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Stereoselective Synthesis of *syn*-γ-Hydroxynorvaline and Related α-Amino Acids

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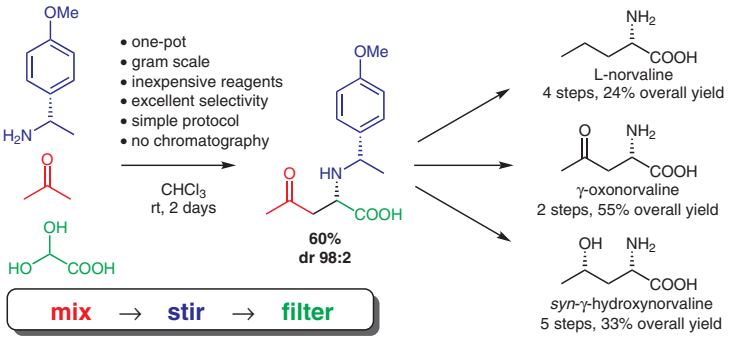

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Abstract The total syntheses of three enantiomerically pure non-proteinogenic amino acids, L-norvaline, γ-oxonorvaline, and *syn*-γ-hydroxynorvaline, are reported. The chromatography-free route pivoted on the construction of highly enantiomerically enriched substituted α-amino-γ-oxopentanoic acid, from which all three members were accessed divergently *via* chemoselective and stereoselective reductions. The rapid synthesis of this key α-amino-γ-oxopentanoic acid was achieved by a highly diastereoselective crystallisation-driven three-component Mannich reaction from the readily available building blocks acetone, glyoxylic acid monohydrate, and (*S*)-(4-methoxyphenyl)ethylamine. The enantiomeric purity of all target molecules was confirmed by HPLC analysis, either of the amino acids or their derivatives.

Key words stereoselective synthesis, α-amino acids, Mannich reaction, crystallisation-induced, norvaline, γ-hydroxynorvaline, aza-Michael addition

The immense quantity of enantiomerically pure proteinogenic α-amino acids found in nature forms the foundation of all living organisms. Although their non-proteinogenic counterparts are far less abundant, they play vital roles in various biogenic processes, cell signalling, and enzyme inhibition[1] and allow industrial exploration of biological activities as antibiotics and metal chelators.[2] Naturally, synthesis of enantiomerically pure α-amino acids has always been one of the most studied parts of modern stereoselective synthesis.[3] A vast array of diverse traditional approaches including resolution,[4] efficient organocatalysis,[5] cooperative catalysis,[6] metal catalysis,[7] and auxiliary-based synthesis[8] has been developed. However, as the industrial and academic demands for greener, waste-free, and time- and cost-efficient processes never cease, α-amino acids have always also been hugely popular model substrates for the development of alternative methodologies. Amongst the less frequently used, but elegant and efficient methods of stereoselective synthesis, crystallisation-induced asymmetric transformation (CIAT) stands out.[9] This method allows the formation of enantiomerically pure crystalline compounds due to a preferential crystallisation of one isomer from a solution containing a mixture of simultaneously equilibrating species.

In sharp contrast to its sophisticated principles[10] is the usual technical simplicity of CIAT, making the method very attractive compared to many traditional approaches. Typically, the process involves stirring a heterogeneous reaction mixture at room or slightly elevated temperature followed by simple filtration of a crystalline product. Arguably, filtration represents by far the most straightforward purification operation in organic chemistry and has gained undeniable popularity amongst all practising chemists. Due to such simple workup and multiple attractive ecological and economic features, CIAT has been frequently implemented in various industrial processes[11] and was recognised for its environmentally friendly character.[12]

Enantiomerically pure norvalin (**1**) and its γ-oxygenated analogues γ-oxonorvaline (**2**) and especially *syn*-γ-hydroxynorvaline (**3**) have been popular subjects of numerous synthetic studies (Scheme 1).[13] Despite its structural simplicity, norvaline (**1**) as an arginase inhibitor has been recently used in the treatment of Alzheimer disease,[14] has anti-inflammatory effects,[15] and is even used as a common food supplement. *syn*-γ-Hydroxynorvaline (**3**), first isolated in 1966 by Fowden from *Lathyrus odoratus* seed[16] and later by Eugster from the mushroom *Boletus satanas* Lenz,[17] has been reported to show several biological activities, including anti-diabetic properties.[18] The α-amino-γ-hydroxy acid

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Biographical Sketches

From left to right:

Dominika Valachová received her bachelor's degree in 2018 from the Slovak University of Technology in Bratislava. She is now continuing her studies under the guidance of Dr. Jakubec in Prof. Berkeš research group. Her undergraduate research focused on the preparation of enantiomerically pure amino acids by crystallisation-driven processes.

Branislav Ferko received his PhD from the Slovak University of Technology in 2019, working under the supervision of Prof. Berkeš. His work focused on the synthesis of novel and potent fluorescence labelled analogues of arylceramides for application in PET tomography. During his PhD studies he joined the group of Prof. Darren J. Dixon at the University of Oxford, where he participated in two independent projects: the development of a novel photocatalytic method for the construction of α-tertiary ethers and a first total synthesis of a potent antibiotic. Currently he is a postdoctoral research assistant at the Slovak University of Technology, where he is involved in the development of novel cross-coupling reactions.

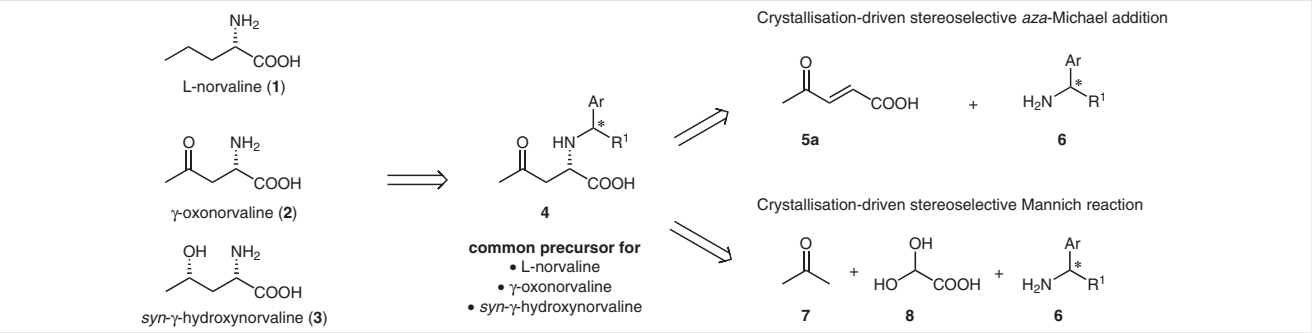
Eva Puchľová studied organic chemistry at the Slovak University of Technology in Bratislava and obtained her MSc degree in 2016. Currently, she is a PhD student and R&D chemist in the flavour industry, focusing on stereoselective (bio)transformations in the synthesis of aroma compounds.

Oľga Caletková graduated in 2007 at the Slovak Technical University of Technology in Bratislava. In 2008 she received an MPhil degree from the University of Manchester under the supervision of Prof. Jonathan P. Clayden. After returning to Slovakia she carried out her PhD studies, working on the synthesis of natural products in the group of Prof. Gracza. In 2012 she worked as a postdoctoral researcher in the group of Prof. Michal Hocek at the Academy of Sciences of the Czech Republic. Since 2016 she has been working as a research assistant at the Slovak University of Technology in Bratislava.

Dušan Berkeš was born in Nové Zámky (Slovakia) in 1957. He studied chemistry and pharmaceutical technology at the Slovak Technical University in Bratislava, where he received his PhD in 1987 under the supervision of Prof. J. Kovac for studies on furan derivatives. He was a postdoctoral fellow in the group of Prof. Henry-Basch at the University Paris-Sud (1988–1989) and research fellow at the University of Le Havre (1992–1993) in the group of Professor Morel, on stereoselective synthesis of nitrogen heterocycles. In 2002 he was appointed as Associate Professor of Organic Chemistry at the Slovak Technical University in Bratislava. From 2012 he has been the head of the detached university laboratory in the Saneca pharmaceuticals company. His current research is on stereoselective nonproteinogenic amino acid synthesis and crystallisation-induced asymmetric transformations, with applications towards the synthesis of sphingolipid metabolism inhibitors.

Andrej Kolarovič obtained his PhD in 2003 from the Slovak University of Technology in Bratislava (advisor: Prof. Dušan Berkeš). During his doctoral studies he spent a period as a visiting researcher at the Degussa-Hüls AG labs in Hanau (Germany), under the supervision of Dr. Kai Rossen. He performed his postdoctoral research with Prof. Giulia Licini (University of Padova; (pseudo)-C_3-symmetric ligands) and Prof. Eriks Rozners (Northeastern University, Boston; formaldehyde-bridged oligonucleotides; NSF-NATO Fellowship). In 2006 he returned to his *alma mater* in Bratislava as an Assistant Professor while in parallel he further broadened his knowledge as a postdoc in the groups of Prof. Marko D. Mihovilovic (Vienna University of Technology; catalytic decarboxylations; Ernst Mach Jubilee Fellowship) and Prof. Helma Wennemers (ETH Zürich; stereoselective (organo)catalysis; SCIEX Fellowship). Since 2016 he has been an Associate Professor at the Trnava University in Slovakia.

Pavol Jakubec received his PhD in 2005 from the Slovak University of Technology in Bratislava (supervisor Prof. Dušan Berkeš). In 2006 he joined the group of Prof. Darren J. Dixon and spent two years as a postdoctoral researcher at the University of Manchester. Then he followed Darren to the University of Oxford where he worked on the total synthesis of manzamine alkaloids and the development of new methodologies. In 2014 he moved to the US, and as a postdoctoral researcher he worked for Prof. Andrew G. Myers at Harvard University on macrolide antibiotics. After returning to Slovakia in 2016, he became a research assistant at the Slovak University of Technology in Bratislava. He has co-authored 29 scientific papers, including 2 articles in *Nature* with Profs. Schrock, Hoveyda, and Myers.

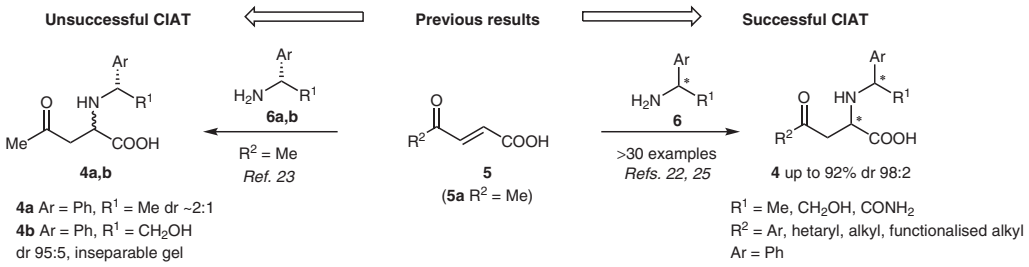


Scheme 1 Retrosynthetic analysis of norvaline (**1**) and its γ-oxygenated analogues γ-oxonorvaline (**2**) and γ-hydroxynorvaline (**3**)

fragment is found in some biologically active peptides including the antifungal agent theonellamide F.[19] But perhaps the most notable biological properties are of the cyclic form of γ-hydroxynorvaline, the α-amino-γ-butyrolactones. They form a core structural element in a series of natural products and pharmaceutical drugs, including pesticides, ACE inhibitors, and bacteriostatic agents.[20]

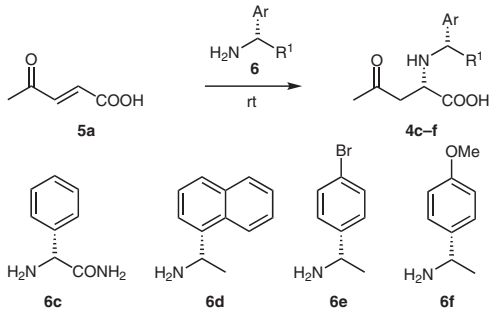
Intrigued by the broad spectrum of the biological activities and the frequent natural abundance of these structurally similar compounds, we envisaged that a unified synthetic approach featuring CIAT from a common intermediate could enhance the existing syntheses. All three target amino acids possess the same structural backbone and differ only in the oxidation state at C-4. The structural similarities led us to believe that amino ketone **4** could be the key common intermediate (Scheme 1). Further retrosynthesis revealed that ketone **4** could be accessed *via* a stereoselective aza-Michael addition from unsaturated acid **5a**[21] or Mannich reaction from acetone (**7**), glyoxylic acid monohydrate (**8**), and a suitable chiral mediator **6** (Scheme 1). CIAT approaches featuring stereoselective aza-Michael addition to various related γ-aryl- and γ-alkyl-substituted γ-oxobutenoic acids **5** have already been developed (Scheme 2).[22] However, as we reported, the attempted CIAT in the aza-Michael addition to unsaturated acid **5a** remained elusive due to gel formation or low stereoselectivity (Scheme 2).[23] Therefore, our primary goal was to significantly improve the stereocontrol in the aza-Michael addition to acetylacrylic acid (**5a**).

Our synthetic endeavour began with a critical analysis of our previously reported reactions of amines **6a** (R^1 = Me) and **6b** (R^1 = CH_2OH) with **5a** (R^2 = Me) (Scheme 2). The outcomes were scrutinised in the light of the recently emerged successful applications of CIAT in aza-Michael and nitro-Mannich reactions, where scarcely used chiral mediators **6c** and **6d** (Table 1) were employed.[24–26] The latest advancements prompted us to return to the disappointing aza-Michael addition and react acetylacrylic acid (**5a**) with a broader range of enantiomerically pure amines **6** (Table 1). Under conditions suitable for the crystallisation-driven processes, four commercially available enantiomerically pure chiral amines **6c–f** were investigated in the reaction monitored by reverse-phase HPLC. Selected results are reported in Table 1.[27] Pleasingly, already after a brief screening of the reaction conditions, several highly diastereoselective reactions were discovered when amines **6e** and **6f** were employed in chlorinated solvents. The aza-Michael addition with amine **6e** afforded adduct **4e** in 75% yield and excellent diasteroselectivity (dr 99:1) when performed in chloroform. The most outstanding datapoint was obtained with amine **6f** when the addition was performed in chloroform at room temperature. Without any precautions to exclude moisture or light or special demands for solvent purity, amino acid **4f** was isolated by simple filtration in excellent yield (88%) and dr (99:1) after five days of stirring. In good agreement with the previous investigations, the origin of the highly diastereoselective reaction was confirmed as crystallisation-induced asymmetric transformation.



Scheme 2 Crystallisation-induced asymmetric transformation of N-nucleophiles in aza-Michael addition to acylacrylic acids **5**

Table 1 Attempted CIAT: Screening of Chiral Amines **6** in Reaction with **5a**[a]

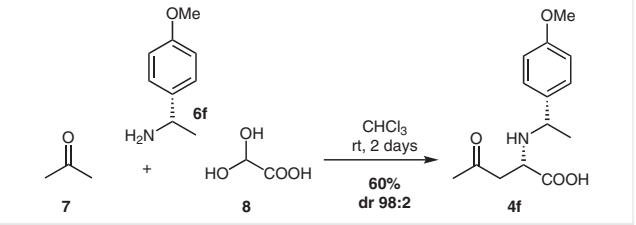


Amine	Conditions	Results	Isolated
6c (1.3 equiv)	$CHCl_3$, 7 d	–[b]	–[b]
6d (1.3 equiv)	$CHCl_3$, 7 d	–[b]	–[b]
6e (1.1 equiv)	CH_2Cl_2, 7 d	suspension, dr 49:51	**4e**, dr 49:51, 42%
6e (1.1 equiv)	$CHCl_3$, 6 d	suspension, dr 97:3	**4e**, dr 99:1, 75%
6f (1.1 equiv)	$CHCl_3$, 5 d	suspension, dr 92:8	**4f**, dr 99:1, 65%
6f (1.3 equiv)	$CHCl_3$, 5 d	suspension, dr 92:8	**4f**, dr 99:1, 88%

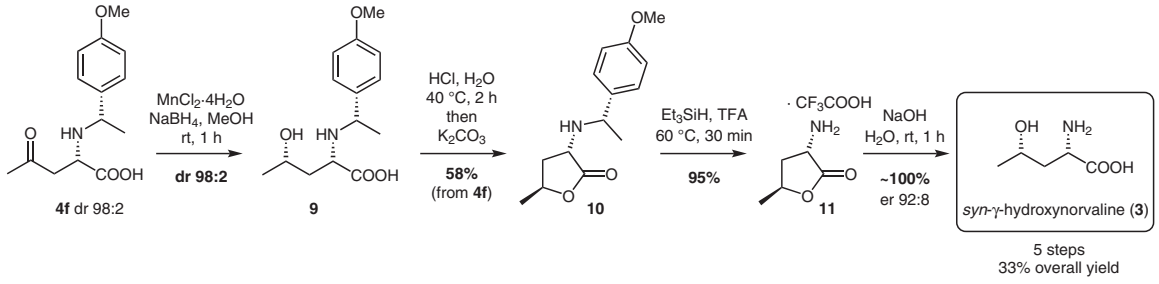
[a] Reaction conditions: **5a** (1 equiv), **6**, solvent, rt, 5–7 d.
[b] The reaction mixture did not form a suspension.

Encouraged by the feasibility of the stereoselective crystallisation-driven aza-Michael reaction, the accessibility of **4f** *via* a three-component Mannich reaction from acetone (**7**), amine **6f**, and glyoxylic acid monohydrate (**8**) was assessed (Scheme 3).[28] Such an ambitious process would benefit not only from a potentially reduced overall step-count but also from the much easier commercial access to the starting materials. Having already identified chloroform as the optimal solvent for CIAT and amine **6f** as the most suitable chiral mediator, the starting point for the three-component Mannich reaction was well set. To our delight, there was no need for further extensive optimisation, because the usage of acetone as a co-solvent allowed the swift formation of **4f** with an initial dr of ~1:1. Similar to the aza-Michael reaction, the rapid epimerisation of (*S*,*R*)-**4f** accompanied by crystallisation of the desired (*S*,*S*)-adduct enabled a smooth transformation of the three inexpensive, commercially available components into enantiomerically pure amino acid **4f**. Simple filtration of the solid precipitate formed over the course of the reaction afforded **4f** in 60% yield and 98:2 dr. The reaction was successfully performed already on a multigram scale, but the indisputable simplicity of the reaction execution ('mix → stir → filter') holds promises for even more significant scale-up.

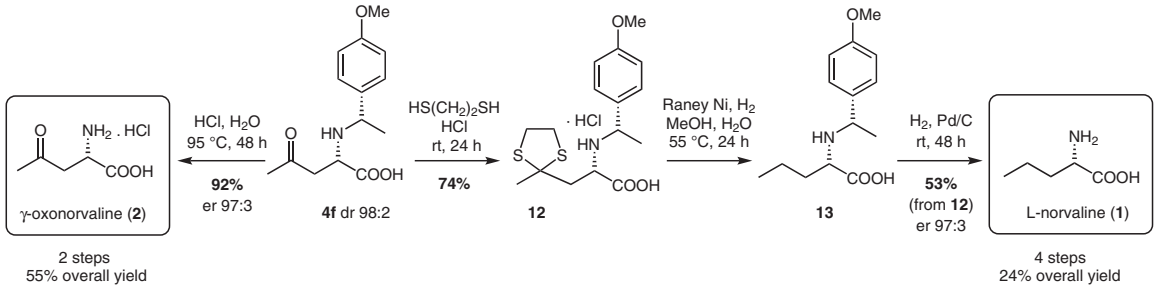
With the straightforward approach to amino acid **4f** *via* the Mannich reaction established, its envisaged utility in the stereoselective synthesis of norvaline (**1**) and its oxygenated analogues was surveyed. Firstly, the synthesis of γ-hydroxynorvaline (**3**), the most complex target, was investigated, and the results are presented in Scheme 4. According to our retrosynthetic analysis (Scheme 1), a controlled *syn*-1,3-induction was required to install the stereogenic centre at C-4. We employed a highly stereoselective method taking advantage of a pre-organised six-membered Mn chelate formed *in situ* from amino ketone **4f** and manganese dichloride.[29] After a smooth *syn*-stereoselective reduction with sodium borohydride in MeOH, α-amino-γ-hydroxy acid **9** was formed in an excellent 98:2 dr, as determined by HPLC. Due to the highly polar nature of the molecule, after a mild lactonization, we isolated its cyclic form, lactone **10**. The following removal of the chiral mediator was achieved by a mild reductive debenzylation by using trifluoroacetic acid as the solvent and triethylsilane as the reducing agent.[30] Our synthesis of *syn*-γ-hydroxynorvaline (**3**) was completed by a gentle lactone opening, yielding the natural product in 33% yield over five steps. The spectroscopic data (^1H and ^{13}C NMR), melting point, and specific rotation of our material were in excellent agreement with the published data.[13c] HPLC analysis of the *N*-tosyl derivative of



Scheme 3 Crystallisation-driven stereoselective three-component Mannich reaction



Scheme 4 Stereoselective synthesis of *syn*-γ-hydroxynorvaline (**3**)



Scheme 5 Synthesis of norvaline (**1**) and γ-oxonorvaline (**2**) *via* chemoselective reductions of amino acid **4f**

hydroxynorvaline confirmed a high enantiomeric purity (er 92:8).[31] To the best of our knowledge, this is the first time that the enantiomeric purity of *syn*-γ-hydroxynorvaline was determined by HPLC analysis instead of the traditional measurement of optical rotation.

Unlike preparation of γ-hydroxynorvaline (**3**), the synthesis of norvaline (**1**) required complete but chemoselective removal of two latent functional groups – the *N*-benzyl moiety and the oxo group in the γ-position (Scheme 5). Although undeniable progress has been made in the deoxygenation of organic compounds,[32] especially *via* advanced Clemmensen[33] or Wolff–Kishner reactions,[34] epimerisation-prone substrate **4f** restricted the available arsenal to only a few options. While the classical Clemmensen reduction has met with only limited success, the two-step Mozingo desulfuration of thioacetal **12** proved to be a highly reliable alternative. Firstly, thioacetal **12**, available from ketone **4f** in excellent yield, was treated with Raney nickel under a hydrogen atmosphere at 55 °C, resulting in the formation of amino acid **13** (Scheme 5). Without any purification, the intermediate underwent Pd-catalysed debenzylation that completed the envisaged global deprotection. Norvaline (**1**) was isolated in a respectable 53% yield and 97:3 er, thus indicating a high stability of the present stereogenic centre at C-2.[31] Featuring another acid-promoted chemoselective debenzylation, γ-oxonorvaline (**2**) was obtained directly from key intermediate **4f** in just one step in an excellent 92% chemical yield (Scheme 5). HPLC analysis of γ-oxonorvaline (**2**) confirmed again only negligible erosion of the stereochemical purity during the synthesis; an excellent 97:3 er was detected.[31]

In conclusion, we have developed short and highly stereoselective syntheses of three enantiomerically pure non-proteinogenic amino acids: L-norvaline (**1**), γ-oxonorvaline (**2**), and *syn*-γ-hydroxynorvaline (**3**). The unified, chromatography-free strategy pivots on a highly diastereoselective crystallisation-driven Mannich reaction using acetone (**7**), glyoxylic acid monohydrate (**8**), and amine **6f** as inexpensive, commercially available starting materials. Further chemoselective and/or stereoselective reductive manipulation of key intermediate **4f** allowed the preparation of all three amino acids from the same common intermediate. The high enantiomeric purities of norvaline (**1**), γ-oxonorvaline (**2**), and *syn*-γ-hydroxynorvaline (**3**) were confirmed by HPLC analysis, either directly of the amino acids or of their derivatives.

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian VXR-300 and 600 MHz spectrometers (300 MHz, 600 MHz and 75.4 MHz, 151 MHz, respectively). High-resolution mass spectra were recorded on an Orbitrap Velos PRO, Thermo Scientific 5 machine. Optical rotations were measured on a JASCO P-1020 or POLAR L-mP (IBZ Mestechnik) polarimeter (concentration, *c*, is given as g/100 mL). The reaction progress was monitored by reverse-phase HPLC using a UV-VIS-205 detector (at 205 nm), Varian ProStar 310 pump (1.0 mL/min flow), Clarity DataApex software, and Nucleodur® Phenyl-Hexyl C18 column (Macherey-Nagel, 250 × 4.0, 5 µm). H_2O–MeCN based eluents were used for most of the analyses, with Et_3N

and 85% aq H_3PO_4 (v/v 1:1) as additives (1% v/v compare to the H_2O–MeCN mixture). (*E*)-4-Oxopent-2-enoic acid (**5a**) was prepared by a published method.[21a]

2-[1-(4-Bromophenyl)ethylamino]-4-oxopentanoic Acid (4e)

To a solution of acid **5a** (0.228 g, 2.00 mmol) in $CHCl_3$ (10 mL) was added amine (*S*)-**6e** (0.440 g, 2.20 mol, 1.1 equiv) and the resulting mixture was stirred at rt and monitored by HPLC. After 6 d, the insoluble solid was collected by filtration, washed (Et_2O), and dried, yielding amino acid **4e**.

Yield: 0.471 g, 75%, dr 99:1; white solid; mp 128 °C; $[\alpha]_D^{25}$ –18.6 (*c* 1, MeOH–5% aq HCl, 9:1).

^{1}H NMR (300 MHz, DMSO-d_6 + DCl): δ = 7.63 (d, *J* = 8.5 Hz, 2 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 4.54 (q, *J* = 6.5 Hz, 1 H), 3.72 (t, *J* = 4.9 Hz, 1 H), 3.25–3.03 (m, 2 H), 2.10 (s, 3 H), 1.59 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6 + DCl): δ = 203.8, 169.4, 135.8, 132.1, 130.8, 122.7, 57.0, 52.0, 42.7, 29.7, 19.9.

HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}BrNO_3$: 314.03863; found: 314.03849.

2-[1-(4-Methoxyphenyl)ethylamino]-4-oxopentanoic Acid (4f)

By Michael addition: To a solution of acid **5a** (4.0 g, 35 mmol) in $CHCl_3$ (175 mL) was added amine (*S*)-**6f** (6.3 g, 6.2 mL, 42 mmol, 1.2 equiv) and the resulting mixture was stirred at rt and monitored by HPLC. After 5 d, the insoluble solid was collected by filtration, washed (Et_2O), and dried, yielding amino acid **4f**.

Yield: 8.3 g, 88%, dr 99:1; white solid.

By Mannich reaction: glyoxylic acid monohydrate (**8**; 4.6 g, 50 mmol) was suspended in a mixture of $CHCl_3$ (200 mL) and acetone (74 mL), which was cooled to 0 °C. Amine (*S*)-**6f** (9.1 g, 8.9 mL, 60 mmol, 1.2 equiv) was added dropwise within 10 min to this solution, and the reaction mixture was stirred at 0 °C. After 30 min, the mixture was warmed to rt. The reaction was monitored by HPLC and after 48 h the precipitate was collected by filtration, washed with Et_2O (15 mL), and dried, yielding amino acid **4f**.

Yield: 7.9 g, 60%, dr 98:2; white solid; mp 120 °C (dec.); $[\alpha]_D^{25}$ –27.8 (*c* 1, MeOH–5% aq HCl, 9:1).

^{1}H NMR (300 MHz, DMSO-d_6 + DCl): δ = 7.41 (d, *J* = 8.7 Hz, 2 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 4.44 (q, *J* = 6.8 Hz, 1 H), 3.71 (s, 3 H), 3.65 (m, 1 H), 3.15–3.00 (m, 2 H), 2.05 (s, 3 H), 1.55 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6 + DCl): δ = 204.4, 169.7, 160.3, 130.2, 128.2, 114.9, 57.5, 55.8, 52.1, 43.0, 30.0, 20.4.

HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_4$: 266.13868; found: 266.13868.

Lactone 10

Amino acid **4f** (2.84 g, 10.7 mmol) and $MnCl_2{\cdot}4H_2O$ (424 mg, 2.14 mmol, 20 mol%) were suspended in MeOH (100 mL), and the mixture was cooled to 0 °C. $NaBH_4$ (605 mg, 16.1 mmol, 1.5 equiv) was added portionwise during 30 min, and the reaction mixture was allowed to warm to rt. The reaction was monitored by HPLC, and after 1 h it was concentrated *in vacuo*, affording crude hydroxy acid **9**. To the crude acid was added 8 M aq HCl (55 mL) and the reaction mixture was stirred at 40 °C. After 2 h, the mixture was concentrated *in vacuo*. The residue was diluted with 10% aq K_2CO_3 (55 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised (Et_2O–hexane), yielding lactone **10**.

Yield: 1.54 g, 58% (over 2 steps from **4f**), dr 98:2; white crystalline solid; mp 69–70.4 °C; $[\alpha]_D^{25}$ –114.3 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2 H), 6.89–6.85 (m, 2 H), 4.62 (dqd, *J* = 7.7, 6.5, 3.5 Hz, 1 H), 4.07 (q, *J* = 6.6 Hz, 1 H), 3.81 (s, 3 H), 3.46 (t, *J* = 8.5 Hz, 1 H), 1.94 (ddd, *J* = 13.0, 8.6, 7.7 Hz, 1 H), 1.71 (ddd, *J* = 13.0, 8.4, 3.5 Hz, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.26 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 177.8, 158.9, 137.0, 128.2, 113.9, 74.8, 57.2, 55.4, 54.7, 37.8, 24.8, 21.3.

HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_3$: 250.14377; found: 250.14358.

Lactone 11

To a mixture of lactone **10** (2.92 g, 11.7 mmol) and Et_3SiH (1.4 g, 1.9 mL, 12 mmol) was added TFA (9 mL) and the resulting mixture was stirred at 60 °C. After 30 min, the mixture was concentrated *in vacuo* and the crude product was triturated with cold Et_2O (30 mL). The precipitated white solid was collected by filtration, washed with Et_2O (5 mL), and dried, yielding lactone **11**.

Yield: 2.56 g, 95%, dr 98:2; white solid; mp 132–134 °C; $[\alpha]_D^{25}$ –11.8 (*c* 1, MeOH).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.76 (br s, 3 H), 4.86–4.81 (m, 1 H), 4.49 (t, *J* = 9.7 Hz, 1 H), 2.39 (ddd, *J* = 12.8, 9.9, 8.7 Hz, 1 H), 2.27 (ddd, *J* = 12.8, 9.3, 2.2 Hz, 1 H), 1.34 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 172.9, 158.4 (q, *J* = 31.1 Hz), 117.2 (q, *J* = 301.2 Hz), 75.2, 47.2, 32.3, 20.6.

HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{10}NO_2$: 116.07061; found: 116.07069.

syn-γ-Hydroxynorvaline (3)

To a mixture of lactone **11** (229 mg, 1.00 mmol) and H_2O (2.3 mL) was added 2 M aq NaOH (1.4 mL) at rt. The reaction mixture was stirred for 1 h and passed through a column of Dowex 50WX8 ion exchange resin (H^+ form, 3 g). The column was washed thoroughly with H_2O (50 mL) and the amino acid was eluted with NH_4OH (25–27% NH_3 in H_2O, 20 mL). The ammoniacal eluate was lyophilized to dryness *in vacuo* affording *syn*-γ-hydroxynorvaline (**3**).

Yield: 133 mg, ~100%, er 92:8[31]; white solid; mp 213 °C (dec.) (Lit.[13c] 228–230 °C, EtOH–H_2O); $[\alpha]_D^{25}$ +18 (*c* 1.3, H_2O) [Lit.[13c] $[\alpha]_D^{25}$ +21 (*c* 1.3, H_2O)].

^{1}H NMR (300 MHz, D_2O): δ = 4.11–4.01 (m, 1 H), 3.74 (dd, *J* = 9.1, 4.3 Hz, 1 H), 2.06 (dt, *J* = 15.0, 4.3 Hz, 1 H), 1.77 (dt, *J* = 15.0, 9.1 Hz, 1 H), 1.24 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (75 MHz, D_2O): δ = 175.3, 66.6, 54.2, 38.9, 22.7.

All data are in good agreement with previously published data.[13c]

Thioacetal 12

To a mixture of amino acid **4f** (2.65 g, 10.0 mmol) and 12 M aq HCl (10 mL) was added dropwise ethane-1,2-dithiol (1.2 g, 1.1 mL, 0.013 mol); the resulting mixture was stirred at rt. After 24 h the insoluble solid was collected by filtration and washed with Et_2O (3 × 20 mL), yielding thioacetal **12**.

Yield: 2.8 g, 74%; white solid; mp 182–183 °C; $[\alpha]_D^{25}$ –29.4 (*c* 1.0, DMSO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.26 (br s, 1 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 6.96 (d, *J* = 8.7 Hz, 2 H), 4.26 (q, *J* = 6.5 Hz, 1 H), 3.76 (s, 3 H), 3.40 (dd, *J* = 9.2, 2.5 Hz, 1 H), 3.34–3.06 (m, 4 H), 2.77 (dd, *J* = 14.4, 2.0 Hz, 1 H), 2.46 (m, 1 H), 1.61 (m, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.7, 159.6, 129.9, 128.0, 114.1, 64.0, 56.6, 56.3, 55.2, 44.1, 39.6, 30.9, 20.8.

HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{24}NO_3S_2$: 342.11921; found: 342.11935

Norvaline (1)

To a mixture of thioacetal **12** (0.754 g, 2.00 mmol) in H_2O (10 mL) and MeOH (10 mL) was added Raney Ni (W-2, 3.8 g) and the heterogeneous mixture was stirred under H_2 (balloon) at 55 °C. After 1 h, the mixture was cooled to rt, Raney Ni (W-2, 3.9 g) was added, and the mixture was stirred again under H_2 (balloon) at 55 °C. After 24 h, the mixture was filtered through a pad of Celite, the filter cake was washed with boiling MeOH (5 × 20 mL), and the filtrate was concentrated *in vacuo*. H_2O (10 mL) was added and the insoluble solid was collected by filtration, washed (Et_2O), and dried, affording a white solid. This residue was dissolved in MeOH (20 mL), and 10% Pd/C (100 mg) was added under argon. The mixture was degassed and stirred under H_2 (balloon) at rt. After 48 h (complete conversion by LCMS), the mixture was filtered through a pad of Celite, the filter cake was washed with MeOH (2 × 10 mL), and the combined filtrates were concentrated *in vacuo*, affording norvaline (**1**).

Yield: 0.123 g, 53%, er 97:3[31]; white solid; mp 290 °C (dec.) (Lit.[35] 297 °C); $[\alpha]_D^{25}$ +4.9 (*c* 1, H_2O) [Lit.[35] $[\alpha]_D^{25}$ +6.5 (*c* 2, H_2O); Lit.[4b] (91% ee) $[\alpha]_D^{20}$ +4.6 (*c* 1.0, H_2O)].

^{1}H NMR (300 MHz, D_2O): δ = 3.82 (t, *J* = 5.9 Hz, 1 H), 1.97–1.82 (m, 2 H), 1.44 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, D_2O): δ = 175.1, 54.7, 32.5, 17.8, 12.9.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{12}NO_2$: 118.1; found: 118.2.

γ-Oxonorvaline Hydrochloride (2)

A mixture of amino acid **4f** (1.33 g, 500 mmol) and 6 M aq HCl (100 mL) was stirred at 95 °C. After 48 h, the mixture was cooled to rt and extracted with Et_2O (3 × 100 mL). The combined organics were discarded. The aqueous layer was concentrated *in vacuo*, yielding a yellow solid. To this residue was added Et_2O (100 mL) and the mixture was stirred at rt. After 1 h, the insoluble solid was collected by filtration, washed with Et_2O (3 × 50 mL), and dried, yielding γ-oxonorvaline hydrochloride (**2**).

Yield: 0.60 g, 92%, er 97:3[31]; yellow solid; mp 147 °C (Lit.[36] 135–137 °C); $[\alpha]_D^{25}$ +8.9 (*c* 1, H_2O) [Lit.[36] $[\alpha]_D^{25}$ +8 (*c* 1, H_2O)].

^{1}H NMR (300 MHz, D_2O): δ = 4.34–4.30 (m, 1 H), 3.43–3.28 (m, 2 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, D_2O): δ = 209.6, 171.4, 48.5, 42.1, 29.0.

HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{10}NO_3$: 132.06552; found: 132.06571.

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Supporting Information

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(31) (a) For further details, see the Supporting Information. (b) The observed negligible difference in the dr of adduct **4f** (98:2), the er of norvaline (**1**) (er 97:3), and the er of γ-oxonorvaline (**2**) (97:3) could be attributed to the precision limits/accuracy of the HPLC measurements. The apparent erosion of the enantiomeric purity of *syn*-γ-hydroxynorvaline (**3**) (er 92:8) could be caused by a partial epimerisation of the intermediates during the transformations of **4f** to *syn*-γ-hydroxynorvaline (**3**).
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