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Solid-phase synthesis of hydroxamic acid based TNF-α convertase inhibitors[1]

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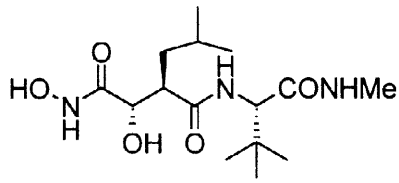
Abstract: An acid-sensitive linker for the solid phase synthesis of hydroxamic acids is described. Hydroxamic acid based TNFα inhibitors have been prepared by solid phase synthesis: derivatisation of N^2-[4-(N-oxyamino)-2R-isobutyl-3S-aminosuccinyl]-L-tert-leucine-N^1-methylamide grafted on Sasrin® resin and subsequent acidic cleavage afforded hydroxamic acids in good yields and with good purity.

Keywords: *hydroxamic acid, solid-phase synthesis, reductive amination, acylation*

Hydroxamic acids are very effective ion chelators. They have been extensively used as zinc binding ligands in the field of zinc metalloenzyme inhibitors, especially as MMP (matrix metalloprotease) inhibitors. This approach has led to pseudopeptide and non peptide hydroxamic acids which are potent MMP inhibitors (as exemplified by Marimastat): several of them have advanced into human clinical trials for the treatment of cancer, arthritis and corneal ulceration.[2]



Marimastat

We have previously reported on the preparation and use of O-2,4-dimethoxybenzylhydroxylamine for the synthesis of hydroxamic acid based inhibitors of biological interest.[3]

As part of our on-going interest in the design and synthesis of TACE (tumour necrosis factor α convertase[4]) inhibitors, a zinc metalloenzyme, we have been developing effective solid-phase syntheses of these compounds. We report here the preparation of **1**[5], a solid phase equivalent of O-2,4-dimethoxybenzylhydroxylamine and its use in solid phase synthesis of TACE and MMP inhibitors **2a-c**, where we have widely varied the R residue in a multiparallel mode.

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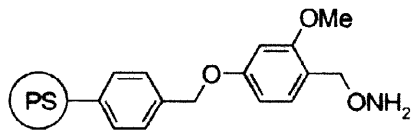
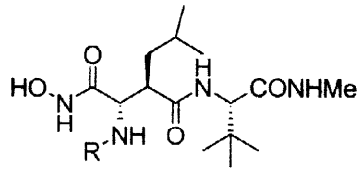
PII: S0040-4020(99)00347-6



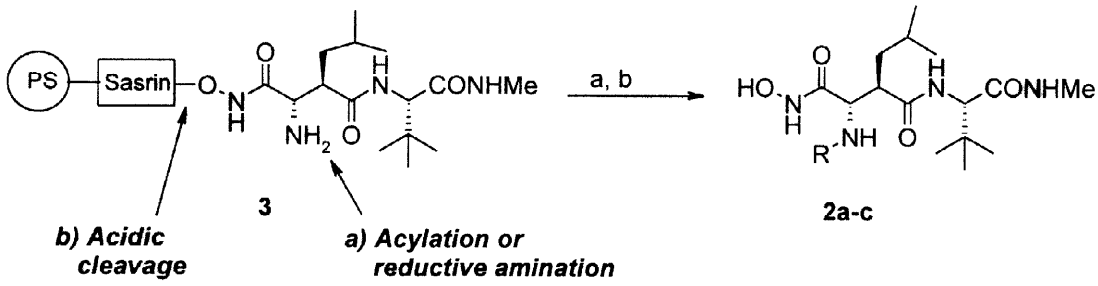
1 (Sasrin-ONH_2)



2a-c **2a:** R= R_1SO_2
2b: R= R_2CO
2c: R= R_3CH_2

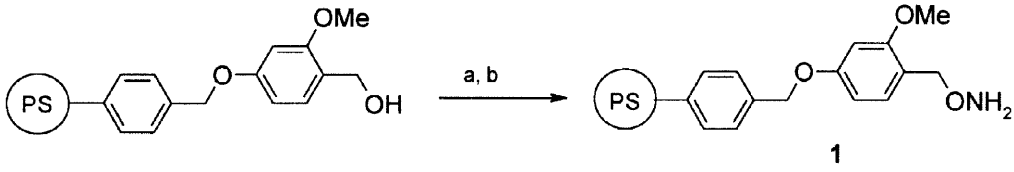
We conceived a synthetic route where the R group was introduced in the penultimate step (by robust reactions), followed by cleavage of the desired hydroxamic acid from the resin. Resin **1** was chosen for its ease of cleavage under mild acidic conditions.

For this approach, we required the key intermediate **3**, that could further be functionalised by sulfonamide/amide coupling or reductive amination, and finally be cleaved under acidic conditions to give hydroxamic acids **2a-c** (scheme 1).



Scheme 1

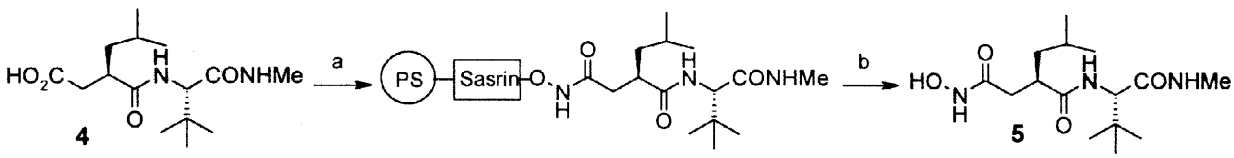
1 was synthesised from SASRIN® resin in a similar way to that described by Floyd and Lewis[5a] using Wang resin (scheme 2).



a) PPh_3 (8 eq.), DEAD (8 eq.), N-hydroxyphthalimide (8 eq.), CH_2Cl_2, 72h; b) NH_2NH_2, MeOH

Scheme 2

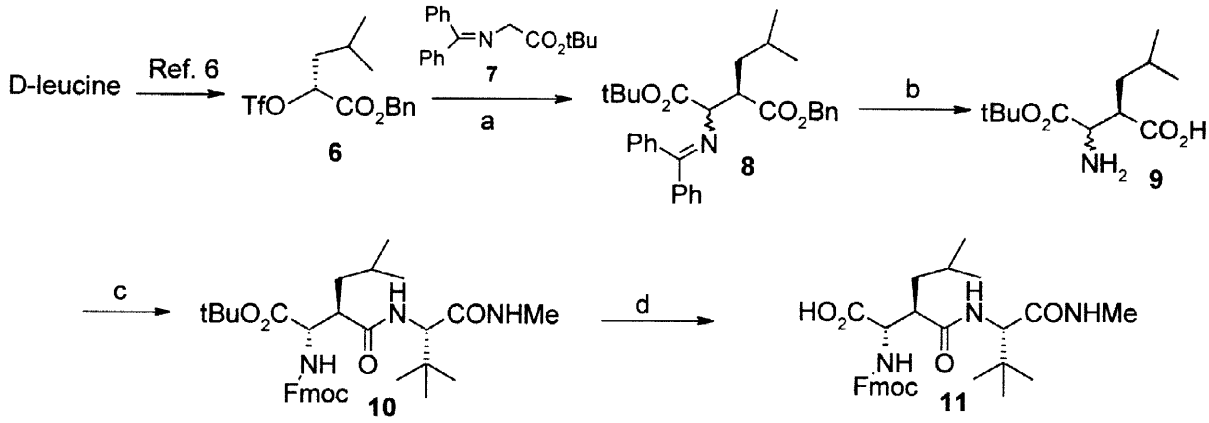
We first checked that a highly functionalised carboxylic acid can be coupled with **1** and cleanly cleaved from the resin to give the corresponding hydroxamic acid: carboxylic acid **4** was reacted with **1** under peptide coupling conditions to give the corresponding protected hydroxamic acid grafted on resin. Cleavage under mild acidic conditions (5% TFA/dichloromethane) afforded hydroxamic acid **5** with good purity as illustrated below in scheme 3.



a) Acid **4** (1.5 eq.), resin **1** (1 eq.), EDCI (5 eq.), DMAP (1 eq.), DMF; b) 5% TFA - CH_2Cl_2, 15 min

Scheme 3

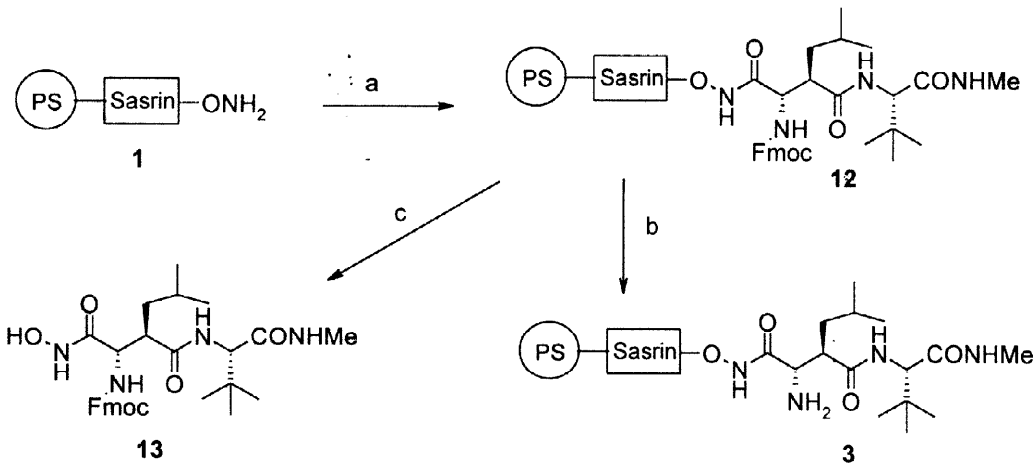
Intermediate **3** was prepared from D-leucine according to schemes 4 and 5: Triflate **6**[6] was displaced by the anion of **7** according to Stork's procedure[7] to give **8**, predominantly as the desired anti diastereoisomer[8] (syn/anti ratio: 1/3). **8** was further processed to acid **11**.



a) **7**, LDA (1 eq.), THF-DMPU, -78°C, then **6** (1 eq.), 99%, syn/anti ratio 1:3; b) H_2, Pd/C, MeOH, 82%, c) FmocCl, dioxane, aq. Na_2CO_3; L-tert-leucine methylamide (1.4 eq.), EDCI (1.2 eq.), CH_2Cl_2; seperation of isomers, 35% from **9**; d) TFA - CH_2Cl_2 (1:1), 99%

Scheme 4

Coupling of **11** with resin **1** provided the required intermediate **3** after Fmoc deprotection with piperidine/DMF. Validation of the coupling was assessed by cleavage of **12** with 5% TFA/dichloromethane which gave hydroxamic acid **13** with good purity (scheme 5).

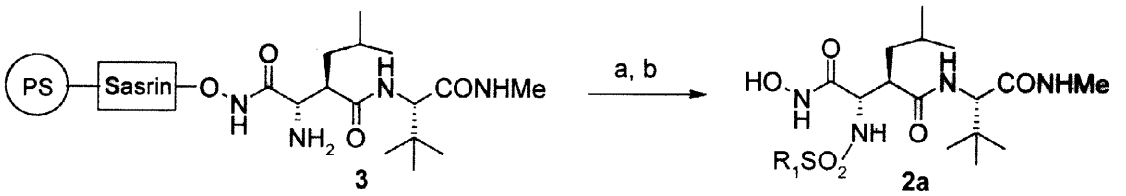


a) Acid **11** (1.3 eq.), resin **1** (1 eq.), EDCI (5 eq.), DMAP (1.3 eq.), DMF; b) piperidine - DMF 1: 3
c) 5% TFA - CH_2Cl_2, 15 min.

Scheme 5

With intermediate **3** in hand, we were ready to derivatise the amino group. Subsequent cleavage of the adduct from the resin would afford hydroxamic acids **2a-c** ready for biological evaluation.

Sulfonamide synthesis was performed under classical conditions [R_1SO_2Cl (5 eq), CH_2Cl_2-pyridine (4:1), 2 h, ultrasonication]. Cleavage of the resin with 5% TFA/dichloromethane afforded the corresponding sulfonamides **2a** (scheme 6).



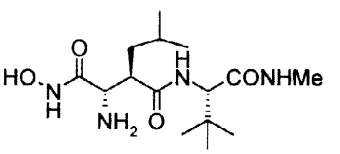
3

a) R_1SO_2Cl (5 eq.), CH_2Cl_2 - pyridine 4:1, ultrasonication; b) 5%TFA - CH_2Cl_2, 15 min

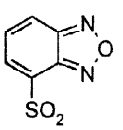
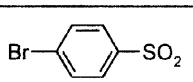
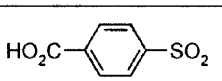
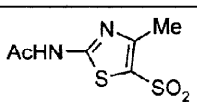
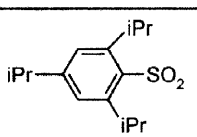
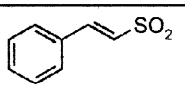
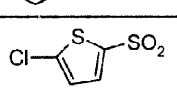
Scheme 6

Representative examples of sulfonamides are described in Table 1. Quality control (e.g. purity and structure assignment) was assessed by HPLC with light scattering detection, UV detection at 254 nm and mass spectrometry. ^1H NMR was performed on representative examples to further determine the structural integrity of compounds **2a**.

The reaction proceeded equally well with aromatic and aliphatic sulfonyl chlorides, in good yields and with good purity (see Table 1). However, bulky aliphatic sulfonyl chlorides (such as isopropylsulfonyl chloride) or hydrolysis-sensitive sulfonyl equivalents (such as trifluoromethanesulfonyl anhydride) gave mixtures containing the unreacted amine **14**.



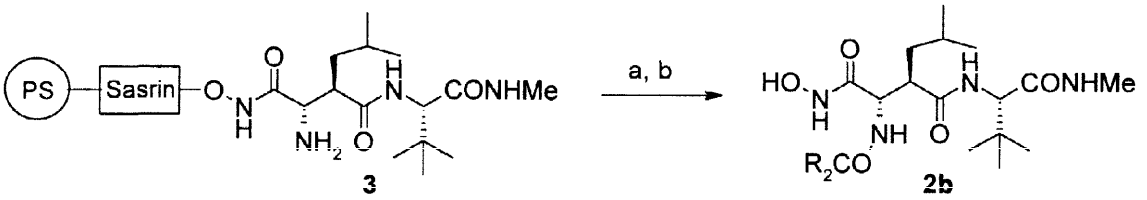
14

Entry	Compound 2a R= R_1SO_2	Yield [9] mg (%)	MS (ESI) (MH^+)	HPLC t_R (min)
1	n-$BuSO_2$	14 (62)	451	7.6
2	$PhSO_2$	16 (68)	471	4.8[a]
3	$PhCH_2SO_2$	15 (62)	485	7.8
4		16 (63)	513	7.5
5		11.8 (43)	549 (^{79}Br) 551 (^{81}Br)	8.8
6		13.5 (52)	515	6.7
7		20.1 (73)	549	7.0
8		22.3 (75)	597	12.6
9		24.1 (97)	497	8.4
10		14.3 (56)	511 (^{35}Cl) 513 (^{37}Cl)	8.6

a) eluting with 45% methanol in 1% acetic acid-water

Table 1

Similarly, amide formation was performed under classical conditions [diisopropylcarbodiimide (6 eq.), R_2CO_2H (5 eq), CH_2Cl_2/DMF, ultrasonication]. Cleavage from the resin with 5% TFA/dichloromethane afforded the corresponding amides **2b**. (scheme 7)



a) R_2COOH (5 eq.), diisopropylcarbodiimide (6 eq.), DMF - CH_2Cl_2 1:3, ultrasonication; b) 5% TFA - CH_2Cl_2, 15 min

Scheme 7

Representative examples of carboxamides are described in Table 2.

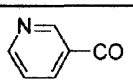
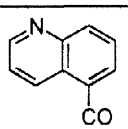
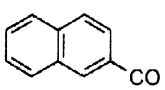
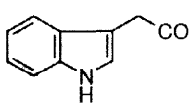
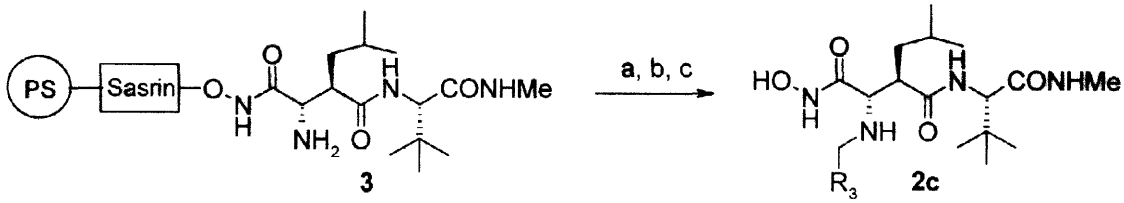
Entry	Compound 2b R= R_2CO	Yield [9] mg (%)	MS (ESI) (MH^+)	HPLC t_R (min)
1	$Ph(CH_2)_4CO$	18.3 (75)	471	10.5
2	n-HexCO	14.8 (67)	443	10.5
3		21 (97)	436	5.8
4		26.1 (108)	486	6.9
5		22.6 (93)	485	9.5
6	$MeO_2C(CH_2)_4CO$	23.7 (100)	473	7.5
7		13.1 (54)	488	8.4

Table 2

To further investigate the versatility of resin **1**, we also functionalised the amino group of **3** by reductive amination.

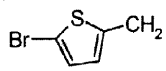
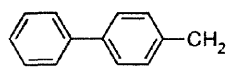
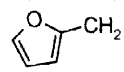
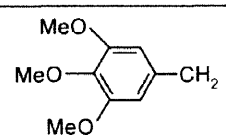
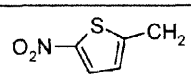
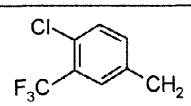
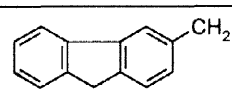
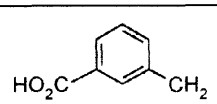
Reductive amination can lead to dialkylation of the amine.[10] To prevent it, the reaction was performed in two steps using Look's reductive amination procedure:[11] formation of the imine in the presence of trimethylorthoformate as dehydrating agent and subsequent reduction with excess of $NaBH_3CN$ in 1% acetic acid-methanol (Scheme 8).



a) R_3CHO (10 eq.), trimethylorthoformate - CH_2Cl_2 1:1, ultrasonication; b) $NaBH_3CN$ (20 eq.), 1% AcOH/MeOH ultrasonication; c) 5% TFA - CH_2Cl_2, 15 min

Scheme 8

Representative examples of amines are described in Table 3.

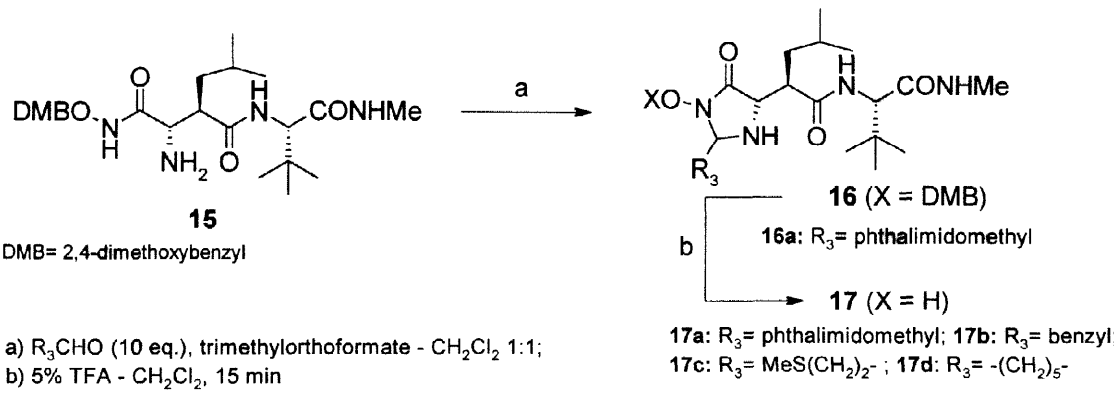
Entry	Compound 2c R= R_3CH_2	Yield [9] mg (%)	MS (ESI) (MH^+)	HPLC t_R (min)
1	$PhCH_2$	10 (48)	421	6.4
2		15.8 (63)	505(^{79}Br) 507 (^{81}Br)	10.0
3	$tBuCH_2$	21.6 (104)	415	5.6
4		25 (100)	497	10.2
5		25.7 (105)	411	5.4
6		23.7 (93)	511	6.2
7	$MeS(CH_2)_3$	22.4 (107)	419	4.0
8		20.5 (87)	472	8.8
9		27.4 (105)	523 (^{35}Cl) 525 (^{37}Cl)	11.2
10		27 (106)	509	10.2
11		25 (108)	465	6.2
12[a]	cyclohexyl	22 (106)	413	5.2
13[a]	3-pentyl	21 (105)	401	4.6

(a) Reduction step: 2x3h with 20 eq. $NaBH_3CN$ in 1% AcOH-methanol, ultrasonication.

Table 3

The procedure worked well with a wide range of aldehydes. However, with a few aldehydes, we did not obtain the expected amine, but we isolated the corresponding imidazolinone **17** (respectively **17a** and **17b** for phthalimidoacetaldehyde and phenylacetaldehyde).

Formation of **17** was confirmed in solution. Reaction of **15** with phthalimidoacetaldehyde gave imidazolinone **16a** which could not be reduced to the corresponding amine with an excess of $NaBH_3CN$ in 1% AcOH-methanol. Cleavage of the 2,4-dimethoxybenzyl group gave the corresponding deprotected imidazolinone **17a**. Similarly, methylthiopropionaldehyde reacted with **15** to give imidazolinone **17c** after deprotection of the dimethoxybenzyl group with 5% TFA (scheme 9).



15

DMB= 2,4-dimethoxybenzyl

a) R_3CHO (10 eq.), trimethylorthoformate - CH_2Cl_2 1:1;
b) 5% TFA - CH_2Cl_2, 15 min

17a: R_3= phthalimidomethyl; **17b**: R_3= benzyl;
17c: R_3= $MeS(CH_2)_2$- ; **17d**: R_3= -$(CH_2)_5$-

Scheme 9

These results[12] suggest that during the reductive amination process, reaction of an aldehyde with **3** affords first the corresponding imidazolinone which is reduced in most cases with $NaBH_3CN$ to amine **2c** after acidic cleavage from the resin.

The reductive amination procedure was also applied to aliphatic ketones (entry 12 and 13 in Table 3). However, reduction of the corresponding imidazolinones[13b] could only be completed by longer reaction times (2 x 3h with an excess of $NaBH_3CN$ in 1% AcOH-methanol). In entry 12 (cyclohexanone), shorter reaction times led to subsequent amounts of unreduced imidazolinone **17d** after cleavage.

Under trimethylorthoformate activation, no imine formation was observed with aromatic ketones: reductive amination with acetophenone gave only the unreacted amine **14**.

In conclusion, we have developed an O-protected hydroxylamine **1** grafted on resin. Coupling of carboxylic acid **11** (obtained by chiral synthesis) with **1** gave the key synthon **3** after removal of the Fmoc group. Sulfonamide/amide coupling or reductive amination on **3** followed by mild acidic cleavage gave the corresponding MMP/TACE inhibitors **2a-c**[13] in an m.p.s. (multiple parallel synthesis) mode.

Acknowledgements: We warmly thank Dr. T.G.C. Bird for early work in this area and fruitful discussions. Many thanks to Mr C. Delvare for recording gel ^{13}C NMR spectra of resins.

Experimental

All experiments were carried out under an inert atmosphere unless otherwise stated. Flash chromatography was carried out on Merck Kieselgel 60 (Art. 9385). TLCs were performed on precoated silica gel plates (Merck Art. 5715). Melting points were determined on a Kofler Block or with a Büchi melting point apparatus and are uncorrected. Proton and ^{13}C NMR spectra were recorded on a JEOL JMM-EX400 spectrometer at 400 MHz and 100 MHz respectively with TMS as an internal standard. Chemical shifts are expressed in units of δ (ppm), and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; br s, broad

singlet; m, multiplet. Gel ^{13}C NMR was performed on resin swollen in $CDCl_3$ (unless otherwise stated), typically 100 mg of resin in 0.5 ml of solvent. Pulse delay was reduced from 2.3 s to 0.7 s. The IR spectra were recorded with a Bruker Vector 22 FTIR spectrophotometer. Mass spectra were obtained on a Finnigan SSQ7000 mass spectrometer by electronic impact (EI) or electrospray (ESI) ionisation techniques. Elemental analyses were performed on a Carlo Erba EA1108 instrument. Unless otherwise stated, HPLC retention times were measured on a 125/4.6 mm Kromasil C_{18}, 5 μm HPLC column, eluant: methanol and water/1%AcOH; linear gradient from 30:70 to 90:10 for 10 min then 100:0 for 5 min; flow rate 1.5 ml/min, UV detection 254 nm and light scattering. SASRIN® resin was prepared from chloromethyl-copoly(styrene-1% divinylbenzene)-resin (Merrifield resin, supplied by Bachem, loading: 0.8-1 mmol/g, crosslinked with 1% DVB, 200-400 mesh) according to Ref 14.

4-(Aminoxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1% divinylbenzene)-resin 1. 4-(Hydroxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1% divinylbenzene)-resin (SASRIN® resin) (2.6 g, ca 0.7 mmol/g loading, 1.8 mmol) was suspended in dry chloroform (100 ml) and gently agitated for 30 min under a blanket of argon. N-hydroxyphthalimide (2.71 g, 16.6 mmol) and triphenylphosphine (4.36 g, 16.6 mmol) were added. The mixture was stirred for 15 min at 0°C. Diethylazodicarboxylate (2.6 ml, 16.6 mmol) was added dropwise and the mixture was shaken for 72 h at room temperature. The resin was collected by filtration, washed successively with chloroform (3x100 ml), methanol (3x100 ml), dichloromethane (3x100 ml), ether (3x100 ml) and dried to give 4-(phthalimidoxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1% divinylbenzene)-resin. ^{13}C NMR (gel in $CDCl_3$): 163.4, 99.1, 74.2, 69.7, 55.4; IR: 1730.
4-(Phthalimidoxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1% divinylbenzene)-resin (3.6 g, ca. 0.6 mmol/g) was suspended in methanol (100 ml) for 30 min. To this mixture was added hydrazine hydrate (0.77 ml, 15.8 mmol). The mixture was stirred at room temperature for 18 h. The resin was collected by filtration, washed successively with methanol (3x100 ml), dichloromethane (3x100 ml), ethyl acetate (3x100 ml), ether (3x100 ml) and dried to give resin **1**. (Estimation of the loading was assessed by titration of the liberated phthalhydrazide: 0.7-0.8 mmol/g). ^{13}C NMR (gel in THF-d_8): 102.2, 75.4, 73.0, 58.1.

N^2-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide 5. Resin **1** (115 mg, 0.08 mmol) was suspended in DMF (7.5 ml) for 30 min. To this mixture were added acid **4**[6] (36 mg, 0.12 mmol), DMAP (10 mg, 0.08 mmol) and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (80 mg, 0.4 mmol). The mixture was agitated for 18 h. The resin was collected by filtration and washed with DMF (4 x 10 ml), methanol (4 x 10 ml), CH_2Cl_2 (4 x 10 ml) and ether (4 x10 ml) to give 95 mg of a white resin. This resin was suspended in 5% TFA-CH_2Cl_2 (5 ml). The mixture was agitated for 15 mn. The resin was filtered off and washed with CH_2Cl_2 (10 ml). Evaporation of the filtrate with toluene, followed by trituration in ether afforded **5** as a white powder (13 mg, 82%). ^1H NMR (DMSO-d_6): 10.4 (m, 1H), 8.7 (m, 1H), 7.85 (m, 1H), 7.66 (d, 1H, J= 9 Hz), 4.16 (d, 1H, J= 9 Hz), 2.84 (m, 1H), 2.55 (d, 3H, J= 4.3 Hz), 2.15 (dd, 1H, J= 14.4 Hz, J'= 7 Hz), 2.01 (dd, 1H, J= 14.4 Hz, J = 7.4 Hz), 1.41 (m, 2H), 1.10 (m, 1H), 0.88 (s, 9H), 0.83 (d, 3H, J= 5.9 Hz), 0.79 (d, 3H, J= 5.9 Hz); MS (ESI): 316 (MH^+); HPLC (linear gradient 40% to 90% MeOH-1% AcOH/H_2O in 10 min): t_R= 4 min

1-Benzyl-4-tert-butyl-3(R/S)-(N-diphenylmethylene)amino-2R-isobutylbutan-1,4-dioate 8. To a stirred solution of LDA [75.2 mmol; prepared by addition of 1.6 M n-butyl lithium (47 ml, 75.2 mmol) in hexane to a solution of diisopropylamine (10.53 ml, 80.3 mmol) in dry THF (120 ml) at -78°C] cooled at -78°C under argon atmosphere was added dropwise tert-butyl N-(diphenylmethylene)glycinate[15] **7** (22.2 g, 75.2 mmol) in dry THF (170 ml). The mixture was stirred for 15 min at -78°C and DMPU (18 ml, 149 mmol) was added dropwise. The mixture was stirred for 30 min at -78°C. A solution of benzyl 2R-trifluoromethanesulfonyloxy-4-methylvalerate[6] **6** (26.3 g, 74.2 mmol) in dry THF (170 ml) was added dropwise to the reaction mixture at -78°C. The mixture was stirred at -78°C for 1 h and at room temperature for 18 h. The solution was diluted in petroleum ether (1000 ml), washed with saturated aqueous ammonium chloride (2 x 600 ml), water (600 ml) and brine (600 ml), dried over $MgSO_4$ and filtered. The solvents were removed and the residue was purified by flash chromatography on silica using petroleum ether-ethyl acetate with 0.5% triethylamine (gradient from 95/5 to

90/10) as eluant to give **8** (36.6 g, 99%, S/R (anti/syn isomers) 3:1 mixture): ^{1}H NMR ($CDCl_3$): 7.7-7.1 (m, 5H), 5.16 (d, 1H, J= 12.5 Hz, 3S isomer), 5.10 (d, 1H, J= 12.8 Hz, 3R isomer), 5.07 (d, 1H, J= 12.5 Hz, 3S isomer), 5.03 (d, 1H, J= 12.8 Hz, 3R isomer), 4.29 (d, 1H, J= 7 Hz, 3R isomer), 4.12 (d, 1H, J= 6.6 Hz, 3S isomer), 3.38 (m, 1H, 3S isomer), 3.22 (m, 1H, 3R isomer), 1.8-1.1 (m, 3H), 1.40 (s, 9H, 3R isomer), 1.39 (s, 9H, 3S isomer), 0.90-0.81 (m, 6H); MS (ESI): 500 (MH^+); Elemental analysis for $C_{32}H_{37}NO_4$ 0.1H_2O: Calculated: C, 76.65; H, 7.48; N, 2.79; Found: C, 76.42; H, 7.45; N, 2.73.

3(R/S)-Amino-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester 9. A solution of **8** (20 g, 40 mmol, R/S 1:3 mixture) in methanol (250 ml) was hydrogenated in the presence of palladium on charcoal (1.5 g, 10%) under 1 bar for 24 h. The catalyst was removed by filtration and the solvents were removed in vacuo. The yellow solid was triturated with petroleum ether to give **9** (8.07 g, 82%, R/S 1:3 mixture) as a white solid; ^{1}H NMR (DMSO-d_6, CD_3CO_2D): 3.86 (s br, 1H, 3R isomer), 3.63 (s br, 1H, 3S isomer), 2.68 (m, 1H), 1.7-1.25 (m, 3H), 1.44 (s, 9H, 3R isomer), 1.42 (s, 9H, 3S isomer), 0.89-0.84 (m, 6H); MS (EI): 246 (MH^+); Elemental analysis for $C_{12}H_{23}NO_4$: Calculated: C, 58.75; H, 9.45; N, 5.71; Found: C, 58.48; H, 9.76; N, 5.69; m.p.: 184-186°C.

N^2-[2R-Isobutyl-3S-(9-fluorenylmethoxycarbonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide 10. To a solution of **9** (4.7 g, 19.1 mmol, R/S 1:3 mixture) in a mixture of dioxane (50 ml) and 10% aqueous sodium carbonate (100 ml) cooled at 0°C was added a solution of 9-fluorenylmethyl chloroformate (5 g, 19.3 mmol) in dioxane (80 ml) dropwise. The mixture was warmed to room temperature and stirred for 1 h. The mixture was acidified to pH 3 by the addition of 4N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and the solvents were evaporated in vacuo to give 3(R/S)-(9-fluorenylmethoxycarbonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester as a white solid. To a solution of this crude compound in dichloromethane (70 ml) was added L-tert-leucine methylamide (3.8 g, 26.4 mmol), and EDCI (4.4 g, 23.0 mmol). The mixture was stirred for 3 h, diluted with ethyl acetate, washed with 1N hydrochloric acid and brine. The organic layer was dried over $MgSO_4$. The residue was purified by chromatography on silica gel using dichloromethane/acetonitrile (85:15) as eluant to give pure isomer **10** (4.0 g, 35%) as a white foam. ^{1}H NMR ($CDCl_3$): 7.76 (m, 2H), 7.63 (m, 2H), 7.39 (m, 2H), 7.30 (m, 2H), 6.40 (m, 2H), 5.70 (m, 1H), 4.50-4.20 (m, 4H), 4.14 (d, 1H, J= 9.2 Hz), 2.99 (m, 1H), 2.82 (d, 3H, J= 4.8 Hz), 1.7-1.4 (m, 3H), 1.44 (s, 9H), 1.00 (s, 9H), 0.93 (d, 6H, J= 6.3 Hz); MS (ESI): 594 (MH^+); Elemental analysis for $C_{34}H_{47}N_5O_6$: Calculated: C, 68.78; H, 7.98; N, 7.08; Found: C, 68.80; H, 7.98; N, 7.04; m.p.: 105-110°C.

N^2-[2R-Isobutyl-3S-(9-fluorenylmethoxycarbonylamino)-4-hydroxysuccinyl]-L-tert-leucine-N^1-methylamide 11. To a solution of **10** (4 g, 6.74 mmol) in dichloromethane (20 ml) was added trifluoroacetic acid (20 ml). The mixture was stirred for 18 h at 0°C. The solvents were evaporated in vacuo. The residue was taken up in toluene and the solvent was removed in vacuo (3 times). The residue was triturated in a mixture of pentane/ether (1:1) to give a while solid which was collected and dried: **11** (3.6 g, 99%). ^{1}H NMR (DMSO-d_6): 7.90-7.10 (m, 11H), 4.35-4.10 (m, 4H), 3.97 (m, 1H), 2.97 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 1.52 (m, 1H), 1.37 (m, 1H), 1.10 (m, 1H), 0.83 (m, 15H); MS (ESI): 538 (MH^+); Elemental analysis for $C_{30}H_{39}N_5O_6$ 0.50 H_2O: Calculated: C, 65.91; H, 7.38; N, 7.69; Found: C, 65.76; H, 7.74; N, 7.47; m.p.: 150-160°C.

Resin 12. Resin **1** (7.5 g, ca 0.7 mmol/g loading, 5.25 mmol) was suspended in DMF (200 ml) and gently agitated for 30 min. To this slurry was successively added **11** (3.67 g, 6.83 mmol), EDCI (5 g, 26.3 mmol) and DMAP (840 mg, 6.9 mmol). The mixture was shaken for 72 h. The resin was collected by filtration, washed successively with DMF (2x100 ml), dichloromethane (100 ml), methanol (2x100 ml), dichloromethane (100 ml), ether (100 ml) and dried.

Resin 3. Resin **12** (from above) was shaken with a solution of 25% piperidine in DMF (v/v, 200 ml) for 4 h. The resin was collected by filtration, washed with DMF (2x100 ml), methanol (2x100 ml), dichloromethane (2x100 ml), ether (100 ml) and dried to give resin **3** (8.65 g, theoretical loading 0.5-0.6 mmol/g).

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(9-fluorenylmethoxycarbonylamino)succinyl]-L-tert-leucine-N^1-methylamide 13. Resin **12** (50 mg, ca 0.025 mmol) was suspended in 5% TFA-CH_2Cl_2 (2.5 ml). The mixture was agitated for 15 min. Filtration and washing of the resin with CH_2Cl_2 (10 ml) afforded **13** (6 mg, 43%) as a white powder after addition of toluene and evaporation of the solvents. ^{1}H NMR (DMSO-d_6): 10.8 (s br, 1H), 8.9 (s br, 1H), 7.88 (m, 3H), 7.67 (m, 2H), 7.44-7.23 (m, 6H), 4.28-4.11 (m, 4H), 3.84 (m, 1H), 2.79 (m, 1H), 2.55

(d, 3H, J= 4.6 Hz), 1.54 (m, 1H), 1.30 (m, 1H), 0.80 (s, 9H), 0.77 (m, 7H); MS (ESI): 575 (MNa^+); HPLC (linear gradient 60% to 90% MeOH 1% AcOH/H_2O in 7 min): t_R= 6.6 min

General procedure for the synthesis of sulfonamides 2a: A gas dispersion tube with resin **3** (100 mg, ca 0.05 mmol) inside was placed in a test tube and 25% pyridine in dichloromethane (3 ml, v/v) was added, followed by a sulfonyl chloride (0.25 mmol) in dichloromethane (1 ml). The mixture was agitated in a ultrasonicated bath for 2 h. The gas dispersion tube was drained and purged with nitrogen. The standard protocol for washing the resin consisted in adding dichloromethane (2x6 ml), methanol (2x6 ml) and dichloromethane (2x6 ml) into the gas dispersion tube, followed by agitation by ultrasonication for 5 min, and finally draining and purging with nitrogen. 5% TFA in dichloromethane (5 ml) was added to the resin in the gas dispersion tube (itself placed in a clean test tube). The mixture was agitated in a ultrasonicated bath for 15 min. The resin was drained, washed with methanol (3 ml), drained and purged with nitrogen. The filtrates were concentrated in vacuo. Toluene (2 ml) and methanol (2 ml) were added and evaporated in vacuo to give the corresponding sulfonamide **2a**.

Sulfonamide 2a (entry 2: R = $PhSO_2$): ^{1}H NMR (DMSO-d_6): 10.74 (s, 1H), 8.82 (s, 1H), 7.89 (m, 1H), 7.75 (d, 2H, J= 7.7 Hz), 7.67-7.52 (m, 4H), 7.27 (m, 1H), 4.12 (d, 1H, J= 9.2 Hz), 3.70 (t br, 1H, J= 9.2 Hz), 2.73 (m, 1H), 2.59 (d, 3H, J= 4.4 Hz), 1.47 (m, 1H), 1.31 (m, 1H), 0.92 (m, 1H), 0.91 (s, 9H), 0.79 (d, 3H, J= 5.9 Hz), 0.77 (d, 3H, J= 5.9 Hz).

General procedure for the synthesis of carboxamides 2b: A gas dispersion tube with resin **3** (100 mg, ca 0.05 mmol) inside was placed in a test tube containing dichloromethane (3 ml). A solution of a carboxylic acid (0.25 mmol) and diisopropylcarbodiimide (0.3 mmol) in DMF (1 ml) was added and the mixture was agitated in a ultrasonicated bath for 4 h. The gas dispersion tube was drained and purged with nitrogen. Washing of the resin was performed as above with the following solvents: methanol (3x5 ml), dichloromethane (1x5 ml), methanol (1x5 ml) and finally dichloromethane (2x5 ml). Cleavage with 5% TFA in dichloromethane was performed as above to give the corresponding carboxamide **2b**.

General procedure for the synthesis of amines 2c (via reductive amination): A gas dispersion tube with resin **3** (100 mg, ca 0.05 mmol) inside was placed in a test tube containing dichloromethane (2 ml), trimethylorthoformate (2 ml), and an aldehyde (0.5 mmol). The mixture was agitated in a ultrasonicated bath for 2 h. The gas dispersion tube was drained and purged with nitrogen. Washing of the resin was performed as above with dichloromethane (4x5 ml). The resin in the gas dispersion tube was placed in a clean test tube containing $NaBH_3CN$ (1 mmol) in 1% acetic acid - methanol (5 ml). The mixture was agitated in a ultrasonicated bath for 2 h. The gas dispersion tube was drained and purged with nitrogen. Washing of the resin was performed as above with the following solvents: methanol (4 ml), 5% aqueous diethanolamine (4 ml), water (5 ml), 20% aqueous acetic acid (4 ml), methanol (3x4 ml) and dichloromethane (3x4 ml). Cleavage with 5% TFA in dichloromethane was performed as above to give the corresponding amine **2c**.

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-aminosuccinyl]-L-tert-leucine-N^1-methylamide 14.
^{1}H NMR (DMSO-d_6): 10.4 (s br, 1H), 8.8 (m, 1H), 7.82 (m, 1H), 7.73 (d br, 1H, J= 9.5 Hz), 4.19 (d, 1H, J= 9.5 Hz), 3.01 (d, 1H, J= 9.5 Hz), 2.63 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 1.5-1.3 (m, 2H), 0.9 (m, 1H), 0.93 (s, 9H), 0.82 (d, 3H, J= 6.6 Hz), 0.78 (d, 3H, J= 6.6 Hz); MS (ESI): 331 (MH^+), 353 (MNa^+); HPLC (standard gradient) t_R= 1.7 min; HPLC (20% MeOH-1% AcOH/H_2O) t_R= 3.4 min.

N^2-[4-(N-2,4-Dimethoxybenzyloxyamino)-2R-isobutyl-3S-aminosuccinyl]-L-tert-leucine-N^1-methylamide 15. A mixture of acid **11** (6.7 g, 12.4 mmol), O-2,4-dimethoxybenzylhydroxylamine[3] (2.75 g, 15 mmol) and EDCI (3.1 g, 16 mmol) in DMF (60 ml) was stirred for 18 h at room temperature. The mixture was diluted with ethyl acetate, washed twice with water and brine. The organic layer was diluted with an equal volume of petroleum ether. After crystallisation, the white solid was filtered, washed with ether-petroleum ether (1:1) and dried under vacuum to give the O-protected hydroxamic acid as white crystals (6.5 g, 75%). ^{1}H NMR (DMSO-d_6): 11.35 (s, 1H), 7.88 (m, 3H), 7.68 (d, 2H, J= 7.3 Hz), 7.5-7.15 (m, 7H), 6.55 (s, 1H), 6.47 (d, 1H, J=

8.4 Hz), 4.71 (s, 2H), 4.3-4.1 (m, 5H), 3.77 (s, 3H), 3.74 (s, 3H), 2.80 (m, 1H), 2.55 (d, 3H, J= 4.4 Hz), 1.51 (m, 1H), 1.29 (m, 1H), 0.81 (m, 13H), 0.76 (d, 3H, J= 6.6 Hz); MS (ESI): 703 (MH^+).

This compound (3.4 g, 4.8 mmol) in piperidine/DMF (40 ml, 1:3) was stirred for 1 h. The mixture was diluted with ethyl acetate (250 ml) and washed with water (2 x 250 ml). The aqueous layers were extracted with dichloromethane (3 x 200 ml). The dichloromethane layers were dried on $MgSO_4$ and evaporated in vacuo. The solid residue was triturated with 1:1 ether/petroleum ether to give **15** as a white solid (2.14 g, 92%). ^1H NMR (DMSO-d_6): 7.82 (m, 1H), 7.73 (d, 1H, J= 9.5 Hz), 7.23 (d, 1H, J= 8.1 Hz), 6.56 (s, 1H), 6.51 (d, 1H, J= 8.1 Hz), 4.74-4.70 (AB system, 2H, J= 11 Hz), 4.17 (d, 1H, J= 9.5 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 2.99 (m, 1H), 2.62 (m, 1H), 2.55 (d, 3H, J= 4.4 Hz), 1.5-1.3 (m, 2H), 0.91 (s, 9H), 0.90 (m, 1H), 0.80 (d, 3H, J= 7.6 Hz), 0.76 (d, 3H, J= 7.6 Hz); MS (ESI): 481 (MH^+); Elemental analysis for $C_{24}H_{40}N_4O_6$ 0.6 H_2O Calculated: C, 58.66; H, 8.45; N, 11.40; Found: C, 59.01; H, 8.85; N, 10.97; m.p.: 114-116°C.

Imidazolinones 16. A solution of **15** (0.1 mmol) and the corresponding aldehyde (1.2 eq) in dichloromethane (2 ml) - trimethylorthoformate (2 ml) was stirred for 2 h at room temperature. After evaporation of the solvents, the residue was triturated with ethyl acetate-petroleum ether (3:7). The solid was filtered, washed with petroleum ether and dried.

16a (aldehyde: phthalimidoacetaldehyde hydrate): 57%; ^1H NMR ($CDCl_3$ + CD_3COOD): 8.05 (d br, 1H, J= 10 Hz), 7.87 (m, 2H), 7.73 (m, 2H), 7.25 (d, 1H, J= 7.9 Hz), 6.91 (m, 1H), 6.44 (m, 2H), 5.10 (d, 1H, J= 9.8 Hz), 4.96 (d, 1H, J= 9.8 Hz), 4.48 (dd, 1H, J= 8.5 Hz, J'= 3 Hz), 4.40 (d, 1H, J= 10 Hz), 4.25 (dd, 1H, J= 14.1 Hz, J'= 3.7 Hz), 3.87 (s, 3H), 3.81 (s, 3H), 3.71 (dd, 1H, J= 14.1 Hz, J'= 8.5 Hz), 3.55 (d, 1H, J= 4.2 Hz), 3.06 (m, 1H), 2.79 (d, 3H, J= 4.4 Hz), 1.64 (m, 1H), 1.48 (m, 2H), 0.97 (s, 9H), 0.86 (d, 3H, J= 5.8 Hz), 0.85 (d, 3H, J= 5.8 Hz); ^{13}C NMR ($CDCl_3$): 172.6, 172.4, 170.8, 168 (2C), 162.1, 159.7, 134.1 (2C), 133.0 (2C), 132.0, 123.5 (2C), 115.4, 104.1, 98.7, 72.8, 71.3, 60.8, 58.8, 55.5, 55.4, 45.1, 40.3, 38.0, 34.4, 26.7 (3C), 26.1, 25.9, 22.9, 22.0; MS (ESI): 652 (MH^+).

Imidazolinones 17. A solution of **16** (0.25 mmol) in 5% TFA-dichloromethane (10 ml) was stirred at room temperature for 15 min. After evaporation of the solvents, methanol was added and the solid was filtered. The filtrate was evaporated, triturated in ether-pentane (1:1) and dried.

17a (phthalimidoacetaldehyde hydrate): 63%, white solid; ^1H NMR (DMSO-d_6): 9.7 (s br, 1H), 8.0-7.7 (m, 6H), 4.58 (m, 1H), 4.11 (d, 1H, J= 9.5 Hz), 3.99 (dd, 1H, J= 13.9 Hz, J'= 4.4 Hz), 3.68 (dd, 1H, J= 13.9 Hz, J'= 6.6 Hz), 3.43 (m, 1H), 2.73 (m, 1H), 2.55 (d, 3H, J = 4.4 Hz), 1.5-1.3 (m, 2H), 0.90 (m, 1H), 0.84 (s, 9H), 0.80 (d, 3H, J= 6.2 Hz), 0.76 (d, 3H, J= 6.2 Hz); MS (ESI): 502 (MH^+); Elemental analysis for $C_{25}H_{35}N_5O_6$ 0.4 TFA: Calculated: C, 56.63; H, 6.52; N, 12.80; Found: C, 56.64; H, 6.95; N, 12.79; HPLC: t_R= 9.8 min; m.p.: 142-144°C (decomposition).

17b (phenylacetaldehyde) obtained on solid phase, not purified: MS (ESI): 433 (MH^+); HPLC t_R= 10 mn

17c (methylthiopropionaldehyde): 20%, white solid; ^1H NMR (DMSO-d_6): 9.6 (m, 1H), 7.97 (d, 1H, J= 9.5 Hz), 7.88 (m, 1H), 4.20 (m, 1H), 4.18 (d, 1H, J= 9.5 Hz), 3.22 (m, 1H), 2.71 (m, 1H), 2.55 (d, 3H, J= 4.4 Hz), 2.05 (s, 3H), 1.95 (m, 1H), 1.76 (m, 1H), 1.64 (m, 1H), 1.5-1.4 (m, 3H), 0.90 (m, 1H), 0.89 (s, 9H), 0.84 (d, 3H, J= 6.3 Hz), 0.80 (d, 3H, J= 6.3 Hz); MS (ESI): 417 (MH^+); Elemental analysis for $C_{19}H_{36}N_4O_4S$: Calculated: C, 54.78; H, 8.71; N, 13.45; Found: C, 54.36; H, 9.20; N, 13.54.

17d (cyclohexanone) obtained on solid phase, not isolated: MS (ESI): 411 (MH^+); HPLC t_R= 9.2 min

β-Lactam 18. To a solution of **9** (14 mg, 0.057 mmol, 3:1 diastereoisomeric ratio) in acetonitrile (1.5 ml) was added triphenylphosphine (19 mg) and 2,2'-dipyridyl disulfide (17 mg). The mixture was stirred for 18 h. After evaporation of the solvents, the residue was chromatographed on silica [eluant: ethyl acetate / petroleum ether (1:3)] to give the corresponding β-lactam **18** (9 mg, 70%). Only traces of the β-lactam **19** were isolated.

18: ^1H NMR ($CDCl_3$): 5.93 (s br, 1H), 3.76 (d, 1H, J= 2.5 Hz), 3.26 (m, 1H), 1.9-1.2 (m, 3H), 1.49 (s, 9H), 0.98 (d, 3H, J= 6.2 Hz), 0.94 (d, 3H, J= 6.2 Hz); MS (EI): 228 (MH^+).

19: ^1H NMR ($CDCl_3$): 5.94 (s br, 1H), 4.14 (d, 1H, J= 5.9 Hz), 3.56 (m, 1H), 1.88 (m, 1H), 1.6-1.4 (m, 2H), 1.50 (s, 9H), 0.94 (d, 6H, J= 6.6 Hz); MS (EI) : 228 (MH^+).

References and notes

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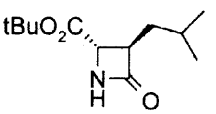
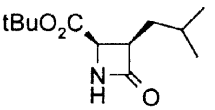
8. Relative stereochemistry was proven by cyclising **9** under Kobayashi's conditions[16] (2,2'-dipyridyl disulfide, PPh_3, CH_3CN) to give the trans β-lactam **18** (coupling constant $J_{H1,H2}$ = 2.5 Hz) and only traces of the cis β-lactam **19** (coupling constant $J_{H1,H2}$ = 5.9 Hz).



18



19

9. Loading of resin **3** may vary from batch to batch. Yields have been calculated with loading of resin **3** set to 0.5 mmol/g. Compounds **2a-c** have been isolated without further purification; they may contain traces of solvents and/or minor impurities. All these factors may explain that yields were found greater than 100% in some cases.
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13. a) Barlaam, B *PCT Int. Appl.* WO 9807742 (Zeneca); *Chem. Abst.* 128:205148. Biological activities of these MMP/TACE inhibitors will be reported elsewhere in due course; b) For the synthesis of similar compounds in solution, see: Alpegiani, M.; Abrate, F.; Bissolino, P.; Palladino, M.; Perrone, E. *PCT Int. Appl.* WO 9749674 (Pharmacia-Upjohn); *Chem. Abst.* 128:089110. In this patent, Alpegiani et al. reported a adduct similar to **17** with acetone.
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