Asymmetric Synthesis of All Stereoisomers of α-Methylthreonine Using an Organocatalytic Steglich Rearrangement Reaction as a Key Step

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Abstract: An efficient synthetic route to all four stereoisomers of α-methylthreonine has been established. Each type of stereoisomer has been isolated in diastereomerically pure form and with an enantiomeric excess of at least 86% ee. The key step in this multi-step synthesis is an enantioselective organocatalytic Steglich rearrangement reaction of O-acetylated azlactones. The Steglich rearrangement was also extended to other substrates.

Key words: acylation, amino acids, asymmetric catalysis, rearrangements, stereoselective synthesis

α-Amino β-hydroxy acids **1** represent an important class of amino acids that occur naturally in proteinogenic (e.g. threonine, serine) and non-proteinogenic forms. Such types of molecules are also integrated as structural motifs in complex natural products such as antibiotics, e.g. vancomycin and chloramphemicol.[1] Furthermore, α-amino β-hydroxy acids are useful chiral building blocks in organic chemistry. The amino acids could be efficiently prepared by chemocatalytic as well as by enzymatic methods.[2] Another important class of amino acids are α,α-dialkylated amino acids **2**. As peptides containing these amino acids often show an enhanced stability under metabolic conditions, α,α-dialkylated amino acids are used in the synthesis of protein-based drugs, and numerous methods for their synthesis exist.[3]

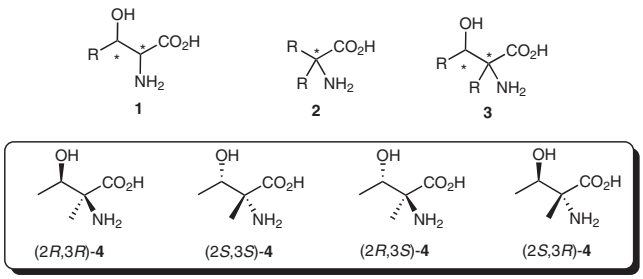

Figure 1 Structure of different types of amino acids **1**–**3** and all stereoisomers of α-methylthreonine **4**

The aim of our work was to prepare amino acids that combine the structural motifs of both the above mentioned classes of amino acids, namely β-hydroxy α-amino acids bearing a quaternary α-carbon of type **3**. Although elegant stereoselective methods for their preparation already exist,[4a–g] the synthesis of such types of amino acids **3** is still challenging. One of the most important representatives of this class is α-methylthreonine (**4**; Figure 1), which is used as a key building block for the preparation of pharmaceutically relevant molecules such as potential enzyme inhibitors.[4h,i] Here we report a new synthetic route to all four stereoisomers of α-methylthreonine (**4**; Figure 1), in high enantiomeric excesses up to 89% by means of an organocatalytic enantioselective Steglich rearrangement reaction as a key step.[5]

The synthetic concept, which is shown in Scheme 1, is based on the use of azlactone **5** as an easily accessible starting material. The key step of this route is an enantioselective organocatalytic Steglich rearrangement, which represents an acyl migration (step B) from oxygen to carbon, thus forming a quarternary stereogenic center. Subsequent ring opening and diastereoselective reduction with borohydrides (steps C and D) then delivers the *l*-diastereomer as the major diastereomer. The formation of *l*-**9** as the major diastereomer was proven in preliminary work when starting from racemic product **7**.[5] Access to the minor diastereomers of type *u*-**9** should be given by inversion of the β-stereogenic center when starting from the *l*-diastereomer.

Since asymmetric Steglich rearrangement is the key step within this multi-step synthesis, we studied in detail the impact of different types of catalysts on this reaction. In our preliminary work we found that the dimethylaminopyridine derivative (*S*)-**10** and (*S*)-tetramisole [(*S*)-**12**] were able to catalyse this reaction enantioselectively.[5] Encouraged by these results, we focused on a detailed investigation of these and related catalysts for enantioselective acyl migration according to step B in Scheme 1 starting from prochiral O-acetylated azlactone **6**.

To start with the commercially available catalysts (*S*)-**10** and (*S*)-**11**, which were developed by the Fu group and turned out to be highly efficient for a range of asymmetric reactions,[6] these compounds were employed as catalysts to give generally high conversions (up to 95%) at a low catalytic loading of only 2 mol% (Table 1). However, the resulting enantioselectivities remained in a moderate range and did not exceed 50% ee. In general, both higher enantioselectivities and higher conversions were obtained with the Fu-catalyst (*S*)-**11** compared to the initially tested catalyst (*S*)-**10**. For example, in the presence of 2 mol% of (*S*)-**10** in dichloromethane as a solvent, azlactone **6** rear-

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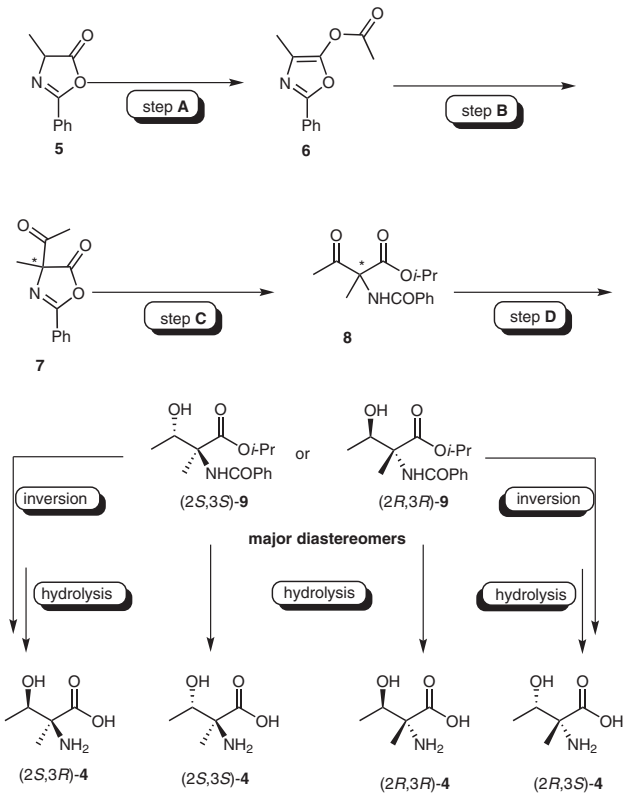
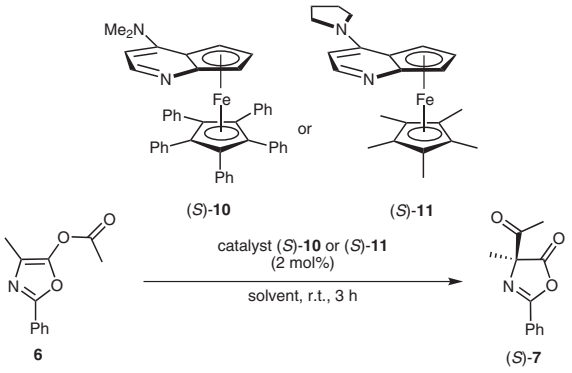


Scheme 1 Concept for the synthesis of all α-methylthreonine stereoisomers of type **4**

ranged to the desired key intermediate **7** with 84% conversion and 25% ee (Table 1, entry 1), whereas under identical reaction conditions the product (*S*)-**7** was formed with 95% conversion and 41% ee when using catalyst (*S*)-**11** (entry 3). When carrying out the reaction in *tert*-amyl alcohol (TAA), which was reported to be an excellent solvent for enantioselective Steglich rearrangements of alkoxycarbonyl and benzyloxycarbonyl groups,[6b] the enantioselectivity further increased up to 50% ee when using the Fu catalyst (*S*)-**11** (entry 5).

We observed a further improvement in the enantioselectivity when using (*S*)-tetramisole [(*S*)-**12**] as a catalyst. Notably, (*S*)-**12** represents an economically attractive and commercially readily available organocatalyst, since this molecule is produced on large scales for medicinal and veterinarian purposes in enantiomerically pure form as a hydrochloride under the trade name 'Levamisole'. As an organocatalyst, (*S*)-**12** was introduced by Birman et al. for kinetic resolution processes.[7] In the presence of a catalytic amount (32 mol%) of (*S*)-**12**, we observed enantioselectivities up to 63% ee in the asymmetric Steglich rearrangement of **6** (Table 2, entries 1 and 2). In order to further improve the reaction rate we increased the reaction temperature. Whereas at 40 °C the reaction was completed within one day, the enantioselectivity turned out to be somewhat lower (entry 3). A further catalyst with a related structure, which was also introduced by the Birman group, is (*R*)-benzotetramisole [(*R*)-**13**];[7] this catalyst can be easily synthesized (and is also commercially available).

Table 1 Enantioselective Acetyl Migration in Steglich Rearrangement Using Fu-Type Catalysts (*S*)-**10** and (*S*)-**11**[a]



Entry[a]	Catalyst	Solvent	Conv. (%)[b]	ee (%)[c]
1	(*S*)-**10**	CH_2Cl_2	84	25
2	(*S*)-**10**	*tert*-amyl alcohol	93	30
3	(*S*)-**11**	CH_2Cl_2	95	41
4	(*S*)-**11**	MTBE	92	20
5	(*S*)-**11**	*tert*-amyl alcohol	94	50

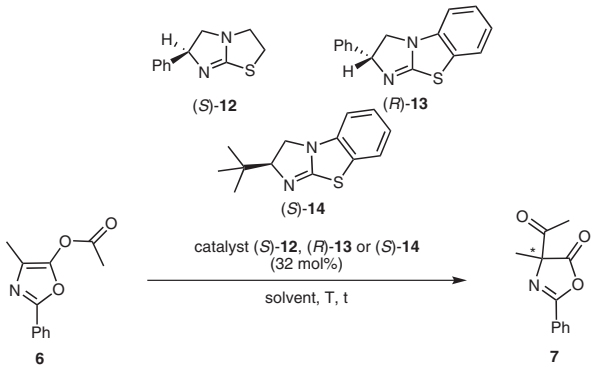
[a] For experimental details, see experimental section.
[b] All conversions given in the table are product-related conversions; consumption of substrate **6** was complete in all cases (>95%) according to NMR spectroscopic data.
[c] Enantiomeric excess was determined after DMAP-catalyzed ring opening to keto ester (*S*)-**8**.

When using (*R*)-**13** as an organocatalyst, similar conversion and enantioselectivity was obtained (up to 61% ee, entries 5–7). The catalyst (*R*)-**13** led to the opposite enantiomeric form of **7** compared to the use of (*S*)-tetramisole [(*S*)-**12**]. Since the *R*-enantiomer of tetramisole is not commercially available, (*R*)-benzotetramisole [(*R*)-**13**] represents an advantageous complementary catalyst to (*S*)-**12**, thus offering access to both enantiomers of the desired product **7** with enantiomeric excesses of about 60% ee by means of these organocatalysts (*S*)-**12** and (*R*)-**13**.

The introduction of a *tert*-butyl group into a chiral catalyst is a well-known technology in order to improve selectivity.[8] For this reason, we decided to examine the new tetramisole analogue catalyst (*S*)-**14** as an organocatalyst. This compound was synthesized in an analogous manner to (*R*)-**13**, starting from (*S*)-*tert*-leucinol instead of (*R*)-phenylglycinol. However, (*S*)-**14** showed very low catalytic activity in the Steglich rearrangement of **6** (entry 8); even after one week reaction time, conversion did not exceed 35%. Complete consumption of the substrate **6**, however, is essential, because the catalyst for the ring opening (DMAP) would otherwise rearrange the remaining substrate, leading to racemic product and thus decreasing the overall enantiomeric excess of the product **7**.

Next, we studied the substrate range of this type of asymmetric Steglich rearrangement. Toward this end, O-acylated azlactones **15a–d** were prepared via their azlactones from the corresponding amino acids (for details, see ex-

Table 2 Enantioselective Acetyl Migration in Steglich Rearrangement Using Birman-Type Catalysts [(*S*)-**12**, (*R*)-**13** and (*S*)-**14**][a]



Entry[a]	Catalyst	Solvent	Temp	Time (h)	Conv. (%)[b]	ee (%)[c]
1	(*S*)-**12**	CH_2Cl_2	r.t.	68	82	59
2	(*S*)-**12**	$CDCl_3$	r.t.	48	80	63
3	(*S*)-**12**	CH_2Cl_2	40 °C	24	84	52
4	(*S*)-**12**	TAA	r.t.	24	74	60
5	(*R*)-**13**	CH_2Cl_2	r.t.	96	69	50
6	(*R*)-**13**	$CDCl_3$	r.t.	48	79	61
7	(*R*)-**13**	TAA	r.t.	24	84	52
8	(*S*)-**14**	CH_2Cl_2	r.t.	168	35	n.d.[d]

[a] For experimental details, see experimental section.
[b] All conversions given in the table are product-related conversions; consumption of substrate **6** was in the range of 95–100%, except for entry 8 (93%) according to NMR spectroscopic data.
[c] Enantiomeric excess was determined after DMAP-catalyzed ring opening to keto ester **8**. The absolute configuration was *S* for entries 1–4 and *R* for entries 5–7.
[d] n.d. = not determined.

perimental section).[9] In these experiments we carried out the Steglich rearrangement of **15** under in situ-formation of **16**, followed by (non-selective) ring-opening to β-keto α-amino esters **17**. Yields and enantioselectivities were determined for **17a–d** (Table 3).

Azlactone **15a**, bearing an α-branched alkyl side chain on C4, did not undergo Steglich rearrangement using (*S*)-**11** as a chiral organocatalyst (Table 3, entry 1). This observation is in accordance with reports in the literature about Steglich rearrangements of alkoxycarbonyl and benzyloxycarbonyl groups.[10] In contrast, we were pleased to find that azlactone **15b**, bearing a sterically demanding isobutyl group at the C4-position of the azlactone, undergoes Steglich rearrangement with a high enantioselectivity of 85% ee when using (*S*)-**12** as a catalyst (entry 2). Reaction rates were, however, lower compared to those for azlactone **6**, bearing a methyl group, and yields are low due to decomposition in the ring-opening step.

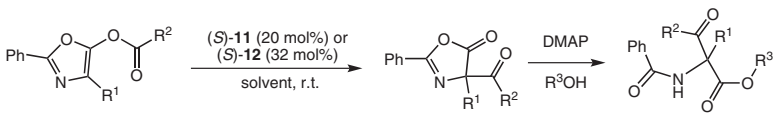
Furthermore, we tried to rearrange acyl groups other than acetyl. The rearrangement of the butanoyl group of substrate **15c** only worked when applying the Fu-type catalysts (*S*)-**10** and (*S*)-**11**. In addition, higher catalytic loadings (20 mol% compared to 2 mol% with substrate **6**) were required, and the enantioselectivity was lower. For example, the desired product **16c** was obtained at 80% conversion and with 24% ee when using 20 mol% of (*S*)-**11** as a catalyst (Table 3, entry 3). Tetramisole-type catalysts (*S*)-**12** and related (*R*)-**13** were not able to complete consumption of the substrate (data not shown). When using azlactone **15d**, bearing a benzoyl group, which would allow access to α-methyl β-phenyl serine, Steglich rearrangement only proceeded very slowly with catalyst (*S*)-**11** in a catalytic loading of 20 mol%. Complete consumption of **15d** was achieved after a reaction time of one week. Product-related conversion and yield, however, were only moderate even though the enantiomeric excess was comparable to those using substrate **6** (entry 4). In summary, it has been demonstrated that the Steglich rearrangement of several substrates proceeds enantioselectively, with O-acylated azlactone **6** being the most suitable substrate tested so far.

After successfully constructing the first stereogenic center (at the amino moiety) by means of Steglich rearrangement, the next step toward the desired stereoisomers of α-methylthreonine (**4**) required the development of a method for the construction of the second stereogenic center in the β-position via diastereoselective reduction of the keto moiety. Initial experiments were carried out using racemate *rac*-**8**. Initially, we tried to use borane as reducing agent, applying the CBS reduction methodology.[11,12] However, these reduction experiments were unsuccessful, and led to the formation of complex crude reaction mixtures due to side reactions (presumably, for example, reduction of the ester moiety in *rac*-**8**).

As we had good experiences using sodium borohydride as reducing agent during our initial synthesis of racemic α-methylthreonine,[5] we decided to continue using borohydrides as reducing agent. In 1979, Umino et al. reported that the use of enantiomerically pure N-protected amino acids as chiral additives to sodium borohydride leads to an enantioselective reduction of ketones.[13] Later, this method was enhanced by using three equivalents of an N-protected amino acid.[14] As *N*-Boc-proline was reported to be one of the most efficient additives, we reduced racemic β-keto-α-amino acid ester *rac*-**8** using sodium borohydride and three equivalents of L-*N*-Boc-proline as reducing agent. The diastereomeric ratio of the reaction improved to 80:20 (at 62% conversion) compared to 73:27 (at 100% conversion) when using only borohydride but, even more important, we were able to obtain the main product (*R*,*R*)-**9** with a conversion of 62%, in 40% yield and with an enantiomeric excess of 36% ee, thus indicating an asymmetric induction of the reducing agent (Scheme 2). Unfortunately, it was not possible to improve the relative low conversions by applying longer reaction times or more equivalents of the reducing agent.

These results showed that the combination of an enantioselective organocatalytic Steglich rearrangement and subsequent diastereoselective reduction using sodium

Table 3 Enantioselective Acyl Migration in Steglich Rearrangement of Azlactones **15a–d**[a]



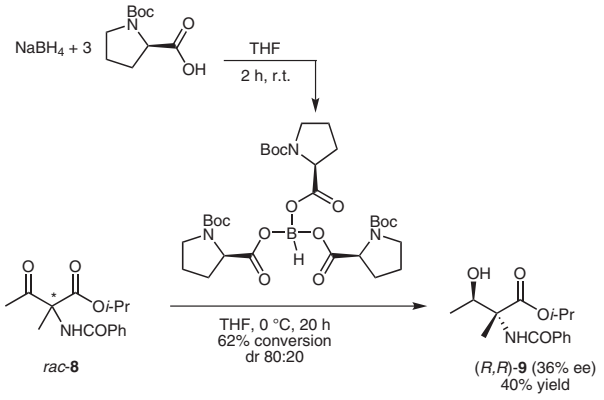
a R^1 = *i*-Pr, R^2 = Me, R^3 = *i*-Pr
b R^1 = *i*-Bu, R^2 = Me, R^3 = Me
c R^1 = Me, R^2 = *n*-Pr, R^3 = *i*-Pr
d R^1 = Me, R^2 = Ph, R^3 = *i*-Pr

Entry[a]	Substrate	Catalyst	Solvent	Time	Conv. to **16** (%)[b]	Yield of **17** (%)[c]	ee (%)[d]
1	**15a**	(*S*)-**11**	$CDCl_3$	7 d	<5	n.d.[e]	n.d.[e]
2	**15b**	(*S*)-**12**	TAA	75 h	59	17	85
3	**15c**	(*S*)-**11**	$CDCl_3$	24 h	80	54	24
4	**15d**	(*S*)-**11**	$CDCl_3$	7 d	48	29	45

[a] For experimental details, see experimental section.
[b] All conversions given in the table are product-related conversions; consumption of **15a–d** was complete in all cases (>90%) except entry 1 according to NMR spectroscopic data.
[c] Yield after chromatography.
[d] Enantiomeric excess was determined after DMAP-catalyzed ring opening to keto ester **17a–d**.
[e] n.d. = not determined.

borohydride and *N*-Boc-proline as reducing agent is a suitable and practical synthetic route towards (enantiomerically enriched) α-methylthreonine. Furthermore, asymmetric induction is possible at both stages, thus offering the potential for obtaining a high 'overall' enantiomeric excess.

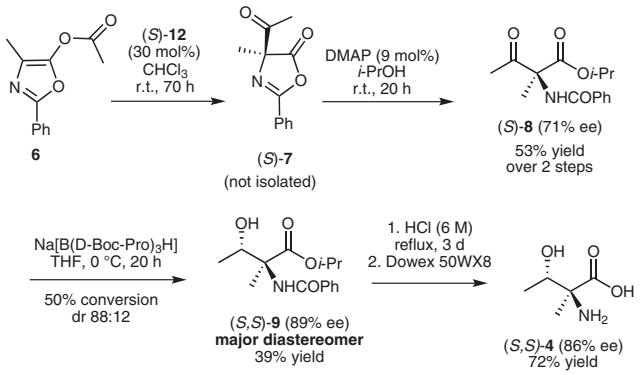
To prove the power of this new synthetic route and to study the suitability of enantiomerically enriched β-keto-α-amino acid ester **8** (resulting from asymmetric Steglich rearrangement) in the diastereoselective reduction, we focused on the synthesis of both enantiomers of *l*-α-methylthreonine in high enantiomeric excess starting from easily available azlactone **6** using this developed two-step synthesis (enantioselective organocatalytic Steglich rearrangement followed by diastereoselective reduction).



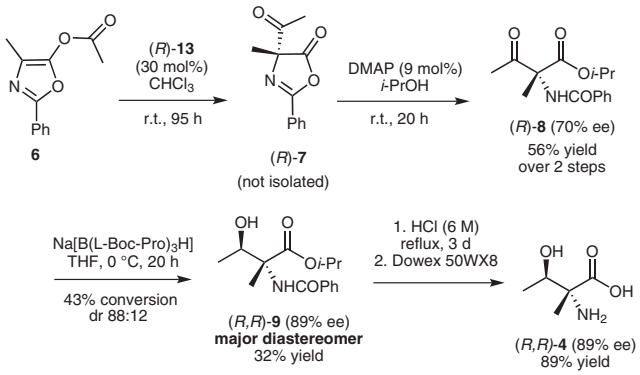
Scheme 2 Diastereoselective reduction of β-keto α-amino ester *rac*-**8**

For the synthesis of (*S*,*S*)-α-methylthreonine, we used (*S*)-tetramisole [(*S*)-**12**] in a catalytic amount of 30 mol% for initial enantioselective Steglich rearrangement in chloroform (Scheme 3). To ensure complete consumption of azlactone **6**, we applied a longer reaction time of 70 hours. After subsequent ring opening in the presence of DMAP as a catalyst and subsequent column chromatography, the β-keto ester (*S*)-**8** was obtained in 53% yield with an enantiomeric excess of 71% ee. The enantiomeric excess of the ester (*S*)-**8** in this experiment, which was performed on a 4.0 mmol scale, was higher compared to the enantiomeric excess obtained in the small scale experiment (0.23 mmol scale; see Table 2, entry 2), since the reaction time had been extended to ensure complete conversion. The reduction was carried out using sodium borohydride and D-Boc-proline as a chiral additive, leading to isopropyl (*S*,*S*)-2-benzoylamino-3-hydroxy-2-methylbutyrate [(*S*,*S*)-**9**] in 39% yield after chromatography. This reduction proceeded diastereoselectively, with a diastereomeric ratio of 88:12, yielding the product (*S*,*S*)-**9** with an enantiomeric excess of 89% ee. Hydrolysis of diastereomerically pure and enantiomerically enriched ester [(*S*,*S*)-**9**] with 86% ee gave diastereomerically pure (*S*,*S*)-α-methylthreonine [(*S*,*S*)-**4**] in 72% yield and with 86% ee.

(*R*,*R*)-α-Methylthreonine was prepared in an analogous manner using (*R*)-benzotetramisole [(*R*)-**13**] as catalyst for the Steglich rearrangement. The intermediate isopropyl (*R*)-2-benzoylamino-2-methyl-3-oxobutyrate [(*R*)-**8**] was obtained in 56% yield and with an enantiomeric excess of 70% ee after subsequent ring-opening (Scheme 4). Reduction with a sodium borohydride complex bearing L-Boc-proline as a ligand, led to isopropyl (*R*,*R*)-2-benzoylamino-3-hydroxy-2-methylbutyrate [(*R*,*R*)-**9**] in 32% yield as the major diastereomer in 89% ee after chromatography. Hydrolysis in hydrochloric acid and subsequent purification on ion-exchange resin led to diastereomeri-



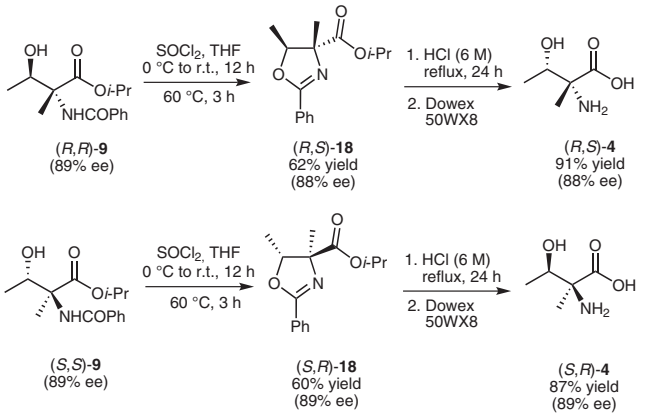
Scheme 3 Synthesis of (*S*,*S*)-α-methylthreonine [(*S*,*S*)-**4**]



Scheme 4 Synthesis of (*R*,*R*)-α-methylthreonine [(*R*,*R*)-**4**]

cally pure (*R*,*R*)-α-methylthreonine [(*R*,*R*)-**4**] in 89% yield and with 89% ee.

With respect to formation of the remaining two diastereomers, namely the *R*,*S*- and *S*,*R*-stereoisomers of α-methylthreonine (**4**), application of the diastereoselective reduction of **8** turned out to be difficult. Those diastereomers represent the minor diastereomers and attempts to reverse the diastereoselectivity in the reducing step were not successful. Thus, we focused on the preparation of the *R*,*S*- and *S*,*R*-diastereoisomers starting from the major *R*,*R*- and *S*,*S*-diastereoisomers, respectively, by inversion of the absolute configuration of the stereogenic centers in the β-position. Such a concept has previously been successfully applied by Hamada et al. for the inversion of configuration of the β-hydroxy group of a protected β-hydroxy α-amino acid of type **1** in the synthesis of all four stereoisomers of 3-hydroxyleucine.[15] Using this technique, preparation of oxazole **18** by dehydration with thionyl chloride, subsequent ring-opening and deprotection with hydrochloric acid, led to the desired remaining diastereoisomers (*R*,*S*)-α-methylthreonine [(*R*,*S*)-**4**] and (*S*,*R*)-α-methylthreonine [(*S*,*R*)-**4**; Scheme 5]. The (*R*,*S*)-oxazole [(*R*,*S*)-**18**] could be isolated in 62% yield, when starting with (*R*,*R*)-**9**. The enantiomeric excess of this product (88% ee) was nearly the same as that of the starting material. Hydrolysis in hydrochloric acid and work up using ion-exchange resin led to diastereomerically pure (*R*,*S*)-α-methylthreonine [(*R*,*S*)-**4**] in 91% yield and with



Scheme 5 Synthesis of (*R*,*S*)-α-methylthreonine [(*R*,*S*)-**4**] and (*S*,*R*)-α-methylthreonine [(*S*,*R*)-**4**]

88% ee. Starting from (*S*,*S*)-**9** with 89% ee, the oxazoline formation leads to diastereomerically pure (*S*,*R*)-**18** with 89% ee in 60% yield. Subsequent hydrolysis furnished diastereomerically pure (*S*,*R*)-α-methylthreonine [(*S*,*R*)-**4**] in 87% yield and with 89% ee.

In conclusion, we have developed an efficient synthetic route towards all four stereoisomers of α-methylthreonine (**4**). The desired stereoisomers of type **4** have been obtained in diastereomerically pure form and with high enantiomeric excesses in the range of 86–89% ee. The key step in this multi-step synthesis is an enantioselective organocatalytic Steglich rearrangement reaction of O-acetylated azlactones. The substrate spectrum of this type of Steglich rearrangement was also studied.

Materials and reagents were used without further purification. Chromatography was performed using Merck silica gel 60 (40–63 nm). Benzotetramisole (**13**) was synthesized according to the literature.[7] As 4-acyl-4-alkyl-2-phenyloxazol-5-ones (**7** and **16a–d**) are not stable under chromatography conditions, they were only characterized by ^{1}H NMR and afterwards further transformed into the corresponding, stable 2-benzoylamino-2-alkyl-3-oxo esters (**8** and **17a–d**), which were completely characterized. For the same reason, analysis of enantiomeric excess was performed with compounds **8**, **17a–d**.

^{1}H and ^{13}C NMR spectra were recorded on Jeol JNM GX 400, Jeol JNM EX 400, Bruker Avance 300 and Bruker Avance 400 spectrometers. Chemical shifts (δ) are reported in ppm using TMS as a reference. A Micromass Zabspec spectrometer was used for FAB mass spectrometry measurements using 3-nitrobenzyl alcohol as matrix. Analytical HPLC was performed using Daicel Chiralcel OD, OJ-H and Chiralpak AD-H (4 mm, 250 mm) columns.

4-Methyl-2-phenyloxazol-5-yl Acetate (6)

4-Methyl-2-phenyloxazol-5(4*H*)-one[17] (**5**; 4.0 g, 22.8 mmol) and AcCl (2.5 mL, 2.7 g, 34.4 mmol) were dissolved in absolute THF (70 mL) and cooled in an ice bath. Et_3N (4.8 mL, 3.5 g, 34.6 mmol) in THF (20 mL) was added dropwise over 10 min, then the solution was stirred for 1 h at 0 °C and the precipitated white solid was filtered off. The solvent was evaporated, and the residue was dissolved in MTBE (50 mL) and washed with 1 M HCl (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated, yielding a white solid. The NMR spectroscopic properties of **6** are in accordance with those reported by Steglich and Höfle.[16]

Yield: 4.05 g (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.35 (s, 3 H), 7.38–7.41 (m, 3 H), 7.90–7.92 (m, 2 H).

4-Isopropyl-2-phenyloxazol-5-yl Acetate (15a)

4-Isopropyl-2-phenyloxazol-5(4*H*)-one[17] (2.5 g, 12.3 mmol) and AcCl (960 μL, 1.06 g, 13.5 mmol) were dissolved in absolute THF (40 mL) and cooled in an ice bath. Et_3N (1.9 mL, 1.4 g, 13.5 mmol) in THF (10 mL) was added dropwise over 10 min. The solution was stirred for 1 h at 0 °C and the precipitated white solid was filtered off. The solvent was evaporated, and the residue was dissolved in MTBE (30 mL) and washed with 1 M HCl (30 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated, yielding an orange oil, which was purified by column chromatography (EtOAc–cyclohexane, 1:10).

Yield: 1.28 g (42%); R_f = 0.45 (EtOAc–cyclohexane, 1:10).

IR (powder film): 3066, 2966, 2881, 1784, 1653 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 7.0 Hz, 6 H), 2.32 (s, 3 H), 2.82 (sept, *J* = 7.0 Hz, 1 H), 7.38–7.40 (m, 3 H), 7.91–7.94 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 21.0, 25.4, 118.6, 125.9, 127.6, 128.6, 129.8, 130.0, 144.2, 155.0, 167.8.

MS (FAB): *m*/*z* = 246 [MH$^+$], 204 [MH$^+$ – $COCH_3$].

4-Isobutyl-2-phenyloxazol-5-yl Acetate (15b)

4-Isobutyl-2-phenyloxazol-5(4*H*)-one[17] (1.85 g, 8.5 mmol) and AcCl (670 μL, 740 mg, 9.4 mmol) were dissolved in absolute THF (30 mL) and cooled in an ice bath. Et_3N (1.3 mL, 950 mg, 9.4 mmol) in THF (10 mL) was added dropwise over 10 min. The solution was stirred for 1 h at 0 °C and the precipitated white solid was filtered off. The solvent was evaporated, and the residue was dissolved in MTBE (30 mL) and washed with 1 M HCl (30 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated, yielding a white solid.

Yield: 1.91 g (86%); mp 45–47 °C.

IR (powder film): 3061, 2961, 2868, 1791, 1729, 1660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.8 Hz, 6 H), 2.02 (m, 1 H), 2.29 (d, *J* = 6.8 Hz, 2 H), 2.33 (s, 3 H), 7.38–7.40 (m, 3 H), 7.91–7.94 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 22.2, 27.5, 33.9, 124.0, 125.9, 127.4, 128.7, 130.1, 146.2, 155.1, 167.5.

MS (FAB): *m*/*z* = 260 [MH$^+$], 218 [MH$^+$ – $COCH_3$].

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.65; H, 6.63; N, 5.17.

4-Methyl-2-phenyloxazol-5-yl Butyrate (15c)

4-Methyl-2-phenyloxazol-5(4*H*)-one[17] (**5**; 1.0 g, 5.7 mmol) and butanoyl chloride (600 μL, 610 mg, 5.7 mmol) were dissolved in absolute THF (20 mL) and cooled in an ice bath. Et_3N (791 μL, 575 mg, 5.7 mmol) in THF (5 mL) was added dropwise over 10 min, then the solution was stirred for 2 h at 0 °C and the precipitated white solid was filtered off. The solvent was evaporated, and the residue was dissolved in MTBE (30 mL) and washed with 1 M HCl (30 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (EtOAc–cyclohexane, 1:3), yielding a colorless oil.

Yield: 1.0 g (72%); R_f = 0.38 (EtOAc–cyclohexane, 1:3).

IR (powder film): 3069, 2968, 2934, 2880, 1791, 1752, 1660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.4 Hz, 3 H), 1.74–1.84 (m, 2 H), 2.08 (s, 3 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 7.39–7.42 (m, 3 H), 7.90–7.93 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 13.4, 18.1, 35.3, 120.5, 125.8, 127.4, 128.7, 130.1, 145.9, 155.0, 170.0.

MS (FAB): *m*/*z* = 248 [MH$^+$], 177 [MH$^+$ – $COCH_2CH_2CH_3$].

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.92; H, 6.23; N, 5.62.

4-Methyl-2-phenyloxazol-5-yl Benzoate (15d)

4-Methyl-2-phenyloxazol-5(4*H*)-one[17] (**5**; 1.0 g, 5.7 mmol) and benzoyl bromide (739 μL, 1.16 g, 6.3 mmol) were dissolved in absolute THF (20 mL) and cooled in an ice bath. Et_3N (870 μL, 632 mg, 6.3 mmol) in THF (10 mL) was added dropwise over 10 min, then the solution was stirred for 4 h at 0 °C and the precipitated white solid was filtered off. The solvent was evaporated, and the residue was dissolved in MTBE (30 mL) and washed with 1 M HCl (30 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (EtOAc–cyclohexane, 1:6), yielding a white solid. The analytical data of **15d** are identical to those reported by Steglich and Höfle.[16]

Yield: 880 mg (55%); R_f = 0.33 (EtOAc–cyclohexane, 1:6).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H), 7.40–7.42 (m, 3 H), 7.51–7.55 (m, 2 H), 7.66–7.70 (m, 1 H), 7.94–7.97 (m, 2 H), 8.19–8.21 (m, 2 H).

***rac*-4-Acetyl-4-methyl-2-phenyloxazol-5-one (*rac*-7)**

5-Acetyloxy-4-methyl-2-phenyloxazole (**6**; 2.0 g, 9.3 mmol) and DMAP (90 mg, 0.7 mmol) were dissolved in CH_2Cl_2 (50 mL) at r.t. After 3 h stirring, the solvent was removed to give **7** as a yellow oil. The analytical data of *rac*-**7** are in accordance with those reported by Steglich and Höfle.[16]

Yield: 2.05 g (quantitative, purity >95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 3 H), 2.26 (s, 3 H), 7.46–7.59 (m, 3 H), 8.00–8.02 (m, 2 H).

Isopropyl *rac*-2-Benzoylamino-2-methyl-3-oxobutyrate (*rac*-8)

rac-4-Acetyl-4-methyl-2-phenyloxazol-5-one (*rac*-**7**, 1.5 g, 6.9 mmol) and DMAP (90 mg, 0.7 mmol) were dissolved in *i*-PrOH (40 mL). The reaction mixture was stirred for 16 h and the excess of *i*-PrOH was removed in vacuo. The resulting crude product was purified by column chromatography (EtOAc–cyclohexane, 1:3) to give a colorless oil.

Yield: 1.62 g (84%); R_f = 0.36 (EtOAc–cyclohexane, 1:3).

HPLC (Chiralcel OD column; hexanes–*i*-PrOH, 97:3; 1.0 mL/min): t_R = 9.0, 10.8 min.

IR (thin film): 3412, 3327, 2984, 1722, 1664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.3 Hz, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.79 (s, 3 H), 2.21 (s, 3 H), 5.08 (sept, *J* = 6.3 Hz, 1 H), 7.40–7.44 (m, 2 H), 7.47–7.51 (m, 1 H), 7.71 (br s, 1 H), 7.78–7.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 21.30, 21.32, 23.9, 68.6, 70.5, 127.1, 128.6, 131.9, 133.6, 166.0, 168.7, 200.4.

MS (EI): *m*/*z* = 278 [MH$^+$], 234 [MH$^+$ – $COCH_3$].

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05; Found: C, 64.61; H, 6.88; N, 4.89.

***rac*-4-Acetyl-4-isopropyl-2-phenyloxazol-5-one (*rac*-16a)**

5-Acetyloxy-4-isopropyl-2-phenyloxazole (**15a**; 100 mg, 0.4 mmol) and DMAP (5 mg, 0.04 mmol) were dissolved in CH_2Cl_2 (5 mL) at r.t. After 3 h stirring, the solvent was removed to give crude **16a** as yellow oil, which was applied for ring opening to **17a**. The analytical data of *rac*-**16a** are in accordance with those reported by Steglich and Höfle.[16]

Yield: 102 mg (quantitative, purity >70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 2.32 (s, 3 H), 2.76 (sept, *J* = 6.8 Hz, 1 H), 7.47–7.60 (m, 3 H), 8.03–8.07 (m, 2 H).

Isopropyl *rac*-2-Benzoylamino-2-isopropyl-3-oxobutyrate (*rac*-17a)

rac-4-Acetyl-4-isopropyl-2-phenyloxazol-5-one (*rac*-**16a**, 102 mg), containing DMAP and side products was dissolved in *i*-PrOH (5 mL). The reaction mixture was stirred for 16 h and the excess of *i*-PrOH was removed in vacuo. The resulting crude product was purified by column chromatography (EtOAc–cyclohexane, 1:6) to give a colorless oil.

Yield: 75 mg (61%); R_f = 0.20 (EtOAc–cyclohexane, 1:6).

IR (thin film): 3391, 2974, 2935, 2881, 1722, 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.19 (d, *J* = 6.3 Hz, 3 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 2.14 (s, 3 H), 2.85 (sept, *J* = 6.8 Hz, 1 H), 5.11 (sept, *J* = 6.3 Hz, 1 H), 7.42–7.53 (m, 4 H), 7.80–7.82 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 18.3, 21.3, 24.7, 26.8, 32.7, 70.3, 74.6, 127.1, 128.7, 131.9, 133.9, 166.4, 168.0, 199.1.

MS (EI): *m*/*z* = 306 [MH$^+$], 262 [MH$^+$ – *i*-PrOH], 201 [MH$^+$ – PhCO], 158 [MH$^+$ – *i*-PrOH – PhCO].

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.58; H, 7.79; N, 4.57.

***rac*-4-Acetyl-4-isobutyl-2-phenyloxazol-5-one (*rac*-16b)**

5-Acetyloxy-4-isobutyl-2-phenyloxazole (**15b**; 400 mg, 1.4 mmol) and DMAP (15 mg, 0.1 mmol) were dissolved in CH_2Cl_2 (20 mL) at r.t. After 4 h stirring, the solvent was removed to give crude *rac*-**16b** as a yellow oil, which was applied for ring opening to *rac*-**17b**.

Yield: 402 mg (quantitative, purity >85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.91 (m, 6 H), 1.61–1.73 (m, 1 H), 1.97–2.02 (m, 1 H), 2.19–2.25 (m, 1 H), 2.28 (s, 3 H), 7.48–7.51 (m, 2 H), 7.57–7.61 (m, 1 H), 8.02–8.05 (m, 2 H).

Methyl *rac*-2-Benzoylamino-2-isobutyl-3-oxobutyrate (*rac*-17b)

4-Acetyl-4-isopropyl-2-phenyloxazol-5-one (*rac*-**16b**; 380 mg), and DMAP (80 mg, 0.6 mmol) were dissolved in CH_2Cl_2 (50 mL). MeOH (5 mL) was added and the reaction mixture was stirred for 16 h. The excess solvent was removed in vacuo, then the resulting crude product was purified by column chromatography (EtOAc–cyclohexane, 1:3) to give pure racemic *rac*-**17b** as a colorless oil.

Yield: 137 mg (32%); R_f = 0.47 (EtOAc–cyclohexane, 1:3).

HPLC (Chiralcel OJ-H-column; hexanes–*i*-PrOH, 90:10; 1.0 mL/min): t_R = 12.2, 19.9 min.

IR (thin film): 3408, 2961, 1749, 1722, 1664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.86 (m, 6 H), 1.46–1.55 (m, 1 H), 2.22 (s, 3 H), 2.37–2.42 (m, 1 H), 2.49–2.54 (m, 1 H), 3.76 (s, 3 H), 7.43–7.54 (m, 3 H), 7.75 (br s, 1 H), 7.81–7.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 23.6, 24.3, 24.4, 39.5, 53.5, 72.1, 127.2, 128.8, 132.1, 133.4, 165.9, 169.8, 200.6.

MS (FAB): *m*/*z* = 292 [MH$^+$].

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.53; H, 7.36; N, 4.65.

***rac*-4-Butyryl-4-methyl-2-phenyloxazol-5-one (*rac*-16c)**

4-Methyl-2-phenyloxazol-5-yl butyrate (**15c**; 200 mg, 0.8 mmol) and DMAP (20 mg, 0.16 mmol) were dissolved in CH_2Cl_2 (5 mL) at r.t. After 3 h stirring, the solvent was removed to give crude *rac*-**16c** as a yellow oil, which was applied for ring opening to *rac*-**17c**.

Yield: 210 mg (quantitative, purity ~90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.90 (m, 3 H), 1.55–1.63 (m, 2 H), 1.70 (s, 3 H), 2.42–2.69 (m, 2 H), 7.46–7.62 (m, 3 H), 8.01–8.04 (m, 2 H).

Isopropyl *rac*-2-Benzoylamino-2-methyl-3-oxohexanoate (*rac*-17c)

A sample of the mixture from the reaction mentioned above (210 mg), containing 4-butyryl-4-methyl-2-phenyloxazol-5-one (*rac*-**16c**; ~90%), and DMAP (~10%) were dissolved in *i*-PrOH (5 mL). The reaction mixture was stirred for 16 h, then the excess alcohol was removed in vacuo. The resulting crude product was purified by column chromatography (EtOAc–cyclohexane, 1:3) to give pure racemic *rac*-**17c** as a colorless oil.

Yield: 140 mg (56%); R_f = 0.53 (EtOAc–cyclohexane, 1:3).

HPLC (Chiralpak AD-H-column; hexanes–*i*-PrOH, 97:3; 1.0 mL/min): t_R = 13.3, 14.9 min.

IR (thin film): 3408, 2968, 2937, 2880, 1745, 1718, 1664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.4 Hz, 3 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 1.19 (d, *J* = 6.3 Hz, 3 H), 1.57–1.66 (m, 2 H), 1.78 (s, 3 H), 2.41–2.56 (m, 2 H), 5.07 (sept, *J* = 6.3 Hz, 1 H), 7.39–7.43 (m, 2 H), 7.46–7.50 (m, 1 H), 7.76 (br s, 1 H), 7.77–7.80 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 17.0, 19.8, 21.32, 21.34, 38.0, 68.5, 70.3, 127.0, 128.6, 131.8, 133.7, 165.9, 168.7, 202.7.

MS (FAB): *m*/*z* = 307 [MH$^+$].

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.39; H, 7.57; N, 4.39.

***rac*-4-Benzoyl-4-methyl-2-phenyloxazol-5-one (*rac*-16d)**

4-Methyl-2-phenyloxazol-5-yl benzoate (**15d**; 260 mg, 0.93 mmol) and DMAP (23 mg, 0.19 mmol) were dissolved in CH_2Cl_2 (5 mL) at r.t. After 5 h stirring, the solvent was removed to give crude **16d** as a yellow oil, which was applied for ring opening to *rac*-**17c**.

Yield: 280 mg (quantitative, purity ~70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (s, 3 H), 7.43–7.59 (m, 6 H), 8.01–8.20 (m, 4 H).

Isopropyl *rac*-2-Benzoylamino-2-methyl-3-oxo-3-phenylpropanoate (*rac*-17d)

A sample of the mixture from the reaction mentioned above (280 mg), containing 4-benzoyl-4-methyl-2-phenyloxazol-5-one (*rac*-**16d**; ~70%), DMAP (~10%) and deacylated side product were dissolved in *i*-PrOH (20 mL). The reaction mixture was stirred for 16 h, then the excess alcohol was removed in vacuo. The resulting crude product was purified by column chromatography (EtOAc–cyclohexane, 1:3) to give pure racemic *rac*-**17d** as a white solid.

Yield: 100 mg (33%); mp 128–130 °C; R_f = 0.46 (EtOAc–cyclohexane, 1:3).

HPLC (Chiralcel OJ-H-column; hexanes–*i*-PrOH, 90:10; 1.0 mL/min): t_R = 13.7, 29.4 min.

IR (powder film): 3408, 2984, 1737, 1698, 1652 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.3 Hz, 3 H), 1.15 (d, *J* = 6.3 Hz, 3 H,), 1.95 (s, 3 H), 5.12 (sept, *J* = 6.3 Hz, 1 H), 7.34–7.49 (m, 6 H), 7.71–7.73 (m, 2 H), 7.93–7.95 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.3, 22.0, 66.8, 71.0, 127.0, 128.4, 128.56, 128.58, 131.8, 133.0, 133.6, 134.4, 165.4, 170.3, 192.1.

MS (FAB): *m*/*z* = 341 [MH$^+$].

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.71; H, 5.97; N, 3.92.

Isopropyl *rac*-2-Benzoylamino-3-hydroxy-2-methylbutyrate (*rac-l*-9, *rac-u*-9)

Isopropyl 2-benzoylamino-2-methyl-3-oxobutyrate (*rac*-**8**, 100 mg, 0.36 mmol) was dissolved in absolute THF (5 mL) and cooled in an ice bath. After adding $NaBH_4$ (7.2 mg, 0.18 mmol), the mixture was stirred at ice-bath temperature for 2 h. Subsequently, dilute HCl was added until no further hydrogen was evolved. After addition of H_2O the reaction mixture was extracted with MTBE (3 × 10 mL). Removal of the solvent furnished a crude product of the resulting racemic diastereomers *l*-**9** and *u*-**9** (diastereomeric ratio of 73:27), which were separated by column chromatography (EtOAc–cyclohexane, 1:3) to give both diastereomers as white solids.

***rac-l*-9**

Yield: 60 mg (60%); mp 70–71 °C; R_f = 0.16 (EtOAc–cyclohexane, 1:3).

HPLC (Chiralcel OD column; hexanes–*i*-PrOH, 97:3; 1.0 mL/min): t_R = 9.9, 12.5 min.

IR (powder film): 3516, 3242, 2984, 1706, 1633 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.5 Hz, 3 H), 1.25–1.29 (m, 6 H), 1.69 (s, 3 H), 4.14–4.22 (m, 1 H), 5.09 (sept, *J* = 6.4 Hz, 1 H), 5.49 (d, *J* = 10.1 Hz, 1 H), 7.41–7.45 (m, 2 H), 7.49–7.53 (m, 1 H), 7.61 (br s, 1 H), 7.79–7.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 20.1, 21.4, 65.9, 70.5, 71.2, 127.2, 128.7, 132.1, 133.9, 168.0, 173.6.

MS (FAB): *m*/*z* = 280 [MH^+].

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.14; H, 7.58; N, 4.93.

***rac-u*-9**

Yield: 16 mg (16%); mp 111–112 °C; R_f = 0.06 (EtOAc–cyclohexane, 1:3).

IR (powder film): 3412, 3331, 2976, 1733, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.26 (m, 9 H), 1.57 (s, 3 H), 3.71 (br s, 1 H), 4.13–4.19 (m, 1 H), 5.09 (sept, *J* = 6.0 Hz, 1 H), 6.86 (br s, 1 H), 7.38–7.42 (m, 2 H), 7.46–7.50 (m, 1 H), 7.74–7.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.5, 21.56, 21.62, 64.6, 69.6, 71.3, 127.1, 128.6, 131.7, 134.5, 167.9, 172.2.

MS (FAB): *m*/*z* = 280 [MH^+].

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.13; H, 7.61; N, 4.87.

***rac-l*-α-Methylthreonine (*rac-l*-4)**

A mixture of *rac-l*-**9** (106 mg, 0.38 mmol) in HCl (6 M, 10 mL) was refluxed for 3 d then, after cooling to r.t., the mixture was washed with MTBE (10 mL). The aqueous phase was evaporated to dryness and the resulting hydrochloride was converted into free *rac-l*-**4** by ion-exchange resin (Dowex 50WX8; eluent: 1 M ammonia). The spectroscopic properties are in accordance with those reported by Avenoza et al.[4g]

Yield: 45 mg (89%).

^1H NMR (400 MHz, D_2O): δ = 1.14 (d, *J* = 6.6 Hz, 3 H), 1.36 (s, 3 H), 3.96 (q, *J* = 6.6 Hz, 1 H).

***rac-u*-α-Methylthreonine (*rac-u*-4)**

A mixture of *rac-u*-**9** (200 mg, 0.72 mmol) in HCl (6 M, 20 mL) was refluxed for 3 d. After cooling to r.t., the mixture was washed with MTBE (20 mL). The aqueous phase was evaporated to dryness and the resulting hydrochloride was converted into free *rac-u*-**4** by ion-exchange resin (Dowex 50WX8; eluent: 1 M ammonia). The spectroscopic properties are in accordance with those reported by Avenoza et al.[4g]

Yield: 70 mg (73%).

^1H NMR (400 MHz, D_2O): δ = 1.27 (d, *J* = 6.6 Hz, 3 H), 1.42 (s, 3 H), 4.19 (q, *J* = 6.6 Hz, 1 H).

(*S*)-*N*-(Thiazolyl-2)-2-hydroxy-1-*tert*-butylethylamine

A pressure tube charged with 2-chlorobenzothiazole (1.32 mL, 1.72 g, 10.1 mmol), (*S*)-*tert*-leucinol (1.23 g, 10.4 mmol), DIPEA (2.7 mL, 15 mmol) and a stir bar was flushed with nitrogen several times, stoppered and heated at 130 ±5 °C for 24 h. After cooling the tube to r.t., the viscous reaction mixture was treated with CH_2Cl_2 (10 mL) and left at r.t. to dissolve overnight. The diluted reaction mixture was applied directly to a chromatographic column (*i*-PrOH–CH_2Cl_2, 2.5%) to afford a white solid.

Yield: 1.48 g (58%); mp 155–157 °C; $[\alpha]_D$ –34.8 (*c* 1.0, MeOH).

IR (powder film): 3223, 3196, 2964, 2891, 1722, 1668, 1644, 1598, 1522 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.97 (s, 9 H), 3.52 (dd, *J* = 8.1, 11.3 Hz, 1 H), 3.77–3.78 (m, 1 H), 3.85 (dd, *J* = 3.5, 11.4 Hz, 1 H), 6.95–7.00 (m, 1 H), 7.14–7.19 (m, 1 H), 7.32–7.34 (m, 1 H), 7.48–7.50 (m, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 27.4, 35.7, 63.0, 67.2, 118.8, 121.7, 122.5, 126.9, 131.2, 153.3, 170.9.

MS (FAB): *m*/*z* = 251 [MH^+], 233 [$MH^+ - H_2O$].

Anal. Calcd for $C_{13}H_{18}N_2OS$: C, 62.37; H, 7.25; N, 11.19; S, 12.81. Found: C, 62.24; H, 7.31; N, 11.09; S, 12.35.

(*S*)-2,3-Dihydro-2-*tert*-butylimidazo[2,1-*b*]benzothiazole (14)

A solution of (*S*)-*N*-(thiazolyl-2)-2-hydroxy-1-*tert*-butylethylamine (0.63 g, 2.5 mmol) in anhydrous CH_2Cl_2 (25 mL) was cooled to 0 °C under a nitrogen atmosphere and treated with Et_3N (1.05 mL, 7.5 mmol) followed by MsCl (0.29 mL, 3.75 mmol). The mixture was stirred at 0 °C for 1 h and then warmed to r.t.; MeOH (0.15 mL) was then added to quench the excess amount of MsCl, then Et_3N (3.5 mL) was added and the mixture was refluxed overnight. The cooled mixture was washed with a small amount of H_2O, dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by chromatography (*i*-PrOH–hexanes, 5% containing 1% Et_3N) to give the crude product as a white solid. The compound was recrystallized (MTBE–hexanes), yielding a white solid.

Yield: 280 mg (48%); mp 75–76 °C; $[\alpha]_D^{20}$ –154.9 (*c* 1.0, MeOH).

IR (powder film): 2957, 2903, 2864, 1606, 1475 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9 H), 3.52–3.56 (m, 1 H), 3.73–3.78 (m, 1 H), 4.29–4.34 (m, 1 H), 6.63 (d, *J* = 7.8 Hz, 1 H), 6.90 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.14 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.22 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 34.3, 45.4, 82.7, 108.1, 121.1, 123.0, 126.4, 127.2, 137.3, 165.0.

MS (FAB): *m*/*z* = 233 [MH^+], 175 [MH^+ – *t*-Bu].

Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06; S, 13.80. Found: C, 66.91; H, 7.05; N, 11.96; S, 13.55.

Enantioselective Steglich Rearrangement of 6 Using Fu-Type Catalysts 10 and 11; Typical Procedure (Table 1, entry 1)

5-Acetyloxy-4-methyl-2-phenyloxazole (**6**; 50 mg, 0.23 mmol) and (*S*)-4-dimethylaminopyridinyl(pentaphenylcyclopentadienyl)iron [(*S*)-**10**; 4 mg, 0.005 mmol] were dissolved in CH_2Cl_2 (1 mL) and stirred at r.t. for 3 h. Subsequently, the solvent was removed to give 4-acetyl-4-methyl-2-phenyloxazol-5-one (**7**; 52 mg) as an oily crude product. The conversion (84%) was determined by ^1H NMR spectroscopy. The enantioselectivity (25% ee) was determined by

chiral HPLC chromatography after derivatization to isopropyl 2-benzoylamino-2-methyl-3-oxobutyrate (**8**), which was performed as follows: The crude product was dissolved in *i*-PrOH (5 mL) and DMAP (5 mg, 4.1 mmol) was added. After 16 h stirring, the solvent was evaporated in vacuo. The spectroscopic properties are in accordance with those of the racemic products *rac*-**7** and *rac*-**8**. Reactions were stirred until complete consumption of substrate **6** was observed.

Enantioselective Steglich Rearrangement of 6 Using Birman-Type Catalysts 12–14; Typical Procedure (Table 2, entry 1)

5-Acetyloxy-4-methyl-2-phenyloxazole (**6**; 50 mg, 0.23 mmol) and (*S*)-tetramisole [(*S*)-**12**; 15 mg, 0.07 mmol] were dissolved in CH_2Cl_2 (1 mL) and stirred at r.t. for 68 h. Subsequently, the solvent was removed to give 4-acetyl-4-methyl-2-phenyloxazol-5-one (**7**; 63 mg) as a crude oily product. The conversion (82%) was determined by ^{1}H NMR spectroscopy. The enantioselectivity (59% ee) was determined by chiral HPLC chromatography after derivatization to isopropyl 2-benzoylamino-2-methyl-3-oxobutyrate (**8**), which was performed as follows: The crude product was dissolved in *i*-PrOH (5 mL) and DMAP (5 mg, 4.1 mmol) was added. After 16 h stirring, the solvent was evaporated in vacuo. The spectroscopic properties are in accordance with those of the racemic products *rac*-**7** and *rac*-**8**. Reactions were stirred until complete consumption of substrate **6** was observed (except Table 2, entry 8).

Enantioselective Steglich Rearrangement of Substrate 15a

5-Acetyloxy-4-isopropyl-2-phenyloxazole (**15a**; 50 mg, 0.20 mmol) and (*S*)-**11** (15 mg, 0.04 mmol) were dissolved in $CDCl_3$ (1 mL). After shaking this mixture for 7 d, conversion was determined by ^{1}H NMR spectroscopy. As conversion was lower than 5%, no further reaction or purification was carried out.

Enantioselective Steglich Rearrangement of Substrate 15b: Synthesis of Methyl 2-Benzoylamino-2-isobutyl-3-oxobutyrate (17b)

5-Acetyloxy-4-isobutyl-2-phenyloxazole (**15b**, 104 mg, 0.40 mmol) and (*S*)-tetramisol [(*S*)-**12**; 26 mg, 0.13 mmol] were dissolved in *tert*-amyl alcohol (2 mL). After stirring this mixture for 75 h, the solvent was removed to give crude **16b**. Conversion was determined by ^{1}H NMR spectroscopy. The mixture was dissolved in CH_2Cl_2 (4 mL), and DMAP (10 mg, 0.08 mmol) and MeOH (200 μL) were added. After an additional 16 h stirring, the solvent was evaporated to give crude **17b**, which was purified by column chromatography (EtOAc–cyclohexane, 1:4). The spectroscopic properties are in accordance with those of the racemic compound *rac*-**17b**.

Yield: 21 mg (17%); 85% ee.

Enantioselective Steglich Rearrangement of Substrate 15c: Synthesis of Isopropyl 2-Benzoylamino-2-methyl-3-oxohexanoate (17c)

4-Methyl-2-phenyloxazol-5-yl butyrate (**15c**; 50 mg, 0.20 mmol) and (*S*)-**11** (15 mg, 0.04 mmol) were dissolved in $CDCl_3$ (1 mL). After shaking this mixture for 24 h, conversion was determined by ^{1}H NMR spectroscopy. The mixture was rotary evaporated, dissolved in *i*-PrOH (5 mL) and DMAP (10 mg, 0.08 mmol) was added. After an additional 16 h stirring, the solvent was evaporated to give crude **17c**, which was purified by column chromatography (EtOAc–cyclohexane, 1:3). The spectroscopic properties are in accordance with those of the racemic compound *rac*-**17c**.

Yield: 33 mg (54%); 24% ee.

Enantioselective Steglich Rearrangement of Substrate 15d: Synthesis of Isopropyl 2-Benzoylamino-2-methyl-3-oxo-3-phenylpropanoate (17d)

4-Methyl-2-phenyloxazol-5-yl benzoate (**15d**; 50 mg, 0.18 mmol) and (*S*)-**11** (14 mg, 0.036 mmol) were dissolved in $CDCl_3$ (1 mL). After shaking this mixture for 7 d, conversion was determined by ^{1}H NMR spectroscopy. The mixture was rotary evaporated, dissolved in *i*-PrOH (5 mL) and DMAP (10 mg, 0.08 mmol) was added. After an additional 16 h stirring, the solvent was evaporated to give crude **17d**, which was purified by column chromatography (cyclohexane–EtOAc, 3:1). The spectroscopic properties are in accordance with those of the racemic compound *rac*-**17d**.

Yield: 18 mg (29%); 45% ee.

Isopropyl (*S*)-2-Benzoylamino-2-methyl-3-oxobutyrate [(*S*)-8]

5-Acetyloxy-4-methyl-2-phenyloxazole (**6**; 880 mg, 4.0 mmol) and (*S*)-tetramisol [(*S*)-**12**; 248 mg, 1.2 mmol] were dissolved in $CHCl_3$ (17 mL). After stirring this mixture for 70 h, *i*-PrOH (21.5 mL) and DMAP (44 mg, 0.36 mmol) were added. After an additional 16 h stirring, the solvent was evaporated to give crude (*S*)-**8**, which was purified by column chromatography (cyclohexane–EtOAc, 3:1). The spectroscopic properties are in accordance with those of the racemic compound *rac*-**8**.

Yield: 588 mg (53%); 71% ee.

Isopropyl (*S*,*S*)-2-Benzoylamino-3-hydroxy-2-methylbutyrate [(*S*,*S*)-9]

$NaBH_4$ (106 mg, 2.79 mmol) was suspended in absolute THF (15 mL) and cooled in an ice-bath. D-*N*-Boc-proline (1800 mg, 8.36 mmol) in THF (30 mL) was added through an additional funnel. After 2 h stirring at r.t., the mixture was cooled in an ice bath and isopropyl (*S*)-2-benzoylamino-2-methyl-3-oxobutyrate [(*S*)-**8**; 580 mg, 2.09 mmol, 71% ee] in THF (30 mL) was added dropwise. After 20 h stirring at ice-bath temperature, the excess $NaBH_4$ was quenched by adding HCl (2 M) and most of the solvent was evaporated. The resulting aqueous solution was basified with $NaHCO_3$ and extracted with EtOAc (3 × 50 mL). After drying of the combined organic phases over $MgSO_4$, the solvent was removed to give a crude mixture of starting material (*S*)-**8** and both diastereomers of product **9**. The diastereomeric ratio and conversion were determined by ^{1}H NMR spectroscopy. Diastereomerically pure (*S*,*S*)-**9** was obtained after column chromatography (cyclohexane–EtOAc, 3:1). The spectroscopic properties are in accordance with those of the racemic compound *rac*-*l*-**9**.

Yield: 230 mg (39%); 89% ee.

(*S*,*S*)-α-Methylthreonine [(*S*,*S*)-4]

Isopropyl (*S*,*S*)-2-benzoylamino-3-hydroxy-2-methylbutyrate [(*S*,*S*)-**9**; 126 mg, 0.45 mmol, 86% ee] was dissolved in HCl (6 M, 10 mL) and refluxed for 60 h. After cooling to r.t., the mixture was washed with MTBE (10 mL). The aqueous phase was evaporated to dryness and the resulting hydrochloride was converted into free (*S*,*S*)-**4** by ion-exchange resin (Dowex 50WX8; eluent: 1 M ammonia). The spectroscopic properties are in accordance with those given above for the racemic compound *rac*-*l*-**4** and those reported by Avenoza et al.[4g] Enantiomeric excess was examined by optical rotation.

Yield: 43 mg (72%); 86% ee; $[\alpha]_D^{20}$ +10.0 (*c* 0.85, H_2O).

Isopropyl (*R*)-2-Benzoylamino-2-methyl-3-oxobutyrate [(*R*)-8]

5-Acetyloxy-4-methyl-2-phenyloxazole (**6**; 861 mg, 4.0 mmol) and (*R*)-benzotetramisol [(*R*)-**13**; 300 mg, 1.2 mmol] were dissolved in $CHCl_3$ (17 mL). After stirring this mixture for 95 h, *i*-PrOH (21.5 mL) and DMAP (43 mg, 0.35 mmol) were added. After an additional 16 h stirring, the solvent was evaporated to give crude (*R*)-**8**, which was purified by column chromatography (cyclohexane–EtOAc, 3:1). The spectroscopic properties are in accordance with those of the racemic compound *rac*-**8**.

Yield: 615 mg (56%); 70% ee.

Isopropyl (*R*,*R*)-2-Benzoylamino-3-hydroxy-2-methylbutyrate [(*R*,*R*)-9]

$NaBH_4$ (109 mg, 2.89 mmol) was suspended in absolute THF (15 mL) and cooled in an ice bath. L-*N*-Boc-proline (1868 mg, 8.68 mmol) in THF (30 mL) was added through an additional funnel. After 2 h stirring at r.t., the mixture was cooled in an ice bath and isopropyl (*R*)-2-benzoylamino-2-methyl-3-oxobutyrate [(*R*)-**8**; 600 mg, 2.17 mmol, 70% ee) in THF (30 mL) was added dropwise. After 20 h stirring at ice-bath temperature, the excess $NaBH_4$ was quenched by adding HCl (2 M) and most of the solvent was evaporated. The resulting aqueous solution was basified with $NaHCO_3$ and extracted with EtOAc (3 × 50 mL). After drying the combined organic phases over $MgSO_4$, the solvent was removed to give a crude mixture of starting material (*R*)-**8** and both diastereomers of product **9**. The diastereomeric ratio and conversion were determined by ^{1}H NMR spectroscopy. Diastereomerically pure (*R*,*R*)-**9** was obtained after column chromatography (cyclohexane–EtOAc, 3:1). The spectroscopic properties are in accordance with those of the racemic compound *rac*-*l*-**9**.

Yield: 195 mg (32%); 89% ee.

(*R*,*R*)-α-Methylthreonine [(*R*,*R*)-4]

Isopropyl (*R*,*R*)-2-benzoylamino-3-hydroxy-2-methylbutyrate [(*R*,*R*)-**9**; 106 mg, 0.38 mmol, 89% ee] was dissolved in HCl (6 M, 10 mL) and refluxed for 60 h. After cooling to r.t., the mixture was washed with MTBE (10 mL) and the aqueous phase was evaporated to dryness. The resulting hydrochloride was converted into free (*R*,*R*)-**4** by ion-exchange resin (Dowex 50WX8; eluent: 1 M ammonia). The spectroscopic properties are in accordance to those given above for the racemic compound *rac*-*l*-**4** and those reported by Avenoza et al.[4g] Enantiomeric excess was examined by optical rotation.

Yield: 45 mg (89%); 89% ee; $[\alpha]_D^{20}$ –10.4 (*c* 0.85, H_2O).

***rac*-*u*-4-Isopropoxycarbonyl-4,5-dimethyl-2-phenyl-1,3-oxazoline (*rac*-*u*-18)**

Isopropyl *rac*-*l*-2-benzoylamino-3-hydroxy-2-methylbutyrate (*rac*-*l*-**9**; 140 mg, 0.5 mmol) was dissolved in THF (5 mL) and cooled in an ice bath. After $SOCl_2$ (55 μL, 89 mg, 0.75 mmol) was added, the mixture was allowed to come to r.t. overnight. After an additional 3 h stirring at 60 °C, the solution was cooled in an ice bath and the excess $SOCl_2$ was quenched with sat. $NaHCO_3$ (30 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (cyclohexane–EtOAc, 9:1) to yield a colorless oil.

Yield: 94 mg (72%).

HPLC (Chiralcel OJ-H-column; hexanes–*i*-PrOH, 90:10; 1.0 mL/min): t_R = 8.9, 12.5 min.

IR (thin film): 2984, 1725, 1644 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.3 Hz, 6 H), 1.39 (s, 3 H), 1.40 (d, *J* = 6.7 Hz, 3 H), 4.95 (q, *J* = 6.7 Hz, 1 H), 5.03 (sept, *J* = 6.3 Hz, 1 H), 7.32–7.36 (m, 2 H), 7.40–7.44 (m, 1 H), 7.92–7.93 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 19.2, 21.4, 68.8, 75.4, 80.7, 127.6, 128.2, 128.4, 131.5, 163.7, 173.3.

MS (FAB): *m*/*z* = 262 [MH$^+$], 220 [MH$^+$ – *i*-Pr].

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.50; H, 7.38; N, 5.33.

(*R*,*S*)-4-Isopropoxycarbonyl-4,5-dimethyl-2-phenyl-1,3-oxazoline [(*R*,*S*)-18]

Isopropyl (*R*,*R*)-2-benzoylamino-3-hydroxy-2-methylbutyrate [(*R*,*R*)-**9**; 180 mg, 0.7 mmol, 89% ee] was dissolved in THF (5 mL) and cooled in an ice-bath. After $SOCl_2$ (73 μL, 119 mg, 1.0 mmol) was added, the mixture was allowed to come to r.t. overnight. After an additional 3 h stirring at 60 °C, the solution was cooled in an ice-bath and the excess $SOCl_2$ was quenched with sat. $NaHCO_3$ (30 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (cyclohexane–EtOAc, 9:1) to yield a colorless oil. The spectroscopic properties are in accordance with those of the racemic compound *rac*-*u*-**18**.

Yield: 105 mg (62%); 88% ee.

(*S*,*R*)-4-Isopropoxycarbonyl-4,5-dimethyl-2-phenyl-1,3-oxazoline [(*S*,*R*)-18]

Isopropyl (*S*,*S*)-2-benzoylamino-3-hydroxy-2-methylbutyrate [(*S*,*S*)-**9**; 230 mg, 0.8 mmol, 89% ee] was dissolved in THF (8 mL) and cooled in an ice bath. After $SOCl_2$ (91 μL, 152 mg, 1.2 mmol) was added, the mixture was allowed to come to r.t. overnight. After an additional 3 h stirring at 60 °C, the solution was cooled in an ice bath and the excess $SOCl_2$ was quenched with sat. $NaHCO_3$ (40 mL) and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (cyclohexane–EtOAc, 9:1) to yield a colorless oil. The spectroscopic properties are in accordance with those of the racemic compound *rac*-*u*-**18**.

Yield: 127 mg (60%); 89% ee.

(*R*,*S*)-α-Methylthreonine [(*R*,*S*)-4]

(*R*,*S*)-4-Isopropoxycarbonyl-4,5-dimethyl-2-phenyl-1,3-oxazoline [(*R*,*S*)-**18**; 100 mg, 0.38 mmol, 88% ee] was dissolved in HCl (6 M, 15 mL) and refluxed for 24 h. After cooling to r.t., the mixture was washed with MTBE (2 × 10 mL) and the aqueous phase was evaporated to dryness. The resulting hydrochloride was converted into free (*R*,*S*)-**4** by ion-exchange resin (Dowex 50WX8; eluent: 1 M ammonia). The spectroscopic properties are in accordance to those given above for the racemic compound *rac*-*u*-**4** and those reported by Avenoza et al.[4g] Enantiomeric excess was examined by optical rotation.

Yield: 46 mg (91%); 88% ee; $[\alpha]_D^{20}$ +11.8 (*c* 0.75, H_2O).

(*S*,*R*)-α-Methylthreonine [(*S*,*R*)-4]

(*S*,*R*)-4-Isopropoxycarbonyl-4,5-dimethyl-2-phenyl-1,3-oxazoline [(*S*,*R*)-**18**; 127 mg, 0.49 mmol, 89% ee] was dissolved in HCl (6 M, 15 mL) and refluxed for 24 h. After cooling to r.t., the mixture was washed with MTBE (2 × 10 mL) and the aqueous phase was evaporated to dryness. The resulting hydrochloride was converted into free (*S*,*R*)-**4** by ion-exchange resin (Dowex 50WX8; eluent: 1 M ammonia). The spectroscopic properties are in accordance to those given above for the racemic compound *rac*-*u*-**4** and those reported by Avenoza et al.[4g] Enantiomeric excess was examined by optical rotation.

Yield: 56 mg (87%); 89% ee; $[\alpha]_D^{20}$ –11.9 (*c* 0.75, H_2O).

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