The Total Synthesis of Antrimycin D_v; II:[1] Synthesis of Tetrahydropyridazinecarboxylic Acid and Its Incorporation into Peptides[2]

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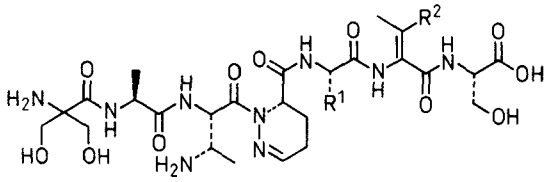
Appropriately protected di- and tripeptides containing (*R,S*)-tetrahydropyridazine-3-carboxylic acids were synthesized via protected γ-formyl-α-hydrazinobutyric acids. The latter compounds are obtained from acetals of either ethyl γ-formylbutyrate or ethyl γ-formyl-α-oxobutyrate.

The closely related (and, in parts, identical) cirratiomycins **1**[3] and antrimycins **2**[4] have been isolated from *Streptomyces xanthocidicus* and *S. cirratus*. These compounds contain the non-proteinogenic amino acids (hydroxymethyl)serine, dehydrovaline or dehydroisoleucine, (*S,S'*)-α,β-diaminobutyric acid, and (*S*)-tetrahydropyridazinecarboxylic acid. The latter has been found for the first time whereas its 4-hydroxy derivative has been found as a residue of luzopeptin,[5] a DNA intercalating, cancerostatic cyclopeptide.



1, 2

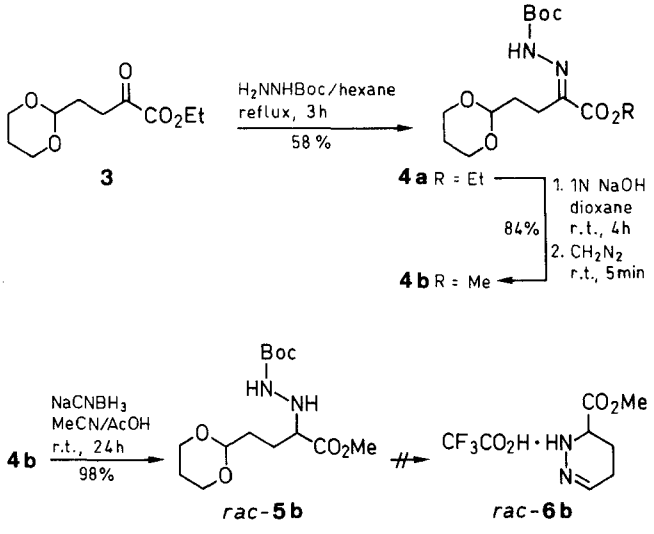
	R^1	R^2		R^1	R^2
1A	*i*-Bu	Et	**2B**	Et	Et
1B	Me	Et	**2C$_v$**	Pr	Me
2A$_v$	Me	Me	**2C**	Pr	Et
2A	Me	Et	**2D$_v$**	*i*-Bu	Me
2B$_v$	Et	Me	**2D**	*i*-Bu	Et

On the other hand, hexahydropyridazinecarboxylic acid has been identified as a residue in several non-ribosomal, biologically active peptides such as, e.g., the immunosuppressive depsidomycin.[6] Most of these peptides contain both enantiomeric forms of the hexahydropyridazinecarboxylic acid.

The antrimycins and cirratiomycins combine tuberculostatic activity with a low toxicity and are structurally related to lavendomycin;[7] we reported on the synthesis of the latter very recently.[8]

We have described the synthesis of antrimycin D_v in a preliminary communication[1] and now present the experimental details. In the meantime we have become aware of a short communication by Japanese authors[9] in which the synthesis of tetrahydropyridazinecarboxylic acid esters and the construction of a tetrapeptide possessing an *N*-terminal tetrahydropyridazinecarboxylic acid are described. However, this report does not contain any experimental details, the products are not sufficiently characterized by spectroscopy,[10] and some of the results deviate substantially from our work. The concept of the Japanese authors for the synthesis of antrimycins involves the coupling of a tetrapeptide possessing an *N*-terminal tetrahydropyridazinecarboxylic acid group with the tripeptide (hydroxymethylserylalanyldiaminobutyric acid. This step should only be realizable with exceptional difficulty; we have, for example, not yet been able to acylate a tetrahydropyridazinecarboxylic acid derivative.[11] The formation of a peptide containing a tetrahydropyridazinecarboxylic acid via dehydrogenation of the corresponding hexahydro compounds by *tert*-butyl hypochlorite and pyridine was recently mentioned in a patent.[12] First of all, we synthesized all the non-proteinogenic amino acids of antrimycin since our initial strategy comprised the synthesis of the two fragments alanyldiaminobutyryltetrahydropyridazinecarboxylic acid and leucyldidehydrovalylserine, the combination of these two tripeptides, and subsequent acylation with protected (hydroxymethyl)serine. However, unforeseen difficulties were encountered in the synthesis of peptides containing tetrahydropyridazinecarboxylic acid. We have thus investigated two approaches to the synthesis of this amino acid in which the ring is built up through intramolecular hydrazone formation from a 2-hydrazino-5-oxopentanoic acid.

1) Starting from the readily accessible acetal of ethyl 2,5-dioxopentanoate **3**,[13] the *tert*-butoxycarbonylhydrazones **4a** and **4b** were formed and the C=N bond reduced. However, attempts to cleave the acetal **5b** and close the ring in trifluoroacetic acid only gave rise to decomposition products. It was later found that only N_1,N_2-diacyl compounds of the type **8** are suitable for ring closure to tetrahydropyridazine derivatives **6**.

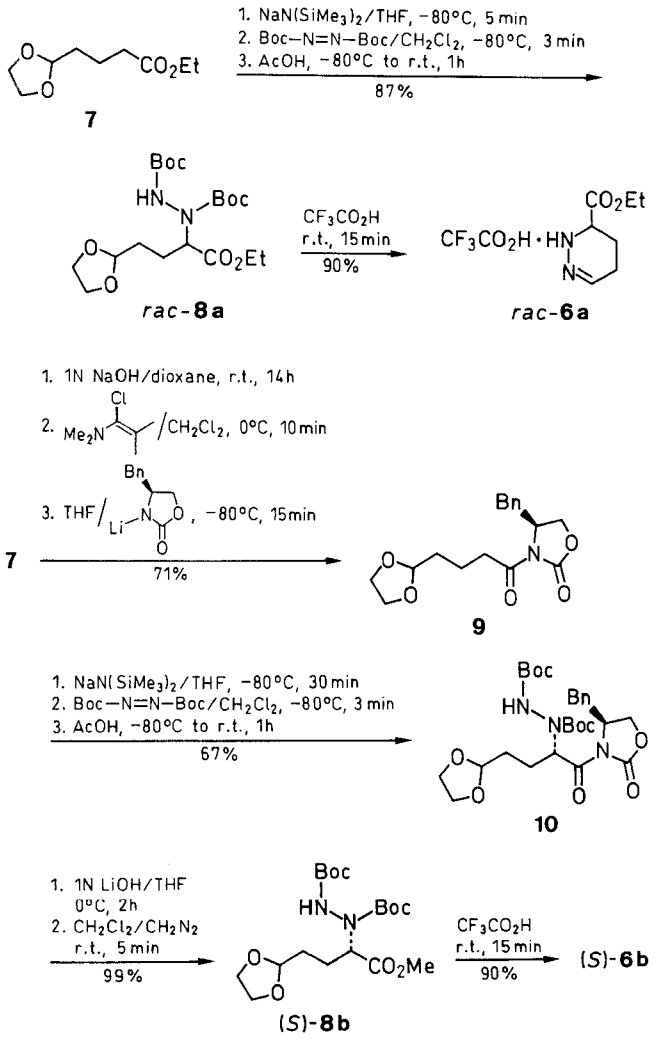


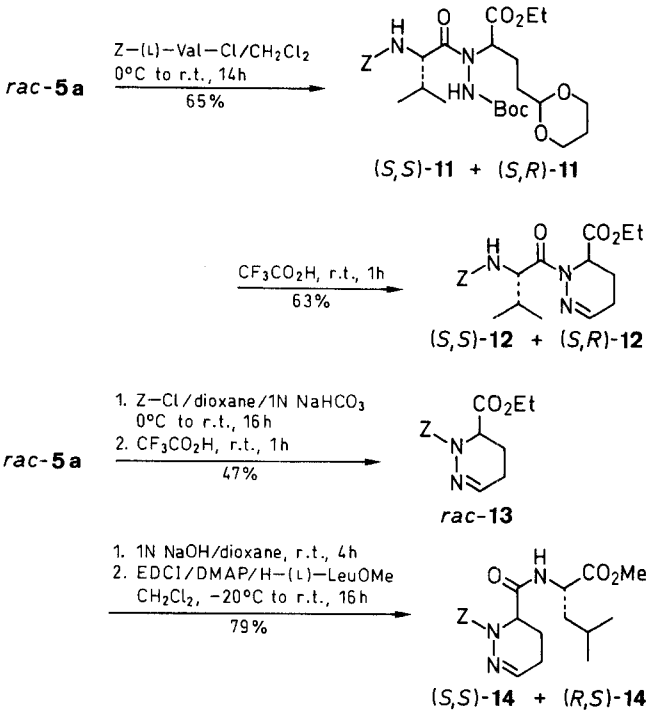
The conversion of the ethyl ester of **5** into the trifluoroacetate of the tetrahydropyridazinecarboxylic acid ester (ethyl ester of **6**) has been described in an American thesis.[13] A highly contaminated compound

was obtained (yield: 126%!); the ^{13}C NMR spectrum of the product did not contain any signals for the trifluoroacetate.[13] It was also concluded in this thesis that the generation and acylation of the free tetrahydropyridazinecarboxylic acid esters are not possible.

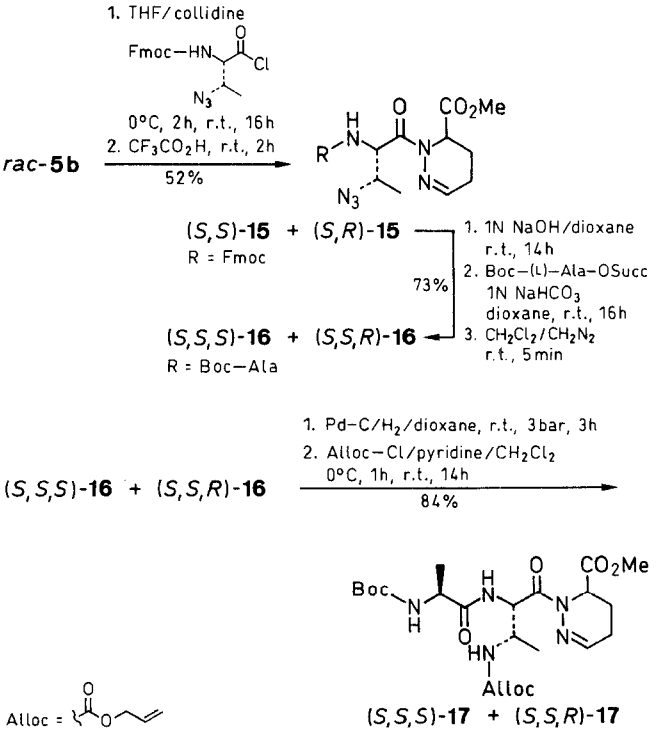
2) The acetal of ethyl 5-oxopentanoate **7**[14] was prepared by a malonic ester synthesis, metalated, and converted to the hydrazino compound **8a** by treatment with di-*tert*-butyl azodicarboxylate. Ring closure of **8a** in trifluoroacetic acid was successful and gave the racemic tetrahydropyridazine-3-carboxylic acid ester trifluoroacetate **6a**. This approach can also be used to prepare the optically active compound (*S*)-**6b** when, according to the method of Evans,[15] the optically active acyloxazolidinone **9** is employed in place of ester **7** and the hydrazine function is introduced diastereoselectively (> 99%) to furnish **10**.

An analogous sequence employing the dimethyl acetal (corresponding to **8b**) has been reported.[9] We have also repeated this reaction but we cannot confirm the high yield claimed.[11] Our previous experience has shown that the five-membered ring acetals **8b** are particularly suitable for ring closure of diacylhydrazine compounds. Since the free tetrahydropyridazinecarboxylic acid ester in Ref. 9 is insufficiently characterized by spectroscopy[10], we now report our experimental results on the formation of the trifluoroacetates **6a** and **6b**.





Even so, the free tetrahydropyridazinecarboxylic acid ester, generated from **6** by treatment with triethylamine, cannot be used in the peptide synthesis since it decomposes very rapidly. Model experiments, however, have shown that N_α-acylated hydrazines are able to form stable *N*-acyl derivatives of tetrahydropyridazinecarboxylic acid in trifluoroacetic acid.[16] For example, Z-valyl chloride has been allowed to react with the hydrazine **5a**; ring closure in trifluoroacetic acid furnished the Z-Val-tetrahydropyridazine-3-carboxylic acid ester **12**. The stable Z-tetrahydropyridazine-3-carboxylic acid ester **13** was prepared analogously and coupled with leucine ester to yield the Z-protected dipeptide **14**.



An analogous sequence was used to obtain the protected alanyldiaminobutyryltetrahydropyridazine-3-carboxylic acid **17** as follows. A suitably protected diaminobutyric acid derivative[17] was available from our previous synthesis of lavendomycin.[8] This was coupled with the protected hydrazine **5b**, acid treatment then gave rise to the dipeptide **15**. Subsequent cleavage of the Fmoc group, coupling with Boc-alanine to furnish **16**, reduction of the azide group, and protection gave the tripeptide **17** as a mixture of diastereomers (1:1). The mixture of the diastereomers (*S,S,S*)-**16** and (*S,S,R*)-**16** as well as the mixture of (*S,S,S*)-**17** and (*S,S,R*)-**17** can be separated easily by MPLC. At a later stage – protected hexapeptides and epimeric antrimycins – it is also possible to deduce their assignments by NMR spectroscopy.

The ^{1}H NMR spectra were recorded on a Varian T 60 (60 MHz), a Bruker WP 80 (80 MHz), a Bruker AC-F (250 MHz) and a Bruker CXP (300 MHz), respectively. The ^{13}C NMR spectra were recorded on a Bruker AC-F (63 MHz). Optical rotation values were determined with a Perkin-Elmer 241 polarimeter. Melting points (Reichert microscope) are uncorrected. TLC was done on silica gel (Merck Silica 60 F_{254} sheets) and MPLC used Merck LiChroprep Si 60 (15–25 μ). HPLC was done with an LKB instrument and a silica gel column (Merck Hibar, LiChrosorb Si 60 7 μ). Satisfactory microanalyses obtained for **4a,b, 5a, 8a,b, 9, 10, 13, 14, 16:** C ± 0.24, H ± 0.14, N ± 0.26.

Ethyl 5,5-(1,3-Propanediyldioxy)-2-oxopentanoate (3):[13]

2-(2-Bromoethyl)-1,3-dioxane (5.86 g, 30 mmol) was added to a stirred mixture of Mg (0.97 g, 40 mmol) and anhydr. THF (20 mL). The mixture was heated carefully until an exothermic reaction occurred. After the exothermic reaction had ceased the mixture was refluxed for 20 min. After cooling to r.t. the mixture was added slowly to a solution of diethyl oxalate (17.5 mL, 129 mmol) in anhydr. THF (175 mL) maintained at −10 °C. The resulting mixture was stirred and allowed to equilibrate to r.t. over 1 h. After quenching with sat. aq NH_4Cl (50 mL) the solvent was removed under reduced pressure. The residue was extracted with EtOAc (3 × 100 mL). After drying ($MgSO_4$) and evaporation under reduced pressure the excess diethyl oxalate was distilled off (60 °C, 0.3–0.4 Torr). The crude product was purified by filtration through silica gel (eluent: hexane/EtOAc 6:4) to give 5.24 g (81 %) of **3** as a colorless oil. R_f = 0.34 (hexane/EtOAc, 1:1). The product was converted into the hydrazone **4a** without further purification.

***E/Z*-Mixture of Ethyl 2-(*tert*-Butoxycarbonylhydrazono)-5,5-(1,3-propanediyldioxy)pentanoate**[13] **(4a):**

A solution of **3** (5.24 g, 24.3 mmol) and *tert*-butylcarbazate (3.2 g, 24.3 mmol) in anhydr. hexane (40 mL) was heated for 3 h under reflux. The mixture was allowed to equilibrate slowly to r.t. over 4 h. During this period product **4a** precipitated. Filtration gave **4a** as a mixture of *E*- and *Z*-isomers. Yield: 4.61 g (58 %); R_f (of the inseparable *E/Z*-mixture) = 0.29 (hexane/EtOAc, 1:1); mp 93–94 °C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.33 (t, 3 H, *J* = 7.2 Hz), 1.49 + 1.52 (2 s, 9 H), 1.85–1.91 (m, 2 H), 2.56–2.65 (m, 2 H), 3.84 (t, 2 H, *J* = 5.6 Hz), 4.09 (dt, 2 H, *J* = 11.9, 5 Hz), 4.26 (q, 2 H, *J* = 7.3 Hz), 4.45–4.48 (m, 2 H), 4.51 + 4.56 (2 t, 1 H, *J* = 5 Hz), 9.3 + 11.6 (2 s, 1 H).

Methyl 2-(*tert*-Butoxycarbonylhydrazono)-5,5-(1,3-propanediyldioxy)pentanoate (4b):

2-(tert-Butoxycarbonylhydrazono)-5,5-(1,3-propanediyldioxy)pentanoic Acid:

To a stirred solution of **4a** (8.92 g, 24.9 mmol) in dioxane (50 mL) 1 N NaOH (26 mL) was added. After stirring at r.t. for 4 h the dioxane was removed under reduced pressure, the aqueous layer was acidified with 1 N H_2SO_4 and extracted with EtOAc (3 × 30 mL). After drying ($MgSO_4$) and evaporation under reduced pressure the product was isolated as a colorless solid. Yield: 6.5 g (86 %); mp 123–124 °C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.37–1.49 (m, 2 H), 1.55 (s, 9 H), 1.88–1.95 (m, 2 H), 2.07–2.19 (m, 1 H), 2.59–2.65 (m, 2 H), 3.75 (dd, 1 H, *J* = 12.2, 2.4 Hz), 3.82–3.87 (m, 1 H), 4.10–4.17 (m, 2 H), 4.55 (t, 1 H, *J* = 4.4 Hz), 9.55 (s, 1 H).

Methyl 2-tert-Butoxycarbonylhydrazono)-5,5-(1,3-propanediyldioxy)pentanoate **(4b):**

The acid obtained above (6.04 g, 20 mmol) was converted into the methyl ester **4b** by reaction with CH_2N_2 in Et_2O. After evaporation under reduced pressure and crystallization from Et_2O/hexane **4b** was obtained as colorless needles. Yield: 6.2 g (98 %); R_f = 0.31 (hexane/EtOAc, 1:1); mp 111 °C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.33–1.43 (m, 1 H), 1.53 (s, 9 H), 1.85–1.92 (m, 2 H), 2.03–2.20 (m, 1 H), 2.6 (dd, 2 H, *J* = 8, 6.6 Hz), 3.75 (dt, 2 H, *J* = 10.7, 9.9 Hz), 3.81 (s, 3 H), 4.13 (ddd, 2 H, *J* = 11.95, 4.8 Hz), 4.50 (t, 1 H, *J* = 4.7 Hz), 9.37 (s, 1 H).

Ethyl (*RS*)-2-(*N'-tert*-Butoxycarbonylhydrazino)-5,5-(1,3-propanediyldioxy)pentenoate *rac*-(5a):[13]

To a stirred solution of **4a** (2.38 g, 7.22 mmol) and $NaCNBH_3$ (1.93 g, 30.8 mmol) in anhydr. MeCN (50 mL) AcOH (6.8 mL) was added. The mixture was stirred at r.t. until no more **4a** was detected (TLC control). After evaporation of the solvent under reduced pressure the residue was dissolved in H_2O/Et_2O (80:160 mL) and brought to pH 13 (KOH solid). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 80 mL). Drying ($MgSO_4$) and evaporation under reduced pressure gives *rac*-**5a** as a colorless solid. Yield: 2.39 g (98 %). R_f = 0.33 (hexane/EtOAc, 4:6).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, *J* = 7.2 Hz), 1.38 (s, 9 H), 1.67–2.00 (m, 6 H), 3.55 (br, 1 H), 3.70 (t, 2 H, *J* = 12.6 Hz), 4.00 (dd, 2 H, *J* = 10.6, 6.5 Hz), 4.15 (q, 2 H, *J* = 7.2 Hz), 4.50 (br, 1 H), 4.51 (t, 1 H, *J* = 4.2 Hz), 6.65 (br, 1 H).

Methyl (*R,S*)-2-(*N'-tert*-Butoxycarbonylhydrazino)-5,5-(1,3-propanediyldioxy)pentanoate *rac*-(5b):

Hydrazone **4b** was reduced in the same manner as **4a** to give hydrazine *rac*-**5b** as a colorless oil. Yield: 6.3 g (98 %); R_f = 0.30 (hexane/EtOAc, 4:6).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.32–1.39 (m, 1 H), 1.45 (s, 9 H), 1.73–2.15 (m, 6 H), 3.76 (s, 3 H), 3.62–3.81 (m, 3 H), 4.06–4.12 (m, 2 H), 4.57 (t, 1 H, *J* = 4.5 Hz), 6.47 (br, 1 H).

Methyl (*S*)-2,3,4,5-Tetrahydropyridazine-3-carboxylate · Trifluoroacetic Acid [(*S*)-6b]:

Compound (*S*)-**8b** (418 mg, 1 mmol) was treated with CF_3CO_2H (5 mL) for 15 min at r.t. under N_2. The solvent was removed under aspirator vacuo followed by high vacuo (60 °C) to yield 290 mg (90 %) of (*S*)-**6b** as a slightly yellow oil.

$[\alpha]_D^{20}$ + 51.8° (*c* = 2.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 2.19–2.36 (m, 2 H), 2.51–2.59 (m, 2 H), 3.80 (s, 3 H), 4.12 (t, 1 H, *J* = 5.3 Hz), 7.15–7.20 (m, 1 H), 9.83 (s, 2 H).

Ethyl (*RS*)-2,3,4,5-Tetrahydropyridazine-3-carboxylate · Trifluoroacetatic Acid [(*RS*)-6a]:

Hydrazine *rac*-**8a** was treated in the same manner as (*S*)-**8b** to give (*RS*)-**6a** as a slightly yellow oil. Yield 1.29 g (98 %).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.21 (t, 3 H, *J* = 7.1 Hz), 2.23–2.32 (m, 2 H), 2.43–2.58 (m, 2 H), 4.05 (t, 1 H, *J* = 5.3 Hz), 4.16 (q, 2 H, *J* = 7.1 Hz), 7.21 (t, 1 H, *J* = 3 Hz), 10.24 (br, 2 H).

^{13}C NMR ($CDCl_3$/TMS, 62.5 MHz): δ = 19.06, 21.11, 52.60, 62.25, 115.59 (q, *J* = 288.1 Hz), 143.53, 161.24 (q, *J* = 91.3 Hz), 169.79.

Ethyl (*RS*)-2-[*N,N'*-Bis(*tert*-butoxycarbonyl)hydrazino-5,5-ethylenedioxypentanoate *rac*-(8a):

To a solution of $NaN(SiMe_3)_2$ (8.62 g, 47 mmol) in anhydr. THF (100 mL), stirred at −80 °C under N_2, a solution of **7** (7.08 g, 37.6 mmol) in anhydr. THF (100 mL) was added dropwise and stirring at −80 °C was continued for 5 min. A solution of di-*tert*-butyl azodicarboxylate (9.4 g, 40.7 mmol) in anhydr. CH_2Cl_2

(100 mL) was added dropwise to the above enolate solution. After 3 min of stirring the reaction was quenched with glacial AcOH (7.2 mL) and allowed to warm up to r.t. The mixture was partitioned between CH_2Cl_2 and 1 N $NaHCO_3$ (50:300 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography (eluent: hexane/EtOAc, 6:4) to give *rac*-**8a** as a colorless oil. Yield: 13.74 g (87%); R_f = 0.5 (hexane/EtOAc, 1:1).

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.27 (t, 3 H, J = 7.1 Hz), 1.46 (s, 9 H), 1.47 (s, 9 H), 1.71–2.07 (m, 4 H), 3.82–3.97 (m, 4 H), 4.17 (q, 2 H, J = 7.1 Hz), 4.92 (br, 1 H), 6.32 (br, 1 H).

Methyl (*S*)-2-[*N,N'*-Bis(*tert*-butoxycarbonyl)hydrazino]-5,5-ethylenedioxypentanoate [(*S*)-8b]:

An ice cooled solution of **10** (1.1 g, 2 mmol) in THF (8 mL) was treated in one portion with a cold (0 °C) solution of LiOH (112 mg, 4.8 mmol) in H_2O (4 mL). The resulting two-phase mixture was stirred at 0 °C until the reaction was complete (TLC). The mixture was partitioned between CH_2Cl_2 (60 mL) and H_2O (60 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 40 mL). The combined organic layers contain the chiral auxiliary. The aqueous layer was acidified with 1 N H_2SO_4 (10 mL) and extracted with EtOAc (3 × 50 mL). The EtOAc extracts were combined, dried ($MgSO_4$) and concentrated in vacuo. The residue was converted into the methyl ester by addition of CH_2N_2 at 0 °C. After evaporation in vacuo the crude product was purified by flash chromatography (eluent: hexane/EtOAc, 1:1) to yield 800 mg (99%) of (*S*)-**8b** as a colorless oil; R_f = 0.43 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 13.64° (c = 1.96, CH_2Cl_2).

^{1}H NMR ($CDCl_3$/TMS, 80 MHz): δ = 1.40 (s, 18 H), 1.60–2.10 (m, 4 H), 3.55 (s, 3 H), 3.65–3.90 (m, 4 H), 4.50–4.90 (br, 2 H), 6.35 (s, 1 H).

(*S*)-4-Benzyl-3-(5,5-ethylenedioxypentanoyl)-2-oxazolidinone (9):

5,5-Ethylenedioxypentanoic Acid:

A solution of **7**[14] (8 g, 42.5 mmol) in dioxane (50 mL) was treated with 1 N NaOH (45 mL). After stirring for 14 h at r.t. the dioxane was distilled off under reduced pressure. The aqueous layer was extracted with Et_2O (2 × 30 mL), acidified with 1 N H_2SO_4 (50 mL) and extracted with EtOAc (3 × 60 mL). Drying ($MgSO_4$) and removing the solvent under reduced pressure gave 5,5-ethylenedioxypentanoic acid as a colorless oil which became solid after standing in the refrigerator. Yield: 6.36 g (93%).

^{1}H NMR (60 MHz, $CDCl_3$/TMS): δ = 1.60–1.95 (m, 4 H), 2.20–2.60 (m, 2 H), 3.65–4.00 (m, 4 H), 4.75–4.95 (m, 1 H), 10.90 (s, 1 H).

(S)-4-Benzyl-3-(5,5-ethylenedioxypentanoyl)-2-oxazolidinone (**9**):

Solution A: 5,5-Ethylenedioxypentanoyl chloride:

To a solution of 5,5-ethylenedioxypentanoic acid (4 g, 25 mL) in anhydr. CH_2Cl_2 (50 mL) was added 1-chloro-*N,N*-2-trimethyl-1-propen-1-amine[18] (3.5 mL, 26 mmol) at 0 °C, stirred at this temperature for 10 min and then the mixture was used immediately without isolation of the acid chloride.

To a solution of (*S*)-4-benzyl-2-oxazolidinone[19] (4.07 g, 23.4 mmol) in anhydr. THF (47 mL) maintained at − 80 °C one drop of benzylidenebenzylimine was added. To this solution 1.7 N BuLi in hexane was added dropwise until the mixture turns red. Now solution A was added dropwise (− 80 °C). After stirring for 15 min at − 80 °C the cooling bath was removed and the mixture was allowed to warm up to 0 °C. After quenching with 1 N $NaHCO_3$ (40 mL) the mixture was extracted with EtOAc (3 × 70 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by MPLC (hexane/EtOAc, 1:1). The product **9** was isolated as a colorless oil. Yield 6.05 g (76%); R_f = 0.4 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 41.4° (c = 1.34, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.73–1.88 (m, 4 H), 2.76 (dd, 1 H, J = 13.3, 9.6 Hz), 3.0 (q, 2 H, J = 7.2 Hz), 3.29 (dd, 1 H, J = 13.4, 3.2 Hz), 3.83–3.88 (m, 2 H), 3.96–4.23 (m, 2 H), 4.14–4.23 (m, 2 H), 4.63–4.71 (m, 1 H), 4.91 (t, 1 H, J = 4.5 Hz), 7.19–7.22 (m, 2 H), 7.24–7.36 (m, 3 H).

(*S*)-4-Benzyl-3-[(*S*)-2-(*N,N'*-bis(*tert*-butoxycarbonyl)hydrazino-5,5-ethylenedioxypentanoyl]-2-oxazolidinone (10):

To a solution of $NaN(SiMe_3)_2$ (4.31 g, 23.5 mmol) in anhydr. THF (62 mL), stirred at − 80 °C under N_2, a solution of acyloxazolidinone **9** (6.0 g, 18.8 mmol) in 95 mL of anhydr. THF (95 mL) was added dropwise. Residual **9** was rinsed in with two 1 mL portions of anhydr. THF and stirring continued at − 80 °C for 30 min. A solution of di-*tert*-butyl azodicarboxylate (4.7 g, 20.34 mmol) in anhydr. CH_2Cl_2 (100 mL) was added dropwise to the above enolate solution. After 3 min of stirring the reaction was quenched with glacial AcOH (3.6 mL, 64 mmol) and allowed to warm up to r.t. The mixture was partitioned between CH_2Cl_2 and 1 N $NaHCO_3$ (50:200 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. No other diastereomer was detectable by HPLC. The product was purified by crystallization from Et_2O/hexane. Yield: 8.61 (67%) of a colorless solid; mp 162–163 °C; R_f = 0.4 (hexane/EtOAc, 6:4); $[\alpha]_D^{20}$ + 50.76° (c = 1.01, CH_2Cl_2).

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.49 (s, 9 H), 1.48 (s, 9 H), 1.90–2.09 (m, 4 H), 2.79 (br, 1 H), 3.26 (br, 1 H), 3.79–3.87 (m, 2 H), 3.91–3.96 (m, 2 H), 4.19–4.25 (m, 2 H), 4.58 (br, 1 H), 4.91 (br, 1 H), 5.77 (br, 1 H), 6.48–6.75 (br, 1 H), 7.20–7.38 (m, 5 H).

Ethyl (*S*)-2-[(*S*)-2-(Benzyloxycarbonylamino)-3-methylbutyryl]-2,3,4,5-tetrahydropyridazine-3-carboxylate [(*S,S*)-12] and the 3*R*-Diastereomer (*S,R*)-12:

To a solution of Z–(L)–Val–OH (220 mg, 0.88 mmol) in anhydr. CH_2Cl_2 (2 mL) maintained at 0 °C 1-chloro-*N,N*,2-trimethyl-1-propen-1-amine[18] (1.35 mL, 1 mmol) was added in one portion and the resulting mixture was stirred at 0 °C. After 15 min a solution of *rac*-**5a** (266 mg, 0.8 mmol) and collidine (0.12 mL, 0.88 mmol) in anhydr. CH_2Cl_2 was added slowly. After stirring for 2 h at 0 °C and 14 h at r.t. the solvent was removed under reduced pressure. The residue was dissolved in CF_3CO_2H (5 mL) and allowed to stand at r.t. for 1 h. After removing the solvent under reduced pressure the crude product was purified by filtration through silica gel (eluent: hexane/EtOAc, 1:1) and by MPLC (eluent: hexane/EtOAc, 7:3) to give **12** as a mixture of the diastereomers (*S,S*)-**12** and (*S,R*)-**12**. They were separated by MPLC (eluent: hexane/EtOAc, 7:3).

Yield: 101 mg (32%) 1. diasteromer and 100 mg (32%) 2. diastereomer.

MS: m/z (%) = 389.19 (M^+, 2.3); R_f = 0.45 (hexane/EtOAc, 1:1).

1. Diastereomer: HPLC: t_R = 4.85 min (eluent: hexane/EtOAc, 65:35).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, 3 H, J = 6.9 Hz), 0.96 (d, 3 H, J = 6.8 Hz), 1.19 (t, 3 H, J = 7.1 Hz), 1.80–1.92 (m, 1 H), 1.99–2.34 (m, 3 H), 2.36 (dd, 1 H, J = 4, 2 Hz), 4.14 (q, 2 H, J = 7.1 Hz), 5.03–5.12 (m, 3 H), 5.19 (dd, 1 H, J = 9.6, 5 Hz), 5.57 (d, 1 H, J = 9.5 Hz), 6.92 (t, 1 H, J = 1.6 Hz), 7.25–7.36 (m, 5 H).

2. Diastereomer: HPLC: t_R = 5.25 min (eluent: hexane/EtOAc, 65:35).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.8 (d, 3 H, J = 6.9 Hz), 1.02 (d, 3 H, J = 6.8 Hz), 1.25 (t, 3 H, J = 7.2 Hz), 1.83–2.39 (m, 5 H), 4.18 (q, 2 H, J = 7.1 Hz), 5.05–5.22 (m, 3 H), 5.27 (dd, 1 H, J = 10, 4.3 Hz), 5.51 (d, 1 H, J = 9.7 Hz), 6.94 (d, 1 H, J = 3.5 Hz), 7.28–7.43 (m, 5 H).

Ethyl (3*RS*)-2-Benzyloxycarbonyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate *rac*-(13):

Ethyl (RS)-2-(N-Benzyloxycarbonyl-N'-tert-butoxycarbonylhydrazino)-5,5-(1,3-propanediyldioxy)pentanoate:

A solution of *rac*-**5a** (2.22 g, 6.68 mmol) in dioxane (20 mL) was treated with 1 N $NaHCO_3$ (12 mL), cooled to 4 °C and benzyloxycarbonyl chloride (1.76 g, 1.42 mL) was added in one portion. The mixture was stirred and allowed to warm up to r.t. during 16 h. After removing the dioxane the residue was dissolved in EtOAc/H_2O

(50:30 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (eluent: hexane/EtOAc, 1:1) and by MPLC (eluent: hexane/EtOAc, 65:35) to give the product as a colorless oil. Yield: 2.30 g (74%); $R_f = 0.43$ (hexane/EtOAc, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22–1.30 (m, 3H), 1.38–1.46 (m, 9H), 1.81–2.07 (m, 6H), 3.36–3.8 (m, 2H), 4.04–4.19 (m, 4H), 4.54 (s, 1H), 4.71–4.96 (m, 1H), 5.07–5.17 (m, 2H), 5.20–6.64 (br, 1H), 7.24–7.38 (m, 5H).

Ethyl (RS)-2-Benzyloxycarbonyl-2,3,4,5-tetrahydro-3-pyridazinecarboxylate rac-(**13**)

The 2-hydrazinopentanoate obtained above (180 mg, 3.9 mmol) was diluted in CF_3CO_2H and allowed to stand at r.t. for 1 h. Evaporation, resolving the residue with EtOAc (100 mL), washing with 1 N $NaHCO_3$ (2 × 100 mL) and brine (50 mL), drying ($MgSO_4$), flash chromatography (hexane/EtOAc 1:1) and MPLC (hexane/EtOAc, 6:4) gave *rac*-**13** as a colorless oil. Yield: 700 mg (63%); $R_f = 0.26$ (hexane/EtOAc, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (t, 3H, J = 7 Hz), 1.75–2.45 (m, 4H), 4.20 (q, 2H, J = 7 Hz), 5.00 (d, 1H, J = 4 Hz), 5.30 (s, 2H), 6.95 (br, 1H), 7.20–7.50 (m, 5H).

Methyl (*S*)-2-[(*S*)-2-Benzyloxycarbonyl-2,3,4,5-tetrahydro-3-pyridazinylcarbonylamino]-4-methylpentanoate [(*S,S*)-14] and the 3′*R*-Diastereomer (*R,S*)-14:

(3RS)-2-Benzyloxycarbonyl-2,3,4,5-tetrahydropyridazine-3-carboxylic Acid:

A solution of *rac*-**13** (0.71 g, 2.43 mmol) in dioxane (5 mL) was treated with 1 N NaOH (2.5 mL). After stirring for 14 h at r.t. the dioxane was distilled off under reduced pressure. The aqueous layer was diluted with H_2O (20 mL) and washed with Et_2O (15 mL), acidified with 1 N H_2SO_4 (5 mL) and extracted with EtOAc (3 × 20 mL). Drying ($MgSO_4$) and removing the solvent under reduced pressure gave the free acid as a colorless solid. Yield: 570 mg (90%); mp 139°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.90–2.39 (m, 4H), 5.06 (s, 1H), 5.24–5.38 (m, 2H), 7.02 (s, 1H), 7.29–7.40 (m, 5H), 8.13 (s, 1H).

*Methyl (S)-2-[(S)-2-Benzyloxycarbonyl-2,3,4,5-tetrahydro-3-pyridazinylcarbonylamino]-4-methylpentanoate [(S,S)-*14] *and the 3′R-Diastereomer (R,S)-*14:

To a stirred solution of the acid obtained above (500 mg, 1.9 mmol), H–Leu–OMe (410 mg, 2.8 mmol) and 4-(dimethylamino)pyridine (DMAP) (10 mg) in anhydr. CH_2Cl_2 (5 mL) maintained at −20°C, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) (415 mg, 2.1 mmol) was added in one portion. The mixture was allowed to warm up to r.t. over 16 h. After removing the CH_2Cl_2, the residue was dissolved in EtOAc (50 mL) and washed with 1 N H_2SO_4, 1 N $NaHCO_3$ and brine. Drying ($MgSO_4$) evaporation and flash chromatography (eluent: hexane/EtOAc, 3:7) gave **14** as a mixture of diastereomers.

Yield: 650 mg (88%); $R_f = 0.27$ (hexane/EtOAc, 3:7).

The diastereomers were separable by MPLC (hexane/EtOAc, 4:6):

1. Diastereomer: mp 114°C, $[\alpha]_D^{20}$ +41.11° (c = 0.9, CH_2Cl_2); HPLC: t_R = 5.43 min (eluent: hexane/EtOAc, 3:7).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (d, 3H, J = 6.1 Hz), 0.87 (d, 3H, J = 6.1 Hz), 1.38–1.64 (m, 3H), 1.73–2.01 (m, 1H), 2.1–2.47 (m, 3H), 3.68 (s, 3H), 4.49–4.58 (m, 1H), 4.99 (d, 1H, J = 6.4 Hz), 5.32 (s, 2H), 6.27 (br, 1H), 7.12 (s, 1H), 7.28–7.44 (m, 5H).

2. Diastereomer: mp 138°C, $[\alpha]_D^{20}$ −43.22° (c = 1.35, CH_2Cl_2); HPLC: t_R = 6.16 min (eluent: hexane/EtOAc, 3:7).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (d, 3H, J = 6.1 Hz), 0.88 (d, 3H, J = 6.1 Hz), 1.39–1.66 (m, 3H), 1.70–1.85 (m, 1H), 2.12–2.44 (m, 3H), 3.70 (s, 3H), 4.48–4.57 (m, 1H), 4.99 (d, 1H, J = 4.4 Hz), 5.34 (s, 2H), 6.59 (br, 1H), 7.06 (s, 1H), 7.29–7.46 (m, 5H).

Methyl (*S*)-2-[(2*S*,3*S*)-3-Azido-2-(fluoren-9-ylmethoxycarbonylamino)butyryl]-2,3,4,5-tetrahydropyridazine-3-carboxylate [(*S,S,S*)-15] and the 3*R*-Diastereomer (*S,S,R*)-15:

To a stirred solution of (2*S*,3*S*)-3-azido-2-(fluoren-9-ylmethoxycarbonylamino)butyric acid[17] (3.3 g, 9 mmol) in anhydr. THF (18 mL) maintained at 0°C 1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine[18] (1.44 mL, 10.8 mmol) was added in one portion and the resulting mixture was stirred at 0°C. After 20 min a solution of *rac*-**5b** (3.69 g, 11.58 mmol) and collidine (1.44 mL, 10.8 mmol) in anhydr. THF (21 mL) was added slowly. After stirring for 2 h at 0°C and 16 h at r.t. the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed as follows: 1 N $NaHCO_3$, 1 N H_2SO_4 and brine. After drying ($MgSO_4$) and evaporating the solvent under reduced pressure the residue was dissolved in CF_3CO_2H (30 mL) and allowed to stand at r.t. for 2 h. After removing the solvent under reduced pressure the crude product was purified by filtration through silica gel (eluent: hexane/EtOAc, 1:1) and by MPLC (eluent: hexane/EtOAc, 6:4) to give a mixture of (*S,S,S*)-**15** and (*S,S,R*)-**15** as a colorless foam. Yield: 2.28 g (52%). The diastereomers were separated by two MPLC runs (eluent: hexane/EtOAc, 1:1) to give (*S,S,S*)-**15** (1.14 g) and (*S,S,R*)-**15** (1.14 g).

1. Diastereomer: HPLC: t_R = 14.29 min (eluent: hexane/EtOAc, 6:4).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (d, 3H, J = 7.7 Hz), 1.85–2.29 (m, 3H), 2.37–2.45 (m, 1H), 3.72 (s, 3H), 3.85 (t, 1H, J = 6.3 Hz), 4.25 (dd, 1H, J = 7.4, 6.6 Hz), 4.33–4.49 (m, 2H), 5.2 (br, 1H), 5.58–5.64 (m, 1H), 5.75 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 4.1 Hz), 7.28–7.43 (m, 4H), 7.61–7.64 (m, 2H), 7.76 (d, 2H, J = 7.1 Hz).

2. Diastereomer: HPLC: t_R = 15.56 min (eluent: hexane/EtOAc, 6:4).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (d, 3H, J = 7.7 Hz), 1.85–2.29 (m, 3H), 2.37–2.45 (m, 1H), 3.72 (s, 3H), 3.85 (t, 1H, J = 6.3 Hz), 4.25 (dd, 1H, J = 7.4, 6.6 Hz), 4.33–4.49 (m, 2H), 5.2 (s, 2H), 5.58–5.64 (m, 1H), 5.75 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 4.1 Hz), 7.28–7.43 (m, 4H), 7.62 (d, 2H, J = 7.3 Hz), 7.76 (d, 2H, J = 7.1 Hz).

Methyl (*S*)-2-[(2*S*,3*S*)-3-Azido-2-[(*S*)-2-(*tert*-butoxycarbonylamino)-propanoylamino]butyryl]-2,3,4,5-tetrahydropyridazine-3-carboxylate [(*S,S,S*)-16] and the 3*R*-Diastereomer (*S,S,R*)-16:

A solution of (*S,S,S*)-**15** and (*S,S,R*)-**15** (1.9 g, 3.87 mmol) in dioxane (10 mL) was treated with 1 N NaOH (8.5 mL) and stirred for 14 h at r.t. Then, 1.4 mL of 6 N H_2SO_4 was added and the resulting solution was stirred for 5 min at r.t. After neutralization ($NaHCO_3$) Boc–(L)–Ala–OSu[20] (2.24 g, 8 mmol) was added and the resulting mixture was stirred at r.t. for 16 h. After evaporating the solvent in vacuo the residue was taken up in EtOAc/H_2O (50:50 mL). The aqueous layer was separated, acidified with 1 N H_2SO_4 and extracted with EtOAc (3 × 70 mL). After drying ($MgSO_4$) and removing the solvent in vacuo, the residue was dissolved in CH_2Cl_2 (10 mL) and treated with CH_2N_2 until the solution remained yellow. Evaporation of the solvent and flash chromatography (hexane/EtOAc, 3:7) gave a mixture of the diastereomers (*S,S,S*)-**16** and (*S,S,R*)-**16**. They were separated by one MPLC run on a silica gel column of 40 × 420 mm (eluent: hexane/EtOAc, 4:6). Yield: 0.62 g (37%) of (*S,S,S*)-**16** as a colorless solid and 0.62 g (37%) of (*S,S,R*)-**16** as a colorless foam.

1. Diastereomer (*S,S,R*)-**16**: $R_f = 0.33$ (hexane/EtOAc, 3:7); mp 132°C; $[\alpha]_D^{20}$ +47.06° (c = 1.55, CH_2Cl_2); HPLC: t_R = 6.14 min (eluent: hexane/EtOAc, 4:6).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.23 (d, 3H, J = 6.8 Hz), 1.35 (d, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.84–2.43 (m, 4H), 3.71 (s, 3H), 3.73–3.88 (m, 1H), 4.12–4.20 (m, 1H), 5.17–5.19 (m, 2H), 5.78 (dd, 1H, J = 9.1, 6.6 Hz).

2. Diastereomer (*S,S,S*)-**16**: $R_f = 0.33$ (hexane/EtOAc, 3:7); $[\alpha]_D^{20}$ +1.77° (c = 1.32, CH_2Cl_2); HPLC: t_R = 7.00 min (eluent: hexane/EtOAc, 4:6).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (d, 3 H, J = 6.8 Hz), 1.36 (d, 3 H, J = 7.1 Hz), 1.44 (s, 9 H), 1.84–2.42 (m, 4 H), 3.73 (s, 3 H), 3.94–4.04 (m, 1 H), 4.21–4.26 (m, 1 H), 5.13–5.24 (m, 2 H), 5.83 (dd, 1 H, J_1 = 9.2, J_2 = 6.6 Hz), 7.0–7.06 (m, 2 H).

Methyl (*S*)-2-[(2*S*,3*S*)-3-(Allyloxycarbonylamino)-2-[(*S*)-2-(*tert*-butoxycarbonylamino)propanoylamino]butyryl]-2,3,4,5-tetrahydropyridazine-3-carboxylate [(*S,S,S*)-17] and the 3*R*-Diastereomer (*S,S,R*)-17:

A solution of (*S,S,S*)-**16** and (*S,S,R*)-**16** (610 mg, 1.4 mmol) and Et_3N (10 mg) in dioxane (25 mL) was hydrogenated using Pd–C as catalyst (70 mg) for 3 h under H_2 pressure (3 bar). After removal of the catalyst by filtration and evaporation of the solvent under reduced pressure the residue was dissolved in CH_2Cl_2 (7 mL). To this solution allyl chloroformate (0.35 mL, 3.3 mmol) and pyridine (0.27 mL, 3.3 mmol) was added and the resulting mixture stirred for 1 h at 0 °C and 14 h at r.t. Afer removing the solvent in vacuo and flash chromatography (EtOAc) the crude product was purified by MPLC (eluent: hexane/EtOAc, 3:7) to give **17** as a mixture of diastereomers. These were separated by one MPLC run on a silica gel column of 40 × 420 mm (eluent: hexane/EtOAc, 3:7).

Yield: 292 mg (42 %) of (*S,S,R*)-**17** and 292 mg (42 %) of (*S,S,S*)-**17** as a colorless foam;

1. Diastereomer (*S,S,R*)-**17**: R_f = 0.22 (hexane/EtOAc, 3:7); $[\alpha]_D^{20}$ + 15.94° (c = 1.16, CH_2Cl_2); HPLC: t_R = 7.11 min (eluent: hexane/EtOAc, 4:6).

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.01 (d, 3 H, J = 6.7 Hz), 1.32 (d, 3 H, J = 7.0 Hz), 1.34 (s, 9 H), 1.81–2.11 (m, 2 H), 2.16–2.38 (m, 2 H), 3.68 (s, 3 H), 4.11–4.17 (m, 2 H), 4.48–4.51 (m, 2 H), 5.12–5.28 (m, 4 H), 5.57 (d, 1 H, J = 7.7 Hz), 5.86 (ddt, 1 H, J = 16.1, 10.8, 5.6 Hz), 6.18 (d, 1 H, J = 7.8 Hz), 6.98 (d, 1 H, J = 3.5 Hz), 7.18 (d, 1 H, J = 7.8 Hz).

Ion Spray MS: m/z = 498 $(M + H)^+$.

2. Diastereomer (*S,S,S*)-**17**; R_f = 0.22 (hexane/EtOAc, 3:7); $[\alpha]_D^{20}$ − 22.8° (c = 1.6, CH_2Cl_2); HPLC: t_R = 8.62 min (eluent: hexane/EtOAc, 4:6).

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.08 (d, 3 H, J = 6.8 Hz), 1.32 (d, 3 H, J = 7 Hz), 1.40 (s, 9 H), 1.80–1.97 (m, 1 H), 2.08–2.20 (m, 2 H), 2.32–2.43 (m, 1 H), 3.69 (s, 3 H), 4.09–4.18 (m, 1 H), 4.26 (br, 1 H), 4.49–4.51 (m, 2 H), 5.12–5.29 (m, 4 H), 5.61 (dd, 1 H, J = 8.3, 3.1 Hz), 5.82–5.92 (m, 2 H), 6.99 (d, 1 H, J = 3.6 Hz), 7.09 (d, 1 H, J = 8.2 Hz).

Ion spray MS: m/z = 498 $(M + H)^+$.

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