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Practical approaches to the matrix metalloproteinase inhibitor Trocade® (Ro 32-3555) and to the TNF-α converting enzyme inhibitor Ro 32-7315☆

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Abstract—Stereoselective methods were found to efficiently prepare 2- and 3-substituted succinates with *anti* configuration. In the synthesis of Trocade® **1**, the hydantoinmethyl residue was introduced by alkylation of the non-chelated potassium enolate **19** with the bromomethyl hydantoin **9** to give a 92:8 mixture favouring the 2,3-*anti* configurated succinate **18**. The preparation of TNF-α converting enzyme (TACE) inhibitor **2** was accomplished by a highly stereoselective protonation of the dialkylated enolate **23** using CF_3CONH_2 affording a 98:2 mixture in favour of the 2,3-*anti* configurated succinate **24**.

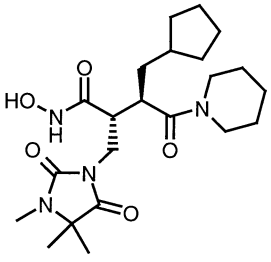
1. Introduction

Hydroxamic acid derivatives have been reported as potent inhibitors of matrix metalloproteinases (MMPs) and for the recently characterized TNF-α converting enzyme (TACE), both enzymes are involved in degrading all components of the extracellular matrix.[1] This process has been implicated in rheumatoid and osteoarthritis, a chronic inflammatory disease leading to the loss of normal joint function. For the clinical evaluation of the MMP inhibitor **1** (Trocade®, Ro 32-3555)[2] and the TACE inhibitor **2** (Ro 32-7315)[3] stereoselective syntheses were required. Herein we report on efficient and practical methods to specifically prepare *anti* configurated succinates (Fig. 1).

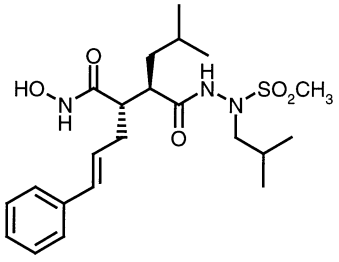
2. Results and discussion

2.1. Synthesis of Trocade® 1

The synthesis of hydroxamic acid **1** employed the new and readily available homoallyl nosylate **6** (Scheme 1) prepared by the enantioselective glyoxylate ene reaction[4] of benzyl glyoxylate (**3**)[5] and methylenecyclopentane (**4**). The enantioselectivity of this reaction proved to be highly sensitive to the water content of the molecular sieve[6,7] required for the preparation of the catalyst (1.5 mol%) generated in situ from $(i\text{-PrO})_2TiBr_2$ and (*R*)-1,1′-binaphthol. Thus, high water contents of 6–10% resulted in ee of 95–98% whereas activated, dry molecular sieves containing 3% or less of water reduced the ee to 20–30%.



1 (Ro 32-3555)



2 (Ro 32-7315)

Figure 1. *anti* Configurated succinates as inhibitors of MMPs and TACE.

☆ Part of these results were previously communicated: Hilpert, H., VIII Ischia Advanced School of Organic Chemistry, September 26, 1998, Ischia, Italy.

Keywords: anti-inflammatory compounds; chelation; ene reactions; enolates; hydroxamic acids and derivatives.

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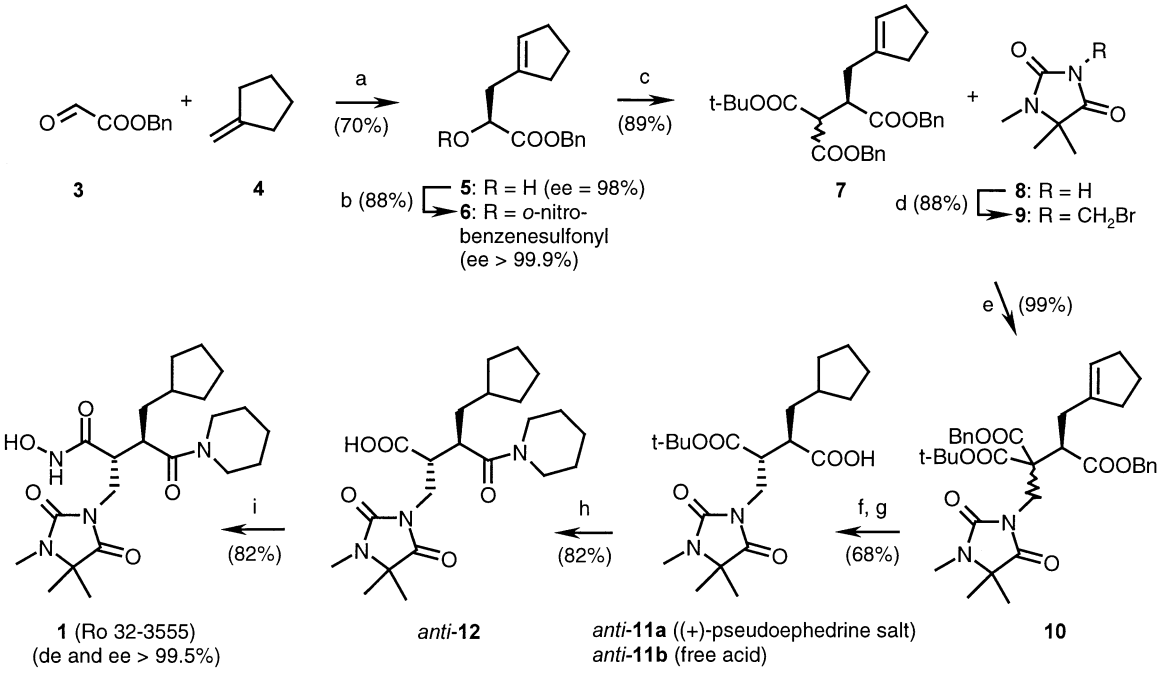


Scheme 1. *Reagents and conditions*: (a) (i) (*R*)-1,1′-binaphthol, powdered molecular sieves 4 Å (containing 8% H_2O), $(i\text{-PrO})_2TiBr_2$, CH_2Cl_2, 22°C, 1.3 h; (ii) **4**, **3**/toluene, 22°C, 16 h; (b) **5**, *o*-nitrobenzenesulfonyl chloride, NEt_3, toluene, −15°C, 22 h; (c) (i) benzyl *tert*-butyl malonate, NaH, DMF, 22°C, 30 min; (ii) **6**, 22°C, 28 h; (d) **8**, paraformaldehyde, HBr/AcOH, 80°C, 4.5 h; (e) **7**, NaH, DMF, 22°C, **9**, DMF, 0°C, 4 h; (f) (i) **10**, Pd/C (5%), *i*-PrOH, 22°C, 24 h; (g) (i) *N*-methylmorpholine, *i*-PrOAc, 90°C, 4 h; (ii) (+)-pseudoephedrine; (h) (i) **11a**, partitioning between AcOEt and 1N HCl; (ii) **11b**, piperidine, *N*-hydroxy-2-pyridone, *N*,*N*′-dicyclohexylcarbodiimide, AcOEt, 22°C, 20 h; (iii) HBr/AcOH, 0°C, 3 h; (i) (i) **12**, *N*-hydroxy-2-pyridone, 2-morpholinoethyl isocyanide, CH_2Cl_2, 22°C, 19 h; (ii) TMSO–NH_2, 0°C, 7 h; (iii) $NaHCO_3/H_2O$.

Activation of crude **5** was achieved by formation of the triflate, *p*- and *o*-nosylate with the advantage of the latter to crystallize readily from acetone/H_2O 3:1 at 40°C leading to **6** in high yield (88%) and high enantiomeric purity (ee=>99.9%). Alkylation of **6** was accomplished with the mixed benzyl *tert*-butyl malonate furnishing a 1:1 mixture of the epimers of **7**, which upon treatment with the bromomethyl hydantoin **9** led to the triester **10** in quantitative yield. Compound **9** was expediently prepared from trimethyl hydantoin **8**[8] in high yield (88%) employing paraformaldehyde/HBr.[9] Hydrogenation and hydrogenolysis of **10** followed by decarboxylation of the intermediate di-acid preferably in the presence of 1 equiv. of *N*-methylmorpholine and *i*-PrOAc gave a 5:1 mixture of the *anti*-/*syn*-succinates **11** which was efficiently separated via the (+)-pseudoephedrine or the ethanolamine salt affording pure *anti*-**11a** in 68% yield over the two steps. The relative and absolute configuration of *anti*-**11** was unambiguously established by an X-ray analysis[10] of the corresponding (+)-pseudoephedrine salt **11a** (Fig. 2).

Introduction of the two amide residues in **1** was readily achieved via the corresponding active esters prepared in situ from *N*-hydroxy-2-pyridone[11] and DCC furnishing *anti*-**12** after cleavage of the *tert*-butyl group or, in the ultimate step, 2-morpholinoethyl isocyanide[12] a potent dehydrating agent giving 2-morpholinoethyl formamide, readily removed by an acidic extraction. Formation of the

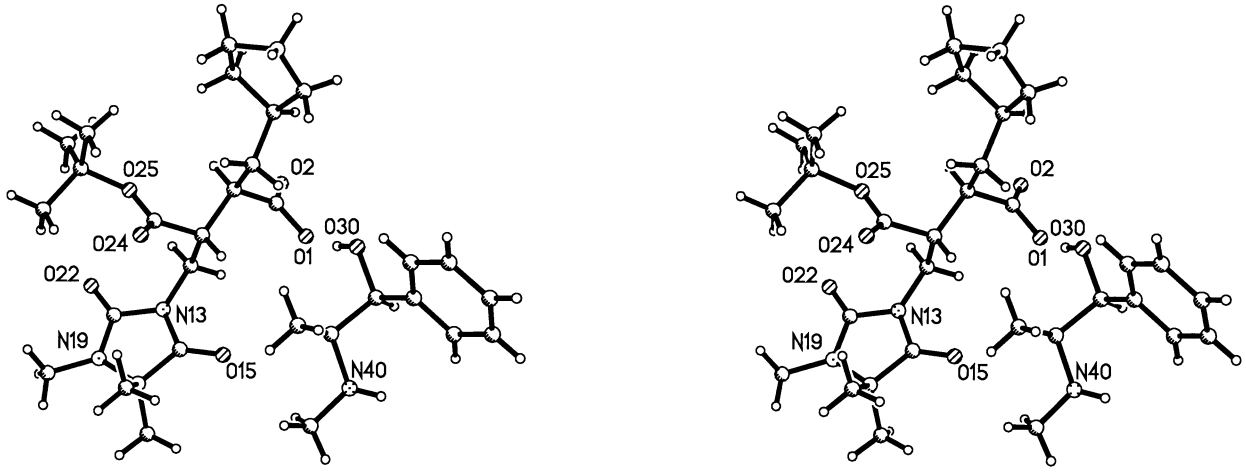
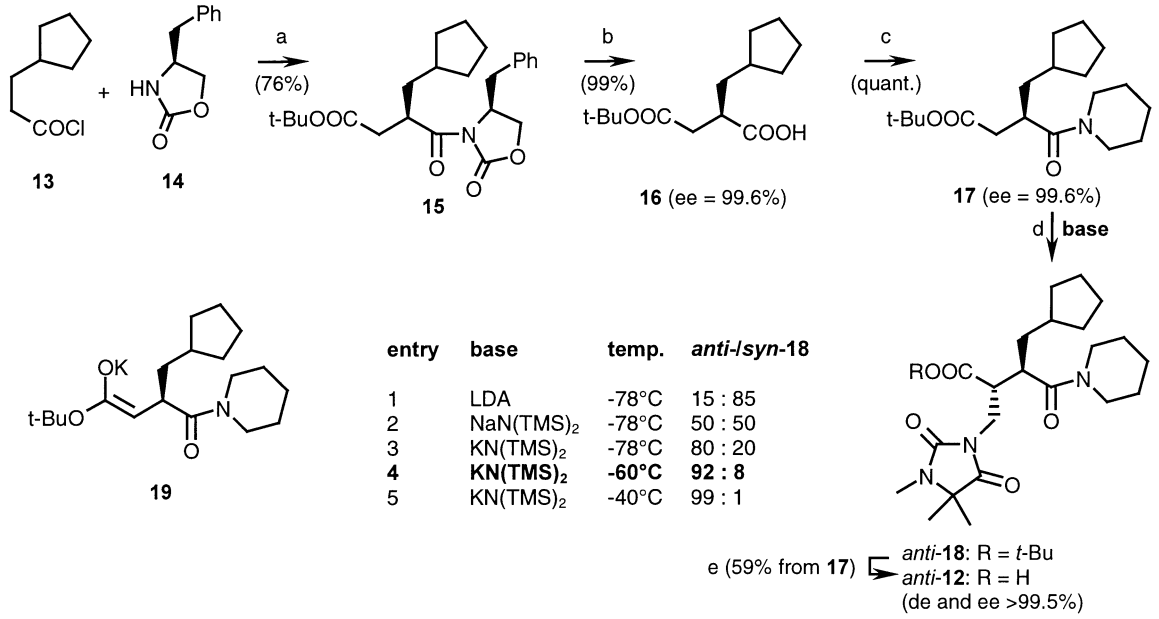


Figure 2. Stereoview of the (+)-pseudoephedrine salt *anti*-**11a**.



Scheme 2. *Reagents and conditions*: (a) (i) **14**, *n*-BuLi, THF, −45°C; (ii) **13**, −45°, 1 h; (iii) LDA, −45°C, 1.5 h; (iv) *tert*-butyl bromoacetate, −45°C, 4 h; (b) **15**, *i*-PrOH, then $NaOH/H_2O$, H_2O_2, 0°C, 10 min, 22°C, 1 h; (c) **16**, piperidine, *N*-hydroxy-2-pyridone, *i*-PrOAc, 0°C, then *N*,*N*′-dicyclohexylcarbodiimide, 0°C, 1 h, 22°C, 16 h; (d) $KN(TMS)_2$, THF, −60°C, then **17** in THF, −60°C, 30 min, then **9** in THF, −60°C, 1.5 h; (e) HBr/AcOH, 0°C, 1.5 h.

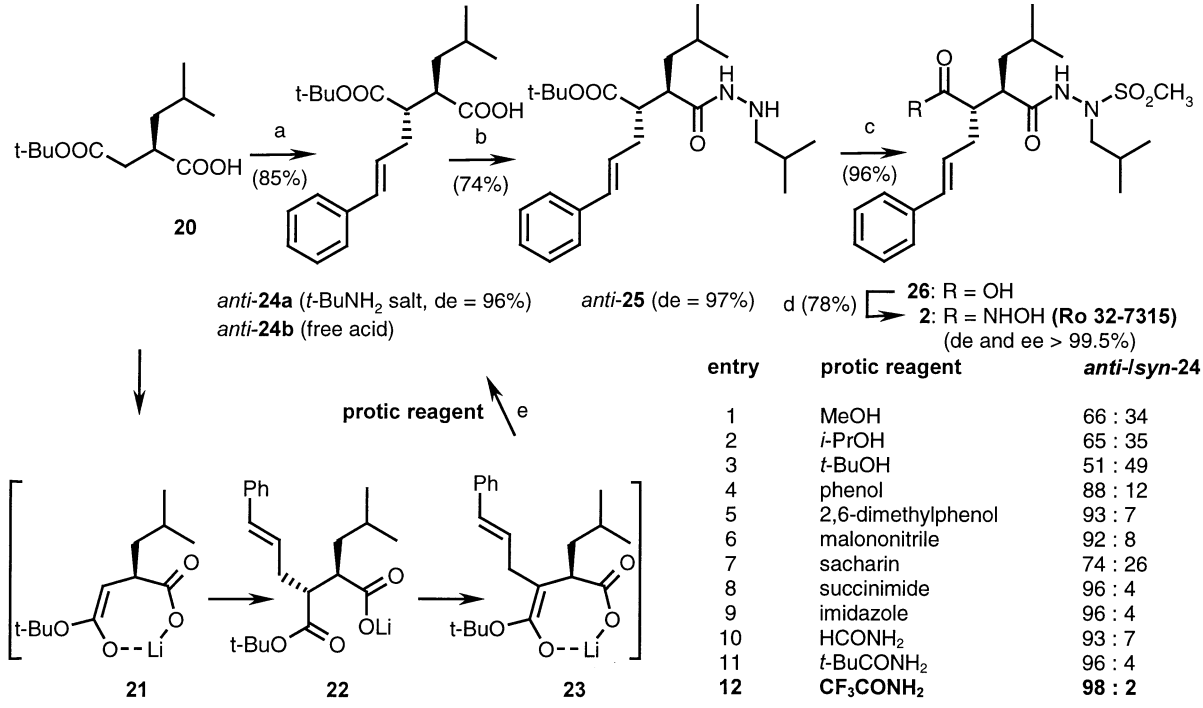
hydroxamic acid residue was best accomplished with *O*-TMS protected hydroxylamine thus avoiding *O*-acylation followed by hydrolysis during work-up to furnish the pure and crystalline hydroxamic acid **1** in 82% yield and a high stereoisomeric purity (de and ee>99.5%) after crystallization.

In search of a shorter and even more efficient route to **1**, the alkylation of the piperidine amide **17** (Scheme 2), prepared from the homochiral succinic acid **16**,[13] was investigated. Attempts to alkylate the precursors, i.e. the enolates of **15** or **16** with **9** under various conditions resulted in mixtures of multiple products or were lacking selectivity, respectively. However, the reaction of the amide **17** with **9** proceeded with a surprisingly high degree of selectivity leading either to the *syn*- or to the *anti*-succinate **18** depending on the counter ion of the base used. Thus, lithium bases such as LDA furnished preferentially *syn*-**18** whereas potassium bases like $KN(TMS)_2$ provided *anti*-**18** with reasonable degrees of selectivity (Scheme 2, entry 1 and 3). These results are consistent with the assumption of a lithium enolate chelating with the adjacent carbonyl amide group thereby controlling the alkylation from the sterically less hindered side leading to the *syn* isomer as proposed earlier by Crimmin et al.[14] Alternatively, a potassium enolate is assumed to favour the non-chelated, thermodynamically more stable conformation **19** consequently affording *anti* alkylation. Running the reaction at a higher temperature, e.g. −40°C (entry 5) influenced the result significantly affording a 99:1 ratio of *anti*-/*syn*-**18** but at a reduced yield of about 40%. This ratio and yield is a result of a concomitant β-elimination preferentially of the *syn* isomer to give the hydantoin **8** and the corresponding acrylate. At the optimal temperature of −60°C (entry 4), a 92:8 mixture of *anti*-/*syn*-**18** was obtained which was deprotected and crystallized furnishing isomerically pure *anti*-**12** in 59% yield over the two steps.

2.2. Synthesis of the TACE inhibitor 2

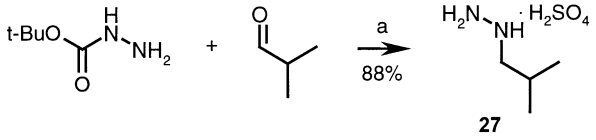
The key step in the synthesis of the TACE inhibitor **2** (Scheme 3) comprises of the stereoselective alkylation of the succinic acid **20**[14] with cinnamyl bromide followed by a deprotonation/protonation sequence to give *anti*-**24**. A related alkylation of **20** using allyl bromide at −78°C described by Crimmin et al.[14] afforded a 94:6 mixture in favour of the corresponding *syn* isomer followed by a repeated epimerisation involving deprotonation with LDA and protonation with methanol at −78°C then providing preferentially the *anti*-isomer in a ratio of 83:17. In search of a significantly higher selectivity, we investigated the protonation of the enolate **23** at −80–−90°C testing three categories of protic reagents, namely O–H (Scheme 3, entry 1–5), C–H (entry 6) and N–H acidic compounds (entry 7–12). Alkylation of **20** with cinnamyl bromide gave as expected, a 93:7 mixture favouring the *syn*-isomer. After an additional deprotonation with LDA and protonation with CF_3CONH_2 (entry 12), a remarkably high selectivity of 98:2 in favour of *anti*-**24** (85% yield after isolation) was observed. These selectivities can be rationalized by a chelation effect of the enolate **21** which is alkylated on the sterically less hindered side leading to syn-**22**. A second deprotonation of **22** to the chelated enolate **23** and protonation again from the sterically less hindered side accounts for *anti*-**24**. The general tendency of N–H acidic compounds towards highest selectivities is rationalized by protonation of the enolate **23** occurring at the softer carbanion center which is closer to the adjacent stereo center.

Formation of the hydrazide *anti*-**25** was accomplished in 74% yield employing *i*-butyl hydrazine·H_2SO_4 (**27**, Scheme 4) conveniently prepared by a one-pot procedure starting with the Schiff base formation of *tert*-butyl carbazate and *i*-butylaldehyde, followed by hydrogenation of the hydrazone and cleavage of the BOC protecting group



entry	protic reagent	*anti*-/*syn*-24
1	MeOH	66 : 34
2	*i*-PrOH	65 : 35
3	*t*-BuOH	51 : 49
4	phenol	88 : 12
5	2,6-dimethylphenol	93 : 7
6	malononitrile	92 : 8
7	sacharin	74 : 26
8	succinimide	96 : 4
9	imidazole	96 : 4
10	$HCONH_2$	93 : 7
11	*t*-$BuCONH_2$	96 : 4
12	**CF_3CONH_2**	**98 : 2**

Scheme 3. *Reagents and conditions*: (a) (i) **20**, LDA, THF, −20°C, 1 h, then cinnamyl bromide, −20°C, 40 min, 22°C, 2 h, then LDA, −20°C, 30 min, then CF_3CONH_2/THF, −90°C, 1 h; (ii) *tert*-$BuNH_2$/*i*-PrOAc, 0°C, 3 h; (b) **24a** (i) partitioning between *i*-PrOAc and 1N HCl; (ii) **24b**, *N*-hydroxy-2-pyridone, *N*,*N*′-dicyclohexylcarbodiimide, *i*-PrOAc, 0°C, 4 h, then *N*-ethylmorpholine, **27**, 22°C, 17 h, 45°C, 8 h; (c) (i) **25**, CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0°C, 30 min; (ii) HBr/AcOH, −15°C, 1.5 h; (d) **26**, *N*-hydroxy-2-pyridone, *N*,*N*′-dicyclohexylcarbodiimide, THF, 22°C, 22 h, then NH_2-OH·H_2O, 22°C, 4 h.



Scheme 4. *Reagents and conditions*: (i) *tert*-butyl carbazate, *i*-butylaldehyde, *i*-PrOH, 0°C, 2 h; (ii) H_2, Pt/C (5%), *i*-PrOH, 30°C, 42 h; (iii) H_2SO_4, 50°C, 5 h.

using sulfuric acid to give **27** in 88% overall yield. Mesylation of *anti*-**25** followed by in situ deprotection provided the acid **26** (96%) ready to introduce the hydroxamic acid residue, accomplished with unprotected hydroxylamine hydrate. This reaction proved to be highly solvent dependent leading in dichloromethane to an approximately 1:1 mixture of *N*- and *O*-acylated products. However, in THF a 94:6 mixture favouring the desired *N*-acylated compound **2** was obtained. A final crystallization from ethanol/water provided the pure hydroxamic acid **2** in 78% yield with a de and ee of >99.5%.

3. Summary

Two methods of general interest were found to synthesize *anti* configurated 2- and 3-alkylated succinates. The first one involves the alkylation of the potassium enolate **19** particularly suited for base sensitive products such as **18** that cannot be enolized without concomitant β-elimination. The second method proceeds via a *syn* alkylation to **22** followed by a highly stereoselective protonation of the dialkylated enolate **23** providing *anti*-**24**. Two linear six step syntheses were developed to efficiently prepare Trocade® **1** and the TACE inhibitor **2** in overall yields of 36 and 31 (including the preparation of **20**) and avoiding chromatographic purifications, which were applied on a multi ton and multi kilogram scale.

4. Experimental

4.1. General

Melting points: Tottoli or Büchi 535, uncorrected. IR spectra: Nicolet, FT-IR 20 SXB. ^{1}H NMR spectra: Bruker AC 250, internal standard TMS, *J* values in Hz. MS spectra: Finnigan MAT SSQ 7000, EI at 70 eV. HPLC: Agilent 1100. GLC: Perkin–Elmer AutoSystem. Monitoring of the reactions and quality control of the products by TLC (silica gel) or by HPLC (RP-18, CH_3CN/buffered water of various ratios). HPLC columns: Chiralpak AS and Chiracel OJ: Daicel Chemical, LTD; Symmetry™ C18: Waters, Lichrospher 100, RP-18: Merck. Benzyl glyoxylate: Hoechst France; Powdered molecular sieves: Aldrich (containing ca. 8% of water); Diisopropoxytitanium dibromide prepared according to Ref. 4; benzyl *tert*-butyl malonate: Lancaster; Pd/C (5%) and Pt/C (5%, type F 101 R/D): Degussa; *N*-hydroxy-2-pyridone, 2-morpholinoethyl isocyanide, TMSO–NH_2 and LDA in THF/heptane: Fluka; $KN(TMS)_2$: Callery.

4.1.1. (*R*)-3-Cyclopent-1-enyl-2-(2-nitro-phenylsulfonyl-oxy)-propionic acid benzyl ester (6). To a solution of (*R*)-(+)-1,1′-bi-2-naphthol (0.453 g, 1.58 mmol) in dichloromethane (40 ml) was subsequently added at 22°C powdered molecular sieves (4 Å, 7.93 g) and a solution of diisopropoxytitanium dibromide in toluene (20%,

1.49 mmol). The suspension was stirred at 22°C for 1.3 h and subsequently treated with methylene–cyclopentane (**4**, 8.22 g, 100 mmol) and with a solution of benzyl glyoxylate (**3**, 19.83 g, 82.8% pure, 100 mmol) in toluene (46 ml) over 40 min keeping the temperature at 22°C. Prior to the addition of the solution, the benzyl glyoxylate (**3**) should be depolymerized by heating the solution to reflux temperature for 5 h followed by rapid cooling. The brown suspension was stirred at 22°C for 16 h, filtered, the residue was washed with dichloromethane (100 ml) and the combined filtrates were evaporated. The residue containing crude **5** (ee=98%, HPLC, Chiralpak AS, *n*-hexane/EtOH 98:2) was dissolved in toluene (185 ml) and treated at 22°C with *o*-nitrobenzenesulfonyl chloride (18.69 g, 84.3 mmol) in one portion. The orange solution was cooled to −15°C, treated with NEt_3 (14.22 g, 140.5 mmol) over 30 min and stirring was continued at −10–−15°C for 3 h. The suspension was treated again with *o*-nitrobenzenesulfonyl chloride (3.11 g, 14.0 mmol) and NEt_3 (3.55 g, 35.1 mmol), stirring was continued for 3 h and this operation was repeated again to drive the reaction to completion. The suspension was stirred at −20°C for 16 h, warmed to 0°C, treated with water (31 ml), the mixture was stirred for 15 min and filtered. The residue containing the crude nosylate **6** was washed with toluene (2×50 ml) and with water (2×50 ml) and wet **6** was dissolved in acetone (265 ml) at 40°C. The solution was diluted with water (81 ml) over 20 min, the suspension was cooled to 22°C over 2 h and filtered. The residue was washed with a solution of acetone/water (2:1, 2×30 ml) and dried at 22°C/9 mbar overnight to give the pure title compound **6** (26.68 g, 62% yield) as pale yellow crystals, mp 123–125°C. ee=>99.9% (HPLC, Chiracel OJ, *n*-hexane/EtOH 40:60). *Caution*: neat **6** can decompose vigorously above 80°C. IR (KBr): 1736 s (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): 8.10 (d, *J*=6.9 Hz, 1H), 7.77–7.60 (m, 3H), 7.35–7.25 (m, 5H), 5.45 (s, br. 1H), 5.28 (dd, *J*=5.4, 7.0 Hz, 1H), 5.11 (s, 2H), 2.90–2.60 (m, 2H), 2.27–2.10 (m, 4H), 1.85–1.65 (m, 2H). MS (EI): 413/1 $[M-H_2O]^+$, 186/10, 137/85, 91/100. $C_{21}H_{21}NO_7S$ requires: C 58.46%, H 4.91%, N 3.25%, S 7.43%; found: C 58.41%, H 4.88%, N 3.15%, S 7.33%.

4.1.2. 1:1 Mixture of (2*R*,3*R*)- and (2*S*,3*R*)-2-*tert*-butoxycarbonyl-3-cyclopent-1-enylmethyl-succinic acid dibenzyl ester (7). To a suspension of NaH (3.17 g, 55–65% pure, 79.2 mmol, pre-washed with *n*-hexane) in dimethylformamide (30 ml) was added at 22°C, a solution of benzyl *tert*-butyl malonate (18.02 g, 72.0 mmol) in dimethylformamide (30 ml) over 30 min (gas evolution ceased) which was followed by the portionwise addition of the nosylate **6** (31.06 g, 72.0 mmol) over 35 min and stirring was continued at 22°C for 6 h. The mixture was treated again with **6** (6.21 g, 14.4 mmol) and stirring was continued for 22 h after which time the conversion was complete. The red solution was cooled to 10°C, diluted with *n*-hexane (100 ml) and water (200 ml) and stirring was continued at 10°C for 1 h. The mixture was filtered (the residue contained 4.18 g of recovered and pure **6**), the organic layer of the filtrate was washed with water (2×100 ml), dried and evaporated to give the crude title compound **7** (35.15 g, 87.4% pure, 89% yield) as a yellow oil which was further processed without purification.

4.1.3. 1-(Bromomethyl)-3,4,4-trimethyl-2,5-imidazolidinedione (9). A suspension of 3,4,4-trimethyl-2,5-imidazolidinedione[8] (**8**, 21.3 g, 150 mmol) and paraformaldehyde (5.86 g, 195 mmol) in HBr/AcOH (33%, 34 ml, 195 mmol) was heated to 80°C for 2 h, the yellow solution was treated again with HBr/AcOH (33%, 7.9 ml, 45 mmol) and stirring was continued at 80°C for 2.5 h after which time the reaction was complete. The solution was cooled to 0°C, diluted with dichloromethane (100 ml) and ice-cold water (100 ml) keeping the temperature at 0°C. The organic layer was washed with water (2×100 ml), dried and evaporated. The residual oil was dissolved in *tert*-butyl methyl ether (20 ml), the solution was rapidly diluted with *n*-hexane (100 ml), the suspension was cooled to 0°C and stirring was continued for 20 min. The suspension was filtered, the residue washed with *n*-hexane (3×40 ml) and dried at 22°C/12 mbar overnight to give the pure title compound **9** (30.89 g, 88% yield) as white crystals, mp 86–88°C. IR (KBr): 1779 m and 1733 s (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): 5.30 (s, 2H), 2.92 (s, 3H), 1.41 (s, 6H). MS (EI): 155/100 $[M-Br]^+$. $C_7H_{11}N_2BrO_2$ requires: C 35.77%, H 4.72%, N 11.92%, Br 33.99%; found: C 36.03%, H 4.79%, N 12.02%, Br 33.62%.

4.1.4. 1:1 Mixture of (2*R*,3*R*)- and (2*S*,3*R*)-2-*tert*-butoxycarbonyl-3-cyclopent-1-enylmethyl-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-succinic acid dibenzyl ester (10). To a suspension of NaH (3.15 g, 55–65% pure, 78.8 mmol, pre-washed with *n*-hexane) in dimethylformamide (30 ml) was added at 22°C, a solution of the crude triester **7** (34.95 g, 87.4% pure, 63.8 mmol) in dimethylformamide (60 ml) over 50 min and stirring was continued for 30 min after which gas evolution ceased. The solution obtained was added at 0°C to a freshly prepared solution of the bromomethyl hydantoin **9** (20.20 g, 85.93 mmol) in dimethylformamide (30 ml) over 15 min and stirring was continued at 0°C for 4 h. The suspension was diluted at 0–10°C with cyclohexane (300 ml) and with water (300 ml) and the organic layer was washed with aqueous NaOH (0.1N, 150 ml), with aqueous HCl (0.1N, 150 ml) and with water (2×150 ml). The organic layer was dried and evaporated to give the crude title compound **10** (47.33 g, 84.5% pure, 99% yield) as a pale yellow oil which was further processed without purification.

4.1.5. 4-*tert*-Butyl-2(*R*)-(cyclopentylmethyl)-3(*R*)-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate (+)-pseudoephedrine salt (*anti*-11a). A vigorously stirred suspension of the crude triester **10** (47.33 g, 84.5% pure, 63.2 mmol) and Pd/C (5%, 9.47 g) in *i*-PrOH (475 ml) was hydrogenated at 25–30°C for 24 h after which hydrogen up-take ceased. The suspension was filtered, the residue was washed with *i*-PrOH (2×50 ml) and the combined filtrates were evaporated at 25°C/12 mbar. To remove traces of residual *i*-PrOH, the residue was dissolved in *i*-PrOAc (200 ml) and evaporated again. The residue was treated with *i*-PrOAc (465 ml) and with *N*-methylmorpholine (7.25 g, 71.7 mmol) and the mixture was heated to reflux temperature for 4 h after which gas evolution ceased. The solution containing a 83:17-mixture of *anti*-/*syn*-**11** was treated at reflux temperature with (+)-pseudoephedrine (11.83 g, 71.6 mmol), the solution was slowly cooled to 22°C over 1 h and stirring was continued for 4 h. The

suspension was filtered and the residue was washed with cold (0°C) *i*-PrOAc (2×100 ml) to give the pure title compound *anti*-**11a** (24.73 g, 68% yield) as white crystals, mp 169–170°C. IR (KBr): 3433 m and 3234 m (NH, OH), 1771 s and 1714 s (C═O). ^{1}H NMR (250 MHz, $CDCl_3$): 8.54 (s, br., 3H), 7.45–7.20 (m, 5H), 4.67 (d, *J*=9.5 Hz, 1H), 3.93 (dd, *J*=11.0, 13.0 Hz, 1H), 3.56 (dd, *J*=13.0, 4.0 Hz, 1H), 3.20 (m, 1H), 2.90 (m, 1H), 2.82 (s, 3H), 2.71 (s, 3H), 2.55 (m, 1H), 1.90–1.10 (m, 11H), 1.41 (s, 9H), 1.33 (s, 3H), 1.32 (s, 3H), 1.08 (d, *J*=6.6 Hz, 3H). MS (neg. ion spray): 409 $[M-H]^-$. $C_{31}H_{49}N_3O_7$ requires: C 64.67%, H 8.58%, N 7.30%; found: C 64.44%, H 8.44%, N 7.39%.

4.1.6. 1-[2(*R*)-[1(*R*)-Carboxy-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-cyclopentylpropionyl]piperidine (*anti*-12). *anti*-**11a** (38.92 g, 67.6 mmol) was partitioned between EtOAc (150 ml) and aqueous HCl (1N, 100 ml), the organic layer was washed with water (2×150 ml) and the aqueous layers were back extracted with EtOAc (100 ml). The combined organic layers were dried over $MgSO_4$, the suspension was filtered and the filtrate was evaporated to a weight of 163 g. The solution containing the free acid *anti*-**11b** was treated at 22°C with *N*-hydroxy-2-pyridone (3.00 g, 27.0 mmol), the solution was cooled to 0°C and treated subsequently with piperidine (6.04 g, 70.9 mmol) and with a solution of *N*,*N*′-dicyclohexylcarbodiimide (15.34 g, 74.35 mmol) in EtOAc (45 ml). The suspension was stirred at 0°C for 2 h and at 22°C for 20 h, the yellow mixture was cooled to 0°C, filtered and the residue was washed with cold (0°C) EtOAc (2×15 ml). The combined filtrates were treated at 0°C with HBr/AcOH (33%, 47.5 ml, 271 mmol) and stirring was continued at 0°C for 3 h. The suspension was treated at 0–10°C with aqueous NaOH (2N, 325 ml) until the pH was adjusted to 5 and the suspension was filtered. The aqueous layer of the filtrate was extracted with EtOAc (2×200 ml), the organic layers were washed with brine (2×200 ml) and the combined organic layers were dried and evaporated at 30°C/12 mbar. To remove traces of acetic acid disturbing the forthcoming crystallization, the residue was diluted with toluene (150 ml) and the solvent was evaporated at 30°C/12 mbar. This procedure was repeated twice. The residue was dissolved in EtOAc (60 ml) and the solution was diluted at 22°C with *n*-hexane (60 ml). After the crystallization sets in, the suspension was further diluted with *n*-hexane (180 ml), the suspension was cooled to 0°C and stirring was continued for 16 h. The suspension was filtered, the residue was washed with *n*-hexane (2×20 ml) and dried to give the pure title compound *anti*-**12** (23.30 g, 82% yield) as pale yellow crystals, mp 116–117°C. IR (KBr): 2600 w, br. (COOH), 1768 m and 1713 s (C═O). ^{1}H NMR (250 MHz, $CDCl_3$): 11.3 (s, br., 1H), 4.03 (dd, *J*=4.4, 14.3 Hz, 1H), 3.80–3.35 (m, 5H), 3.10 (m, 2H), 2.89 (s, 3H), 1.85–1.45 (m, 15H), 1.38 (s, 6H), 1.26 (m, 1H), 1.10 (m, 1H). MS (pos. ion spray): 422/100 $[M+H]^+$. $C_{22}H_{35}N_3O_5$ requires: C 62.69%, H 8.37%, N 9.97%; found: C 62.47%, H 8.51%, N 9.68%.

4.1.7. 1-[3-Cyclopentyl-2(*R*)-[1(*R*)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]piperidine (1). A suspension of *N*-hydroxy-2-pyridone (12.22 g, 110 mmol) in dichloromethane (420 ml) was subsequently treated at 22°C with the acid *anti*-**12** (42.15 g, 97.4% pure, 97.4 mmol) and 2-morpholinoethyl isocyanide (15.42 g, 110 mmol) and stirring was continued for 19 h after which time formation of the intermediate pyridone active ester was complete. The solution was treated at 0°C with TMSO–NH_2 (11.57 g, 97.3% pure, 107 mmol) and stirring was continued at 0°C for 7 h. The solution was washed with sat. aqueous $NaHCO_3$ (440 ml) and with water (3×440 ml), the aqueous layers were extracted with dichloromethane (420 ml), the combined organic layers were diluted with acetic acid (0.6 g, stabilizes the product) and the solution was evaporated at 22°C/400 mbar to a weight of 120 g. The solution was diluted with *tert*-butyl methyl ether (440 ml) and evaporated at 22°C/240 mbar to a weight of 260 g. The residue was diluted with *tert*-butyl methyl ether (145 ml) and with water (4.2 ml) and stirring was continued at 22°C for 16 h. The suspension was diluted with *n*-hexane (220 ml), stirring was continued for 30 min, the suspension was filtered, the residue was washed with *n*-hexane/*tert*-butyl methyl ether (35:15, 260 ml) and dried to give the pure title compound **1** (35.25 g, 96% pure, 79% yield) as white crystals, mp 108–114°C (gas evolution). A second crop yielded an additional 1.50 g (3% yield) of **1**. de=>99.5% (HPLC, Symmetry™ C18); ee=>99.5% (HPLC, Chiralpack AD, *n*-hexane/*i*-PrOH 3:1). IR (nujol): 3570 w and 3302 m (OH, NH), 1765m and 1715 s (C═O).). ^{1}H NMR (250 MHz, $CDCl_3$): 10.4 (s, very br., 1–2H), 3.80–3.35 (m, 6H), 3.26 (m, 1H), 3.15 (m, 1H), 2.86 (s, 3H), 1.80–1.30 (m, 15H), 1.37 (s, 3H), 1.35 (s, 3H), 1.15 (m, 2H). MS (EI): 436/15 $[M]^+$, 404/100. $C_{22}H_{36}N_4O_5$ (containing 0.6 mol% of H_2O) requires: C 59.07%, H 8.38%, N 12.52%; found: C 59.27%, H 8.33%, N 12.68%.

4.1.8. (*R*)-3-Cyclopentylmethyl-4-oxo-4-piperidin-1-yl-butyric acid *tert*-butyl ester (17). A suspension of the acid **16**[13] (ee=99.6%, 34.48 g, 134.5 mmol) and *N*-hydroxy-2-pyridone (5.98 g, 53.8 mmol) in *i*-PrOAc (170 ml) was subsequently treated at 0°C with piperidine (12.03 g, 141.2 mmol) and with a solution of *N*,*N*′-dicyclohexylcarbodiimide (30.53 g, 148.0 mmol) in *i*-PrOAc (90 ml) and stirring was continued at 0°C for 1 h and at 22°C for 16 h. Excess of *N*,*N*′-dicyclohexylcarbodiimide was destroyed by the addition of an aqueous solution of acetic acid (10%, 82 g) and the mixture was stirred for 4 h. The suspension was cooled to 0°C, filtered and the residue washed with *i*-PrOAc (3×40 ml). The organic layer was washed with aqueous Na_2CO_3 (10%, 200 ml) and water (3×200 ml), the aqueous layers were extracted with *i*-PrOAc (200 ml), the combined organic layers were dried and evaporated to give the pure title compound **17** (43.89 g, 98.9% pure, 100% yield) as a pale yellow liquid which solidified on storing at 22°C, mp 38.0–40.5°C. ee=99.6% (HPLC, Chiralpack AD, *n*-hexane/EtOH 95:5). IR (neat): 1729 s and 1641 s (C═O). ^{1}H NMR (250 MHz, $CDCl_3$): 3.65–3.45 (m, 4H), 3.15 (m, 1H), 2.68 (dd, *J*=8.6, 16.3 Hz, 1H), 2.31 (dd, *J*=5.3, 16.3 Hz, 1H), 1.85–1.30 (m, 15H), 1.42 (s, 9H), 1.10 (m, 2H). MS (EI): 324/2 $[M+H]^+$, 185/100.

4.1.9. *anti*-12 from 17. To a solution of $KN(TMS)_2$ (20.2% in THF, 153.6 g, 154 mmol) in THF (155 ml) was added at −60°C a solution of the amide **17** (35.96 g, 98.9% pure, 110 mmol) in THF (180 ml) over 50 min and stirring was continued for 30 min. The yellow solution was treated at

−60°C using a syringe pump with a solution of the bromomethyl hydantoin **9** (28.44 g, 121 mmol) in THF (140 ml) over 1 h keeping the inner temperature strictly at −60°C and stirring was continued at −60°C for 1.5 h. The reaction was quenched at −50–−60°C with brine (20%, 200 ml) over 30 min, the cooling bath was removed and a further portion of brine (20%, 350 ml) was added. The organic layer was washed with brine (20%, 550 ml, containing hydrochloric acid, 25%, 90 ml) and with brine (20%, 2×550 ml), dried and evaporated. The residue containing crude *anti*-**18**/*syn*-**18** (92:8) was dissolved in AcOH (52 ml), treated at 0°C with HBr/AcOH (33%, 47 ml, 268 mmol) and stirring was continued at 0°C for 1.5 h. The mixture was diluted at 0°C with dichloromethane (250 ml) and water (250 ml), the organic layer was washed with ice-cold water (4×250 ml), the aqueous layers were extracted with dichloromethane (250 ml) and the combined organic layers were dried and evaporated. The residue was dissolved in *tert*-butyl methyl ether (100 ml), the solution was diluted at 22°C with *n*-hexane (10 ml) until it became cloudy, crystallization was awaited and the suspension was further diluted with *n*-hexane (75 ml) over 1 h and stirring was continued at 22°C for 1.5 h and at 10°C for 30 min. The suspension was filtered, the residue washed with cold (10°C) *tert*-butyl methyl ether/*n*-hexane (1:1, 3×60 ml) and dried to give the pure title compound *anti*-**12** (27.36 g, 59% yield) as a white solid, mp 110–112°C. IR, ^{1}H NMR and MS are identical with *anti*-**12** from Section 4.1.6.

4.1.10. 4-*tert*-Butyl (*E*)-2(*R*)-isobutyl-3(*S*)-(3-phenyl-allyl)succinate *tert*-butylamine salt (*anti*-24a). A solution of the acid **20**[14] (34.70 g, 150 mmol) in THF (140 ml) was treated at −20°C with a solution of LDA in THF/heptane (2.0 M, 150 ml, 300 mmol) over 40 min and stirring was continued at −20°C for 1 h. The orange solution was treated with a solution of cinnamyl bromide (31.67 g, 98% pure, 157.5 mmol) in THF (50 ml) over 40 min, the yellow solution was allowed to warm to 22°C over 1 h and stirring was continued for 2 h. The solution containing a mixture of *anti*-**24**/*syn*-**24** (7:93, GLC, DB17 capillary column, 50% phenyl–50% methyl-polysiloxane, derivatized with *N*,*O*-bis-(trimethylsilyl)-trifluoroacetamide) was cooled to −20°C and treated with a solution of LDA in THF/heptane (2.0 M, 79 ml, 158 mmol) over 15 min and stirring was continued at −20°C for 30 min. The brown solution was cooled to −90°C and treated with a solution of CF_3CONH_2 (20.35 g, 180 mmol) in THF (20 ml) and stirring was continued at −90°C for 1 h. The yellow solution containing a mixture of *anti*-**24**/*syn*-**24** (98:2) was allowed to warm to 0°C, water (300 ml) was added and the organic solvents were distilled off. The pH of the aqueous solution was adjusted at 0°C to 3 by adding hydrochloric acid (36%, 27 ml), the mixture was diluted with *i*-PrOAc (270 ml), the organic layer was washed with water (3×150 ml) and the aqueous layers were extracted with *i*-PrOAc (270 ml). The combined organic layers were dried and treated at 22°C with *tert*-butylamine (10.97 g, 150 mmol) over 2 min. The suspension obtained was stirred at 22°C for 1 h and at 0°C for 3 h, filtered, the residue was washed with cold (0°C) *i*-PrOAc (50 ml) and dried to give the pure title compound *anti*-**24a** (53.50 g, 85% yield) as a pale yellow solid, mp 155–157°. de=96%, (HPLC, Symmetry™ C18). IR (nujol): 1718 s (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): 7.74 (s, br., 3H), 7.35–7.15 (m, 5H), 6.36 (d, *J*=15.8 Hz, 1H), 6.09 (dt, *J*=15.8, 6.5 Hz, 1H), 2.70–2.35 (m, 4H), 1.75–1.55 (m, 2H), 1.38 (s, 9H), 1.33 (s, 9H), 1.11 (m, 1H), 0.90 (d, *J*=6.4 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H). MS (EI): 290/45 $[M-C_4H_8]^+$, 174/100. $C_{25}H_{41}NO_4$ (containing 0.2 mol% of *i*-PrOAc) requires: C 70.97%, H 9.85%, N 3.18%; found: C 70.97%, H 9.87%, N 3.37%.

4.1.11. *i*-Butylhydrazine·H_2SO_4 (27). A solution of *tert*-butyl carbazate (100 g, 0.757 mol) in *i*-PrOH (1000 ml) was treated at 0°C with *i*-butylaldehyde (54.6 g, 0.757 mol) over 30 min and stirring was continued at 0°C for 2 h and at 22°C for 2 h. To the yellow solution containing the intermediate Schiff base was added a suspension of Pt/C (5%, type F 101 R/D, 9.0 g) in *i*-PrOH (60 ml) and the vigorously stirred mixture was hydrogenated at 30°C/1 bar H_2 for 42 h after which time hydrogen up-take ceased. The suspension was filtered and the filtrate was evaporated to a volume of ca. 720 ml. The pale yellow solution was treated at 0°C with sulfuric acid (65.7 ml) over 20 min and stirring was continued at 50°C for 5 h after which time gas evolution ceased. The suspension was diluted at 22°C with *tert*-butyl methyl ether (580 ml), cooled to −15°C and stirring was continued for 1 h. The suspension was filtered, the residue was washed with cold (−10°C) *tert*-butyl methyl ether/*i*-PrOH (4:1, 3×250 ml) and dried to give the pure title compound **27** (124.09 g, 88% yield) as white crystals, mp 145–147°C (dec.). ^{1}H NMR (250 MHz, CD_3OD): 2.88 (d, *J*=7.1 Hz, 2H), 1.98 (hept., *J*=6.0 Hz, 1H), 1.01 (d, *J*=6.0 Hz, 6H). MS (EI): 88/15 $[M]^+$, 45/100. $C_4H_{14}N_2O_4S$ requires: C 25.80%, H 7.58%, N 15.04%, S 17.22%; found: C 25.91%, H 7.61%, N 15.06%, S 17.18%.

4.1.12. (*E*)-2(*R*)-[1(*S*)-(*tert*-Butoxycarbonyl)-4-phenyl-3-butenyl]-2′-isobutyl-4-methylvalerohydrazide (*anti*-25). A stirred suspension of the *tert*-butylamine salt *anti*-**24a** (41.96 g, 100 mmol) in *i*-PrOAc (400 ml) and water (400 ml) was treated at 0°C with hydrochloric acid (25%, 13.7 ml) until the pH reached a value of 2–3. The organic layer was washed with water (2×200 ml), dried and evaporated to a volume of 200 ml. The solution containing **24b** was treated with *N*-hydroxy-2-pyridone (12.22 g, 110 mmol), the suspension was cooled to 0°C and treated with a solution of *N*,*N*′-dicyclohexylcarbodiimide (22.70 g, 110 mmol) in *i*-PrOAc (25 ml) over 30 min and stirring was continued at 0°C for 4 h. The pale yellow suspension was subsequently treated at 0°C with 4-ethyl morpholine (40.31 g, 350 mmol) and *i*-butylhydrazine H_2SO_4 (**27**, 19.55 g, 105 mmol) and the suspension was stirred at 22°C for 17 h and at 45°C for 7.5 h. The suspension was treated at 0°C with a solution of acetic acid (6.01 g, 100 mmol) in water (60 ml) and stirring was continued at 22°C for 1.5 h. The suspension was cooled to 0°C, diluted with aqueous $NaHCO_3$ (5%, 75 ml), filtered and the residue was washed with *i*-PrOAc (3×45 ml). The combined organic layers were washed with aqueous $NaHCO_3$ (5%, 75 ml), with hydrochloric acid (1N, 2×75 ml), with brine (20%, 2×75 ml) and with water (100 ml). The aqueous layers were extracted with *i*-PrOAc (100 ml), the combined organic layers were dried and evaporated. The residue was diluted with *n*-hexane (200 ml) and evaporated again. The pale yellow solid was treated with *n*-hexane (60 ml), the suspension was stirred at 22°C for 5 h and filtered.

The residue was washed with *n*-hexane (20 ml) and dried to give the pure title compound *anti*-**25** (30.72 g, 74% yield) as white crystals, mp 109–111°C. de=97% (HPLC, (Symmetry™ C18). IR (nujol): 3224 m (NH), 1728 s, 1718 s and 1628 s (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): 7.8 (s, very br., 1H), 7.30–7.15 (m, 5H), 6.38 (d, *J*=15.8 Hz, 1H), 6.10 (dt, *J*=15.8, 7.6 Hz, 1H), 5.6 (s, very br., 1H), 2.75–2.60 (m, 3H), 2.45–2.30 (m, 3H), 1.80 (m, 2H), 1.50 (m, 1H), 1.40 (s, 9H), 1.11 (m, 1H), 0.95 (d, *J*=6.7 Hz, 6H), 0.89 (d, *J*=6.5 Hz, 6H). MS (pos. ion spray): 417/70 $[M+H]^+$, 361/100. $C_{25}H_{40}N_2O_3$ requires: C 72.08%, H 9.68%, N 6.72%; found: C 71.59%, H 9.66%, N 6.74%.

4.1.13. (*E*)-2(*R*)-(1(*S*)-Carboxy-4-phenyl-3-butenyl)-2′-isobutyl-2′-(methanesulfonyl)-4-methylvalerohydrazide (26). To a solution of *anti*-**25** (57.20 g, 137.3 mmol) in dichloromethane (450 ml) was subsequently added at 0°C methansulfonyl chloride (17.30 g, 151.0 mmol) and triethylamine (18.06 g, 178.5 mmol) and stirring was continued at 0°C for 30 min. The pale yellow solution was treated at −15°C with HBr/AcOH (33%, 96.5 ml, 550 mmol) over 30 min and stirring was continued at −15°C for 1.5 h. The reaction mixture was diluted with water (600 ml), the organic layer was washed with water (2×600 ml), the aqueous layers were extracted with dichloromethane (200 ml) and the combined organic layers were dried and evaporated to a weight of 200 g. The stirred solution was diluted at 22°C with *n*-hexane (750 ml) over 5 min, from the suspension obtained 200 ml of solvent were distilled off, a further portion of *n*-hexane (200 ml) was added and stirring was continued for 2 h. The suspension was filtered and the residue was washed with *n*-hexane (200 ml) and dried to give the pure title compound **26** (57.60 g, 96% yield) as white crystals. IR (nujol): 3254 m (NH), 1697 s and 1672 s (C=O), 1347 s and 1158 s (SO_2). ^{1}H NMR (250 MHz, d6-DMSO): 12.4 (s, br. 1H), 10.50 (s, 1H), 7.40–7.15 (m, 5H), 6.37 (d, *J*=15.9 Hz, 1H), 6.20 (dt, *J*=15.9, 7.1 Hz, 1H), 3.30–3.00 (m, 5H), 2.60–2.25 (m, 3H), 1.85–1.20 (m 4H), 1.03 (m, 1H), 0.98–0.80 (m, 12H). MS (pos. ion spray): 461/100 $[M+Na]^+$, 439 $[M+H]^+$. $C_{22}H_{34}N_2O_5S$ (containing 0.8% of dichloromethane) requires: C 59.88%, H 7.77%, N 6.34%, S 7.25%; found: C 59.58%, H 7.87%, N 6.19%, S 7.18%.

4.1.14. (*E*)-2(*R*)-[1(*S*)-(Hydroxycarbamoyl)-4-phenyl-3-butenyl]-2′-isobutyl-2′-(methanesulfonyl)-4-methylvalerohydrazide (2). To a suspension of *N*-hydroxy-2-pyridone (5.50 g, 49.5 mmol) in THF (150 ml) was subsequently added at 22°C the acid **26** (19.74 g, 45.0 mmol) and a solution of *N*,*N*′-dicyclohexylcarbodiimide (10.21 g, 49.5 mmol) in THF (54 ml) and stirring was continued at 22°C for 22 h. The suspension containing the intermediate pyridone active ester was treated with aqueous hydroxylamine (50%, 3.57 g, 54 mmol) and stirring was continued at 22°C for 2 h. The thick suspension was diluted with THF (200 ml) and stirring was continued for 2 h. The mixture was treated with AcOH (3.24 g), stirring was continued for 10 h and the suspension was filtered. The filtrate was evaporated, the residue suspended in *i*-PrOAc (300 ml), the suspension was cooled to 0°C, stirring was continued for 30 min, the suspension was filtered and the residue was washed with *i*-PrOAc (3×50 ml). The combined filtrates were washed with aqueous Na_2CO_3 (13%, 110 ml) and with water (3×110 ml), the aqueous layers were extracted with *i*-PrOAc (200 ml), the combined organic layers were dried and evaporated. The residue was treated with dichloromethane (440 ml), the suspension was stirred at 22°C for 2.5 h, filtered and the residue was washed with dichloromethane (2×150 ml) and dried. The residue (17.56 g) was dissolved in EtOH (176 ml), the solution was diluted at 22°C with water (198 ml) over 20 min and stirring was continued until crystallization sets in. The suspension was diluted with water (154 ml) over 45 min and stirring was continued for 3.5 h. The suspension was filtered, the residue washed with EtOH/water (1:2, 2×35 ml) and dried to give the pure title compound **2** (15.97 g, 78% yield) as a white solid, mp 200–205°C (dec.). de=>99.5% (HPLC, Symmetry™ C18); ee=>99.5% (HPLC, Chiralpak AD, *n*-hexane/*i*-PrOH 7:3). IR (nujol): 3237 m (NH, OH), 1709 m and 1650 s (C=O), 1347 s and 1151 s (SO_2). ^{1}H NMR (250 MHz, d6-DMSO): 10.58 (s, 1H), 10.45 (s, 1H), 8.87 (s, 1H), 7.35–7.15 (m, 5H), 6.30 (d, *J*=15.8 Hz, 1H), 6.09 (dt, *J*=15.8, 6.9 Hz, 1H), 3.30–2.95 (m, 5H), 2.65–2.15 (m, 4H), 1.85–1.15 (m, 3H), 0.98 (m, 1H), 0.95–0.75 (m, 12H). MS (neg. ion spray): 452/100 $[M-H]^-$. $C_{22}H_{35}N_3O_5S$ requires: C 58.26%, H 7.78%, N 9.26%, S 7.07%; found: C 57.95%, H 7.88%, N 9.35%, S 7.16%.

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