196 mL, 4.83 mol) at 10 °C. The reaction mixture was stirred for 30 min at 10 °C and 2 h at room temperature. The reaction mixture was diluted with DCM (400 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by vacuum distillation (120 °C, 2.5×10^{-3} mbar) to provide (*R*)-**1** as a colorless oil; yield 97.3 g (79%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.8 Hz, 3 H), 3.14 (s, 3 H), 3.72 (d, *J* = 13.6 Hz, 1 H), 3.77 (d, *J* = 13.6 Hz, 1 H), 3.93 (d, *J* = 9.4 Hz, 1 H), 4.07 (q, *J* = 6.8 Hz, 1 H), 4.19 (d, *J* = 9.4 Hz, 1 H), 7.16–7.35 (m, 8 H), 7.39–7.45 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 52.6, 55.0, 59.2, 82.5, 126.76, 126.83, 127.5, 128.1, 128.2, 128.8, 139.8, 145.0 ppm. IR (neat): $\tilde{\nu}$ = 3027, 2973, 1602, 1493, 1452, 1165, 1062, 1028, 912, 761, 739, 696 cm^{-1}. $[\alpha]_D^{20}$ = +4.9 (c 5.0, MeOH).

(*S*)-*N*-Benzyl-*N*-(methoxymethyl)-1-phenylethan-1-amine [(*S*)-1]: N,O-Acetal (*S*)-**1** was prepared according (*R*)-**1** using (*S*)-*N*-benzyl-1-phenylethan-1-amine as starting material. Colorless oil; yield 78%; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.8 Hz, 3 H), 3.16 (s, 3 H), 3.72 (d, *J* = 13.6 Hz, 1 H), 3.78 (d, *J* = 13.6 Hz, 1 H), 3.94 (d, *J* = 9.4 Hz, 1 H), 4.07 (q, *J* = 6.8 Hz, 1 H), 4.19 (d, *J* = 9.4 Hz, 1 H), 7.17–7.37 (m, 8 H), 7.40–7.46 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 52.6, 54.9, 59.2, 82.4, 126.75, 126.82, 127.5, 128.1, 128.2, 128.8, 139.7, 145.0 ppm. IR (neat): $\tilde{\nu}$ = 3027, 2973, 1602, 1493, 1452, 1165, 1063, 1028, 911, 761, 739, 696 cm^{-1}. $[\alpha]_D^{20}$ = –5.0 (c 5.0, MeOH).

(*S*)-*N*-Benzyl-*N*-(isopropoxymethyl)-1-phenylethan-1-amine [(*S*)-2]: N,O-Acetal (*S*)-**2** was prepared according (*S*)-**1** using *i*PrOH as starting material. Amorphous solid; yield 59%; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 6.2 Hz, 6 H), 1.45 (d, *J* = 6.8 Hz, 3 H), 3.44 (hept, *J* = 6.2 Hz, 1 H), 3.68 (d, *J* = 13.5 Hz, 1 H), 3.75 (d, *J* = 13.5 Hz, 1 H), 3.96 (d, *J* = 9.4 Hz, 1 H), 4.07 (q, *J* = 6.8 Hz, 1 H), 4.25 (d, *J* = 9.4 Hz, 1 H), 7.17–7.37 (m, 8 H), 7.39–7.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 22.3, 22.4, 52.4, 59.1, 68.1, 78.5, 126.67, 126.74, 127.5, 128.1, 128.2, 128.8, 140.1, 145.4 ppm. IR (neat): $\tilde{\nu}$ = 3028, 2969, 1602, 1493, 1453, 1367, 1162, 1023, 1003, 955, 910, 761, 738, 696 cm^{-1}. $[\alpha]_D^{20}$ = –4.8 (c 5.0, *i*PrOH).

Diastereoselective Mannich Reaction with Isovaleraldehyde. General Procedure for Proline Catalysts C2, C3, C4: D-Proline **C3** (23 mg, 0.2 mmol) was stirred in DMF (4 mL) at room temperature for 5 min. Next, isovaleraldehyde (172 mg, 2.0 mmol) and N,O-acetal (*S*)-**1** (255 mg, 1.0 mmol) were added at –25 °C. The conversion of 20% and the *dr* of 28:72 (*S*,*S*):(*R*,*S*) were determined by ^1H NMR [**(*S*,*S*)-3** 8.94 ppm, (*R*,*S*)-**3** 9.39 ppm, isovaleraldehyde 9.75 ppm] of the reaction mixture after 2 h.

Diastereoselective Mannich Reaction with Isovaleraldehyde. General Procedure for Diarylprolinol Catalysts C5-C16: The Hayashi catalyst **C9** (65 mg, 0.2 mmol), LiBr (35 mg, 0.4 mmol) and AcOH (12 mg, 0.2 mmol) were stirred in DMF (4 mL) at room temperature for 5 min. Next, isovaleraldehyde (172 mg, 2.0 mmol) and N,O-acetal (*S*)-**1** (255 mg, 1.0 mmol) were added at –25 °C. The conversion of 80% and the *dr* of 92:8 (*S*,*S*):(*R*,*S*) were determined by ^1H NMR [**(*S*,*S*)-3** 8.94 ppm, **(*R*,*S*)-3** 9.39 ppm, isovaleraldehyde 9.75 ppm] of the reaction mixture after 2 h.

3-*tert*-Butoxypropanal (4): To a mixture of *p*-toluenesufonic acid monohydrate (7.61 g, 0.040 mol) in *tert*-butanol (741 g, 10.0 mol) was added acrolein ethylene acetal (100.1 g, 2.00 mol) and stirred at room temperature for 24 h. The reaction mixture was quenched with a solution of saturated $NaHCO_3$ (1000 mL) and extracted with TBME (1000/500/500 mL). The organic layers were washed with brine, dried with $MgSO_4$, and concentrated. The residue was diluted with a solution of AcOH (10% in H_2O, 1300 mL) and heated to 85 °C for 2 h. After cooling to room temperature the mixture was extracted with diethyl ether (1000/500/500 mL). The organic layers were washed with a solution of K_2CO_3 (10% in H_2O, 3 × 500 mL), dried with $MgSO_4$, and concentrated. The residue was once more diluted with a solution of AcOH (10% in H_2O, 1300 mL) and heated to 85 °C for 2 h. After workup as described above the crude product was purified by vacuum distillation (65 °C, 40 mbar) to provide **4** as a colorless liquid; yield 110.2 g (42%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 2.60 (td, *J* = 6.1, 1.9 Hz, 2 H), 3.71 (t, *J* = 6.1 Hz, 2 H), 9.78 (t, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 44.4, 55.7, 73.2, 202.1 ppm. IR (neat): $\tilde{\nu}$ = 2974, 1725, 1465, 1391, 1363, 1195, 1088, 976, 864 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_7H_{14}O_2Na^+$ 153.0886 $[M + Na]^+$, found 153.0887.

(*R*,*R*)-6 and (*S*)-3-{Benzyl[(*R*)-1-phenylethyl]amino}-2-(*tert*-butoxymethyl)propan-1-ol [(*S*,*R*)-6]: A suspension of D-proline **C3** (4.61 g, 40 mmol) in DMF (400 mL) was stirred at room temperature overnight. Aldehyde **4** (52.1 g, 400 mmol) was added to the reaction mixture at –25 °C followed by the addition of N,O-acetal (*R*)-**1** (51.1 g, 200 mmol). The reaction mixture was stirred at –25 °C for 18 h. $NaBH_4$ (22.7 g, 600 mmol) was added at < –20 °C followed by dropwise addition of MeOH (130 mL). The reaction mixture was stirred at –25 °C for 30 min and at 0 °C for 2 h. The reaction mixture was slowly poured into a solution of saturated NH_4Cl (700 mL) at <5 °C. The mixture was allowed to stir at 0 °C for 30 min and at room temperature for 1 h. The mixture was extracted with TBME (600/200 mL) and the organic layers were washed with H_2O (300 mL) and brine (300 mL). The organic layers were dried with $MgSO_4$, and concentrated. The diastereoisomers (*dr* of 83:17 in the crude product) were separated by column chromatography (EtOAc/heptane, 2:8) to provide (*R*,*R*)-**6** and (*S*,*R*)-**6** as colorless oils.

(*R*,*R*)-6: Yield 47.1 g (66%); *dr* >99.5:0.5; R_f = 0.25 (EtOAC/heptane, 2:8); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 9 H), 1.37 (d, *J* = 6.9 Hz, 3 H), 1.99–2.16 (m, 1 H), 2.32 (dd, *J* = 12.9, 9.4 Hz, 1 H), 2.54 (dd, *J* = 12.9, 5.3 Hz, 1 H), 3.14 (dd, *J* = 8.8, 7.6 Hz, 1 H), 3.30 (dd, *J* = 8.8, 4.9 Hz, 1 H), 3.40 (dd, *J* = 10.7, 5.6 Hz, 1

H), 3.46 (d, *J* = 13.5 Hz, 1 H), 3.54 (dd, *J* = 10.7, 5.3 Hz, 1 H), 3.70 (d, *J* = 13.5 Hz, 1 H), 3.90 (s, 1 H), 3.98 (q, *J* = 6.9 Hz, 1 H), 7.20–7.38 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 27.4, 38.6, 49.6, 54.8, 56.7, 63.4, 66.1, 73.0, 127.0, 127.1, 128.10, 128.13, 128.4, 129.0, 139.6, 142.6 ppm. IR (neat): $\tilde{\nu}$ = 3431, 3027, 2971, 1602, 1493, 1452, 1362, 1196, 1072, 1025, 748, 730, 697 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{34}NO_2$ 356.2584 [M + H]$^+$, found 356.2588. $[\alpha]_D^{20}$ = –13.8 (c 2.0, $CHCl_3$).

(*S*,*R*)-6: Yield 7.09 g (10%); *dr* 99.5:0.5; R_f = 0.18 (EtOAc/heptane, 2:8); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 2.06–2.20 (m, 1 H), 2.30 (dd, *J* = 13.0, 5.4 Hz, 1 H), 2.50 (dd, *J* = 13.0, 8.9 Hz, 1 H), 3.02 (dd, *J* = 8.9, 7.4 Hz, 1 H), 3.22 (d, *J* = 13.6 Hz, 1 H), 3.29 (dd, *J* = 8.9, 5.0 Hz, 1 H), 3.54 (dd, *J* = 10.5, 6.3 Hz, 1 H), 3.64 (dd, *J* = 10.5, 5.3 Hz, 1 H), 3.80 (d, *J* = 13.6 Hz, 1 H), 3.98 (q, *J* = 7.0 Hz, 1 H), 4.48 (s, 1 H), 7.20–7.38 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 27.3, 38.4, 50.7, 54.8, 57.5, 63.5, 66.8, 73.0, 127.0, 127.1, 128.0, 128.4, 128.5, 129.0, 139.5, 140.8 ppm. IR (neat): $\tilde{\nu}$ = 3431, 3028, 2971, 1602, 1493, 1452, 1362, 1196, 1073, 1026, 748, 730, 697 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{34}NO_2$ 356.2584 [M + H]$^+$, found 356.2594. $[\alpha]_D^{20}$ = +58.4 (c 2.0, $CHCl_3$).

(9*H*-Fluoren-9-yl)methyl (*R*)-[3-(*tert*-Butoxy)-2-(hydroxymethyl)-propyl]carbamate [(*R*)-7]: To a mixture of alcohol (*R*,*R*)-**6** (46.9 g, 131.9 mmol) and Pd/C 10% (4.69 g) in MeOH (1400 mL) was added ammonium formate (41.6 g, 659 mmol) and stirred at 50 °C for 8 h. The mixture was cooled to room temperature, filtered through celite with an excess of MeOH, and concentrated to yield the deprotected amine as a slightly yellow oil. The product was dissolved in DCM (1 L). Triethylamine (26.7 g, 264 mmol) and Fmoc-OSu (43.6 g, 129.3 mmol) was added at 0 °C and stirred 3 h at this temperature. The reaction mixture was extracted with solutions of $NaHSO_4$ (10% in H_2O, 700 mL), saturated $NaHCO_3$ (200 mL) and H_2O (200 mL). The aqueous layers were extracted consecutively with DCM (200 mL). The combined organic layers were dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc/heptane, 1:1) to provide (*R*)-**7** as a colorless oil; yield 49.2 g (97%); R_f = 0.35 (EtOAc/heptane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 1.59 (br. s 0.1 H), 1.89 (hept, *J* = 5.4 Hz, 0.9 H), 3.13 (t, *J* = 5.9 Hz, 1 H), 3.33 (q, *J* = 6.1 Hz, 2 H), 3.44 (d, *J* = 5.4 Hz, 2 H), 3.62 (t, *J* = 5.4 Hz, 2 H), 4.20 (t, *J* = 6.8 Hz, 1 H), 4.35–4.45 (m, 1.8 H), 4.46–4.57 (m, 0.2 H), 5.04 (br. s 0.1 H), 5.32 (t, *J* = 5.8 Hz, 0.9 H), 7.29 (td, *J* = 7.4, 1.1 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.58 (d, *J* = 7.4 Hz, 2 H), 7.75 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 40.2, 41.3, 47.3, 62.5, 62.9, 66.6, 73.3, 120.0, 125.0, 127.0, 127.7, 141.3, 143.9, 157.3 ppm. IR (neat): $\tilde{\nu}$ = 335, 3284, 2971, 2932, 2873, 1697, 1517, 1449, 1363, 1246, 1193, 1075, 1007, 758, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{29}NO_4Na$ 406.1989 [M + Na]$^+$, found 406.1995. $[\alpha]_D^{20}$ = –9.3 (c 2.0, $CHCl_3$).

(9*H*-Fluoren-9-yl)methyl (*S*)-[3-(*tert*-Butoxy)-2-(hydroxymethyl)-propyl]carbamate [(*S*)-7]: Colorless oil; yield 95%; R_f = 0.35 (EtOAc/heptane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 1.59 (br. s 0.1 H), 1.89 (hept, *J* = 5.5 Hz, 0.9 H), 3.17 (t, *J* = 6.1 Hz, 1 H), 3.33 (q, *J* = 6.1 Hz, 2 H), 3.44 (d, *J* = 5.5 Hz, 2 H), 3.62 (t, *J* = 5.5 Hz, 2 H), 4.19 (t, *J* = 6.9 Hz, 1 H), 4.35–4.45 (m, 1.8 H), 4.46–4.57 (m, 0.2 H), 5.10 (br. s 0.1 H), 5.36 (t, *J* = 5.9 Hz, 0.9 H), 7.29 (td, *J* = 7.4, 1.1 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.58 (d, *J* = 7.4 Hz, 2 H), 7.74 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 40.2, 41.3, 47.3, 62.5, 62.9, 66.6, 73.3, 120.0, 125.0, 127.0, 127.7, 141.3, 143.9, 157.3 ppm. IR (neat): $\tilde{\nu}$ = 3352, 3280, 2971, 2933, 2873, 1697, 1517, 1449, 1363, 1246, 1193, 1075, 1007, 758, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{29}NO_4Na$ 406.1989 [M + Na]$^+$, found 406.2000. $[\alpha]_D^{20}$ = +9.4 (c 2.0, $CHCl_3$).

(*S*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-2-(*tert*-butoxymethyl)propanoic Acid [(*S*)-8]: A mixture of alcohol (*R*)-**7** (48.9 g, 127.4 mmol) and TEMPO (1.39 g, 8.92 mmol) in ACN (650 mL) and phosphate buffer (430 mL, 0.67 mol/L, pH = 6.7) was heated to 35 °C. Solutions of sodium chlorite [23.0 g (*w* = 80%) in 130 mL of H_2O, 255 mmol] and sodium hypochlorite [1.46 g (*w* = 13%) in 65 mL of H_2O] were added simultaneously over 2 h. The mixture was stirred at 35 °C for 4 h. The mixture was cooled to room temperature, diluted with H_2O (400 mL), and the pH was adjusted to 8.0 with a 2 M aqueous solution of NaOH. The reaction was quenched by pouring into a 0.5 M aqueous solution of Na_2SO_3 at <20 °C and stirred for 30 min at this temperature. The mixture was extracted with TBME (800/400 mL) and washed with a 0.1 M aqueous solution of Na_2SO_3 (200 mL). The combined organic layers were diluted with TBME (800 mL) and acidified to pH 3 with a 2 M aqueous solution of HCl. The layers were separated and the aqueous layer extracted with TBME (400 mL). The organic layers were washed with H_2O (400 mL), dried with $MgSO_4$, and concentrated. The residue was twice diluted with DCM (300 mL), concentrated, and dried under high vacuum to provide (*S*)-**8** as an amorphous white solid; yield 45.64 g (90%); *er* 99.8:0.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 2.25 H), 1.18 (s, 6.75 H), 2.47–2.64 (m, 0.25 H), 2.82 (p, *J* = 5.5 Hz, 0.75 H), 3.26–3.78 (m, 4 H), 4.15–4.27 (m, 1 H), 4.28–4.41 (m, 1.5 H), 4.42–4.54 (m, 0.5 H), 5.54 (t, *J* = 5.8 Hz, 0.75 H), 6.30–6.47 (m, 0.25 H), 7.28 (t, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.57 (d, *J* = 7.4 Hz, 2 H), 7.73 (d, *J* = 7.4 Hz, 2 H), 10.92 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 40.0, (40.4), 45.8, (46.4), 47.2, (60.3), 60.7, 66.8, (67.3), (73.5), 74.1, 120.0, 125.1, 127.0, 127.7, 141.3, 143.9, 156.6, (157.6), (176.5), 176.8 ppm. IR (neat): $\tilde{\nu}$ = 3342, 3250, 2971, 1705, 1517, 1449, 1363, 1232, 1190, 1080, 758, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{27}NO_5Na$ 420.1781 [M + Na]$^+$, found 420.1782. $[\alpha]_D^{20}$ = +7.3 (c 2.0, $CHCl_3$).

(*R*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-2-(*tert*-butoxymethyl)propanoic Acid [(*R*)-8]: Amorphous white solid; yield 88%; *er* 99.6:0.4; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 2.25 H), 1.18 (s, 6.75 H), 2.47–2.64 (m, 0.25 H), 2.82 (p, *J* = 5.7 Hz, 0.75 H), 3.26–3.78 (m, 4 H), 4.15–4.27 (m, 1 H), 4.28–4.41 (m, 1.5 H), 4.42–4.54 (m, 0.5 H), 5.54 (t, *J* = 5.9 Hz, 0.75 H), 6.30–6.47 (m, 0.25 H), 7.28 (t, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.57 (d, *J* = 7.4 Hz, 2 H), 7.74 (d, *J* = 7.4 Hz, 2 H), 10.92 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 40.0, (40.4), 45.8, (46.3), 47.2, (60.3), 60.7, 66.8, (67.3), (73.5), 74.1, 120.0, 125.1, 127.0, 127.7, 141.3, 143.9, 156.6, (157.6), (176.5), 176.8 ppm. IR (neat): $\tilde{\nu}$ = 3340, 3249, 2972, 1705, 1517, 1449, 1363, 1232, 1191, 1081, 758, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{27}NO_5Na$ 420.1783 [M + Na]$^+$, found 420.1782. $[\alpha]_D^{20}$ = –7.1 (c 2.0, $CHCl_3$).

(*R*)-3-*tert*-Butoxybutanal (9): To a solution of ethyl (*R*)-3-hydroxybutyrate (24.1 g, 188 mmol) and *tert*-butyl 2,2,2-trichloroacetimidate (82.2 g, 376 mmol) in pentane (400 mL) was added DCM (50 mL). Trifluoromethanesulfonic acid (0.14 g, 0.94 mmol) was added at –70 °C and let slowly warmed to –60 °C whereby a suspension was formed. The reaction mixture was stirred at –60 °C for 1 h and after warmed to room temperature. The suspension was diluted with cyclohexane (300 mL), filtered, and concentrated. The crude product was purified by vacuum distillation (56 °C, 5 mbar) to provide ethyl (*R*)-3-*tert*-butoxybutyrate as a colorless liquid; yield 23.3 g (66%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.1 Hz, 3 H) 1.19 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 2.35 (dd, *J* =

14.5, 7.1 Hz, 1 H), 2.50 (dd, *J* = 14.5, 6.2 Hz, 1 H), 3.94–4.27 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 23.4, 28.4, 44.4, 60.2, 64.8, 73.8, 171.8 ppm. IR (neat): $\tilde{\nu}$ = 2976, 2936, 1734, 1465, 1367, 1180, 1077, 1033, 995 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{10}H_{20}O_3Na$ 211.1305 [M + Na]$^+$, found 211.1304. $[\alpha]_D^{20}$ = –15.8 (c 2.0, $CHCl_3$).

To a solution of ethyl (*R*)-3-*tert*-butoxybutyrate (21.7 g, 115 mmol) in pentane/diethyl ether, 9:1 (400 mL) was added dropwise a solution of DIBAL (1.0 M in cyclohexane, 132 mL, 132 mmol) at –70 °C and stirred at this temperature for 3 h. The reaction was quenched by the addition of MeOH (50 mL) and stirred at –70 °C for 10 min. The reaction mixture was warmeded to 0 °C and poured into a solution of saturated aqueous NH_4Cl (400 mL) and warmed to room temperature. The mixture was diluted with H_2O (200 mL) and extracted with TBME (400/200/200 mL). The organic layers were washed with brine (200 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by vacuum distillation (51 °C, 15 mbar) to provide **9** as a colorless liquid; yield 9.40 g (57%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 2.48 (ddd, *J* = 15.9, 6.2, 2.3 Hz, 1 H), 2.58 (ddd, *J* = 15.9, 6.2, 2.3 Hz, 1 H), 4.15 (h, *J* = 6.2 Hz, 1 H), 9.79 (t, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8, 28.4, 52.6, 63.3, 74.0, 202.3 ppm. IR (neat): $\tilde{\nu}$ = 2976, 1729, 1465, 1391, 1365, 1195, 1088, 976, 864 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_{16}O_2Na^+$ 167.1043 [M + Na]$^+$, found 167.1046.

(2*R*,3*R*)-2-({Benzyl[(*R*)-1-phenylethyl]amino}methyl)-3-(*tert*-butoxy)butan-1-ol [(*R*,*R*)-11]: A suspension of D-proline **C3** (230 mg, 2.00 mmol) in DMF (20 mL) was stirred at room temperature for 1 h. Aldehyde **9** (2.88 g, 20.0 mmol) was added to the reaction mixture at –25 °C followed by the addition of N,O-acetal (*R*)-**1** (2.55 g, 10.0 mmol). The reaction mixture was stirred at –25 °C for 18 h. $NaBH_4$ (1.14 g, 30.0 mmol) was added at < –20 °C followed by dropwise addition of MeOH (6 mL). The reaction mixture was stirred at –25 °C for 30 min and at 0 °C for 2 h. The reaction mixture was slowly poured into a solution of saturated aqueous NH_4Cl (35 mL) at <5 °C. The mixture was allowed to stir at 0 °C for 30 min and at room temperature for 1 h. The mixture was extracted with TBME (100/50/50 mL) and the organic layers were washed with H_2O (50 mL) and brine (50 mL). The organic layers were dried with $MgSO_4$, and concentrated. The crude product (*dr* 73:27) was purified by column chromatography [EtOAc/DCM/heptane, 2:3:5] to provide (*R*,*R*)-**11** as a colorless oil; yield 1.67 g (45%); *dr* 99:1; R_f = 0.53 [EtOAc/DCM/heptane, 2:3:5]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.4 Hz, 3 H), 1.15 (s, 9 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 2.02–2.14 (m, 1 H), 2.24 (dd, *J* = 13.0, 8.8 Hz, 1 H), 2.39 (dd, *J* = 13.0, 5.8 Hz, 1 H), 3.32 (dd, *J* = 10.6, 6.0 Hz, 1 H), 3.55 (s, 2 H), 3.56 (dd, *J* = 10.6, 7.4 Hz, 1 H), 3.63–3.76 (m, 1 H), 3.97 (q, *J* = 6.9 Hz, 1 H), 4.39 (s, 1 H), 7.15–7.43 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 18.0, 28.3, 43.3, 49.6, 54.8, 57.1, 64.0, 68.7, 73.9, 127.05, 127.11, 128.1, 128.2, 128.4, 129.1, 139.4, 142.0 ppm. IR (neat): $\tilde{\nu}$ = 3472, 3028, 2971, 1602, 1493, 1451, 1365, 1195, 1120, 1072, 1028, 1005, 748, 730, 698 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{24}H_{36}NO_2$ 370.2741 [M + H]$^+$, found 370.2742. $[\alpha]_D^{20}$ = –1.0 (c 2.0, $CHCl_3$).

(9*H*-Fluoren-9-yl)methyl [(2*R*,3*R*)-3-(*tert*-Butoxy)-2-(hydroxymethyl)butyl]carbamate [(*R*)-12]: To a mixture of alcohol (*R*,*R*)-**11** (1103 mg, 3.00 mmol) and Pd/C 10% (222 mg) in MeOH (40 mL) was added ammonium formate (1.89 g, 30.0 mmol) and stirred at 50 °C for 5 h. The mixture was cooled to room temperature, filtered through celite with an excess of MeOH, and concentrated to yield the deprotected amine as slightly yellow oil. The product was dissolved in DCM (25 mL). Triethylamine (607 mg, 6.00 mmol) and Fmoc-OSu (961 mg, 2.85 mmol) was added at 0 °C and stirred 4 h at this temperature. The reaction mixture was diluted with EtOAc and extracted with a solution of $NaHSO_4$ (10% in H_2O, 100 mL), a solution of saturated aqueous $NaHCO_3$ (100 mL) and H_2O (100 mL). The aqueous layers were extracted consecutively with EtOAc (50 mL). The combined organic layers were dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc/heptane, 4:6) to provide (*R*)-**12** as a colorless oil; yield 918 mg (77%); R_f = 0.25 (EtOAc/heptane, 4:6); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 9 H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.70 (dt, *J* = 10.7, 5.4 Hz, 1 H), 3.15–3.26 (m, 1 H), 3.37–3.48 (m, 1 H), 3.52–3.68 (m, 2 H), 3.77–3.88 (m, 1 H), 4.20 (t, *J* = 6.8 Hz, 1 H), 4.35–4.47 (m, 1.9 H), 4.48–4.53 (m, 0.1 H), 5.11 (br. s 0.05 H), 5.31–5.46 (m, 0.95 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.59 (d, *J* = 7.3 Hz, 2 H), 7.75 (d, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 28.6, 38.7, 46.8, 47.3, 61.6, 66.6, 68.2, 74.1, 120.0, 125.0, 127.0, 127.6, 141.3, 143.9, 144.0, 157.3 ppm. IR (neat): $\tilde{\nu}$ = 3391, 3280, 2972, 2935, 2892, 1698, 1515, 1449, 1365, 1250, 1191, 1075, 1006, 758, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{24}H_{31}NO_4Na$ 420.2145 [M + Na]$^+$, found 420.2154. $[\alpha]_D^{20}$ = –19.5 (c 2.0, $CHCl_3$).

(2*S*,3*R*)-2-[({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)methyl]-3-(*tert*-butoxy)butanoic Acid [(*S*)-13]: To a solution of alcohol (*R*)-**12** (648 mg, 1.63 mmol) in acetone (15 mL) was added Jones reagent (0.5 M $Na_2Cr_2O_7$ in 2 M aqueous H_2SO_4, 6.5 mL, 3.25 mmol) at 0 °C. The reaction was allowed to stir at 0 °C for 1 h and at room temperature for 3 h. The reaction was quenched by addition of *i*PrOH (5 mL) and stirred at room temperature for 20 min. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (100/50/50 mL). The organic layers were washed with H_2O (3× 50 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography (AcOH/EtOAc/heptane, 2:30:70). The residue was twice diluted with DCM (10 mL), concentrated, and dried under high vacuum to provide (*S*)-**13** as an amorphous white solid; yield 498 mg (74%); R_f = 0.35 (AcOH/EtOAc/heptane, 2:30:70); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08–1.20 (m, 1.8 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.27 (s, 7.2 H), 2.5 (br. s 0.2 H), 2.74 (dt, *J* = 8.3, 4.1 Hz, 0.8 H), 3.27 (ddd, *J* = 13.8, 9.0, 4.7 Hz, 1 H), 3.46 (ddd, *J* = 12.0, 8.1, 3.9 Hz, 1 H), 3.82–3.93 (m, 0.2 H), 3.96–4.11 (m, 0.8 H), 4.19 (t, *J* = 7.0 Hz, 1 H), 4.28–4.48 (m, 1.8 H), 4.49–4.53 (m, 0.2 H), 5.47–5.66 (m, 0.8 H), 6.44 (br. s 0.2 H), 7.30 (dt, *J* = 7.4, 1.1 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.57 (d, *J* = 7.4 Hz, 2 H), 7.75 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, (21.3), 28.2, (28.3), 39.3, 47.2, 51.8, (53.0), 66.9, 67.1, (67.3), (74.5), 76.3, 120.0, 125.1, 127.0, 127.7, 141.3, (143.6), 143.8, 143.9, 156.5, (157.8), 174.9, 175.9 ppm. IR (neat): $\tilde{\nu}$ = 3339, 3241, 2973, 1706, 1515, 1449, 1365, 1232, 1190, 1083, 758, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{24}H_{29}NO_5Na$ 434.1938 [M + Na]$^+$, found 434.1948. $[\alpha]_D^{20}$ = +6.4 (c 2.0, $CHCl_3$).

3-(*tert*-Butylthio)propanal (14): To a solution 2-methyl-2-propanethiol (36.1 g, 400 mmol) was added acrolein (31.4 g, 560 mmol) and triethylamine (10.1 g, 100 mmol) at 0 °C. The mixture was allowed to stir at 0 °C for 2 h and at room temperature overnight. The reaction mixture was concentrated, and the crude product was purified by vacuum distillation (59 °C, 5 mbar) to provide **14** as a colorless liquid; yield 50.3 g (86%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 2.67–2.74 (m, 2 H), 2.77–2.85 (m, 2 H), 9.78 (t, *J* = 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 30.8, 42.5, 43.7, 200.7 ppm. IR (neat): $\tilde{\nu}$ = 2962, 2724, 1723, 1460, 1365, 1163, 1054, 1025, 853 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_7H_{14}OSNa^+$ 169.0658 [M + Na]$^+$, found 169.0657.

(*R*)-3-{Benzyl[(*R*)-1-phenylethyl]amino}-2-[(*tert*-butylthio)methyl]-propan-1-ol [(*R*,*R*)-16]: A suspension of D-proline **C3** (173 mg, 1.5 mmol) in DMF (15 mL) was stirred at room temperature for 1 h. Aldehyde **14** (1.95 g, 15.0 mmol) was added to the reaction mixture at –25 °C followed by the addition of N,O-acetal (*R*)-**1** (1.92 g, 7.50 mmol). The reaction mixture allowed stirred at –25 °C for 18 h. $NaBH_4$ (0.85 g, 22.5 mmol) was added at < –20 °C followed by dropwise addition of MeOH (6 mL). The reaction mixture was stirred at –25 °C for 30 min and at 0 °C for 2 h. The reaction mixture was slowly poured into a solution of saturated aqueous NH_4Cl (25 mL) at 0 °C. The mixture was allowed to stir at 0 °C for 30 min and at room temperature for 1 h. The mixture was extracted with TBME (80/40/40 mL) and the organic layers were washed with H_2O (40 mL) and brine (40 mL). The organic layers were dried with $MgSO_4$, and concentrated. The crude product (*dr* 83:17) was purified by column chromatography (EtOAc/heptane, 1.5:8.5) to provide (*R*,*R*)-**16** as a colorless oil; yield 1.42 g (60%); *dr* >99.5:0.5; R_f = 0.30 (EtOAc/heptane, 1.5:8.5); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 9 H), 1.37 (d, J = 6.9 Hz, 3 H), 1.94–2.13 (m, 1 H), 2.18–2.36 (m, 2 H), 2.45 (dd, J = 12.9, 10.6 Hz, 1 H), 2.70 (dd, J = 12.9, 2.9 Hz, 1 H), 3.19 (dd, J = 10.7, 7.2 Hz, 1 H), 3.41 (d, J = 13.2 Hz, 1 H), 3.64 (dd, J = 10.3, 2.0 Hz, 1 H), 3.82 (d, J = 13.2 Hz, 1 H), 3.90–4.08 (m, 2 H), 7.11–7.39 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.9, 28.6, 30.8, 38.0, 42.0, 52.8, 54.9, 56.3, 66.7, 127.1, 127.3, 128.1, 128.2, 128.5, 129.1, 139.0, 142.5 ppm. IR (neat): $\tilde{\nu}$ = 3583, 3422, 3027, 2964, 1602, 1493, 1451, 1362, 1196, 1070, 1028, 748, 729, 697 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{23}H_{34}NOS$ 372.2356 $[M + H]^+$, found 372.2367. $[\alpha]_D^{20}$ = –77.9 (c 2.0, $CHCl_3$).

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