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Synthesis of all four enantiomers of 1-aminoindane-2-carboxylic acid, a new cispentacin benzologue

Ferenc Fülöp,[a,*] Márta Palkó,[a] Judit Kámán,[a] László Lázár[a] and Reijo Sillanpää[b]

[a]*Institute of Pharmaceutical Chemistry, University of Szeged, PO Box 121, H-6701 Szeged, Hungary*
[b]*Department of Chemistry, University of Turku, FIN-20014 Turku, Finland*

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Abstract

Racemic *cis*- and *trans*-1-aminoindane-2-carboxylic acids (**3** and **5**) were prepared from indene by chlorosulphonyl isocyanate addition followed by ring opening and isomerisation. The intermediate racemic hydroxymethylated β-lactam **6** was resolved through the lipase-catalysed asymmetric acylation of the primary hydroxy group at the (*R*)-stereogenic centre. High enantioselectivities (E>200) were observed when the enzymatic reactions were performed with lipase AK or lipase PS as catalyst and vinyl acetate or vinyl butyrate as acyl donor. The hydrolysis and isomerisation resulted in all four enantiomers (**9**, **11**, **13** and **14**) of 1-aminoindane-2-carboxylic acid, a new benzologue of cispentacin.

1. Introduction

Although of less importance than their α-analogues, β-amino acids are also present in peptides and different heterocycles, and their free forms and derivatives exhibit interesting pharmacological effects.[1–6] A decade ago, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin), an antifungal antibiotic, was isolated from *Bacillus cereus*[7] and *Streptomyces setonii*.[8] *cis*-2-Aminocyclopentanecarboxylic acid is also a component of the antibiotic amipurimycin.[9] The research groups of Seebach and Gellman recently reported oligopeptide chains which can fold into stable helical structures.[10,11] Gellman's group synthesised and investigated[12–14] *trans*-2-aminocyclopentane- and *trans*-2-aminocyclohexanecarboxylic acid oligomers which display a stable helical conformation.

Besides the fact that they themselves possess pharmacological activity, the alicyclic β-amino acids can be used as building blocks for the preparation of modified (unnatural) analogues of

* Corresponding author. Tel: 36 62 545564; fax: 36 62 545705; e-mail: fulop@pharma.szote.u-szeged.hu

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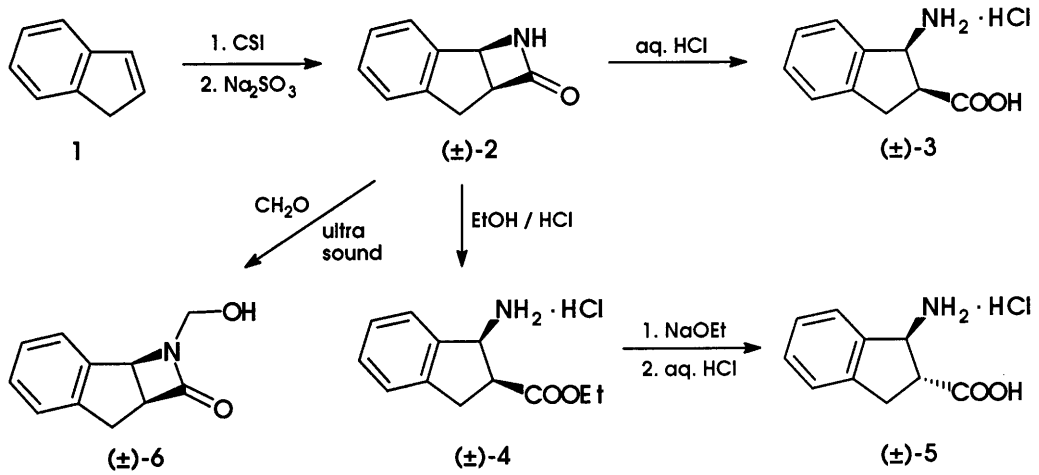
biologically active peptides. In consequence of the natural occurrence and the novel biological activity, chemical interest in investigations of the alicyclic β-amino acids has rapidly increased. Our present aim was the synthesis of the title alicyclic β-amino acids.

2. Results and discussion

2.1. Synthesis of the racemic β-amino acid substrates

The pathways of the syntheses of the racemic amino acids **3** and **5** are shown in Scheme 1. Chlorosulphonyl isocyanate addition[15–17] to indene takes places regio- and stereoselectively, in accordance with the Markovnikov orientation, resulting in β-lactam **2**. Treatment of **2** with hydrochloric acid resulted in amino acid hydrochloride **3**, while treatment with ethanolic hydrogen chloride led to ethyl ester **4**. Sodium ethoxide isomerisation of **4**, followed by acidic hydrolysis, resulted in the *trans* amino acid hydrochloride **5**. The free amino acids of **3** and **5** were liberated by ion-exchange chromatography.

The *N*-hydroxymethylated β-lactam **6**, the starting substance of the enzymatic reactions, was prepared from **2** with paraformaldehyde under sonication.



Scheme 1.

2.2. Enzymatic resolutions

N-Hydroxymethylated β-lactams were earlier readily resolved[18] by means of lipase AK- or lipase PS-catalysed asymmetric acylation of the primary hydroxy group at the (*S*) stereogenic centre. The investigated related substrates were: *N*-hydroxymethylated 7-azabicyclo[3.2.0]heptan-7-one, 7-azabicyclo[4.2.0]octan-8-one, 7-azabicyclo[4.2.0]oct-3-en-8-one and 7-azabicyclo[4.2.0]oct-4-en-8-one.[19,20] The enantioselectivities (*E*) varied in the range 40–200 when vinyl butyrate was used as acyl donor. Acetone proved to be the best solvent for the transformations.

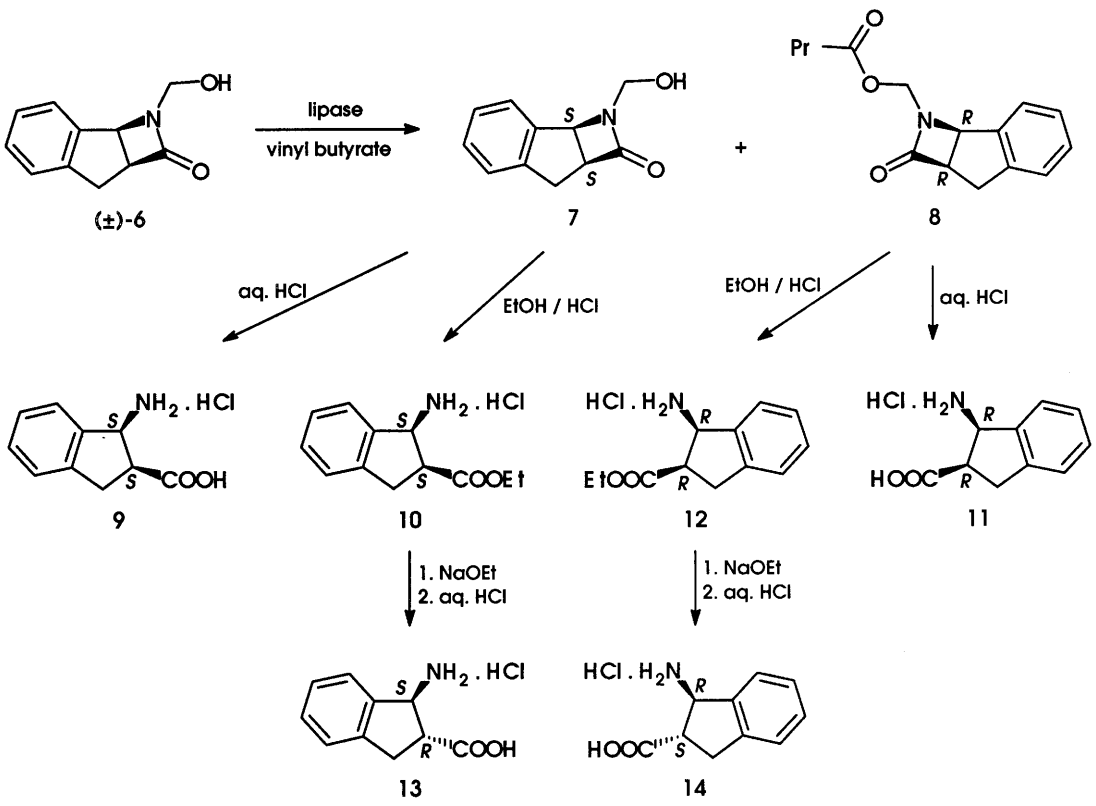
At the beginning of this work, we had some doubt as to whether similarly high selectivities would be achieved, since the steric demand of the benzologue of 7-azabicyclo[3.2.0]heptan-7-one is increased. In the small-scale experiments (Table 1), it was found that lipase AK and lipase PS are each excellent catalysts, both in vinyl acetate- and in vinyl butyrate-mediated acylation

(E>200). In the present case, replacement of acetone by acetonitrile or tetrahydrofuran did not lead to lower E values; excellent selectivities were still attained (E>200). Finally, for the gram-scale resolution of **6**, lipase AK and vinyl butyrate in THF were used. With this method, after a reaction time of 2.5 hours, product **8** was obtained in 44% yield, and substrate **7** in 42% yield, after chromatographic separation, both with ee = 99%.

Table 1
Effects of vinyl esters (0.2 M) and solvent on the acylation of **6** (0.1 M) in the presence of lipase PS[a] or AK[a] (50 mg ml^{-1}) at room temperature

Solvent	Acyl donor[b]	Enzyme	Time (h)	Conv. (%)	Ee_s (%)	Ee_p (%)	E
Acetone	VA	Lipase AK[a]	4	49	94	98	>200
Acetone	VB	Lipase AK[a]	7	47	88	99	>200
Acetone	VB	Lipase PS[a]	7	40	66	99	>200
THF	VB	Lipase PS[a]	7	46	85	98	>200
THF	VB	Lipase AK[a]	2.5	49	96	99	>200
Acetonitrile	VB	Lipase AK[a]	8	49	93	98	>200

[a] Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.
[b] VA = vinyl acetate, VB = vinyl butyrate.



Scheme 2.

Enantiomers **7** and **8** were transformed to the corresponding β-amino acids **9** and **11** and esters **10** and **12**, similarly to the racemic compounds (Scheme 2). Isomerisation of esters **10** and **12**, followed by hydrolysis, resulted in the *trans* enantiomers **13** and **14**, respectively, with high optical purity (ee = 99%).

2.3. Absolute configurations

X-ray investigation revealed the absolute configuration of **12**. Amino ester **12** was transformed to thiourea **15** by reacting it with (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate (DANI), a newly developed chiral derivatising agent.[21,22] The X-ray structure (Fig. 1) clearly shows the (*R*,*R*) configuration of the starting **12**. In the early cases, *S* selectivity was observed[19,20] in the enzyme-catalysed acylation of hydroxymethylated β-lactams, while in the present case *R* selectivity was found. It is necessary to mention that in these reactions the same stereochemical demands are fulfilled around the asymmetric centres, but only the sequence of priority of the substituents on the substrates differs.

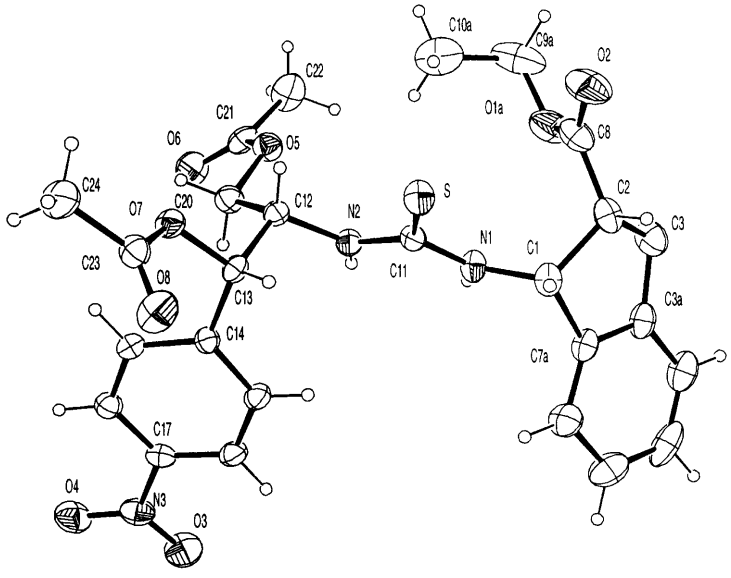


Figure 1. ORTEP plot of the X-ray structure of thiourea **15**. The thermal ellipsoids are drawn at the 25% probability level. Only the main component of the disordered ester chain is shown

3. Conclusions

Starting from indene, the syntheses of all four enantiomers of 1-aminoindane-2-carboxylic acid proved possible by a combination of lipase-catalysed *O*-acylation and some simple synthetic transformations. The synthesised β-amino acids, all four enantiomers (**9**, **11**, **13** and **14**) of 1-aminoindane-2-carboxylic acid, are promising compounds for the synthesis of partially saturated heterocycles, peptides and peptidomimetics, as potential pharmacons.

4. Experimental

4.1. Materials and methods

Vinyl acetate was purchased from Aldrich Chemical Co. and vinyl butyrate from Fluka. Lipase PS and lipase AK were obtained from Amano Pharmaceuticals, and Novozym 435 as an immobilised preparation from Novo Nordisk. Before use, lipase PS (5 g) was dissolved in Tris–HCl buffer (0.02 M; pH 7.8) in the presence of sucrose (3 g), followed by adsorption on Celite (17 g) (Sigma). The lipase preparation thus obtained contained 20% (w/w) of lipase.

The ee values of the unreacted alcohol **7** and the produced ester **8** and amino esters **10** and **12** were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m). Amino esters **10** and **12** were derivatised with acetic anhydride in the presence of 4-dimethylaminopyridine and pyridine before the gas chromatographic analysis. The ee values of the amino acid enantiomers **9**, **11**, **13** and **14** were determined by HPLC on an APEX ODS column (0.46×25 cm, Jones Chromatography Ltd.), with 0.1% aqueous trifluoroacetic acid:methanol (45:55) as eluent. For chiral derivatisation, (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate was used, according to the literature.[21,22]

Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and om (overlapping multiplet). Melting points were determined on a Kofler apparatus.

4.2. 3,4-Benzo-6-azabicyclo[3.2.0]heptan-7-one, (±)-2

A solution of 15.57 g (0.11 mol) *N*-chlorosulphonyl isocyanate in dry diethyl ether (50 ml) was added rapidly to 11.62 g (0.10 mol) freshly distilled indene dissolved in dry diethyl ether (200 ml). The resulting colourless solution was stirred for 2 hours at room temperature, after which *n*-hexane (100 ml) was added and the crystalline product was filtered off. The crystalline *N*-chlorosulphonyl derivative was dissolved in diethyl ether (200 ml) and added, dropwise and with stirring, to a mixture of Na_2SO_3 (10 g) in water (50 ml) and diethyl ether (50 ml). During the addition, the aqueous phase was kept slightly alkaline by addition of 10% KOH solution. (±)-**2** crystallised out and was filtered off (7.92 g) from the mixture. A second crop of (±)-**2** was obtained as follows: from the above filtrate, the organic phase was separated, and the aqueous part was extracted twice with diethyl ether. The combined organic layer was dried (Na_2SO_4) and evaporated. The combined crude products were recrystallised from ethyl acetate–methanol, which afforded 10.03 g (63%) colourless crystals of (±)-**2**, mp 188–189°C, lit.[23] mp 183–184°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.07 (1H, dd, $J=17.5$, 10.5, CH_2), 3.35 (1H, d, $J=17.4$, CH_2), 4.02 (1H, m, CHCO), 5.03 (1H, d, $J=4.2$, CHN), 6.28 (1H, broad s, NH), 7.18–7.36 (4H, om, C$_6H_4$). Analysis: calculated for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80; found: C, 75.61; H, 5.91; N, 8.65.

4.3. cis-1-Aminoindane-2-carboxylic acid hydrochloride, (±)-3

The β-lactam (±)-**2** (1.59 g, 0.01 mol) was refluxed in 36% hydrochloric acid (10 ml) for 12 hours. After standing overnight, the precipitated crystalline product was separated by filtration and recrystallised from ethanol–diethyl ether (1.68 g, 79%), mp 220–222°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.37 (2H, d, $J=8.9$, CH_2), 3.74 (1H, dd, $J=15.9$, 8.7, CHCO), 5.01 (1H, d, $J=7.0$, CHN), 7.42 (3H, m, C_6H_4), 7.53 (1H, d, $J=7.5$, C_6H_4). Analysis: calculated for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; found: C, 56.35; H, 5.56; N, 6.72.

The free amino acid base was liberated by ion-exchange chromatography with DOWEX 50, mp 265–266°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.22 (1H, dd, $J=16.3$, 9.6, CH_2), 3.32 (1H, dd, $J=16.3$, 8.6, CH_2), 3.51 (1H, m, CHCO), 4.85 (1H, d, $J=6.8$, CHN), 7.37 (1H, m, C_6H_4), 7.44 (2H, m, C_6H_4), 7.51 (1H, d, $J=7.5$, C_6H_4). Analysis: calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.49; H, 6.48; N, 7.97.

4.4. *Ethyl* cis-*1-aminoindane-2-carboxylate hydrochloride*, (±)-**4**

The β-lactam (±)-**2** (0.01 mol, 1.59 g) was refluxed in ethanol (50 ml) containing 22% dry hydrogen chloride for 8 hours. The solvent was evaporated off, and the crystalline product was recrystallised from ethanol–diethyl ether (1.98 g, 82%), mp 210–211°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (3H, t, $J=7.1$, CH_3), 3.24 (1H, dd, $J=18.0$, 10.8, CHCH_2), 3.54 (2H, m, CHCH_2, CHCO), 4.20 (2H, q, $J=7.1$, OCH_2), 4.81 (1H, d, $J=6.2$, CHN), 7.25 (3H, m, C_6H_4), 7.80 (1H, d, $J=7.6$, C_6H_4). Analysis: calculated for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79; found: C, 59.82; H, 6.56; N, 5.43.

4.5. trans-*1-Aminoindane-2-carboxylic acid hydrochloride*, (±)-**5**

Sodium (0.60 g) was dissolved in dry ethanol (20 ml), 2.05 g (0.01 mol) base (±)-**4** was added to this solution and the mixture was heated at 70°C for 7 hours. The yellow solution was evaporated and refluxed with 10% hydrochloric acid (20 ml) for 10 hours. After standing overnight, the solution was filtered and evaporated to dryness. The residue was dissolved in hot methanol, and the removal of solvent gave 1.80 g crude product, which was recrystallised from ethanol–diethyl ether (1.45 g, 60%), mp 220–222°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.23 (1H, m, CH_2), 3.51 (2H, m, CH_2, CHCO), 5.17 (1H, d, $J=5.3$, CHN), 7.40 (3H, m, C_6H_4), 7.51 (1H, d, $J=7.0$, C_6H_4). Analysis: calculated for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; found: C, 56.44; H, 5.73; N, 6.40.

The free amino acid base was liberated by ion-exchange chromatography with DOWEX 50, mp 234–235°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.13 (1H, dd, $J=16.0$, 7.0, CH_2), 3.22 (1H, m, CH_2), 3.46 (1H, dd, $J=16.0$, 8.7, CHCO), 5.04 (1H, d, $J=6.0$, CHN), 7.40 (3H, m, C_6H_4), 7.48 (1H, d, $J=7.4$, C_6H_4). Analysis: calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.66; H, 6.38; N, 7.72.

4.6. *Preparation of racemic 3,4-benzo-6-hydroxymethyl-6-azabicyclo[3.2.0]heptan-7-one*, (±)-**6**

Compound **2** (6.00 g, 37.69 mmol) was dissolved in THF (250 ml), and paraformaldehyde (1.36 g), potassium carbonate (0.52 g, 3.77 mmol) and water (3.8 ml) were added. The solution was sonicated for 5 hours. The solvent was evaporated off and the residue was dissolved in ethyl acetate. The solution was dried over Na_2SO_4, the solvent was evaporated off and the product was recrystallised from a THF–diisopropyl ether mixture to afford white crystals of **6** (5.06 g, 71%,), mp 112–114°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.08 (2H, m, CHCH_2, OH), 3.33 (1H, d, $J=17.4$, CHCH_2), 4.01 (1H, m, CHCO), 4.39 (1H, dd, $J=11.6$, 9.0, CH_2OH), 4.87 (1H, dd, $J=11.6$, 5.8, CH_2OH), 5.17 (1H, d, $J=4.3$, CHN), 7.28 (3H, m, C_6H_4), 7.42 (1H, d, $J=7.4$, C_6H_4). Analysis: calculated for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40; found: C, 69.39; H, 6.23; N, 7.30.

4.7. General procedure for small-scale experiments

The *N*-hydroxymethyl-β-lactam (±)-**6** (0.1 M solution) in an organic solvent (1 ml) was added to lipase PS (50 mg ml^{-1}) or lipase AK (50 mg ml^{-1}). Vinyl acetate or butyrate (0.2 M in the reaction mixture) was added and the mixture was shaken at room temperature. The progress of the reaction was followed by taking samples from the reaction mixture at intervals and analysing them by gas chromatography.

4.8. Gram-scale resolution of (±)-6

Racemic **6** (4.00 g, 21.14 mmol) was dissolved in THF (200 ml), lipase AK (10.58 g) and vinyl butyrate (4.83 g, 42.28 mmol) were added and the mixture was stirred at room temperature. After 2.5 hours, a few drops of triethylamine were added in order to enhance the stability of the unreacted acid-labile **7**, and the enzyme was filtered off at 50% conversion. The THF was evaporated off. The residue was chromatographed on silica, with elution with dichloromethane:ethyl acetate (9:1) for separation of the ester (1*R*,5*R*)-**8** (2.43 g, 9.37 mmol; $[\alpha]_D^{25}=-91.8$ ($c=0.51$, $CHCl_3$); ee = 99%) as a colourless oil. Elution with dichloromethane:ethyl acetate (1:1) afforded the unreacted (1*S*,5*S*)-**7** (1.68 g, 8.88 mmol; $[\alpha]_D^{25}=+137$ ($c=0.36$, $CHCl_3$); ee = 99%; mp 138–140°C) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **8**: 0.96 (3H, t, $J=7.4$, CH_3), 1.66 (2H, m, $CH_2CH_2CH_3$), 2.30 (2H, t, $J=7.4$, $CH_2CH_2CH_3$), 3.09 (1H, dd, $J=17.4$, 10.5, CHCH_2), 3.32 (1H, d, $J=17.4$, CHCH_2), 4.00 (1H, m, CHCO), 4.97 (1H, d, $J=11.4$, OCH_2), 5.07 (1H, d, $J=11.4$, OCH_2), 5.11 (1H, d, $J=4.4$, CHN), 7.30 (3H, m, C_6H_4), 7.61 (1H, d, $J=7.4$, C_6H_4). Analysis: calculated for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; found: C, 69.12; H, 6.71; N, 5.48.

The ^{1}H NMR data for **7** are similar to those for (±)-**6**. Analysis found: C, 69.71; H, 5.91; N, 7.35.

4.9. Acid hydrolysis of 7 and 8

Compound **7** (0.40 g, 2.11 mmol) was dissolved in 18% HCl (14 ml) and refluxed for 2 hours at 70°C. The solvent was evaporated off, and the residue was recrystallised from ethanol–diethyl ether, which afforded white crystals of (1*S*,2*S*)-**9** (0.35 g, 1.64 mmol; $[\alpha]_D^{25}=+5.7$ ($c=0.50$, MeOH); mp 281–282°C; ee = 99%).

The ^{1}H NMR data for **9** are similar to those for (±)-**3.** Analysis found: C, 56.34; H, 5.58; N, 6.53.

Similarly, **8** (1.00 g, 3.86 mmol) afforded white crystals of (1*R*,2*R*)-**11** (0.50 g, 2.34 mmol; $[\alpha]_D^{25}=-5.3$ ($c=0.50$, MeOH); mp 273–275°C; ee = 99%). The ^{1}H NMR data for **11** are similar to those for **9** and (±)-**3**. Analysis found: C, 56.29; H, 5.71; N, 6.60.

4.10. Preparation of esters **10** and **12**

Similarly as in Section 4.4, (1*S*,5*S*)-**7** (0.80 g, 4.23 mmol) afforded white crystals of (1*S*,2*S*)-**10** (0.73 g, 3.02 mmol; $[\alpha]_D^{25}=+6.0$ ($c=0.50$, H_2O); mp 208–209°C; ee = 99%). The ^{1}H NMR data for **10** are similar to those for (±)-**4**. Analysis found: C, 59.74; H, 6.61; N, 5.75.

Similarly, (1*R*,5*R*)-**8** (1.00 g, 3.86 mmol) afforded white crystals of (1*R*,2*R*)-**12** (0.70 g, 2.90 mmol; $[\alpha]_D^{25}=-6.2$ ($c=0.50$, H_2O); mp 214–216°C; ee = 99%). The ^{1}H NMR data for **12** are similar to those for **10** and (±)-**4**. Analysis found: C, 59.69; H, 6.59; Cl, 14.62; N, 5.84.

4.11. Preparation of trans-1-aminoindane-2-carboxylic acid hydrochloride enantiomers **13** and **14**

With the procedure described in Section 4.5, (1*S*,2*S*)-**10** (0.40 g, 1.65 mmol) afforded (1*S*,2*R*)-**13** crude material. Since the product contained ~20% *cis* isomer, the isomerisation was carried out again, yielding white crystals of (1*S*,2*R*)-**13** (0.13 g, 0.61 mmol; $[\alpha]_D^{25}=-76.8$ ($c=0.5$, H_2O); mp 217–220°C; ee = 99%). The ^{1}H NMR data for **13** are similar to those for (±)-**5**. Analysis found: C, 56.11; H, 5.69; Cl, 16.47; N, 6.48.

With the above procedure, (1*R*,2*R*)-**12** (0.40 g, 1.65 mmol) afforded (1*R*,2*S*)-**14** (0.21 g, 0.98 mmol; $[\alpha]_D^{25}=+75.8$ ($c=0.5$, H_2O); mp 220–222°C; ee = 99%). The ^{1}H NMR data for **14** are similar to those for **13** and (±)-**5**. Analysis found: C, 56.28; H, 5.62; Cl, 16.52; N, 6.61.

4.12. Preparation of thiourea derivative **15**

The free base of ethyl ester **12** (0.08 g, 0.39 mmol) was dissolved in diethyl ether (10 ml), and (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate (0.14 g, 0.41 mmol) was added. The mixture was allowed to stand at room temperature for a few hours. The white crystals of **15** were separated. The product was recrystallised from diisopropyl ether–diethyl ether, mp 145–148°C.

4.13. X-ray crystallography

All data were collected on a Rigaku AFC5S diffractometer, with graphite-monochromated Mo Kα radiation ($\chi=0.71069$ Å) in the ω–2θ scan mode at room temperature. The lattice parameters were calculated by least-squares refinements of 20 reflections. The weak reflections [$I<10\sigma(I)$] were rescanned up to two times. For **15**, 2819 reflections were collected ($2\theta_{max}=50°$). The data were corrected for Lorentz and polarisation effects.

4.13.1. Crystal data for **15**

$C_{26}H_{27}N_3O_8S$, $M_r=541.57$, orthorhombic, space group $P2_12_12_1$ (no. 19), lattice parameters: $a=11.127(4)$, $b=22.908(3)$, $c=10.665(4)$ Å, $Z=4$, $V=2718.6(14)$ Å^3, $D_c=1.323$ g cm^{-3}, μ (Mo Kα) = 0.172 mm^{-1}, $F(000)=1136$, $T=294$ K; a colourless plate, crystal dimensions 0.22×0.24×0.32 mm.

The structure was solved by direct methods (SIR-92)[24] and refined by full-matrix least-squares techniques (SHELXL-97)[25] to an R_1 value of 0.048 ($wR_2=0.112$). These final R values are based on the reflections with $I>2\sigma(I)$. The heavy atoms were refined anisotropically. The hydrogen atoms on the aliphatic carbons (C1, C2, C12 and C13) and on the nitrogen atoms were refined

with fixed isotropic temperature factors ($1.2U_{eq}$ of the carrying atom) and the remaining hydrogen atoms were included in the calculated positions with fixed isotropic temperature factors (1.2 or 1.5 times U_{eq} of the carrying atom). The ester group at C8 has two orientations. The population of the major component is 56(5)%. Calculations were performed with teXsan for Windows[26] crystallographic software. Fig. 1 was drawn with ORTEP-3 for Windows.[27]

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References

1. *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VHC: New York, 1997.
2. Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905.
3. Abdel-Magid, A. F.; Cohen, J. H.; Maryanoff, C. A. *Curr. Med. Chem.* **1999**, *6*, 955.
4. Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983.
5. Fülöp, F. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed. The chemistry of 2-aminocyclopentanecarboxylic acid. Elsevier Science: New York, 2000; pp. 273–306.
6. Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett* **1993**, 461; Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411; Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595.
7. Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749.
8. Iwamoto, T.; Tsujii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H.; Kawabata, K.; Inamoto, Y.; Sakane, K. *J. Antibiot.* **1990**, *43*, 1.
9. Knapp, S. *Chem. Rev.* **1995**, *95*, 1859.
10. Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381; Porter, E. A.; Wang, X.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
11. Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.
12. Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206.
13. Appella, D. H.; Durell, S. L.; Barchi, J. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309.
14. Barchi, J. J.; Huang, X.; Appella, D. H.; Christianson, L. A.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 2711.
15. Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389.
16. Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437; Kamal, A.; Sattur, P. B. *Heterocycles* **1987**, *26*, 1051.
17. Szakonyi, Z.; Fülöp, F.; Bernáth, G.; Evanics, F.; Riddell, F. G. *Tetrahedron* **1998**, *54*, 1013.
18. Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Chemistry*; Wiley-VHC: Weinheim, 1999.
19. Csomós, P.; Kanerva, L. T.; Bernáth, G.; Fülöp, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1789.
20. Kámán, J.; Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2000**, *11*, 1593.
21. Péter, M.; Péter, A.; Fülöp, F. *Chromatographia* **1999**, *50*, 307.
22. Péter, M.; Péter, A.; Fülöp, F. *J. Chromatogr. A* **2000**, *871*, 115.
23. Murray, R. J.; Cromwell, N. H. *J. Heterocyclic Chem.* **1974**, *11*, 979.
24. Altomare, A.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
25. Sheldrick, G. M. *SHELX-97*; University of Göttingen: Germany, 1997.
26. Molecular Structure Corporation. *teXsan for Windows. Single Crystal Structure Analysis Software. Version 1.01.* MSC: 3200 Research Forest Drive, The Woodlands, TX 77381, USA, 1997.
27. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.