Tetrahedron 64 (2008) 8659–8667

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of β,β′-diamino acids from α-amino acid-derived β-lactams by ring opening with nucleophiles. Utilization in the synthesis of peptidomimetics

Alexander A. Taubinger [a], Dieter Fenske [b], Joachim Podlech [a,*]

[a] Institut für Organische Chemie, Universität Karlsruhe, Karlsruher Institut für Technologie (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
[b] Institut für Anorganische Chemie, Universität Karlsruhe, Karlsruher Institut für Technologie (KIT), Engesserstraße 15, 76131 Karlsruhe, Germany

ARTICLE INFO

Article history:
Received 21 May 2008
Accepted 1 July 2008
Available online 5 July 2008

Keywords:
Amino acids
Diazo compounds
Lactams
Amino alcohols
Peptidomimetics

ABSTRACT

Ring opening of protected 3-aminoalkyl-substituted azetidin-2-ones with *O*-, *N*- or *S*-nucleophiles led to β,β′-diaminocarboxylic esters, amides and thioesters, respectively. The reaction outcome is improved by the addition of catalytic amounts of sodium azide. Utilization of a glycine derivative with unprotected amino function as nucleophile was possible. When bulkier amino acid esters were used, the intermediate acid azide underwent a Curtius rearrangement. The isocynates formed were trapped as the corresponding urea derivatives. Reduction of β-lactam's amide moiety led to diaminoalcohols.

1. Introduction

β-Lactams are not only eminent parts of antibiotics,[1] but were also used as precursors for the production of polyamides[2] and for the preparation of β-amino acids, a class of compounds, which found substantial attention during the last decades.[3] The side chain of the antitumour agent Taxol® (Paclitaxel)[4] is preferentially prepared by nucleophilic ring opening of suitably substituted β-lactams.[5] β-Lactams are usually prepared by Staudinger reaction, in which in situ generated ketenes—preferentially prepared from acid chlorides with tertiary bases—are reacted with imines.[6] Recently, we presented a new variation of the Staudinger reaction, in which ketenes were prepared in situ via a photochemical rearrangement of diazo ketones synthesized from α-amino acids. These react diastereoselectively with imines to yield exclusively trans-arranged[7] aminoalkyl-substituted β-lactams.[8] With this method 4-aryl- or 4-styryl-substituted β-lactams are accessible, while a change to thermal conditions in the decomposition of diazo ketones additionally allows the preparation of 4-vinyl- and 4-crotyl-substituted derivatives.[9]

In this paper, we wish to describe a nucleophilic ring opening of thus obtained β-lactams leading to β,β′-diamino acid derivatives.[10] These compounds, though interesting building blocks, have hardly been investigated.[11] A stereoselective synthesis has been reported only once using the ring opening of pyrazolidines.[12] β,β′-Diamino acids should be useful as synthetic intermediates and as unnatural amino acids,[13] e.g., for the preparation of peptidomimetics. Reductive ring opening would lead to γ,γ′-diaminoalcohols, which could be used as three-dentate ligands[14] or therapeutics.[15]

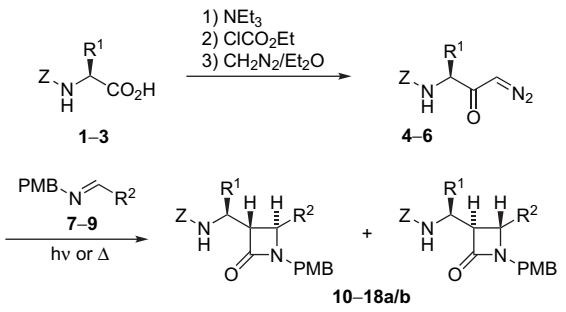
2. Results and discussion

2.1. Preparation of β-lactams

Synthesis of the herein used β-lactams is simply achieved by photolysis of amino acid-derived diazo ketones **4**–**6** in the presence of imines **7**–**9** (Scheme 1, Table 1).[8] Photochemical Staudinger reaction was performed in a quartz immersion photoreactor at −25 °C, while the thermal reaction was performed by heating at 160 °C in dichlorobenzene. Selectivities were ruled by the steric hindrance of amino acid's side chain and ranged from 2:1 (alanine, R=Me) to 7:1 (valine, R=*i*Pr). Starting with L-amino acids the major product was 3*R*,4*S*-configured; the diastereoisomers were separable by flash chromatography or medium pressure liquid chromatography (MPLC). Z protection at the N-terminus was chosen to allow for UV detection at any time of the proposed syntheses. Furthermore, it is an orthogonal protecting group to the *tert*-butyloxycarbonyl (Boc) group, which will be introduced at a later stage of the synthesis. It has to be kept in mind that the Z group is hardly useful in β-lactam synthesis, since a β-lactam (with aryl substituent in position C-4) is cleaved with hydrogenolytic conditions,[16] but is fully applicable when the β-lactam is cleaved as it is in the here proposed reactions.

* Corresponding author. Tel.: +49 721 608 3209; fax: +49 721 608 7652.
E-mail address: joachim.podlech@ioc.uka.de (J. Podlech).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.07.006



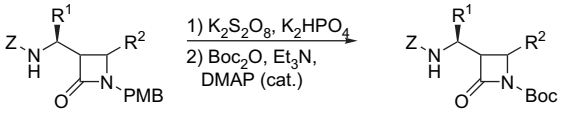
Scheme 1. Preparation of β-lactams in a photochemically or thermally induced Staudinger reaction.

Table 1
Synthesis of β-lactams

No.	Diazo ketone	Imine	R^1	R^{2a}	β-Lactam[b]	Yield [%]	d.r.
1	**4**	**7**	Me	Ph	**10a,b**	59[c]	56:44
2	**4**	**8**	Me	*p*CP	**11a,b**	49	66:34
3	**4**	**9**	Me	(*E*)–CH=CHPh	**12a,b**	48	62:38
4	**5**	**7**	*i*Pr	Ph	**15a,b**	57	87:13
5	**5**	**8**	*i*Pr	*p*CP	**16a,b**	43	81:19
6	**6**	**7**	Bn	Ph	**17a,b**	43[c]	55:45
7	**6**	**8**	Bn	*p*CP	**18a,b**	42	57:43

[a] *p*CP: 4-chlorophenyl.
[b] Isomer **a**: 3*R*,4*S*; **b**: 3*S*,4*R*.
[c] Thermal conditions.

Unfortunately, imines with electron-withdrawing protection groups (e.g., carbamate protections), which would be useful for the further reactions cannot be subjected to the herein used β-lactam synthesis.[8a,b] Therefore, a *para*-methoxybenzyl (PMB) group was introduced with the imine yielding PMB-protected β-lactams. Oxidative cleavage of the PMB group is achieved with potassium peroxodisulfate in a buffered (K_2HPO_4) mixture of acetonitrile and water.[8b,c,17] With this method, an overoxidation of the PMB group (leading to a *para*-methoxybenzoyl group) is minimized (Scheme 2, Table 2). Furthermore, this variation is compatible with an acid-sensitive acetal group, which is obtained by oxidative degradation of the styryl group and subsequent acetal formation (Scheme 3) and with any of the other functional groups present in these

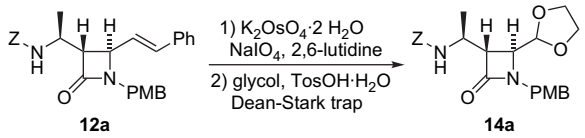


Scheme 2. Preparation of *N*-Boc-protected β-lactams suitable for ring opening.

Table 2
Protection group manipulations

No.	β-Lactam[a]	R^1	R^{2b}	PMB cleavage		Boc protection	
				Yield [%]	Product[a]	Yield [%]	Product[a]
1	**10a**	Me	Ph	56	**19a**	79	**26a**
2	**10b**	Me	Ph	56	**19b**	87	**26b**
3	**11a**	Me	*p*CP	53	**20a**	88	**27a**
4	**11b**	Me	*p*CP	51	**20b**	70	**27b**
5	**14a**	Me	1,3-Dioxolan-2-yl	40	**21a**	70	**28a**
6	**15a**	*i*Pr	Ph	36	**22a**	92	**29a**
7	**16a**	*i*Pr	*p*CP	47	**23a**	88	**30a**
8	**17a**	Bn	Ph	32	**24a**	56	**31a**
9	**17b**	Bn	Ph	40	**24b**	72	**31b**
10	**18b**	Bn	*p*CP	34	**25b**	—	—

[a] Isomer **a**: 3*R*,4*S*; **b**: 3*S*,4*R*.
[b] *p*CP=4-chlorophenyl.

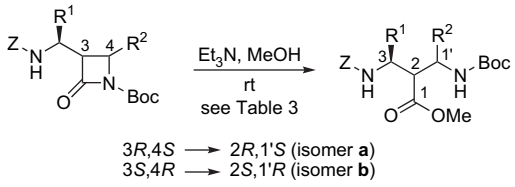


Scheme 3. Oxidative degradation of the styryl group and acetal formation.

substrates. It has to be kept in mind that these oxidative conditions are not compatible with highly electron-rich aromatic rings. Consequently, we tested besides the parent phenyl group a slightly electron-deficient *para*-chlorophenyl (*p*CP) group as substituents of the β-lactam. β-Lactams with an aliphatic substituent or without substituent at the nitrogen are hydrolyzed only with strongly acidic conditions.[18] A mild ring opening is best achieved with an electron-withdrawing group at the nitrogen. The Boc group is an easy to handle protecting group fulfilling this requirement. Introduction of the Boc protection group at β-lactam's nitrogen was achieved with standard conditions using di-*tert*-butyl dicarbonate (Boc_2O), triethyl amine and catalytic amounts of 4-(dimethylamino)pyridine (DMAP).[19] Most of the Boc-protected substrates were obtained as crystalline products (Table 2).

2.2. Ring opening of β-lactams

Ring opening of Boc-protected β-lactam **26a** with sodium methanolate in refluxing methanol led to a poor 33% yield of the corresponding methyl β,β′-diaminocarboxylate **32a** within 5 h. When performing the ring opening at rt in methanol with addition of triethyl amine >97% of methyl esters were obtained, though reaction times had to be extended to about one day. Only substrate **31b** led to a moderate 61% yield caused by a laborious purification procedure (Scheme 4, Table 3). These substrates are *N*,*N*′-protected with orthogonal protecting groups allowing for a selective deprotection and utilization in further reactions. No detectable epimerization at any of the stereogenic centres occurred during these and the following reactions.



Scheme 4. Ring opening of β-lactams with methanol.

N-Unprotected β-lactams were similarly, albeit more sluggishly opened by methanol in the presence of chlorotrimethylsilane as Lewis acid according to a protocol of Palomo et al. (Table 3 entries

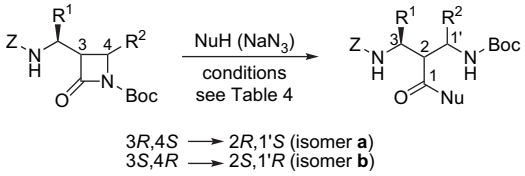
Table 3
Ring opening with methanol (cf. Scheme 4)

No.	β-Lactam[a]	R^1	R^{2b}	PG	Time [h]	Product[a]	Yield [%]
1	**26a**	Me	Ph	Boc	21	**32a**	99
2	**27a**	Me	*p*CP	Boc	24	**33a**	99
3	**28a**	Me	1,3-Dioxolan-2-yl	Boc	22	**34a**	99
4	**29a**	*i*Pr	Ph	Boc	16	**35a**	97
5	**31b**	Bn	Ph	Boc	24	**36b**	61
6	**19a**	Me	Ph	H	66[c]	**37a**	58
7	**25b**	Bn	*p*CP	H	48[c]	**38b**	53
8	**23a**	*i*Pr	*p*CP	H	24[c]	**39a**[d]	51

[a] Isomer **a**: 3*R*,4*S*; **b**: 3*S*,4*R*; the products have accordant configuration.
[b] *p*CP=4-chlorophenyl.
[c] Addition of ClSiMe as Lewis acid.
[d] Amine **39a** was Boc-protected (→**40a**) for analytical reasons.

6–8).[18a,20] Thus obtained unprotected amines could, e.g., for reasons of analysis, be protected with the Boc group using a standard protocol. Nevertheless, they are reasonably stable and crystallized in some cases. The structure of **38b** was proven by X-ray crystallographic analysis.[21]

Ring opening with pyrrolidine and morpholine was cleanly achieved at elevated temperatures without addition of solvent. The respective amides were obtained as analytically pure, crystalline solids in about 80% yield (Scheme 5, Table 4, entries 2–5). Addition of primary amines was very sluggish with similar conditions, but proceeded cleanly at ambient temperatures when sodium azide was added as catalyst (entries 11–13).[22] The stereochemical integrity and the structure of thus obtained amides were proven by X-ray crystallographic analysis of substrates **42a** and **44a**.[21]



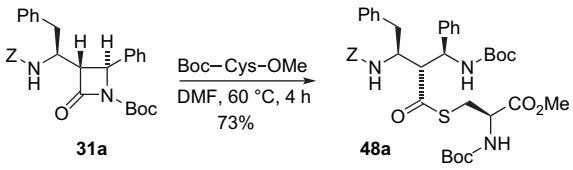
Scheme 5. Ring opening of β-lactams with *N*-nucleophiles.

Though *N*,*O*-dimethyl- and *O*-methylhydroxylamine (liberated from the respective hydrochlorides by addition of triethyl amine) are exceptionally good nucleophiles due to the α-effect, they could not be used successfully in the ring opening of β-lactams, even in the presence of sodium azide.[23] While the former did not react at all, the latter gave only traces of a hydroxamic acid within 5 d. The aimed products (Weinreb amides) would have been useful for further reactions, e.g., for the preparation of ketones.[24]

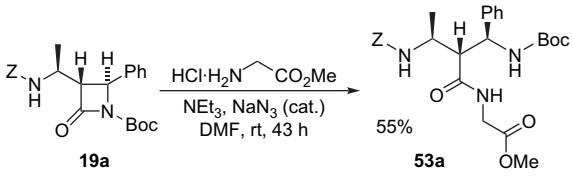
The ring opening with allyl mercaptane or with *N*,*O*-diprotected cysteine (Scheme 6)[25] leading to thiocarboxylates is achieved with high yields in the presence of a base (triethyl amine) at slightly elevated temperatures (Table 4, entries 6–8). The addition of the bulky *tert*-butylthiol proceeded only in the presence of sodium azide as catalyst and with a longer reaction time. With this variation similar yields were obtained as with primary thiols (entry 10).

2.3. Synthesis of peptidomimetics

The ring opening of β-lactams with amines was now applied to the utilization of amino acid derivatives as nucleophiles aiming for peptidomimetics containing β,β′-diamino acids. Similar compounds, obtained via the ring opening of 3-benzyloxy-substituted β-lactams have been synthesized and investigated by Palomo et al.[22a] Since primary amines require the addition of a catalyst in that reaction, we performed a ring opening of the β-lactams with amino esters in the presence of a catalytic amount of sodium azide. The amino function was in situ liberated from the respective hydrochlorides by addition of triethyl amine. With these reaction conditions addition of glycine methyl ester (H–Gly–OMe) was achieved within 43 h with a 55% yield (Scheme 7). Due to the orthogonality of the protection groups in this compound an attachment of further amino acids at any of the termini should be possible without significant problems. The structure of this dipeptidomimetic was unambiguously determined by X-ray crystallographic analysis (Fig. 1).[21]



Scheme 6. Ring opening of β-lactams with a cysteine derivative.



Scheme 7. Azide-catalyzed ring opening with glycine methyl ester.

Ring opening with amino esters bulkier than glycine was not successful. No significant reaction was observed with valine or alanine derivatives and catalytic amounts of sodium azide. With stoichiometric amounts of azide, a reaction was observed only at 60 °C yielding urea derivatives **54a** and **55a**, respectively. Obviously, the intermediately formed acid azide suffers a Curtius rearrangement at elevated temperature forming an isocyanate, which is trapped by the amine yielding the observed urea derivatives (Scheme 8). Nevertheless, these compounds are of significant interest with view on their possible utilization as peptidomimetics.[26]

Table 4
Ring opening of β-lactams with *O*-, *N*-, and *S*-nucleophiles (cf. Scheme 5 and 6)

No.	β-Lactam[a]	R^1	R^{2b}	NuH	Conditions[c]	Product[a]	Yield [%]
1	**26a**	Me	Ph	Allyl–OH	60 °C, 18 h	**41a**	68[d]
2	**26a**	Me	Ph	Pyrrolidine	90 °C, 1 h[e]	**42a**	81
3	**27a**	Me	*p*CP	Pyrrolidine	90 °C, 1 h[e]	**43a**	82
4	**29a**	*i*Pr	Ph	Morpholine	100 °C, 1.5 h[e]	**44a**	72
5	**30a**	*i*Pr	*p*CP	Morpholine	100 °C, 1.5 h[e]	**45a**	78
6	**26a**	Me	Ph	Allyl–SH	NEt_3, 60 °C, 4 h	**46a**	79
7	**27a**	Me	*p*CP	Allyl–SH	NEt_3, 60 °C, 4 h	**47a**	70
8	**31a**	Bn	Ph	Boc–Cys–OMe	NEt_3, 60 °C, 4 h	**48a**	73
9	**30a**	*i*Pr	*p*CP	^{t}BuSH	NEt_3, 60 °C, 4 h	**49a**	0
10	**30a**	*i*Pr	*p*CP	^{t}BuSH	NEt_3, 60 °C, 24 h	**49a**	68[d]
11	**26a**	Me	Ph	nBuNH$_2$	rt, 23 h	**50a**	61[d]
12	**27b**	Me	*p*CP	nBuNH$_2$	rt, 42 h	**51b**	79[d]
13	**31b**	Bn	Ph	Allyl–NH$_2$	rt, 24 h	**52b**	61[d]

[a] Isomer **a**: 3*R*,4*S*; **b**: 3*S*,4*R*; the products have accordant configuration.
[b] *p*CP=4-chlorophenyl.
[c] In DMF.
[d] Addition of sodium azide (cat.).
[e] Neat, without DMF.

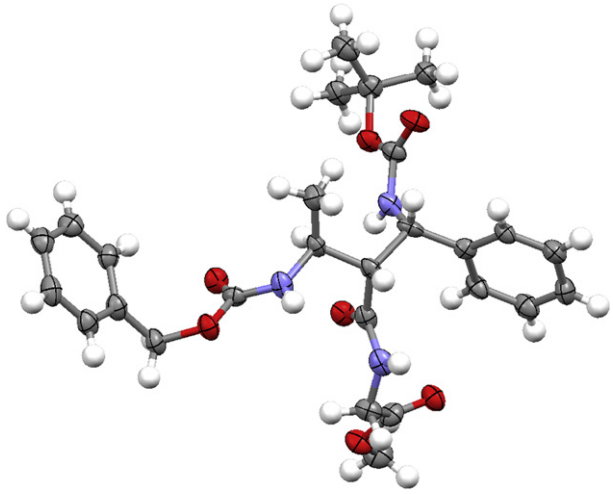
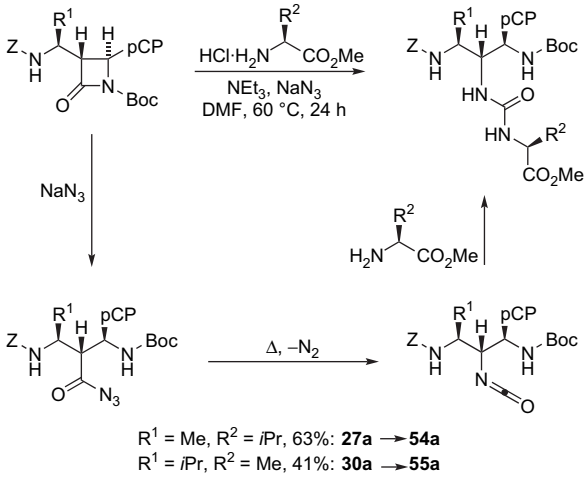


Figure 1. Structure of **53a** in the crystal.[21]

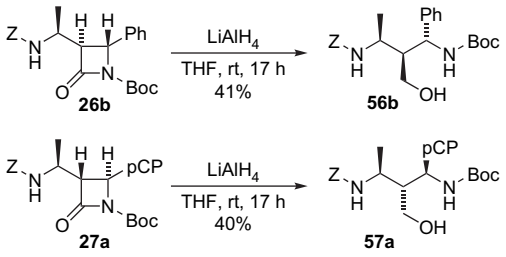


Scheme 8. Preparation of urea-containing peptidomimetics starting with β-lactams. *p*CP=4-chlorophenyl.

We planned to use this Curtius rearrangement for the preparation of triamines with three orthogonal protecting groups. Trapping of the intermediate isocyanate with allyl alcohol would lead to an allyloxycarbonyl (Aloc)-protected amino function. Nevertheless, reaction conditions leading to urea derivatives turned out to be not suitable for the preparation of carbamates (urethanes). Reaction of allyl alcohol with the acid azide (from **26a**) was obviously fast; the respective allyl β,β′-diaminocarboxylate **41a** was isolated with 68% yield (Table 4, entry 1).

2.4. Reductive ring openings

Reductive ring opening of β-lactams to 1,3-aminoalcohols is usually achieved either with lithium aluminium hydride,[27] with sodium borohydride[28] or with lithium borohydride.[29] We used lithium aluminium hydride as reducing agent for β-lactams **26b** and **27a** and obtained diaminoalcohols **56b** and **57a**. The carbamate protecting groups were not reduced with these conditions. To receive filterable granulates after hydrolysis, a basic work-up procedure developed by Amundsen and Nelson was used.[30] With this, chiral, enantiomerically pure γ,γ′-diaminoalcohols with orthogonal protecting groups at the nitrogen atoms were obtained with reasonable yields (Scheme 9).



Scheme 9. Reductive ring opening of β-lactams.

3. Experimental section

3.1. General remarks

The synthesis of protected amino acids **1**–**3**,[19] diazo ketones **4**, **5**[31] and **6**,[32] imine **7**[33] and β-lactams **15a**,**b**,[8b] **19a**,[8c] **22a**[8b] and **29a**[8b] has been published elsewhere. Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl radical. Abbreviations: ethyl acetate, EA; *para*-chlorophenyl, *p*CP. All moisture-sensitive reactions were carried out under oxygen-free argon or N_2 using oven-dried glassware and a vacuum line. Photochemical reactions were performed in a *Heraeus* laboratory UV reactor system 2 (quartz, 150 W). Flash column chromatography[34] was carried out using *Merck* silica gel 60 (230–400 mesh) and thin layer chromatography was carried out using commercially available Merck F_{254} pre-coated sheets. Medium pressure liquid chromatography (MPLC): Pump (*Labomatic* MD-50), detection by UV absorption (*Latek* UVIS 200); *Merck* LiChroprep Si 60 (15–25 μm). HPLC: analyses of diastereoisomer distributions were carried out with a *Merck-Hitachi* LaChrom D7000 apparatus with a L7100 mixer and diode-array detection (L7455) on a LiChrospher Si 60, 5 μm, *Merck* (flow: 1–1.5 ml/min) chromatographic column. ^1H and ^{13}C NMR spectra were recorded on a *Bruker* Cryospek WM-250, an AM-400 or a DRX 500. Chemical shifts are given in parts per million downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT 135 and DEPT 90 experiments. Melting points were measured on a *Büchi* apparatus and were not corrected. IR spectra were recorded on a *Bruker* IFS-88 spectrometer. Elemental analyses were performed on a *Heraeus*, CHN-O-rapid or on an *elementar* vario MICRO. Electrical ionization and high resolution mass spectra were recorded on a *Finnigan* MAT-90. Optical rotations were recorded on a *Perkin Elmer* 241 polarimeter (using the sodium D line, 589 nm) and specific optical rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}.

3.2. Imine syntheses

3.2.1. *N-(4-Methoxybenzyl)-4-chloro-benzaldimine (**8**)*[35]

4-Methoxybenzylamine (790 μl, 6.09 mmol), 4-chlorobenzaldehyde (853 mg, 6.07 mmol) and Al_2O_3 (3.03 g, activated, neutral, mesh 50–200 μm) were placed in a small flask and vigorously shaken. After standing for 2 h, the heterogeneous mixture was placed in a funnel blocked with cotton and Celite® and was extracted with CH_2Cl_2. The filtrate was concentrated and imine **8** was used without further purification (1.57 g, 6.04 mmol, quant.).

3.2.2. *N-(4-Methoxybenzyl)-3-phenyl-propenaldimine (**9**)*[35]

4-Methoxybenzylamine (1.26 ml, 9.71 mmol), cinnamaldehyde (1.22 ml, 9.69 mmol) and Al_2O_3 (4.85 g, activated, neutral, mesh 50–200 μm) were placed in a small flask and vigorously shaken. After standing for 2 h, the heterogeneous mixture was placed in a funnel blocked with cotton and Celite® and was extracted with CH_2Cl_2. The filtrate was concentrated and the slowly crystallizing

product **9** (2.43 g, 9.67 mmol, quant.) was used without further purification.

3.3. β-Lactam syntheses

3.3.1. GP 1: general procedure for the thermally induced synthesis of β-lactams[9]

A flask filled with diazo ketone (1 equiv) and imine (1.1–1.3 equiv) in 1,2-dichlorobenzene is placed in a pre-heated bath (160 °C) and stirred for 30 min. After cooling to rt the mixture is placed on top of a column (silica gel). The solvent is eluted with hexanes and the products are eluted with mixtures of hexanes and EA. The diastereomeric ratio is determined (^{1}H NMR spectroscopy or HPLC) and the isomers were separated by MPLC.

3.3.2. GP 2: general procedure for the photochemically induced synthesis of β-lactams[8b]

A quartz photoreactor is charged with diazo ketone (1 equiv), imine (1.5–2 equiv) and Et_2O (300 ml), flushed with N_2, cooled to −25 °C and irradiated with a UV lamp for 2–4 h (monitoring with TLC) with vigorous stirring. The solution is warmed to rt and the solvent is removed. Excess imine is removed by flash chromatography (silica gel) and the diastereomeric ratio is determined by ^{1}H NMR spectroscopy. Separation and purification of the diastereomers are achieved by MPLC.

*3.3.3. (3R,4S,1′S)- and (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-1-(4-methoxybenzyl)-4-phenyl-azetidin-2-one (**10a**,**b**)*

According to GP 1 Z–Ala–CHN_2 (**4**, 1.91 g, 7.72 mmol) and imine **7** (1.91 g, 8.48 mmol) were reacted in 1,2-dichlorobenzene (44 ml). Filtrative chromatography on silica gel (250 g, hexanes/EA, 5:1→1:2) yielded **10a** and **b** (56:44, ^{1}H NMR), which were separated by MPLC (hexanes/*i*PrOH, 97:3) yielding **10a** (1.19 g, 2.68 mmol, 35%) and **10b** (809 mg, 1.82 mmol, 24%) as colourless solids.

*3.3.4. (3R,4S,1′S)- and (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-4-(4-chlorophenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**11a**,**b**)*

According to GP 2 Z–Ala–CHN_2 (**4**, 1.77 g, 7.16 mmol) and imine **8** (2.72 g, 10.5 mmol) were reacted within 2 h. Excess imine was removed (250 g, silica gel, hexanes/EA, 5:1→1:2) yielding a mixture of isomers (**11a**/**11b**, 66:34), which was separated by MPLC (hexanes/*i*PrOH, 97:3) yielding **11a** (1.06 g, 2.21 mmol, 31%) and **11b** (603 mg, 1.26 mmol, 18%) as colourless solids.

*3.3.5. (E,3R,4S,1′S)- and (E,3S,4R,1′S)-3-(1-Benzyloxycarbonyl-amino-ethyl)-1-(4-methoxybenzyl)-4-(2-phenyl-ethenyl)-azetidin-2-one (**12a**,**b**)*

According to GP 2 Z–Ala–CHN_2 (**4**, 1.38 g, 5.58 mmol) and imine **9** (2.15 g, 8.55 mmol) were reacted within 4 h. Excess imine was removed (200 g, silica gel, hexanes/EA, 5:1→1:2) yielding a mixture of isomers (**12a**/**12b**, 62:38), which was separated by MPLC (hexanes/*i*PrOH, 97:3) yielding **12a** (703 mg, 1.49 mmol, 27%) as a colourless solid and **12b** (539 mg, 1.15 mmol, 21%) as a yellowish waxy solid.

*3.3.6. (3R,4S,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-1-(4-methoxybenzyl)-2-oxo-azetidine-4-carbaldehyde (**13a**)*

To a solution of β-lactam **12a** (837 mg, 1.78 mmol) in 1,4-dioxane/H_2O (3:1, 18 ml) was added at rt and with stirring 2,6-lutidine (410 μl, 3.52 mmol), $NaIO_4$ (1.52 g, 7.11 mmol) and $K_2OsO_4 \cdot 2H_2O$ (13 mg, 35.3 μmol). After stirring for 30 min (monitoring with TLC) H_2O (20 ml) and CH_2Cl_2 (40 ml) were added. The organic layers were separated and the aqueous layers were extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (100 g, silica gel, hexanes/EA, 2:1→1:4) yielding **13a** (396 mg, 999 μmol, 56%) as a colourless oil. Though the product contained some impurities, it was sufficiently clean to be used in the next step.

*3.3.7. (3R,4S,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-4-[1,3]dioxolan-2-yl-1-(4-methoxybenzyl)-azetidin-2-one (**14a**)*

Glycol (1.66 ml, 29.8 mmol) and *p*-TosOH·H_2O (28 mg, 147 μmol) were added with stirring to a solution of aldehyde **13a** (738 mg, 1.86 mmol) in toluene (47 ml) and the mixture was heated with a Dean–Stark trap for 4 h (monitoring with TLC). CH_2Cl_2 (50 ml) was added and the solution was extracted with H_2O (40 ml) and brine (40 ml), dried ($MgSO_4$) and concentrated yielding a brownish oil, which was purified by chromatography (70 g, silica gel, hexanes/EA, 2:1) yielding acetal **14a** (529 mg, 1.20 mmol, 65%) as a colourless solid.

*3.3.8. (3R,4S,1′S)- and (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-2-methyl-propyl)-4-(4-chlorophenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**16a**,**b**)*

According to GP 2 Z–Val–CHN_2 (**5**, 1.70 g, 6.18 mmol) and imine **8** (2.47 g, 9.51 mmol) were reacted within 2 h. Excess imine was removed (230 g, silica gel, hexanes/EA, 6:1→1:1) yielding a mixture of isomers (**16a**/**16b**, 81:19), which was separated by MPLC (hexanes/EA, 4:1) yielding **16a** (1.11 g, 2.19 mmol, 35%) and **16b** (266 mg, 525 μmol, 8%) as yellowish waxy solid.

*3.3.9. (3R,4S,1′S)- and (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-2-phenyl-ethyl)-1-(4-methoxybenzyl)-4-phenyl-azetidin-2-one (**17a**,**b**)*

According to GP 1 Z–Phe–CHN_2 (**6**, 1.70 g, 5.26 mmol) and imine **7** (1.30 g, 5.77 mmol) were reacted in 1,2-dichlorobenzene (40 ml). Filtrative chromatography on silica gel (200 g, hexanes/EA, 5:1→1:1) yielded **17a** and **17b** (55:45, HPLC: hexanes/*i*PrOH, 98:2). Recrystallization (hexanes/EtOAc) gave **17a** (650 mg, 1.25 mmol, 24%) as a colourless solid and purification of the mother liquor by MPLC (hexanes/*i*PrOH, 98:2) yielded **17b** (524 mg, 1.01 mmol, 19%) as a waxy yellowish solid.

*3.3.10. (3R,4S,1′S)- and (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-2-phenyl-ethyl)-4-(4-chlorophenyl)-1-(4-methoxybenzyl)-azetidin-2-one (**18a**,**b**)*

According to GP 2 Z–Phe–CHN_2 (**6**, 1.65 g, 5.10 mmol) and imine **8** (2.12 g, 8.16 mmol) were reacted within 2 h. Recrystallization (hexanes/EA) of the crude product (**18a**/**18b**, 57:43) gave **18a** (473 mg, 52 μmol, 17%) as a colourless solid and purification of the mother liquor by chromatography (hexanes/EA, 5:1→2:1) and MPLC (hexanes/*i*PrOH, 98:2) yielded **18a** (687 mg, 1.24 mmol, 24%) as a colourless solid and **18b** (519 mg, 935 μmol, 18%) as a colourless waxy solid.

3.4. Oxidative cleavage of the PMB group

3.4.1. GP 3: general procedure for the oxidative cleavage of the PMB group[17]

To PMB-protected β-lactam (1.00 mmol) in acetonitrile/H_2O (1:1, 43 ml) was added K_2HPO_4 (600 mg, 3.44 mmol) and $K_2S_2O_8$ (1.80 g, 6.66 mmol). The mixture was heated to 75 °C and stirred for 70 min. The solution was concentrated in vacuo to half the volume and extracted with EA (3×10 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (40 ml) and brine (40 ml). The aqueous layers were re-extracted with EA (10 ml) and the combined organic layers were dried ($MgSO_4$), concentrated and purified by chromatography (silica gel).

*3.4.2. (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-4-phenyl-azetidin-2-one (**19b**)*

According to GP 3 β-lactam **10b** (893 mg, 2.01 mmol) was reacted and purified (90 g, silica gel, hexanes/EA, 4:1→1:1) yielding β-lactam **19b** (362 mg, 1.12 mmol, 56%) as a colourless solid.

*3.4.3. (3R,4S,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-4-(4-chlorophenyl)-azetidin-2-one (**20a**)*

According to GP 3 β-lactam **11a** (196 mg, 409 μmol) was reacted and purified (20 g, silica gel, hexanes/EA, 4:1→1:1) yielding β-lactam **20a** (78 mg, 217 μmol, 53%) as a colourless solid.

*3.4.4. (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-4-(4-chlorophenyl)-azetidin-2-one (**20b**)*

According to GP 3 β-lactam **11b** (641 mg, 1.34 mmol) was reacted and purified (55 g, silica gel, hexanes/EA, 4:1→1:1) yielding β-lactam **20b** (243 mg, 677 μmol, 51%) as a colourless solid.

*3.4.5. (3R,4S,1′S)-3-(1-Benzyloxycarbonylamino-ethyl)-4-[1,3]dioxolan-2-yl-azetidin-2-one (**21a**)*

According to GP 3 β-lactam **14a** (562 mg, 1.28 mmol) was reacted and purified (60 g, silica gel, hexanes/EA, 4:1→1:1) yielding β-lactam **21a** (163 mg, 509 μmol, 40%) as a colourless foam.

*3.4.6. (3R,4S,1′S)-3-(1-Benzyloxycarbonylamino-2-methyl-propyl)-4-(4-chlorophenyl)-azetidin-2-one (**23a**)*

According to GP 3 β-lactam **16a** (1.13 g, 2.23 mmol) was reacted and purified (100 g, silica gel, hexanes/EA, 6:1→4:1) yielding β-lactam **23a** (404 mg, 1.04 mmol, 47%) as a colourless solid.

*3.4.7. (3R,4S,1′S)-3-(1-Benzyloxycarbonylamino-2-phenyl-ethyl)-4-phenyl-azetidin-2-one (**24a**)*

According to GP 3 β-lactam **17a** (500 mg, 960 μmol) was reacted and purified (30 g, silica gel, hexanes/EA, 4:1→2:1) yielding β-lactam **24a** (122 mg, 305 μmol, 32%) as a colourless solid.

*3.4.8. (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-2-phenyl-ethyl)-4-phenyl-azetidin-2-one (**24b**)*

According to GP 3 β-lactam **17b** (618 mg, 1.19 mmol) was reacted and purified (60 g, silica gel, hexanes/EA, 4:1→2:1) yielding β-lactam **24b** (191 mg, 477 μmol, 40%) as a colourless solid.

*3.4.9. (3S,4R,1′S)-3-(1-Benzyloxycarbonylamino-2-phenyl-ethyl)-4-(4-chlorophenyl)-azetidin-2-one (**25b**)*

According to GP 3 β-lactam **18b** (500 mg, 901 μmol) was reacted and purified (40 g, silica gel, hexanes/EA, 4:1→2:1) yielding β-lactam **25b** (135 mg, 310 μmol, 34%) as a colourless solid.

3.5. Synthesis of *N*-Boc-protected β-lactams

3.5.1. GP 4: general procedure for synthesis of N-Boc-protected β-lactams[8b]

To a solution of the β-lactam (500 μmol) in CH_2Cl_2 (10 ml) was added at rt Et_3N (70 μl, 503 μmol), Boc_2O (219 mg, 1.00 mmol) and a catalytic amount of DMAP. After stirring for 4 h brine (10 ml) and Et_2O (10 ml) were added. The organic layer was washed with saturated NH_4Cl solution (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (silica gel).

*3.5.2. tert-Butyl (3R,4S,1′S)-3-(1-benzyloxycarbonylamino-ethyl)-2-oxo-4-phenyl-azetidine-1-carboxylate (**26a**)*

According to GP 4 β-lactam **19a** (230 mg, 709 μmol) was reacted and purified (50 g, silica gel, hexanes/EA, 4:1) yielding β-lactam **26a** (238 mg, 561 μmol, 79%) as a colourless solid.

*3.5.3. tert-Butyl (3S,4R,1′S)-3-(1-benzyloxycarbonylamino-ethyl)-2-oxo-4-phenyl-azetidine-1-carboxylate (**26b**)*

According to GP 4 β-lactam **19b** (195 mg, 601 μmol) was reacted and purified (35 g, silica gel, hexanes/EA, 4:1) yielding β-lactam **26b** (223 mg, 525 μmol, 87%) as a colourless solid.

*3.5.4. tert-Butyl (3R,4S,1′S)-3-(1-benzyloxycarbonylamino-ethyl)-4-(4-chlorophenyl)-2-oxo-azetidine-1-carboxylate (**27a**)*

According to GP 4 β-lactam **20a** (69 mg, 192 μmol) was reacted and purified (20 g, silica gel, hexanes/EA, 5:1→4:1) yielding β-lactam **27a** (78 mg, 170 μmol, 88%) as a colourless solid.

*3.5.5. tert-Butyl (3S,4R,1′S)-3-(1-benzyloxycarbonylamino-ethyl)-4-(4-chlorophenyl)-2-oxo-azetidine-1-carboxylate (**27b**)*

According to GP 4 β-lactam **20b** (142 mg, 396 μmol) was reacted and purified (20 g, silica gel, hexanes/EA, 5:1→4:1) yielding β-lactam **27b** (127 mg, 277 μmol, 70%) as a colourless solid.

*3.5.6. tert-Butyl (3R,4S,1′S)-3-(1-benzyloxycarbonylamino-ethyl)-4-[1,3]dioxolan-2-yl-2-oxo-azetidine-1-carboxylate (**28a**)*

According to GP 4 β-lactam **21a** (114 mg, 356 μmol) was reacted and purified (20 g, silica gel, hexanes/EA, 4:1) yielding β-lactam **28a** (115 mg, 274 μmol, 77%) as a colourless solid.

*3.5.7. tert-Butyl (3R,4S,1′S)-3-(1-benzyloxycarbonylamino-2-methyl-propyl)-4-(4-chlorophenyl)-2-oxo-azetidine-1-carboxylate (**30a**)*

According to GP 4 β-lactam **23a** (404 mg, 1.04 mmol) was reacted and purified (100 g, silica gel, hexanes/EA, 6:1) yielding β-lactam **30a** (447 mg, 918 μmol, 88%) as a colourless foam.

*3.5.8. tert-Butyl (3R,4S,1′S)-3-(1-benzyloxycarbonylamino-2-phenyl-ethyl)-2-oxo-4-phenyl-azetidine-1-carboxylate (**31a**)*

According to GP 4 β-lactam **24a** (102 mg, 255 μmol) was reacted and purified (10 g, silica gel, hexanes/EA, 8:1) yielding β-lactam **31a** (71 mg, 142 μmol, 56%) as a colourless solid.

*3.5.9. tert-Butyl (3S,4R,1′S)-3-(1-benzyloxycarbonylamino-2-phenyl-ethyl)-2-oxo-4-phenyl-azetidine-1-carboxylate (**31b**)*

According to GP 4 β-lactam **24b** (179 mg, 447 μmol) was reacted and purified (30 g, silica gel, hexanes/EA, 8:1) yielding β-lactam **31b** (161 mg, 322 μmol, 72%) as a colourless solid.

3.6. Ring opening with *O*-nucleophiles

*3.6.1. Methyl (2R,3S,1′S)-2-(amino-phenyl-methyl)-3-benzyloxycarbonylamino-butanoate (**37a**)*

TMSCl (158 μl, 1.24 mmol) was added at rt to a solution of β-lactam **19a** (80 mg, 247 μmol) in anhydrous MeOH (4.5 ml), the mixture was stirred for 66 h (monitoring with TLC), volatile components were removed in vacuo and CH_2Cl_2 (30 ml) was added. The solution was extracted with saturated $NaHCO_3$ solution (20 ml), dried ($MgSO_4$), concentrated and chromatographied (10 g, silica gel, hexanes/EA 2:1→1:1) yielding **37a** (51 mg, 143 μmol, 58%) of a slowly crystallizing oil.

*3.6.2. Methyl (2S,3S,1′R)-2-[amino-(4-chlorophenyl)-methyl]-3-(benzyloxycarbonylamino)-4-phenyl-butanoate (**38b**)*

TMSCl (88 μl, 689 μmol) was added at rt to a solution of β-lactam **25b** (60 mg, 138 μmol) in anhydrous MeOH (10 ml) and the mixture was stirred for 48 h (monitoring with TLC). The volatile components were removed and the remnant was dissolved in CH_2Cl_2 (30 ml), washed with saturated $NaHCO_3$ solution (20 ml), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (6 g, silica gel, hexanes/EA, 3:1) yielding **38b** (34 mg, 72.8 μmol, 53%) as a colourless solid.

*3.6.3. Methyl (2R,3S,1′S)-2-[amino-(4-chlorophenyl)-methyl]-3-benzyloxycarbonylamino-4-methyl-pentanoate (**39a**)*

TMSCl (114 μl, 1.13 mmol) was added at rt to a solution of β-lactam **30a** (87 mg, 225 μmol) in anhydrous MeOH (2 ml) and the mixture was stirred for 24 h (monitoring with TLC). The volatile components were removed and the remnant was dissolved in CH_2Cl_2 (30 ml), washed with saturated $NaHCO_3$ solution (20 ml), dried ($MgSO_4$) and concentrated. The residue was chromatographied (8 g, silica gel, hexanes/EA, 3:1) yielding **39a** (48 mg, 115 μmol, 51%) as a yellowish oil containing significant amounts of non-identified side products. This material was transferred into the Boc-protected derivative for analysis (vide infra).

*3.6.4. Methyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-butanoate (**32a**)*

(a) Et_3N (100 μl, 718 μmol) was added to a solution of β-lactam **26a** (102 mg, 240 μmol) in anhydrous MeOH (7 ml) and the mixture was stirred for 21 h at rt (monitoring with TLC), concentrated and purified by chromatography (10 g, silica gel, hexanes/EA, 3:1) yielding methyl ester **32a** (109 mg, 239 μmol, 99%) as a colourless wax.
(b) Methyl ester **32a** is alternatively available by Boc protection of amine **37a** (45 mg, 126 μmol) according to GP 4. Reaction (3 d) and purification (5 g, silica gel, hexanes/EA, 3:1) yielded **32a** (36 mg, 78.9 μmol, 62%) as a colourless wax.

*3.6.5. Methyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-[tert-butyloxycarbonylamino-(4-chlorophenyl)-methyl]-butanoate (**33a**)*

Et_3N (71 μl, 510 μmol) was added at rt to a solution of β-lactam **27a** (78 mg, 170 μmol) in anhydrous MeOH (5 ml) and the mixture was stirred for 24 h (monitoring with TLC). The volatile components were removed at the rotary evaporator and the residue was purified by chromatography (8 g, silica gel, hexanes/EA, 3:1) yielding **33a** (83 mg, 169 μmol, 99%) as a colourless wax.

*3.6.6. Methyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-[1,3]dioxolan-2-yl-methyl)-butanoate (**34a**)*

Et_3N (78 μl, 560 μmol) was added at rt to a solution of β-lactam **28a** (79 mg, 188 μmol) in anhydrous MeOH (4 ml) and the mixture was stirred for 22 h (monitoring with TLC). The volatile components were removed at the rotary evaporator and the residue was purified by chromatography (10 g, silica gel, hexanes/EA, 3:1) yielding **34a** (84 mg, 186 μmol, 99%) as a colourless oil.

*3.6.7. Methyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-4-methyl-pentanoate (**35a**)*

Et_3N (69 μl, 496 μmol) was added at rt to a solution of β-lactam **29a** (75 mg, 166 μmol) in anhydrous MeOH (5 ml) and the mixture was stirred for 16 h (monitoring with TLC). The volatile components were removed at the rotary evaporator and the residue was purified by chromatography (8 g, silica gel, hexanes/EA, 5:1) yielding **35a** (78 mg, 161 μmol, 97%) as a colourless oil.

*3.6.8. Methyl (2S,3S,1′R)-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-4-phenyl-butanoate (**36b**)*

Et_3N (58 μl, 417 μmol) was added at rt to a solution of β-lactam **31b** (69 mg, 138 μmol) in anhydrous MeOH (7 ml) and the mixture was stirred for 24 h (monitoring with TLC). The volatile components were removed at the rotary evaporator and the residue was purified by MPLC (hexanes/EA, 4:1) yielding **36b** (45 mg, 85 μmol, 61%) as a colourless solid.

*3.6.9. Methyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-[tert-butyloxycarbonylamino-(4-chlorophenyl)-methyl]-4-methyl-pentanoate (**40a**)*

Crude amine **39a** (48 mg, 115 μmol) was reacted according to GP 4 within 4 d. Purification (6 g, silica gel, hexanes/EA, 5:1) yielded **40a** (42 mg, 80.9 μmol, 71%) as a colourless solid.

*3.6.10. Allyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-butanoate (**41a**)*

AllylOH (22 μl, 323 μmol) and NaN_3 (16 mg, 246 μmol) were added at rt under an argon atmosphere to a solution of β-lactam **26a** (106 mg, 250 μmol) in anhydrous DMF (1 ml). After stirring for 18 h (monitoring with TLC) at 60 °C the mixture was poured after cooling to brine (10 ml). The aqueous phase was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (18 g, silica gel, hexanes/EA, 3:1) yielding **41a** (82 mg, 170 μmol, 68%) as a colourless oil.

3.7. Ring opening with *N*-nucleophiles

*3.7.1. (2R,3S,1′S)-3-Benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-1-pyrrolidin-1-yl-butan-1-one (**42a**)*

A solution of β-lactam **26a** (87 mg, 205 μmol) in pyrrolidine (0.5 ml) was stirred for 1 h (monitoring with TLC) at 90 °C. After cooling to rt, the volatile components were removed at the rotary evaporator and the residue was purified by chromatography (10 g, silica gel, hexanes/EA, 3:1) to yield **42a** (82 mg, 165 μmol, 81%) as a colourless solid.

*3.7.2. (2R,3S,1′S)-3-Benzyloxycarbonylamino-2-[tert-butyloxy-carbonylamino-(4-chlorophenyl)-methyl]-1-pyrrolidin-1-yl-butan-1-one (**43a**)*

A solution of β-lactam **27a** (80 mg, 174 μmol) in pyrrolidine (1 ml) was stirred for 1 h (monitoring with TLC) at 90 °C. After cooling to rt, the volatile components were removed at the rotary evaporator and the residue was purified by chromatography (11 g, silica gel, hexanes/EA, 3:1) to yield **43a** (76 mg, 143 μmol, 82%) as a colourless solid.

*3.7.3. (2R,3S,1′S)-3-Benzyloxycarbonylamino-2-(tert-butyloxy-carbonylamino-phenyl-methyl)-4-methyl-1-morpholin-4-yl-pentan-1-one (**44a**)*

A solution of β-lactam **29a** (58 mg, 128 μmol) in morpholine (1.1 ml) was stirred for 90 min (monitoring with TLC) at 100 °C. After cooling to rt, the volatile components were removed at the rotary evaporator and the residual yellowish oil was purified by chromatography (13 g, silica gel, hexanes/EA, 3:1) to yield **44a** (50 mg, 93 μmol, 72%) as a colourless solid.

*3.7.4. (2R,3S,1′S)-3-Benzyloxycarbonylamino-2-[tert-butyloxy-carbonylamino-(4-chlorophenyl)-methyl]-4-methyl-1-morpholin-4-yl-pentan-1-one (**45a**)*

A solution of β-lactam **30a** (80 mg, 164 μmol) in morpholine (1 ml) was stirred for 90 min (monitoring with TLC) at 100 °C. After cooling to rt, the volatile components were removed at the rotary evaporator and the residue was purified by chromatography (10 g, silica gel, hexanes/EA, 3:1) to yield **45a** (74 mg, 129 μmol, 78%) as a colourless solid.

*3.7.5. (2R,3S,1′S)-3-Benzyloxycarbonylamino-N-butyl-2-(tert-butyloxycarbonylamino-phenyl-methyl)-butanamide (**50a**)*

n$BuNH_2$ (15 μl, 152 μmol) and NaN_3 (1 mg, 15 μmol) were added at rt to a solution of β-lactam **26a** (50 mg, 118 μmol) in anhydrous DMF (0.5 ml). The mixture was stirred for 23 h (monitoring with

TLC) under argon atmosphere and was poured on brine (5 ml). The organic layer was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (10 g, silica gel, hexanes/EA, 4:1→2:1) yielding **50a** (36 mg, 72.3 μmol, 61%) as a colourless solid.

*3.7.6. (2S,3S,1′R)-3-Benzyloxycarbonylamino-N-butyl-2-[tert-butyloxycarbonylamino-(4-chlorophenyl)-methyl]-butanamide (**51b**)*

*n*BuNH$_2$ (23 μl, 233 μmol) and NaN_3 (2 mg, 31 μmol) were added at rt to a solution of β-lactam **27b** (81 mg, 176 μmol) in anhydrous DMF (1 ml). The mixture was stirred for 42 h (monitoring with TLC) under argon atmosphere and was poured on brine (6 ml). The organic layer was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (16 g, silica gel, hexanes/EA, 4:1→2:1) yielding **51b** (74 mg, 139 μmol, 79%) as a colourless solid.

*3.7.7. (2S,3S,1′R)-N-Allyl-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-4-phenyl-butanamide (**52b**)*

AllylNH$_2$ (8 μl, 107 μmol) and NaN_3 (1 mg, 15 μmol) were added at rt to a solution of β-lactam **31b** (38 mg, 76 μmol) in anhydrous DMF (1.5 ml). The mixture was stirred for 24 h (monitoring with TLC) under argon atmosphere and was poured on brine (2 ml). The organic layer was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (3 g, silica gel, hexanes/EA, 4:1→3:1) yielding **52b** (26 mg, 47 μmol, 61%) as a colourless solid.

3.8. Ring opening with *S*-nucleophiles

*3.8.1. S-Allyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-butanethioate (**46a**)*

Et_3N (28 μl, 201 μmol) and AllylSH (technical grade, 23 μl, 289 μmol) were added under argon atmosphere to a solution of β-lactam **26a** (66 mg, 155 μmol) in anhydrous DMF (1.5 ml). The mixture was heated to 60 °C for 4 h (monitoring with TLC), hydrolyzed with saturated NH_4Cl solution (1 ml) and cooled to rt. The aqueous layer was extracted with Et_2O (3×5 ml) and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×5 ml) and with brine (5 ml), dried ($MgSO_4$) and concentrated at the rotary evaporator. The residue was purified by chromatography (8 g, silica gel, hexanes/EA, 3:1) to yield **46a** (61 mg, 122 μmol, 79%) as a colourless oil.

*3.8.2. S-Allyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-[tert-butyloxycarbonylamino-(4-chlorophenyl)-methyl]-butanethioate (**47a**)*

Et_3N (30 μl, 216 μmol) and AllylSH (technical grade, 25 μl, 314 μmol) were added under argon atmosphere to a solution of β-lactam **27a** (77 mg, 168 μmol) in anhydrous DMF (1.5 ml). The mixture was heated to 60 °C for 4 h (monitoring with TLC), hydrolyzed with saturated NH_4Cl solution (1 ml) and cooled to rt. The aqueous layer was extracted with EA (3×5 ml) and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×5 ml) and with brine (5 ml), dried ($MgSO_4$) and concentrated at the rotary evaporator. The residue was purified by chromatography (17 g, silica gel, hexanes/EA, 3:1) to yield **47a** (63 mg, 118 μmol, 70%) as a colourless solid.

*3.8.3. Methyl (2S,2′R,3′S,1″S)-3-[3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-4-phenyl-butyryl-sulfanyl]-2-tert-butyloxycarbonylamino-propanoate (**48a**)*

Et_3N (25 μl, 180 μmol) and Boc–Cys–OMe (43 mg, 183 μmol) were added under argon atmosphere to a solution of β-lactam **31a** (70 mg, 140 μmol) in anhydrous DMF (1.5 ml). The mixture was heated to 60 °C for 4 h (monitoring with TLC), hydrolyzed with saturated NH_4Cl solution (1 ml), and cooled to rt. The aqueous layer was extracted with EA (3×5 ml) and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated at the rotary evaporator. The residual yellowish oil was purified by chromatography (6 g, silica gel, hexanes/EA, 8:1→6:1) to yield **48a** (75 mg, 102 μmol, 73%) as a colourless oil.

*3.8.4. S-tert-Butyl (2R,3S,1′S)-3-benzyloxycarbonylamino-2-[tert-butyloxycarbonylamino-(4-chlorophenyl)-methyl]-4-methyl-pentanethioate (**49a**)*

Et_3N (47 μl, 338 μmol), *t*BuSH (38 μl, 337 μmol) and NaN_3 (17 mg, 261 μmol) were added at rt under an argon atmosphere to a solution of β-lactam **30a** (127 mg, 261 μmol) in DMF (2.5 ml). After stirring for 24 h (monitoring with TLC) at 60 °C the mixture was poured after cooling to brine (8 ml). The aqueous phase was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (25 g, silica gel, hexanes/EA, 4:1) yielding **49a** (103 mg, 178 μmol, 68%) as a colourless solid.

*3.8.5. Methyl (2′R,3′S,1″S)-[3-benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-butyrylamino]-ethanoate (**53a**)*

Gly–OMe·HCl (46 mg, 366 μmol), Et_3N (51 μl, 366 μmol) and NaN_3 (2 mg, 31 μmol) were added at rt under a nitrogen atmosphere to β-lactam **26a** (120 mg, 283 μmol) in anhydrous DMF (1 ml), the mixture was stirred for 43 h (monitoring with TLC) and poured into brine (8 ml). The aqueous phase was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated at the rotary evaporator. The residue was purified by chromatography (24 g, silica gel, hexanes/EA, 4:1→2:1) yielding **53a** (80 mg, 156 μmol, 55%) as a colourless solid.

*3.8.6. Methyl (2S,1′R,2′S,1″S)-2-(3-{2-benzyloxycarbonylamino-1-[tert-butoxycarbonylamino-(4-chlorophenyl)-methyl]-propyl}-ureido)-3-methyl-butanoate (**54a**)*

Val–OMe·HCl (39 mg, 233 μmol), Et_3N (33 μl, 237 μmol) and NaN_3 (12 mg, 185 μmol) were added at rt under a nitrogen atmosphere to β-lactam **27a** (82 mg, 179 μmol) in anhydrous DMF (1 ml), the mixture was stirred at 60 °C for 24 h (monitoring with TLC) and poured after cooling into brine (6 ml). The aqueous phase was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated at the rotary evaporator. The residue was purified by chromatography (16 g, silica gel, hexanes/EA, 4:1→2:1) yielding **54a** (68 mg, 112 μmol, 63%) as a colourless solid.

*3.8.7. Methyl (2S,1′R,2′S,1″S)-2-(3-{2-benzyloxycarbonylamino-1-[tert-butoxycarbonylamino-(4-chlorophenyl)-methyl]-3-methyl-butyl}-ureido)-propionate (**55a**)*

Ala–OMe·HCl (34 mg, 244 μmol), Et_3N (34 μl, 244 μmol) and NaN_3 (13 mg, 200 μmol) were added at rt under a nitrogen atmosphere to β-lactam **30a** (91 mg, 187 μmol) in anhydrous DMF (1 ml), the mixture was stirred at 60 °C for 24 h (monitoring with TLC) and poured after cooling into brine (6 ml). The aqueous phase was extracted with Et_2O (3×10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated at the rotary evaporator. The

residue was purified by chromatography (12 g, silica gel, hexanes/EA, 4:1→2:1) yielding **55a** (46 mg, 76 μmol, 41%) as a colourless solid.

3.9. Reductive ring openings

*3.9.1. (2S,3S,1′R)-3-Benzyloxycarbonylamino-2-(tert-butyloxycarbonylamino-phenyl-methyl)-butan-1-ol (**56b**)*

β-Lactam **26b** (68 mg, 160 μmol) in anhydrous THF (0.5 ml) was added dropwise at rt under an argon atmosphere to a slurry of $LiAlH_4$ (19 mg, 501 μmol) in anhydrous THF (0.5 ml). After stirring for 14 h (monitoring with TLC), the mixture was carefully hydrolyzed by dropwise (!) addition of 25% aqueous NaOH (0.5 ml). The aqueous phase was extracted with EA (3×5 ml) and the combined organic layers were extracted with brine (10 ml), dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (6 g, silica gel, hexanes/EA, 3:1→2:1) to yield **56b** (28 mg, 65 μmol, 41%) as a colourless solid.

*3.9.2. (2R,3S,1′S)-3-Benzyloxycarbonylamino-2-[tert-butyloxycarbonylamino-(4-chlorophenyl)-methyl]-butan-1-ol (**57a**)*

β-Lactam **27a** (87 mg, 160 μmol) in anhydrous THF (1 ml) was added dropwise at rt under an argon atmosphere to a slurry of $LiAlH_4$ (22 mg, 580 μmol) in anhydrous THF (1 ml). After stirring for 17 h (monitoring with TLC), the mixture was carefully hydrolyzed by dropwise (!) addition of 25% aqueous NaOH (0.5 ml). The aqueous phase was extracted with EA (3×5 ml) and the combined organic layers were extracted with brine (10 ml), dried ($MgSO_4$), concentrated at the rotary evaporator and purified by chromatography (8 g, silica gel, hexanes/EA, 3:1→2:1) to yield **57a** (35 mg, 76 μmol, 40%) as a colourless oil.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft.

Supplementary data

Experimental details and spectroscopic data of all new compounds. X-ray-crystallographic data of compound **53a**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.006.

References and notes

1. Hubschwerlen, C. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, D. J., Eds.; Elsevier: Oxford, UK, 2006; Vol. 7, pp 479–518.
2. (a) Graf, R.; Lohaus, G.; Börner, K.; Schmidt, E.; Bestian, H. *Angew. Chem.* **1962**, *74*, 523–530; *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 481–488; (b) Bestian, H. *Angew. Chem.* **1968**, *80*, 304–312; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 278–285.
3. (a) Matthews, J. L. In *Houben-Weyl, Methods of Organic Chemistry, Synthesis of Peptides and Peptidomimetics*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Georg Thieme: Stuttgart, 2003; Vol. E22c, pp 552–569; (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers.* **2004**, *1*, 1111–1239; (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley & Sons: Hoboken, 2005.
4. Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600.
5. (a) Mukerjee, A. K.; Singh, A. K. *Synthesis* **1975**, 547–589; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley–VCH: New York, NY, 1997; pp 279–357; (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-Interscience: Hoboken, New Jersey, NJ, 2005; pp 477–495; (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492.
6. Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, NY, 1993; pp 295–368.
7. Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2006**, *71*, 6983–6990.
8. (a) Podlech, J. *Synlett* **1996**, 582–584; (b) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873–5883; (c) Podlech, J.; Steurer, S. *Synthesis* **1999**, 650–654; (d) Linder, M. R.; Podlech, J. *Org. Lett.* **1999**, *1*, 869–871; (e) Podlech, J.; Linder, M. R.; Maier, T. C. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rom, 2000; Vol. 4, pp 269–291; (f) Linder, M. R.; Frey, W. U.; Podlech, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2566–2577.
9. Linder, M. R.; Podlech, J. *Org. Lett.* **2001**, *3*, 1849–1851.
10. Taubinger, A. A.; Fenske, D.; Podlech, J. *Synlett* **2008**, 539–542.
11. Ivanov, C.; Dryanska, V. *Dokl. Bulg. Akad. Nauk.* **1969**, *22*, 423–426; *Chem. Abstr.* **1969**, *71*, 123860.
12. Chauveau, A.; Martens, T.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2002**, 1885–1890.
13. Ager, D. J. In *Handbook of Chiral Chemicals*; Ager, D., Ed.; CRC LLC: Boca Raton, 2006; pp 11–30.
14. e. g. Adams, H.; Bradshaw, D.; Fenton, D. E. *J. Chem. Soc., Dalton Trans.* **2002**, 925–930.
15. (a) Ng, J. S.; Przybyla, C. A.; Mueller, R. A.; Vasquez, M. L.; Getman, D. P.; Freskos, J. J.; Decrescenzo, G. A.; Bertenshaw, D. E.; Heintz, R. M.; Zhang, S.; Liu, C.; Laneman S. A. (G. D. Searle and Co., USA), WO 9514653, 1995; *Chem. Abstr.* **1995**, *123*, 339376; (b) Herold, P.; Mah, R.; Stutz, S.; Tschinke, V.; Stojanovic, A.; Marti, C.; Behnke, D.; Jotterand, N.; Quirmbach, M.; Schumacher, C. (Speedel Experimenta AG, Switzerland), EP 1764099, 2007; *Chem. Abstr.* **2007**, *146*, 330872.
16. Ojima, I. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, NY, 1993; pp 197–255.
17. Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron* **1984**, *40*, 1795–1802.
18. (a) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985–7012; (b) Bell, M. R.; Clemans, S. D.; Oesterlin, R. *J. Med. Chem.* **1970**, *13*, 389–394.
19. Podlech, J.; Gurrath, M.; Müller, G.; Lohof, E. In *Houben-Weyl, Methods of Organic Chemistry, Synthesis of Peptides and Peptidomimetics*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Georg Thieme: Stuttgart, 2002; Vol. E22a, pp 41–165.
20. Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571–1579.
21. X-ray crystallographic data of **38** (CCDC 668750), **42** (CCDC 668751) and **44** (CCDC 668749) have already been published.[10] These and the data for the structure of **53** (CCDC 682044) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
22. (a) Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1957–1958; (b) Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett.* **1995**, *36*, 9027–9030.
23. Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *J. Chem. Soc., Chem. Commun.* **1990**, 720–721.
24. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
25. Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1990**, *46*, 4733–4748.
26. (a) Wilson, M. E.; Nowick, J. S. In *Houben-Weyl, Methods of Organic Chemistry, Synthesis of Peptides and Peptidomimetics*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Georg Thieme: Stuttgart, 2003; Vol. E22c, pp 590–605; (b) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287–296; (c) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380–384.
27. (a) Speeter, M. E.; Maroney, W. H. *J. Am. Chem. Soc.* **1954**, *76*, 5810–5811; (b) Testa, E.; Fontanella, L.; Cristiani, G. F. *Liebigs Ann. Chem.* **1959**, *626*, 114–120; (c) Metzger, C. *Chem. Ber.* **1971**, *104*, 59–64; (d) Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron* **2000**, *56*, 5603–5619.
28. Del Buttero, P.; Molteni, G.; Roncoroni, M. *Tetrahedron Lett.* **2006**, *47*, 2209–2211.
29. Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *J. Org. Chem.* **2007**, *72*, 7980–7991.
30. Amundsen, L. H.; Nelson, L. S. *J. Am. Chem. Soc.* **1951**, *73*, 242–244.
31. Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217–1228.
32. Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238–1246.
33. Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549–555.
34. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
35. Texier-Boullet, F. *Synthesis* **1985**, 679–681.