Asymmetric Synthesis of Aliphatic α-Amino and γ-Hydroxy α-Amino Acids and Introduction of a Template for Crystallization-Induced Asymmetric Transformation

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Abstract: The asymmetric synthesis of aliphatic α-amino and γ-hydroxy α-amino acids is described. The key step is an aza-Michael addition controlled by crystallization-induced asymmetric transformation (CIAT), affording excellent diastereomeric ratios (dr ≥96:4). Consecutive deoxygenation or stereoselective reduction (dr 99:1) furnish various α-amino and γ-hydroxy α-amino acids, respectively.

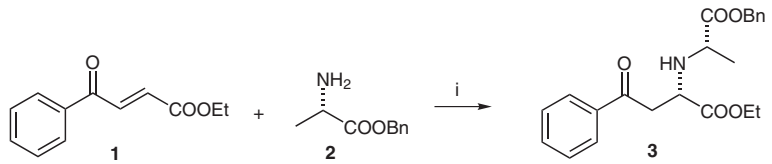
Key words: amino acids, asymmetric synthesis, Michael additions, reductions, solvent effects

We could find an impressive number of papers dealing with asymmetric processes in which amino acids represent either a readily available starting material or an attractive synthetic target.[1] So far, rather little attention has been paid to the synthesis of α-amino acids[2] and their derivatives[3] by application of crystallization-induced asymmetric transformation (CIAT).[4] The main drawback of the method is that it requires suitable and often specific conditions to be effective. Therefore CIAT is frequently reported as an accidental phenomenon observed by a careful experimenter. On the other hand, as CIAT is, by definition, accompanied by crystallization of the target compound, it is a very attractive method, particularly for industrial chemists.[4] Experimental accomplishment of CIAT is usually straightforward and does not require low temperatures, anhydrous conditions, or an inert atmosphere.

Our initial attention was attracted by a paper by Urbach and Henning,[5] describing CIAT based on reversible aza-Michael addition (Scheme 1). The reaction itself gives rise to a mixture of both stereoisomers. However, in the course of the reaction, diastereomer **3** starts to precipitate, and parallel equilibration in solution secures gradual conversion towards this single stereoisomer. Thus one ends up with crystalline compound **3** and a solution containing both stereoisomers, but with **3** the minor one. The question was how to make this approach more general. Even a slight modification in structure of the reagents might cause the target not to crystallize, resulting in the low stereoselectivity typical for this sort of reaction.

Our idea was to employ acylacrylic acids rather than esters. Consequently, the reaction would lead to amino acids, whose solubilities differ significantly compared with the starting reagents. Indeed, addition of (*R*)- or (*S*)-(1-phenylethyl)amine to various aroylacrylic acids led to excellent stereoselectivities, with dr ≥97:3.[6] However, a couple of months after we had launched the project, researchers from Kaneka published similar results.[7] Hence we focused on conditions allowing highly stereoselective reductions of γ-oxo α-amino acids[8] and on applications of amino alcohol auxiliaries in CIAT,[9] enabling oxidative cleavage. Afterwards we employed CIAT on dipeptidic substrates,[10] in simultaneous epimerization at two stereogenic centers,[11] stereoconvergent lactonization,[12] and synthesis of β-furoylalanines.[13] Our findings led us to believe that the acylacrylic subunit, even when variously modified, represents a general template for performing CIAT. Herein we would like to demonstrate the concept on short and efficient syntheses of a wide scale of aliphatic α-amino and γ-hydroxy α-amino acids, as shown in Scheme 2.

The starting acylacrylic acids are readily available and were prepared either by condensation of ketones (Scheme 3) with glyoxylic acid or by ring opening of 2-alkylfurans (Scheme 4).[14] As demonstrated by the condensation reactions of 1,1,1-trichloroacetaldehyde,[15] the first method is suitable only for acetone (**4a**) or α- or β-substituted ketones **4b–d** (Scheme 3).



Scheme 1 *Reagents and conditions*: (i) Et_3N, EtOH, r.t., 77%.

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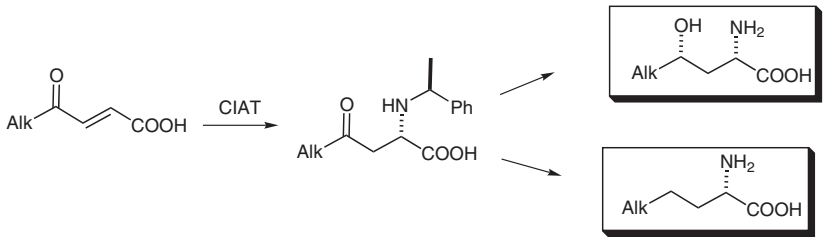
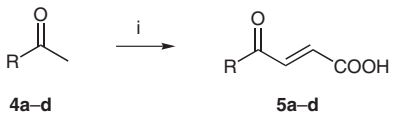
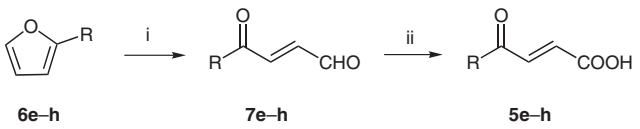


Scheme 2



Scheme 3 *Reagents and conditions*: (i) **5a** (R = Me): $OHCCO_2H$, H_3PO_4, 80 °C, 5 h, 46%; **5b** (R = *t*-Bu): $OHCCO_2H$, H_2SO_4, dioxane, reflux, 2.5 h, 50%; **5c** (R = *i*-Bu): $OHCCO_2H$, H_3PO_4, 100 °C, 2 h, 41%; **5d** (R = cyclopropyl): (a) $OHCCO_2H$, 95 °C, 12 h; (b) toluene, $KHSO_4$, reflux, 3 h, 36% (2 steps).

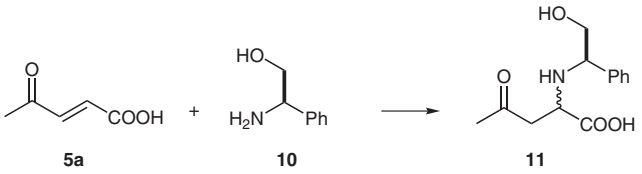
For the 2-alkylfuran oxidations we employed a modified method of Kobayashi.[14] The synthesis was performed in two steps (Scheme 4). Aldehyde intermediates **7** are rather unstable and were immediately used in the next step, the oxidation to β-acylacrylic acids.



Scheme 4 *Reagents and conditions*: (i) NBS, acetone–H_2O (10:1), –15 °C, 0.5 h; (ii) Jones reagent, acetone, 0–5 °C, 2 h; **5e** (R = Et): 44%, **5f** (R = Pr): 64%, **5g** (R = Bu): 46%, **5h** (R = Pent): 44%.

We chose acylacrylic acid **5a** as a model substrate for studies of aza-Michael additions (Scheme 5). Reaction with racemic (1-phenylethyl)amine in dichloromethane was accompanied by preferential crystallization of one diastereomer in high purity (dr >95:5; 39%, configuration undetermined). However, (*S*)-(1-phenylethyl)amine under CIAT conditions only led to a mixture of (*R*,*S*)- and (*S*,*S*)-**9a** (dr ca. 1:1; Scheme 5).

Exchange of the auxiliary for (*R*)-2-phenylglycinol (**10**) and experimenting with various solvents (Scheme 6, Table 1) led to surprisingly high diastereomeric ratios of **11** when 1,4-dioxane was used.



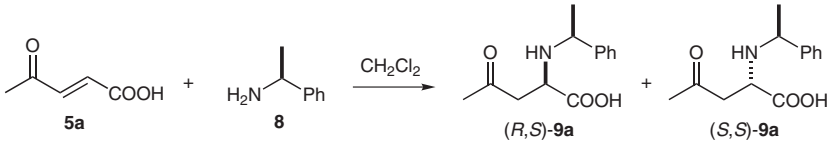
Scheme 6

Table 1 Effect of the Solvent on the Reaction between Acid **5a** and (*R*)-2-Phenylglycinol[a]

Solvent	Appearance	dr[b]
CH_2Cl_2	crystalline	55:45
1,3-dioxolane	crystalline	59:41
THF	crystalline	66:34
1,4-dioxane–CH_2Cl_2, 1:1	crystalline	63:37
1,4-dioxane–Et_2O, 2:1	gel	76:24
1,4-dioxane–H_2O, 98:2	crystalline	56:44
1,4-dioxane–H_2O, 99.2:0.8	gel	80:20
1,4-dioxane–H_2O, 99.6:0.4	gel	92:8
1,4-dioxane–H_2O, 99.8:0.2	gel	94:6
1,4-dioxane	gel	96:4

[a] Reagents and conditions: **10** (1.10 equiv), **5a** (1.00 equiv), r.t., 2 d.
[b] For gel mixtures, the best dr values we obtained are reported; the configurations are unassigned.

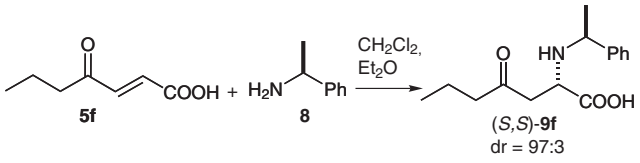
Remarkable is the relation between the consistency of the reaction mixture and diastereomeric enrichment. When modifying the reaction conditions we observed an 'illogical' trend. Increasing gel character of the mixture was accompanied by improved dr values, and, contrarily, crystallinity was reflected in poor diastereomeric ratios. This observation might be considered to be the first example of gelation-induced asymmetric transfomation. How-



Scheme 5

ever, isolation of a configurationally unstable amino acid from the gel mixture is problematic. At the same time, restricted mixing of a gradually forming gel results in fluctuations of dr values (drop of 5–10%).

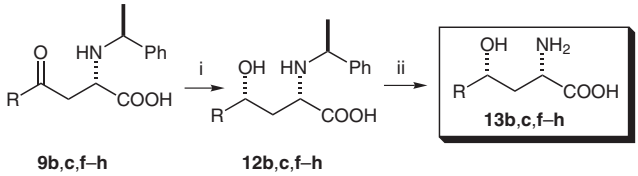
In spite of these complications, we hoped that this phenomenon might have a more general application. Although addition of (*R*)-2-phenylglycinol (**8**) to homologous acids **5e** and **5f** resulted in formation of a gel, the achieved diastereomeric ratios were disappointing. Thus we returned to (*S*)-(1-phenylethyl)amine (**8**). Its addition to acid **5e** resulted again in low dr values, but homologous substrate **5f** (Scheme 7) provided us with a completely different reaction profile. After 4 hours, the dr was 55:45, after 18 hours it rose to 62:38, and in 30 hours the dr was even 70:30. This tendency continued, and after seven days crystalline amino acid (*S*,*S*)-**9f** was isolated in a high yield and purity (dr 97:3). Analogous experiments were performed with the remaining substrates **5b–d** and **5g–h**, providing excellent results (Table 2).



Scheme 7

Apparently, for successful performance of CIAT, several criteria need to be fulfilled, e.g. the right auxiliary needs to be chosen. Structure of the substrate similarly plays an essential role. Exchange of homologue **5e** for **5f** also resulted in a substantial change in the final outcome of the reaction.

γ-Oxo α-amino acids represent straightforward intermediates in the synthesis of α-amino and *syn*-γ-hydroxy α-amino acids. Our method[8] of reducing γ-oxo α-amino acids gave **12b**,**c**,**f–h** in excellent stereoselectivity (dr 98:2) and provided us with a range of aliphatic *syn*-γ-hydroxy α-amino acids (Scheme 8, Table 3). Reductive cleavage of the auxiliary afforded **13b**,**c**,**f–h** in quantitative yields (over one step) after twelve hours (Scheme 8).



Scheme 8 *Reagents and conditions*: (i) $NaBH_4$, $MnCl_2 \cdot 4H_2O$, MeOH, 0–5 °C, 30 min; (ii) H_2/Pd/C, 12 h, r.t., ca. 100%.

Table 3 Stereoselective Reduction of γ-Oxo α-Amino Acids **9b**,**c**,**f–h**

Product	R	dr (*syn*/*anti*)[a]	dr (*syn*/*anti*)[b]	Yield (%)
12b	*t*-Bu	98:2	99:1	92
12c	*i*-Bu	98:2	99:1	77
12f	Pr	98:2	99:1	91
12g	Bu	98:2	99:1	81
12h	pentyl	98:2	99:1	91

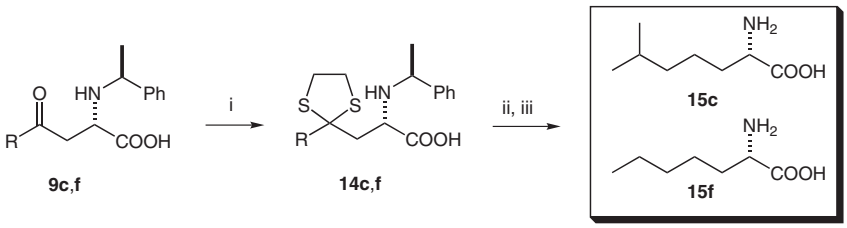
[a] dr of reaction mixture.
[b] dr after isolation.

To show the suitability of this method for the generation of α-amino acids, it was necessary to find proper conditions for deoxygenation of γ-oxo α-amino acids. For choosing the right method we kept in mind the configurational lability of the starting substrate, particularly under

Table 2 Effect of Conditions on the Outcome of Addition of (*S*)-(1-Phenylethyl)amine (**8**) to Acids **5a–h**[a]

Product	R	Solvent	Time	*c* (mol·dm^{-3})	dr of crystals[b]	dr of liquid[c]	Yield (%)
9a	Me	CH_2Cl_2	7 d	0.18	1:1	–	70
9b	*t*-Bu	EtOH	3 d	0.32	98:2	64:36	70
9c	*i*-Bu	CH_2Cl_2–Et_2O, 1:1	7 d	0.12	98:2	63:37	76
9d	*c*-Pr	CH_2Cl_2–Et_2O, 1:1	7–14 d	0.13	96:4	–	80
9e	Et	CH_2Cl_2–Et_2O, 1:1[d]	7 d	0.16	2:3	–	–[e]
9f	Pr	CH_2Cl_2–Et_2O, 1:1	7–14 d	0.14	97:3	71:29	83
9g	Bu	CH_2Cl_2–Et_2O, 1:1	7 d	0.10	98:2	–	92
9h	pentyl	CH_2Cl_2–Et_2O, 1:1	7 d	0.10	97:3	52:48	86

[a] Reagents and conditions: **8** (1.10 equiv), **5** (1.00 equiv), r.t.
[b] dr of isolated crystals.
[c] dr of mother liquors.
[d] Similar results in CH_2Cl_2 and H_2O.
[e] Not isolated from reaction mixture.

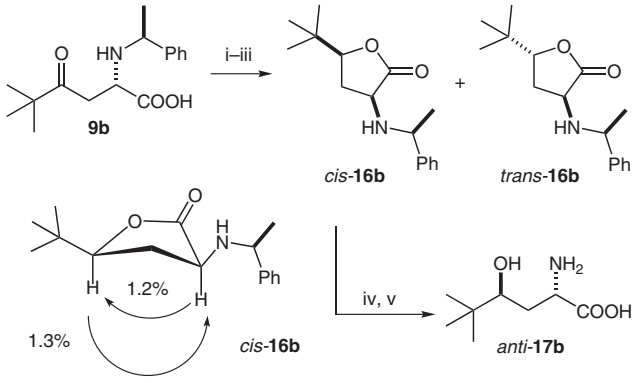


Scheme 9 *Reagents and conditions*: (i) $HS(CH_2)_2SH$, concd HCl, 24 h; **14c** (R = *i*-Bu): 94%, **14f** (R = Pr): 86%; (ii) H_2/Raney Ni, MeOH, 48 h; (iii) H_2/Pd/C, 24 h, r.t.; **15c** (R = *i*-Bu): 55%; **15f** (R = Pr): 65%.

basic conditions and at higher temperatures (i.e., possibility of retro-Michael and retro-Mannich reaction). We have decided to use a sequence based on reaction with sulfur nucleophiles, followed by desulfuration. γ-Oxo α-amino acids **9c**,**f** were smoothly transformed into 1,3-dithiolane derivatives **14c**,**f** (Scheme 9).

By a subsequent simple desulfuration–debenzylation sequence, natural amino acids **15c** and **15f** were obtained (Scheme 9). These amino acids are known to occur naturally and have been isolated from *Streptomyces diastaticus* (subunit of longicatenamycin)[16] and *Claviceps purpurea*,[17] respectively. Until now, reported preparations of **15c** and **15f** have been based on resolution,[18] chiral reagents derived from serine,[19] aziridine ring opening,[20] enantioselective reduction,[21] and conjugate addition of organocuprates.[22] Our methodology might afford a simple and straightforward alternative.

To assign the configuration of the newly built stereogenic centers, model amino acid **9b** was unselectively reduced to a mixture of γ-hydroxy α-amino acids *syn*-**12b** and *anti*-**12b** (*syn*/*anti* 31:69). Successive lactonization and chromatographic separation afforded pure lactones *cis*-**16b** and *trans*-**16b** (Scheme 10).



Scheme 10 *Reagents and conditions*: (i) $NaBH_4$, MeOH, r.t.; (ii) 6 M HCl, 0.5 h; (iii) K_2CO_3, chromatography; *cis*-**16b**: 53%, dr >99:1; *trans*-**16b**: 17%, dr >99:1; (iv) NaOH, MeOH, 1 h; (v) H_2/Pd/C, 12 h, 76% (2 steps).

NOE experiments confirmed the *cis* configuration of lactone *cis*-**16b**. Its ring opening allowed us to identify *anti*-**12b** on HPLC, i.e. the minor diastereomer formed in stereoselective reduction catalyzed by manganese(II) chloride (Scheme 8). Thus, in accordance with our previous results,[8] *syn*-**12b** is the major product of the stereoselective reductive step. Hydrolysis of *cis*-**16b** followed by debenzylation provided us with *anti*-(2*S*,4*S*)-2-amino-4-hydroxy-5,5-dimethylhexanoic acid (**17b**). By analogy, starting with the opposite enantiomer of **9b**, we prepared *anti*-(2*R*,4*R*)-2-amino-4-hydroxy-5,5-dimethylhexanoic acid (**17b**). This has been synthesized and fully characterized by Hegedus.[23] The optical rotation data correspond very well {Lit.[23]: $[\alpha]_D^{25}$ +39.3 (*c* 1.4, H_2O); ours: $[\alpha]_D^{25}$ +40.2 (*c* 0.3, H_2O)}, thus confirming that (*S*)- or (*R*)-(1-phenylethyl)amine induce a stereogenic center at C-2 bearing an (*S*)- or (*R*)-configuration, respectively (Scheme 7, Table 2). Again, this is in accordance with previous observations.[7,8,11] Another proof of this trend was provided by optical rotation data published for amino acid **15f**,[17] confirming the (*S*)-configuration at its C-2 position.

In conclusion, we have demonstrated an efficient CIAT methodology, enabling a short stereoselective synthesis of aliphatic α-amino and *syn*-γ-hydroxy α-amino acids. More importantly, the acylacrylic subunit appears to have a broad potential as a CIAT template. Further studies into the applicability of CIAT are being carried out in our laboratory.

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer (300 and 75.4 MHz, respectively) with TMS as an internal standard. Elemental analyses were performed on the analyzer NA 1500, Series 2, Carlo Erba Instruments. Optical rotations were measured on a JASCO P-1020 or POLAR L-μP (IBZ Mestechnik) polarimeter (concentration, *c* is given as g/100 mL). HPLC analyses were performed on a PU-4015/PU-4021 PYE UNICAM equipment (C_{18} 5-μm reverse-phase column, MeCN–phosphate buffer, 1:9 or 1:4, pH 2.5–3.2). The detector PU-4021 was set in SUM ABS mode, λ = 210–310 nm. (*E*)-4-Oxopent-2-enoic acid (**5a**) was prepared by a published method.[24]

(*E*)-5,5-Dimethyl-4-oxohex-2-enoic Acid (5b)

H_2SO_4 (96%, 15 mL) was added to a mixture of **4b** (10.00 g, 100 mmol) and $OHCCO_2H{\cdot}H_2O$ (13.81 g, 150 mmol) in dioxane (100 mL). The reaction mixture was refluxed for 4 h, allowed to cool to r.t., mixed with H_2O (150 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was washed with H_2O (50 mL) and extracted with 10% aqueous K_2CO_3 (3 × 30 mL). The aq soln was adjusted to pH 2 and extracted with EtOAc (3 × 30 mL), the organic solns were dried (Na_2SO_4) and concentrated. The residue was crystallized from heptane (150 mL); this afforded a pale yellow compound.

Yield: 7.80 g (50%); mp 85–92 °C (Lit.[25] 94–95 °C, Lit.[26] 93–95 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9 H, *t*-Bu), 6.78 (d, *J* = 15.2 Hz, 1 H, H-2), 7.63 (d, *J* = 15.2 Hz, 1 H, H-3).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.5, 43.6, 130.4, 137.3, 170.8, 203.5.

(*E*)-6-Methyl-4-oxohept-2-enoic Acid (5c)

H_3PO_4 (85%, 40 mL) was added to a mixture of **4c** (52.23 g, 521.5 mmol) and $OHCCO_2H{\cdot}H_2O$ (20.00 g, 217.3 mmol). The reaction mixture was stirred at 100 °C for 2 h, allowed to cool to r.t., mixed with H_2O (200 mL), and extracted with EtOAc (3 × 30 mL). The organic layer was washed with H_2O (50 mL) and extracted with 10% aq K_2CO_3 (2 × 50 mL). The aqueous soln was adjusted to pH 1 and extracted with EtOAc (3 × 30 mL), the organic solns were dried (Na_2SO_4) and concentrated. The residue was dissolved in boiling heptane (400 mL), filtered, and crystallized; this afforded a pale yellow compound.

Yield: 13.86 g (41%); mp 76–80 °C (Lit.[27] 91.5–92.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.4 Hz, 6 H, H-7), 2.09–2.28 (m, 1 H, H-6), 2.52 (d, *J* = 7.0 Hz, 2 H, H-5), 6.62 (d, *J* = 16.4 Hz, 1 H, H-2), 7.15 (d, *J* = 16.4 Hz, 1 H, H-3).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 22.5, 24.7, 50.6, 129.7, 141.4, 199.6.

(*E*)-4-Cyclopropyl-4-oxobut-2-enoic Acid (5d)

A mixture of **4d** (2.00 g, 23.8 mmol) and $OHCCO_2H{\cdot}H_2O$ (3.28 g, 35.7 mmol) was stirred at 95 °C for 12 h and then quenched with toluene (15 mL). $KHSO_4$ (3.57 g, 26.2 mmol) was added and the mixture was refluxed. After 3 h the mixture was filtered, and the residue was extracted with boiling toluene (2 × 15 mL). The organic solns were concentrated and the crude product was crystallized from cyclohexane (150 mL); this afforded an off-white solid.

Yield: 1.19 g (36%); mp 94–96 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06–1.24 (m, 4 H, H-2′, H-3′), 2.20–2.28 (m, 1 H, H-1′), 6.73 (d, *J* = 16.1 Hz, 1 H, H-2), 7.26 (d, *J* = 15.4 Hz, 1 H, H-3), 8.98 (br s, 1 H, COOH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 12.5, 12.5, 20.5, 129.4, 141.1, 170.3, 199.7.

(*E*)-4-Oxooct-2-enoic Acid (5g); Typical Procedure

A suspension of **6g** (1.00 g, 8.1 mmol) and $NaHCO_3$ (1.36 g, 16.2 mmol) in acetone–H_2O (10:1, 20 mL) was cooled to –15 °C. A precooled soln of NBS (1.58 g, 8.9 mmol) in acetone–H_2O (10:1, 10 mL) was added. The mixture was allowed to stand at –15 °C for 1 h, afterwards heated to r.t., quenched with EtOAc (30 mL), and the pH was adjusted to 1 with 4 M HCl. The organic layer was washed with H_2O (10 mL) and concentrated, furnishing an emulsion. The organic layer was separated, dissolved in acetone (10 mL), and cooled to 0–5 °C. The Jones reagent (2.5 mL) was added portionwise (100 μL) over 5 min. The mixture was stirred at 0–5 °C for 2 h, afterwards concentrated, mixed with H_2O (15 mL), and extracted with EtOAc (3 × 15 mL). The organic layer was extracted with 10% aq K_2CO_3 (2 × 20 mL). The pH of the aqueous soln was adjusted to 1 and the soln was extracted with EtOAc (3 × 15 mL). The organic solns were washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in boiling heptane (50 mL), filtered, and crystallized; this afforded an off-white solid.

Yield: 0.58 g (46%); mp 103–104 °C (Lit.[28] 98–99.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H, H-8), 1.36 (sext, *J* = 7.5 Hz, 2 H, H-7), 1.64 (quin, *J* = 7.5 Hz, 2 H, H-6), 2.66 (t, *J* = 7.5 Hz, 2 H, H-5), 6.68 (d, *J* = 15.7 Hz, 1 H, H-2), 7.15 (d, *J* = 15.7 Hz, 1 H, H-3), 10.5 (br s, 1 H, COOH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8, 22.2, 25.7, 41.5, 129.6, 141.2, 170.8, 199.8.

(*E*)-4-Oxohex-2-enoic Acid (5e)

Yield: 44%; off-white solid; mp 105–107 °C (Lit.[29] 107–108 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.5 Hz, 3 H, H-6), 2.72 (q, *J* = 7.3 Hz, 2 H, H-5), 6.70 (d, *J* = 15.4 Hz, 1 H, H-2), 7.16 (d, *J* = 15.4 Hz, 1 H, H-3), 11.30 (br s, 1 H, COOH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 7.5, 35.0, 129.5, 140.9, 170.7, 200.0.

(*E*)-4-Oxohept-2-enoic Acid (5f)

Yield: 64%; off-white solid; mp 107–109 °C (Lit.[28] 99 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.6 Hz, 3 H, H-7), 1.69 (sext, *J* = 7.6 Hz, 2 H, H-6), 2.66 (t, *J* = 7.6 Hz, 2 H, H-5), 6.69 (d, *J* = 16.4 Hz, 1 H, H-2), 7.15 (d, *J* = 15.8 Hz, 1 H, H-3), 11.66 (br s, 1 H, COOH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.6, 17.1, 43.6, 129.7, 141.2, 171.0, 199.8.

(*E*)-4-Oxonon-2-enoic Acid (5h)

Yield: 44%; off-white solid; mp 113–114 °C (Lit.[28] 110 °C, Lit.[30] 110–112 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, H-9), 1.26–1.40 (m, 4 H, H-8, H-7), 1.66 (quin, *J* = 7.0 Hz, 2 H, H-6), 2.67 (t, *J* = 7.0 Hz, 2 H, H-5), 6.69 (d, *J* = 15.8 Hz, 1 H, H-2), 7.13 (d, *J* = 15.8 Hz, 1 H, H-2), 11.66 (br s, 1 H, COOH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.8, 22.4, 23.2, 31.2, 41.7, 129.6, 141.1, 171.0, 199.8.

(2*S*)-4-Oxo-2-[(1*S*)-(1-phenylethyl)amino]heptanoic Acid (9f); Typical Procedure

Acid **5f** (0.60 g, 4.2 mmol) was dissolved in CH_2Cl_2–Et_2O (1:1, 60 mL), and amine (*S*)-**8** (0.59 mL, 4.6 mmol) was added. The mixture was stirred at r.t. and monitored by HPLC. After 7 d, the crystalline product was isolated by filtration, washed with Et_2O, and dried; this afforded an off-white solid.

Yield: 0.91 g (83%); dr 97:3; mp 142–143 °C (dec); $[\alpha]_D^{25}$ –14.7 (*c* 0.8, MeOH–1 M HCl, 3:1).

^{1}H NMR (300 MHz, acetone-d_6–DCl): δ = 0.81 (t, *J* = 7.3 Hz, 3 H, H-7), 1.49 (sext, *J* = 7.3 Hz, 2 H, H-6), 1.81 (d, *J* = 6.7 Hz, 3 H, H-2′), 2.39–2.56 (m, 2 H, H-5), 3.28 (dd, *J* = 19.6, 4.9 Hz, 1 H, H-3A), 3.36 (dd, *J* = 19.6, 5.5 Hz, 1 H, H-3B), 3.91 ('t', *J* = 4.9 Hz, 1 H, H-2), 4.78 (q, *J* = 6.7 Hz, 1 H, H-1′), 7.42–7.71 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, acetone-d_6–DCl): δ = 14.6, 18.1, 21.6, 43.5, 45.3, 54.1, 60.3, 130.0, 130.9, 131.1, 137.3, 170.6, C-4 undetected.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 67.81; H, 8.12; N, 5.24.

(2*S*)-5,5-Dimethyl-4-oxo-2-[(1*S*)-(1-phenylethyl)amino]hexanoic Acid (9b)

Reaction in EtOH, 3 d.

Yield: 70%; dr 98:2; off-white solid; mp 213–214 °C (dec); $[\alpha]_D^{25}$ –14.7 (*c* 1.0, MeOH–1 M HCl, 3:1).

^{1}H NMR (300 MHz, acetone-d_6–DCl): δ = 1.09 (s, 9 H, *t*-Bu), 1.85 (d, *J* = 6.8 Hz, 3 H, H-2′), 3.48 (dd, *J* = 19.2, 5.1 Hz, 1 H, H-3A), 3.57 (dd, *J* = 19.2, 5.1 Hz, 1 H, H-3B), 3.89 ('t', *J* = 4.7 Hz, 1 H, H-2), 4.83 (q, *J* = 6.8 Hz, 1 H, H-1′), 7.40–7.48 (m, 3 H, H-Ar), 7.73–7.75 (m, 2 H, H-Ar).

^{13}C NMR (75.4 MHz, acetone-d_6–DCl): δ = 21.8, 27.4, 39.0, 45.1, 54.7, 60.7, 130.3, 131.0, 131.2, 137.6, 170.6, 213.4.

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.27; H, 8.50; N, 4.99.

(2*S*)-6-Methyl-4-oxo-2-[(1*S*)-(1-phenylethyl)amino]heptanoic Acid (9c)

Yield: 76%; dr 98:2; off-white solid; mp 153–156 °C (dec); $[\alpha]_D^{25}$ –12.5 (*c* 0.3, MeOH–1 M HCl, 3:1).

^{1}H NMR (300 MHz, acetone-d_6–DCl): δ = 0.82 (d, *J* = 6.7 Hz, 3 H, H-7), 0.84 (d, *J* = 6.1 Hz, 3 H, H-7), 1.83 (d, *J* = 6.7 Hz, 3 H, H-2′), 2.35 (dd, *J* = 16.5, 6.7 Hz, 1 H, H-5A), 2.43 (dd, *J* = 16.5, 6.7 Hz, 1 H, H-5B), 3.31 (dd, *J* = 18.3, 4.9 Hz, 1 H, H-3A), 3.38 (dd, *J* = 18.3, 5.5 Hz, 1 H, H-3B), 3.92 (dd, *J* = 4.9, 5.5 Hz, 1 H, H-2), 4.80 (q, *J* = 6.7 Hz, 1 H, H-1′), 7.40–7.49 (m, 3 H, H-Ar), 7.69–7.73 (m, 2 H, H-Ar).

^{13}C NMR (75.4 MHz, acetone-d_6–DCl): δ = 21.7, 23.6, 23.6, 25.6, 44.0, 52.3, 54.1, 60.5, 130.2, 131.0, 131.2, 137.5, 170.6, 207.5.

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 68.91; H, 8.42; N, 5.27.

(2*S*)-4-Cyclopropyl-4-oxo-2-[(1*S*)-(1-phenylethyl)amino]butanoic Acid (9d)

Yield: 80%; dr 96:4; off-white solid; mp 145–147 °C.

^{1}H NMR (300 MHz, acetone-d_6–DCl): δ = 0.88–1.01 (m, 4 H, H-2″, H-3″), 1.85 (d, *J* = 6.8 Hz, 3 H, H-2′), 3.50–3.61 (m, 2 H, H-3), 3.93 ('t', *J* = 4.3 Hz, 1 H, H-2), 4.83 (q, *J* = 6.8 Hz, 1 H, H-1′), 7.40–7.51 (m, 3 H, H-Ar), 7.70–7.75 (m, 2 H, H-Ar), H-1′ overlapped by acetone-d_6.

^{13}C NMR (75.4 MHz, acetone-d_6–DCl): δ = 12.3, 12.4, 21.8, 21.9, 43.9, 54.4, 60.5, 130.3, 131.0, 131.2, 137.7, 170.5, C-4 undetected.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.35; H, 7.25; N, 5.58.

(2*S*)-4-Oxo-2-[(1*S*)-(1-phenylethyl)amino]octanoic Acid (9g)

Yield: 92%; dr 98:2; off-white solid; mp 133 °C (dec); $[\alpha]_D^{25}$ –10.7 (*c* 1.0, MeOH–1 M HCl, 3:1).

^{1}H NMR (300 MHz, acetone-d_6–DCl): δ = 0.83 (t, *J* = 7.3 Hz, 3 H, H-8), 1.25 (sext, *J* = 7.3 Hz, 2 H, H-7), 1.47 (quin, *J* = 7.3 Hz, 2 H, H-6), 1.84 (d, *J* = 7.3 Hz, 2 H, H-2′), 2.51 (t, *J* = 7.3 Hz, 2 H, H-5), 3.38 (br s, 2 H, H-3), 3.96 (dd, *J* = 5.1, 5.6 Hz, 1 H, H-2), 4.83 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.43–7.52 (m, 3 H, H-Ar), 7.71–7.75 (m, 2 H, H-Ar).

^{13}C NMR (75.4 MHz, acetone-d_6–DCl): δ = 15.0, 21.7, 23.6, 26.9, 43.3, 43.6, 54.4, 60.6, 130.3, 131.0, 131.2, 137.6, 170.6 (C-1), C-4 undetected.

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 68.82; H, 8.39; N, 5.12.

(2*S*)-4-Oxo-2-[(1*S*)-(1-phenylethyl)amino]nonanoic Acid (9h)

Yield: 86%; dr 97:3; off-white solid; mp 146 °C (dec); $[\alpha]_D^{25}$ –9.0 (*c* 1.0, MeOH–1 M HCl, 3:1).

^{1}H NMR (300 MHz, acetone-d_6–DCl): δ = 0.81 (t, *J* = 6.7 Hz, 3 H, H-9), 1.13–1.30 (m, 4 H, H-8, H-7), 1.47 (quin, *J* = 7.3 Hz, 2 H, H-6), 1.81 (d, *J* = 7.3 Hz, 3 H, H-2′), 2.42–2.57 (m, 2 H, H-5), 3.28 (dd, *J* = 19.6, 5.5 Hz, 1 H, H-3A), 3.36 (dd, *J* = 19.6, 4.9 Hz, 1 H, H-3B), 3.91 (dd, *J* = 5.5, 4.9 Hz, 1 H, H-2), 4.78 (q, *J* = 6.7 Hz, 1 H, H-1′), 7.39–7.69 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, acetone-d_6–DCl): δ = 15.0, 21.7, 23.8, 24.4, 32.6, 43.4, 43.5, 54.2, 60.4, 130.1, 131.1, 131.2, 137.4, 170.6, C-4 undetected.

Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.00; H, 8.78; N, 4.64.

(2*S*,4*S*)-4-Hydroxy-2-[(1*S*)-(1-Phenylethyl)amino]heptanoic Acid (12f); Typical Procedure

Acid **9f** (0.50 g, 1.9 mmol) was suspended in MeOH (25 mL), and $MnCl_2{\cdot}4H_2O$ (0.075 g, 0.4 mmol) was added. The mixture was cooled to 0–5 °C and $NaBH_4$ (0.14 g, 3.8 mmol) was added portionwise over 20 min. The soln was stirred another 30 min, concentrated, and mixed with 10% aq K_2CO_3 (12.5 mL). The resulting suspension was stirred at r.t. for 30 min and filtered. The cake was washed with H_2O. Filtrates were combined and the pH was adjusted to 6–6.5. Precipitated solids were isolated by filtration, washed with H_2O and Et_2O and dried.

Yield: 91%; dr 99:1; off-white solid; mp 215–216 °C (dec); $[\alpha]_D^{25}$ –35.2 (*c* 1.0, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.93 (t, *J* = 6.8 Hz, 3 H, H-7), 1.31–1.44 (m, 4 H, H-5, H-6), 1.47 (d, *J* = 6.8 Hz, 3 H, H-2′), 1.54–1.64 (m, 1 H, H-3A), 1.72–1.81 (m, 1 H, H-3B), 3.01 (dd, *J* = 6.0, 9.4 Hz, 1 H, H-2), 3.67–3.75 (m, 1 H, H-4), 3.79 (q, *J* = 6.8 Hz, 1 H, H-1′), 7.43–7.56 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 16.1, 20.8, 26.3, 41.2, 42.4, 59.4, 63.4, 73.7, 130.1, 130.3, 131.6, 146.8, 184.8.

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.20; H, 8.65; N, 5.51.

(2*S*,4*R*)-4-Hydroxy-5,5-dimethyl-2-[(1*S*)-(1-phenylethyl)amino]hexanoic Acid (12b)

Yield: 92%; dr 99:1; off-white solid; mp 202–205 °C; $[\alpha]_D^{25}$ –38.5 (*c* 1.0, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.79 (s, 9 H, *t*-Bu), 1.36–1.49 (m, 4 H, H-2′, H-3A), 1.71–1.78 (m, 1 H, H-3B), 2.94 (dd, *J* = 7.6, 6.9 Hz, 1 H, H-2), 3.20–3.23 (m, 1 H, H-4), 3.72 (q, *J* = 6.9 Hz, 1 H, H-1′), 7.34–7.47 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 26.4, 27.8, 36.7, 37.0, 59.3, 64.0, 82.2, 130.2, 130.4, 131.6, 146.7, 184.9.

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.29; H, 9.09; N, 5.37.

(2*S*,4*S*)-4-Hydroxy-6-methyl-2-[(1*S*)-(1-phenylethyl)amino]heptanoic Acid (12c)

Yield: 77%; dr 99:1; off-white solid; mp 197–200 °C; $[\alpha]_D^{25}$ –48.4 (*c* 1.0, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.78 [d, *J* = 6.2 Hz, 3 H, $CH(CH_3)_2$], 0.79 [d, *J* = 6.2 Hz, 3 H, $CH(CH_3)_2$], 1.06–1.16 (m, 1 H, H-5A), 1.25–1.70 (m, 7 H, H-5B, H-3, H-2′, H-6), 2.91 (dd, *J* = 8.9, 4.8 Hz, 1 H, H-2), 3.64–3.73 (m, 2 H, H-4, H-1′), 7.33–7.47 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 24.0, 25.4, 26.3, 26.5, 42.9, 48.4, 59.4, 63.4, 72.2, 130.2, 130.4, 131.7, 146.7, 184.8.

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.86; H, 9.08; N, 5.32.

(2*S*,4*S*)-4-Hydroxy-2-[(1*S*)-(1-phenylethyl)amino]octanoic Acid (12g)

Yield: 81%; dr 99:1; off-white solid; mp 195–198 °C (dec); $[\alpha]_D^{25}$ –42.7 (*c* 1.0, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.84 (t, *J* = 7.0 Hz, 3 H, H-8), 1.17–1.35 (m, 6 H, H-7, H-6, H-5), 1.37 (d, *J* = 7.0 Hz, 3 H, H-2′), 1.46–1.51 (m, 1 H, H-3A), 1.65–1.70 (m, 1 H, H-3B), 2.90 (dd, *J* = 5.2, 9.4 Hz, 1 H, H-2), 3.56 –3.62 (m, 1 H, H-4), 3.69 (q, *J* = 7.0 Hz, 1 H, H-1′), 7.35–7.45 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 16.1, 24.8, 26.3, 29.7, 38.7, 42.5, 59.4, 63.5, 74.1, 130.2, 130.4, 131.6, 146.9, 184.9.

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.38; H, 9.11; N, 5.25.

(2*S*,4*S*)-4-Hydroxy-2-[(1*S*)-(1-phenylethyl)amino]nonanoic Acid (12h)

Yield: 91%; dr 99:1; off-white solid; mp 185–187 °C; $[\alpha]_D^{25}$ –35.1 (*c* 0.5, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.85 (t, *J* = 7.0 Hz, 3 H, H-9), 1.17–1.34 (m, 8 H, H-8, H-7, H-6, H-5), 1.37 (d, *J* = 6.4 Hz, 3 H, H-2′), 1.46–1.51 (m, 1 H, H-3A), 1.65–1.69 (m, 1 H, H-3B), 2.89 (dd, *J* = 5.3, 8.8 Hz, 1 H, H-2), 3.57–3.62 (m, 1 H, H-4), 3.69 (q, *J* = 6.4 Hz, 1 H, H-1′), 7.35–7.45 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 16.2, 24.7, 26.3, 27.0, 33.8, 38.9, 42.4, 59.4, 63.4, 74.0, 130.1, 130.3, 131.6, 146.8, 184.8.

Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 68.98; H, 9.37; N, 4.81.

(2*S*,4*S*)-2-Amino-4-hydroxyheptanoic Acid (13f); Typical Procedure

Acid **12f** (0.40 g, 1.5 mmol) was dissolved in MeOH (150 mL). 10% Pd/C (80 mg) was added and the mixture was stirred under a H_2 atmosphere (1.1 atm). The reaction was monitored by HPLC. After complete conversion (typically 12 h), the catalyst was removed by filtration, the cake was washed with MeOH (20 mL), and the combined organic solns were concentrated.

Yield: 100%; dr 99:1; off-white solid; mp 225–230 °C; $[\alpha]_D^{25}$ +5.5 (*c* 0.3, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.92 (t, *J* = 7.6 Hz, 3 H, H-7), 1.29–1.54 (m, 4 H, H-5, H-6), 1.71–1.77 (m, 1 H, H-3A), 2.01–2.14 (m, 1 H, H-3B), 3.75–3.81 (m, 1 H, H-2), 3.88–3.94 (m, 1 H, H-4).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 16.0, 20.8, 40.5, 41.9, 57.3, 73.2, C-1 undetected.

Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 51.02; H, 9.48; N, 8.57.

(2*S*,4*S*)-2-Amino-4-hydroxy-5,5-dimethylhexanoic Acid (13b)

Yield: 100%; dr 99:1; off-white solid; mp 214–219 °C; $[\alpha]_D^{25}$ +41.9 (*c* 1.0, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.87 (s, 9 H, *t*-Bu), 1.45–1.55 (m, 1 H, H-3A), 1.87–1.95 (m, 1 H, H-3B), 3.31–3.40 (m, 2 H, H-2, H-4).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 37.8, 37.0, 38.8, 58.4, 81.2; C-1 undetected.

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 53.93; H, 9.98; N, 7.84.

(2*S*,4*S*)-2-Amino-4-hydroxy-6-methylheptanoic Acid (13c)

Yield: 100%; dr 99:1; off-white solid; mp 216–220 °C; $[\alpha]_D^{25}$ +7.4 (*c* 0.1, MeOH–0.7 M HCl, 3:1).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.91 [d, *J* = 8.8 Hz, 6 H, $CH(CH_3)_2$], 1.27–1.35 (m, 1 H, H-5A), 1.40–1.45 (m, 1 H, H-5B), 1.62–1.75 (m, 2 H, H-3A, H-6), 1.91–2.00 (m, 1 H, H-3B), 3.56 (dd, *J* = 7.0, 6.4 Hz, 1 H, H-2), 3.88–3.96 (m, 1 H, H-4).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 24.0, 25.4, 26.6, 43.0, 48.8, 57.3, 71.4, 182.3.

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.32; H, 9.84; N, 8.05.

(2*S*,4*S*)-2-Amino-4-hydroxyoctanoic Acid (13g)

Yield: 100%; dr 99:1; off-white solid; mp 227–232 °C; $[\alpha]_D^{25}$ +5.2 (*c* 0.4, 0.1 M NaOH).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.89 (t, *J* = 5.9 Hz, 3 H, H-8), 1.25–1.60 (m, 7 H, H-7, H-6, H-5, H-3A), 1.80–1.84 (m, 1 H, H-3B), 3.34 (dd, *J* = 7.0, 6.4 Hz, 1 H, H-2), 3.74–3.81 (m, 1 H, H-4).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 16.2, 24.8, 29.7, 38.8, 44.5, 57.4, 72.9, 186.1.

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.80; H, 9.86; N, 8.08.

(2*S*,4*S*)-2-Amino-4-hydroxynonanoic Acid (13h)

Yield: 100%; dr 99:1; off-white solid; mp 210–215 °C; $[\alpha]_D^{25}$ +7.8 (*c* 0.1, MeOH–0.7 M HCl, 3:1).

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.88 (t, *J* = 6.4 Hz, 3 H, H-9), 1.24–1.60 (m, 9 H, H-8, H-7, H-6, H-5, H-3A), 1.79–1.86 (m, 1 H, H-3B), 3.34 ('t', *J* = 7.0 Hz, 1 H, H-2), 3.75–3.82 (m, 1 H, H-4).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 16.2, 24.8, 27.1, 33.9, 39.1, 44.5, 57.4, 73.0, 186.1.

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 56.69; H, 10.08; N, 7.22.

(2*S*)-3-(2-Isobutyl-1,3-dithiolan-2-yl)-2-[(1*S*)-(1-phenylethyl)amino]propanoic Acid (14c); Typical Procedure

Acid **9c** (4.00 g, 14.4 mmol) was dissolved in 37% aq HCl (40 mL) at r.t. Ethane-1,2-dithiol (1.76 g, 1.57 mL, 18.7 mmol) was added dropwise over 1 min. The mixture was stirred at r.t. for 24 h. Subsequently it was placed in a cooling bath, the pH was adjusted to 6–6.5, and the resulting suspension was stirred for 15 min. The precipitated solids were isolated by filtration, washed with H_2O (3 × 100 mL) and Et_2O and dried; this afforded an off-white solid.

Yield: 1.79 g (94%); dr >95:5 (by NMR); mp 204–205 °C (MeOH); $[\alpha]_D^{25}$ –34.2 (*c* 0.7, 0.1 M NaOH).

^{1}H NMR (300 MHz, CD_3OD–DCl): δ = 0.94 (d, *J* = 6.4 Hz, 3 H, H-7A), 0.95 (d, *J* = 6.4 Hz, 3 H, H-7B), 1.75–1.89 (m, 6 H, H-2′, H-5, H-6), 2.33 (dd, *J* = 15.8, 8.8 Hz, 1 H, H-3A), 2.54 (dd, *J* = 15.8, 2.9 Hz, 1 H, H-3B), 2.80–2.96 (m, 2 H, SCH_2CH_2S), 3.13–3.24 (m, 2 H, SCH_2CH_2), 3.66 (dd, *J* = 8.8, 2.9 Hz, 1 H, H-2), 4.46 (q, *J* = 6.4 Hz, 1 H, H-1′), 7.47–7.56 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, CD_3OD–DCl): δ = 20.4, 24.8, 25.1, 27.4, 39.9, 41.2, 43.8, 54.0, 60.2, 60.8, 71.2, 129.5, 130.5, 130.9, 137.4, C-1 undetected.

Anal. Calcd for $C_{18}H_{27}NO_2S_2$: C, 61.15; H, 7.70; N, 3.96. Found: C, 60.59; H, 7.74; N, 3.88.

(2*S*)-2-[(1*S*)-(1-Phenylethyl)amino]-3-(2-propyl-1,3-dithiolan-2-yl)propanoic Acid (14f)

Yield: 86%; dr >95:5 (by NMR); off-white solid; mp 198–199 °C (MeOH); $[\alpha]_D^{25}$ –29.8 (*c* 0.5, 0.1 M NaOH).

^{1}H NMR (300 MHz, CD_3OD–DCl): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, H-7), 1.38–1.60 (m, 2 H, H-6), 1.76–1.81 (m, 5 H, H-2′, H-5), 2.28 (dd, *J* = 15.8, 8.8 Hz, 1 H, H-3A), 2.52 (dd, *J* = 15.8, 1.8 Hz, 1 H, H-3B), 2.76–2.95 (m, 2 H, SCH_2), 3.09–3.20 (m, 2 H, SCH_2), 3.69 (dd, *J* = 8.8, 1.8 Hz, 1 H, H-2), 4.49 (q, *J* = 7.0 Hz, 1 H, H-1′), 7.49–7.53 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, CD_3OD–DCl): δ = 14.4, 20.3, 20.7, 40.4, 41.5, 43.4, 48.9, 60.1, 60.8, 71.4 (C-4), 129.6, 130.5, 131.0, 137.5, C-1 undetected.

Anal. Calcd for $C_{17}H_{25}NO_2S_2$: C, 60.14; H, 7.42; N, 4.13. Found: C, 59.35; H, 7.38; N, 4.01.

(2*S*)-2-Aminoheptanoic Acid (15f); Typical Procedure

Raney Ni (W-2, 3.00 g) was suspended in MeOH (10 mL) and the mixture was stirred under H_2 (1.1 atm) at 55 °C. After 0.5 h, a soln of acid **14f** (1.00 g, 2.9 mmol) in MeOH (40 mL) was added and the heterogeneous mixture was stirred under H_2 (1.1 atm) at 55 °C. In 1

h, Raney-Ni (W-2, 5.00 g) in H_2O (20 mL) was added, and the mixture was stirred again under H_2 (1.1 atm) at 55 °C. After 48 h the mixture was filtered, the filter cake was washed with MeOH (2 × 20 mL, 50 °C) and H_2O (10 mL). The filtrate was concentrated under reduced pressure to a volume of ca. 10 mL and its pH was adjusted to 6–6.5. The precipitated solid was isolated by filtration, washed with H_2O and Et_2O, and dried; this afforded an off-white solid (470 mg, 65%). This was redissolved in MeOH (20 mL), and 10% Pd/C (90 mg) was added. The mixture was stirred under H_2 (1.1 atm) at r.t. After the conversion was complete (HPLC; typically after 24 h), the mixture was brought to a boil and filtered. The filter cake was washed with hot MeOH (20 mL) and the combined filtrates were concentrated; this afforded an off-white solid.

Yield: 272 mg (ca. 100%; 65% over 2 steps); mp 263–268 °C (MeOH; Lit.[20a] 274–276 °C); $[\alpha]_D^{25}$ +26.0 (*c* 0.1, 6 M HCl) [Lit.[18a] +23.9 (*c* 0.1, 6 M HCl), Lit.[20a] +22.6 (*c* 0.45, 6 M HCl), Lit.[31] +23.3 (*c* 2.0, 6 M HCl), Lit.[21] +23.6 (*c* 0.1, 6 M HCl), Lit.[20b] +27.3 (*c* 0.34, 6 M HCl)].

^{1}H NMR (300 MHz, CD_3OD–DCl): δ = 0.80–1.00 (m, 3 H, H-7), 1.21–1.57 (m, 6 H, H-4, H-5, H-6), 1.84–2.02 (m, 2 H, H-3), 3.99 (dd, *J* = 6.4, 5.9 Hz, 1 H, H-2).

^{13}C NMR (75.4 MHz, CD_3OD–DCl): δ = 14.3, 23.3, 25.5, 31.5, 32.4, 53.9, 172.0.

(2*S*)-2-Amino-6-methylheptanoic Acid (15c)

Yield: 55%; off-white solid; mp 240–245 °C (MeOH; Lit.[32] 240–245 °C); $[\alpha]_D^{25}$ +29.6 (*c* 0.1, 6 M HCl).

^{1}H NMR (300 MHz, CD_3OD–DCl): δ = 0.92 [d, *J* = 6.4 Hz, 6 H, $CH(CH_3)_2$], 1.23–1.66 (m, 5 H, H-4, H-5, H-3A), 1.82–2.00 (m, 2 H, H-6, H-3B), 3.99 (dd, *J* = 5.9, 6.4 Hz, 1 H, H-2).

^{13}C NMR (75.4 MHz, CD_3OD–DCl): δ = 22.9, 22.9, 23.7, 28.9, 31.7, 39.5, 54.0, 172.0.

(3*S*,5*S*)- and (3*S*,5*R*)-5-*tert*-Butyl-3-[(1*S*)-(1-phenylethyl)amino]dihydrofuran-2(3*H*)-one (*cis*- and *trans*-16b)

Acid **9b** (2.00 g, 7.2 mmol) was suspended in MeOH (60 mL), and $NaBH_4$ (0.80 g, 21.6 mmol) was added over 5 min. The mixture was concentrated under reduced pressure, redissolved in 6 M aq HCl (40 mL) and stirred at r.t. After 0.5 h, the precipitated solid was isolated by filtration, dried, and suspended in EtOAc (50 mL). The suspension was washed with 10% aq K_2CO_3 (100 mL) and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic solns were dried (Na_2SO_4) and concentrated; this afforded an off-white solid [1.45 g (77%); *syn*/*anti* 69:31]. The mixture of diastereomers was separated by column chromatography (silica gel, EtOAc–heptane, 1:7).

***cis*-16b**

Yield 0.69 g (53%); dr 99:1; off-white solid; mp 65–67 °C (heptane); $[\alpha]_D^{25}$ –68.4 (*c* 0.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (s, 9 H, *t*-Bu), 1.41 (d, *J* = 6.1 Hz, 3 H, H-2′), 1.53–1.59 (m, 1 H, H-4A), 1.83–1.88 (m, 1 H, H-4B), 3.44 (dd, *J* = 7.7, 11.5 Hz, 1 H, H-3), 3.87 (dd, *J* = 5.4, 11.5 Hz, 1 H, H-5), 4.16 (q, *J* = 6.1 Hz, 1 H, H-1′), 7.25–7.38 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.6, 24.9, 33.0, 33.1, 57.2, 58.1, 84.9, 127.1, 127.4, 128.5, 144.5, 177.8.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.18; H, 8.94; N, 5.47.

***trans*-16b**

Yield 0.23 g (17%); dr 99:1); off-white solid; mp 107–109 °C (EtOAc–heptane); $[\alpha]_D^{25}$ –102.4 (*c* 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 9 H, *t*-Bu), 1.39 (d, *J* = 6.1 Hz, 3 H, H-2′), 1.75–1.80 (m, 1 H, H-4A), 1.87–1.91 (m, 1 H, H-4B), 3.36 (dd, *J* = 6.1, 8.4 Hz, 1 H, H-3), 4.14 (q, *J* = 6.1 Hz, 1 H, H-1′), 4.21 (dd, *J* = 7.7, 5.4 Hz, 1 H, H-5), 7.25–7.38 (m, 5 H, H-Ar).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.2, 24.9, 31.4, 34.0, 55.2, 57.2, 86.1, 127.0, 127.3, 128.5, 144.5, 177.4.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.71; H, 8.93; N, 5.52.

(2*S*,4*S*)-2-Amino-4-hydroxy-5,5-dimethylhexanoic Acid (*anti*-17b)

Compound ***cis*-16b** (0.46 g, 1.8 mmol) was dissolved in MeOH (12 mL). A 1 M aq soln of NaOH (3.5 mmol, 3.5 mL) was added and the soln was stirred at r.t. After 1 h, the mixture was concentrated, redissolved in H_2O (10 mL), and the pH of the soln was adjusted to 6–6.5. The resulting suspension was stirred for 15 min and then filtered. The isolated off-white solid was washed with Et_2O, shortly dried, and redissolved in MeOH (120 mL). 10% Pd/C (70 mg) was added and the mixture was stirred under H_2 (1.1 atm) at r.t. After the conversion was complete (HPLC; typically after 12 h) the mixture was filtered. The filter cake was washed with MeOH (30 mL) and the combined filtrates were concentrated; this afforded an off-white solid.

Yield: 233 mg (76%, 2 steps); dr 99:1; mp 246–249 °C; $[\alpha]_D^{25}$ –40.3 (*c* 0.3, H_2O) [Lit.[23] +39.3 (*c* 1.2, H_2O) for (2*R*,4*R*)-isomer].

^{1}H NMR (300 MHz, NaOD–D_2O): δ = 0.89 (s, 9 H, *t*-Bu), 1.78–1.88 (m, 1 H, H-3A), 1.89–1.97 (m, 1 H, H-3B), 3.41–3.43 (m, 1 H, H-4), 3.69–3.75 (m, 1 H, H-2).

^{13}C NMR (75.4 MHz, NaOD–D_2O): δ = 36.1, 36.1, 37.7, 56.4, 79.5, C-1 undetected.

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