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Simple, Highly Enantioselective Access to Quaternary 1,3,4,4-Tetrasubstituted β-Lactams from Amino Acids: A Solid-Phase Approach

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Abstract: An operationally simple four-step procedure for the solid-phase synthesis of chiral (3*S*,4*S*)-1,3,4,4-tetrasubstituted β-lactams is described. The key step for the four-membered ring formation consisted in the enantioselective phosphazene base-assisted cyclization of resin-bound *N*-(alkyl)-*N*-[(*S*)-2-chloropropionyl]amino acid derivatives. A low-epimerization process during the incorporation of the 2*S*-chloropropionyl moiety into the *N*-alkylamino acid resins was crucial for the final stereochemical outcome, since the 3,4-stereochemistry was exclusively dictated by the configuration of this moiety. To evaluate the scope of this procedure a small library of quaternary, highly functionalized β-lactams has been generated.

Keywords: amino acids; asymmetric synthesis; *cis*-β-lactams; peptidomimetics; phosphazenes; solid-phase synthesis

Introduction

The 2-azetidinone (β-lactam) ring is the central core of the most extensively used class of antibiotics,[1–4] of numerous inhibitors of different proteases,[5–8] and of some anticancer agents.[9,10] Moreover, β-lactams are practical intermediates for the synthesis of a variety of high added value products (β-lactam synthon method).[11,12] In the peptidomimetics field, the β-lactam nucleus has also been used to stabilize peptide conformations, namely reverse β-turns.[13]

The interest of β-lactams in these three fields, biomedicine, organic synthesis and peptidomimetics, has encouraged extensive efforts toward the preparation of new 2-azetidinone derivatives.[14] In addition, to make possible the generation of molecular diversity on the β-lactam scaffold, most synthetic approaches to 2-azetidinones have also been adapted to solid-phase methodologies.[15]

The synthesis of racemic 1,3,4-trisubstituted *cis*- or *trans*-β-lactams *via* a [2+2]Staudinger reaction has profusely been explored from both resin-bound imines and carboxylic acids.[16] Moreover, the asymmetric solid-phase version of this procedure has been achieved through the employment of chiral acid chlorides or chiral aldehydes, leading to 3,4-*cis*-β-lactams as the main isomers in all described cases.[17] The use of appropriate linkers on the polymeric support, such as benzyloxyaniline and Rink amide handles, also allowed the preparation of NH-free 3,4-disubstituted β-lactams by the [2+2]ketene-imine cycloaddition.[18] Alternatively, this type of 3,4-disubstituted β-lactams can also be prepared through the N1-C4 ring closure of serine and threonine derivatives attached to a resin-bound hydroxylamine, followed by reductive cleavage with SmI_2.[19]

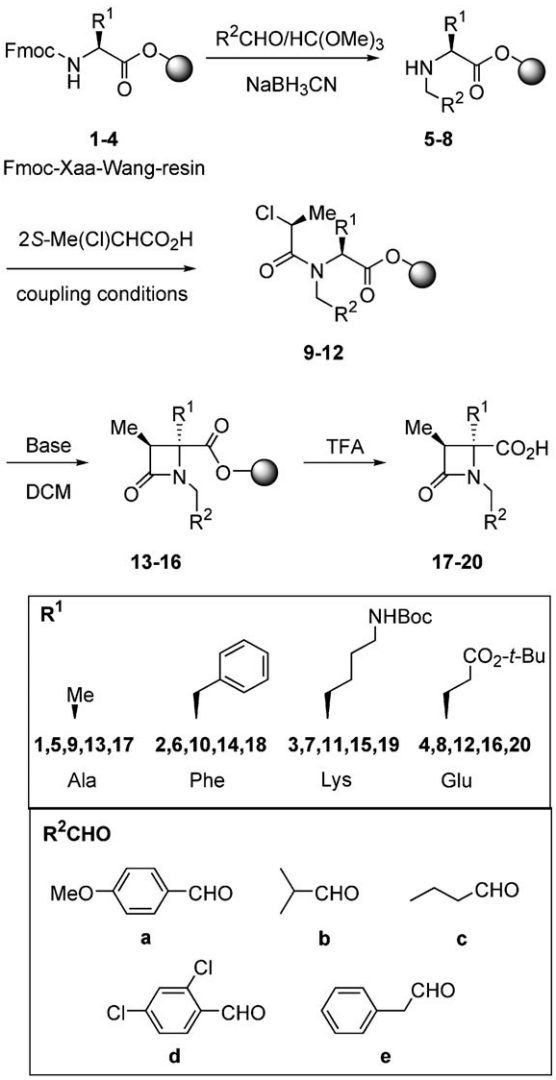
On the other hand, 2-azetidinones with 3,3- or 4,4-disubstitution patterns have also been reported. Thus, quaternary 3,3-disubstituted β-lactams were obtained from immobilized ester enolates in a traceless triazene linker and imines,[20] whereas 1,4,4-trisubstituted derivatives were prepared both in solution and in the solid phase by the base-assisted intramolecular alkylation (C3-C4 bond formation) of *N*-chloroacetylamino acid derivatives.[21,22] These latter derivatives, with an uncommon substitution array, have a 4-carboxy group, like a number of β-lactam-based protease inhibitors, but in contrast to most of these inhibitors

they lack substituents at the C3 position.[5–7] In this context, we have recently described that the base-promoted cyclization of optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionylamino acid derivatives resulted in a diastereo- and enantioselective solution route to valuable 1,3,4,4-tetrasubstituted *cis*-β-lactams.[23] Theoretical calculations on the transition states of deprotonation and intramolecular halide displacement have indicated that the stereochemical course of the reaction is entirely governed by the configuration of the *N*-(2-chloro)propionyl moiety.[24] Taking into account that the 1,3,4-trisubstitution pattern is recurrent in bioactive monocyclic β-lactams, the development of environmentally friendly procedures for the synthesis of unusual 1,3,4,4-analogues could be of major interest in medicinal chemistry programs. To approach the future generation of highly substituted β-lactam combinatorial libraries, we describe here the adaptation of the above recent solution procedure to solid-phase methodology for the expeditious preparation of a small set of tetrasubstituted β-lactams.

Results and Discussion

Four representative amino acids, Ala, Phe, Lys and Glu, were selected for the incorporation of a diversity of appendages at the R^1 position during the solid-phase synthesis of 1,3,4,4-tetrasubstituted β-lactams, while five diverse aldehydes, both aromatic and aliphatic, were used for the decoration of the N atom (R^2) (Scheme 1).[25] By employing the Fmoc-Xaa-Wang resins **1–4** as starting materials, and after removal of Fmoc protecting groups with piperidine, the resulting amines were condensed with a 6-fold molar excess of the corresponding aldehyde in $(MeO)_3CH$ to yield the resin-bound imines, which were satisfactorily reduced with $NaBH_3CN$ (1% AcOH) to the expected *N*-alkylamino acid derivatives **5–8**, according to a reported procedure.[26]

Attempts to acylate resins **5–8** with (*S*)-2-chloropropionic acid, under the same conditions as employed in our previous approach in solution, PyBrop/DIEA, resulted in very low conversions to *N*-alkyl-*N*-chloropropionyl derivatives **9–12** (Figure 1 A, Table 1, Method A). Using resin **6d** as model, the formation of the corresponding acyl derivative **10d** was optimized. Following our first approach to quaternary 1,4,4-trisubstituted β-lactams from amino acids, the reaction of the immobilized Phe derivative **6d** with an excess (5 equiv.) of commercial (*R*,*S*)-2-chloropropionyl chloride, in the presence of propylene oxide as hydrochloric acid scavenger, triggered the total transformation to the expected chloropropionyl derivatives *S,S*-**10d** and *R,S*-**10′d**, with some kinetic resolution (Figure 1 B, Table 1, **10d:10′d** *dr* = 70:30). Therefore, a



Scheme 1. Solid-phase synthetic approach to β-lactams **17–20** and diversity incorporated at R^1 and R^2 positions.

method for the *in situ* conversion of (*S*)-2-chloropropionic acid into (*S*)-2-chloropropionyl chloride was required. The combination of trichloroacetonitrile and triphenylphosphine, as chlorinating agent, and DIEA as HCl scavenger, as reported by Chavarisi,[27] led to very good acylation yield, but the quasi total epimerization of compound **10d** at the chloropropionyl residue was observed (Figure 1 C, Table 1, Method C, **10d:10′d** *dr* = 53:47). Considering that DIEA was also present in Method A, the observed lack of selectivity could probably be due to a high conversion of the activated (*S*)-2-acyl chloride into the (*R*)-2-isomer by means of this base, more likely than the direct epimerization of compound **10d**. A modification of Method C, in which the acid scavenger DIEA was changed to propylene oxide, was evaluated to avoid the presence of any base in the reaction. Under these virtually neutral conditions (Method D), we found the

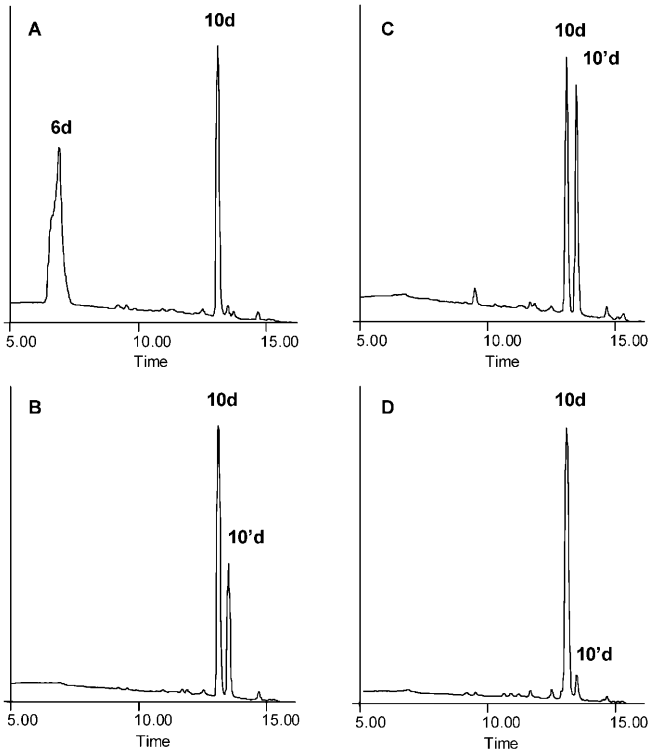


Figure 1. Optimization of the coupling procedure to intermediate **10d.** **A**: 2(*S*)-chloropropionic acid/PyBrop/DIEA/THF (twice). **B**: 2(*R,S*)-chloropropionyl chloride/propylene oxide/THF. **C**: 2(*S*)-chloropropionic acid/Cl_3CCN/PPh_3/DIEA/THF. **D**: 2(*S*)-chloropropionic acid/Cl_3CCN/PPh_3/propylene oxide/THF.

best balance between conversion and selectivity (Figure 1, Table 1, **10:10′d** *dr* = 94:6). Therefore, these conditions were selected for the acylation reactions of all resins **5**–**8**.

With resin-bound amino acid derivatives **9**–**12** in hand, the next question addressed was the search for suitable cyclization conditions, investigating different organic soluble bases (P_1-*t*-Bu, BEMP, BTPP) in different solvents (CH_2Cl_2, THF, DMF). From these optimization experiments, it can be concluded that only stronger phosphazene bases (BEMP and BTTP) in combination with highly polar solvents (DMF) give satisfactory cyclization results to β-lactam **13**–**16**, although the repetition of the process was always necessary. Immobilized β-lactams were finally detached from the resin using TFA to give the expected 1,3,4,4-tetrasubstituted 2-azetidinones **17**–**20**. A simple filtration of the crude β-lactams through silica or reverse-phase SPE cartridges generally resulted in high purity of the final compounds (Table 2).

Each β-lactam was obtained as a single *cis*-diastereoisomer, as deduced from NOE experiments.[23] The enantiomeric purity of one of the β-lactams, namely **18a**, was investigated through transformation to diastereoisomeric dipeptides **21** and **22** (Scheme 2), and evaluation of the crude reaction mixtures by HPLC (see Supporting Information for details). These dipeptides are identical to those previously prepared in solution from the same Phe-derived β-lactam.[23] Although some kinetic resolution was observed, dipeptide derivatives were obtained in about 92:8 diastereoisomeric ratio, quite similar to that the observed in the related starting material *N*-chloropropionyl derivative **10d** (Figure 1, Table 1, **10d:10′d** *dr* = 94:6). This result is an indication of the high enantiomeric purity in which the β-lactams are formed by this solid-phase procedure, despite the absence of either temporary chiral auxiliaries or chiral catalysts. This selectivity was explained through theoretical calculations that indicated a big difference in energy between the transitions states leading to *cis*- and *trans*-β-lactams,[24] and the cyclization to *S,S*- or *R,R*-configured azetidinones exclusively dictated by the configuration at the *N*-chloropropionyl moiety in the starting derivatives **9**–**12**.

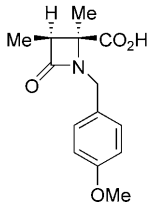
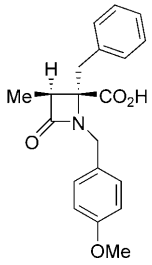
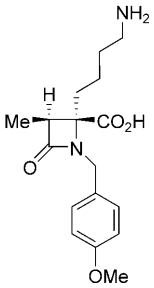
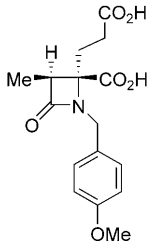
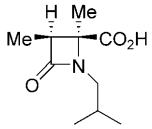
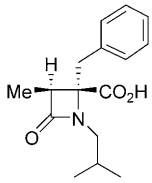
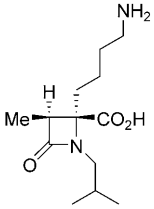
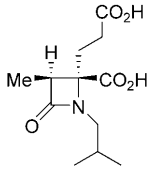
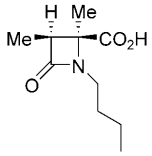
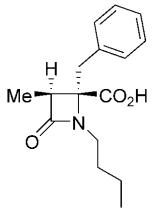
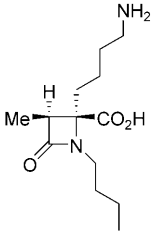
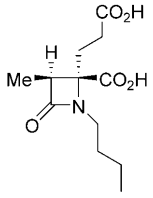
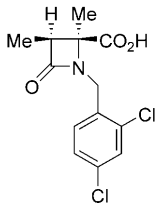
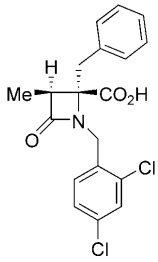
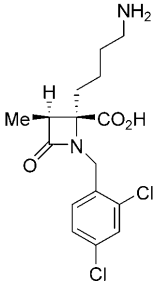
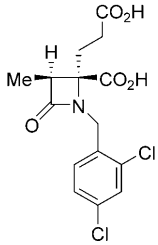
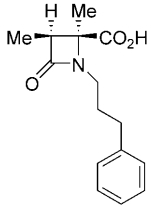
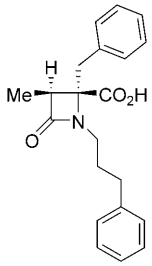
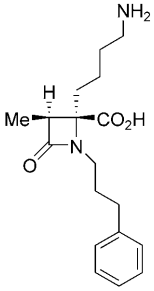
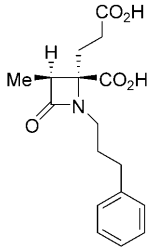
To corroborate this point, acylation of resin **6a** with (*R*)-2-chloropropionic acid to *R,S*-**10′a**, followed by BTPP-mediated cyclization and cleavage with TFA afforded the 3*R*,4*R*-β-lactam **18′a** (Figure 2), an enan-

Table 1. Optimization of acylation of resin **6d**.

Method	Acylation agent	Reaction conditions	% Conversion (1st coupling)[a]		% Conversion (2nd coupling)[a]	
			10d [%]	**6d** [%]	**10d** [%]	**6d** [%]
A	(*S*)-2-Cl(CH_3)$CHCO_2H$	PyBrop/DIEA/THF	27	72	34[b]	65
B	(*R,S*)-2-Cl(CH_3)CHCOCl	Propylene oxide, THF	76	23	99[c]	-
C	(*S*)-2-Cl(CH_3)$CHCO_2H$	Cl_3CCN/Ph_3P/THF, DIEA	74	25	99[d]	-
D	(*S*)-2-Cl(CH_3)$CHCO_2H$	Cl_3CCN/Ph_3P/THF, propylene oxide	90		94[e]	-

[a] Measured by HPLC.
[b] *S,S*-**10d:***R,S*-**10′d** *dr* = 97:3.
[c] *S,S*-**10d:***R,S*-**10′d** *dr* = 70:30.
[d] *S,S*-**10:***R,S*-**3'** *dr* = 53:47.
[e] *S,S*-**3:***R,S*-**10′d'** *dr* = 94:6.

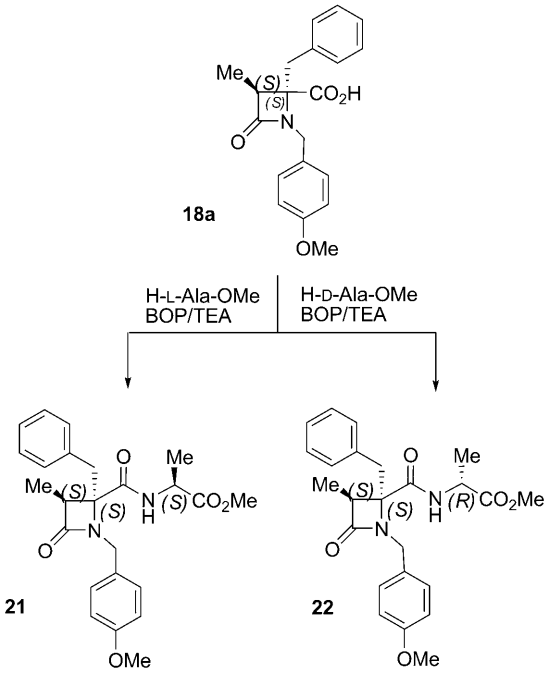
Table 2. Yield and (purity) of the array of β-lactams **17**–**20**.

Product	Yield [%][a] (purity)	Product	Yield [%][a] (purity)	Product	Yield [%][a] (purity)	Product	Yield [%][a] (purity)
	**17a** 14 (92)		**18a** 12 (41)		**19a** 24 (98)		**20a** 12 (69)
	**17b** 47 (98)		**18b** 61 (93)		**19b** 33 (95)		**20b** 24 (98)
	**17c** 26 (97)		**18c** 49 (86)		**19c** 34 (93)		**20c** 24 (45)
	**17d** 47 (98)		**18d** 45 (94)		**19d** 23 (96)		**20d** 40 (83)
	**17e** 29 (93)		**18e** 37 (94)		**19e** 41 (98)		**20e** 11 (82)

[a] Yield of isolated compounds after cartridge purification. Purity was determined by HPLC.

tiomer of **18a**. Therefore, the absolute configuration of the final 2-azetidinone, 3*S*,4*S* or 3*R*,4*R*, can be selected as a function of the configuration of the starting 2-chloropropionic acid. In this respect, our method favorably competes with other reported stereoselective procedures for the generation of β-lactams through the C3-C4 bond formation.[28]

Additionally, the reaction can be extended to the preparation of 2-azetidinones with substituents different from the methyl group at position 3. Thus, acyla-



Scheme 2.

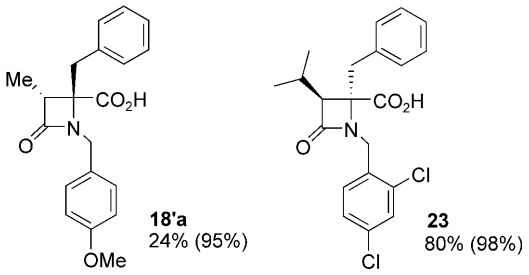
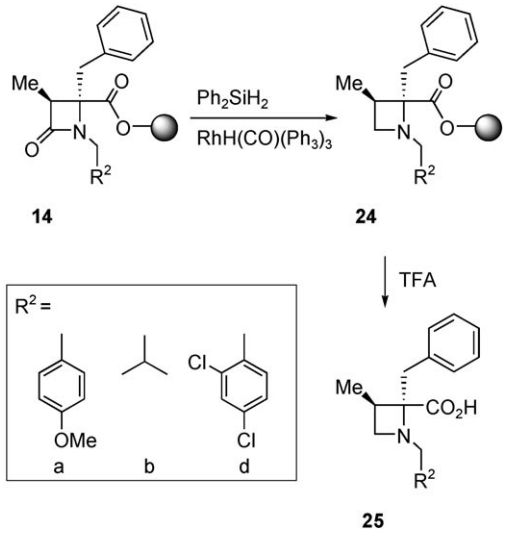


Figure 2.

tion of **6d** with (*S*)-2-chloroisobutyric acid and completion of the remaining three-step procedure gave the 3-isopropyl-β-lactam **23** in excellent yield (Figure 2).

It is interesting to comment that the success of this solid-phase synthesis of β-lactams is highly dependent on the solid support. Thus, while Wang resin gave satisfactory results (see above), the use of Wang-type (MPPA) and Rink amide-type resins should be avoided, due to undesired detachment during the cyclization step and to diketopiperazine formation,[21b] respectively.

In an attempt to apply the "libraries from libraries" concept,[29] the on-resin chemoselective reduction of the 2-CO group in some resin-bound β-lactams **14** was also investigated (Scheme 3).[30] However, the solid-phase version of our previously reported procedure in solution resulted in mixtures of the expected azetidine **25** and the unreacted β-lactam **18**, in an approximately 1:1 ratio. Further efforts to optimize this reaction, by exploring Ph_2SiH_2 or $PhSiH_3$ as reducing agents, THF or DCM as solvent, increasing the percentage of catalyst, and repeating the reaction up to three times were unsuccessful. In any case, pure azetidines **25** were obtained in low-to-moderate yield after careful purification on silica gel cartridges of the azetidine/azetidinone mixtures of reaction.



Scheme 3.

Conclusions

In summary, we report the first expeditious solid-phase procedure for the preparation of optically active quaternary *cis*-β-lactams with an innovative substitution pattern. The route, which is based on the cyclization of chiral *N*-2-chloroalkanoylamino acid derivatives, does not require any chiral auxiliary or catalyst, since the high enantioselectivity observed in the formation of the four-membered ring is exclusively directed by the configuration of the 2-chloroalkanoyl substituent. In addition, the versatility of the method was demonstrated by means of the satisfactory results obtained with the combination of different starting amino acids and aldehydes. Notably, the procedure also permits different configurations of the final β-lactams just by changing the configuration of the 2-chloroalkyl carboxylic acid incorporated in the second step. It is expected that this procedure could complement other approaches for the synthesis of highly substituted β-lactams. Further exploration of the applications of this methodology is currently underway.

Experimental Section

General Procedures for the Solid-Phase Synthesis of Quaternary β-Lactams from Amino Acids

Reductive Amination (Resins 5–8)

Fmoc-Xaa-Wang resins (0.2 mmol) were washed with DCM/DMF/DCM/DMF (5×0.5 min) and piperidine/DMF (1:4 v/v, 1×1 min, 3×10 min). After the cleavage of the Fmoc protecting group, the resins were washed with DMF/DCM/DMF/DCM (5×0.5 min) and TMOF (2×0.5 min). Then, TMOF and the corresponding aldehyde (1.2 mmol) were successively added. In the case of isobutyraldehyde and butyraldehyde an additional 1% of MeOH was also added to the reaction mixture. Formation of the imine overnight at room temperature was followed by filtration, and washing with TMOF (1×0.5 min). To the resulting resin-bound imines were added TMOF, and treated with $NaBH_3CN$ (0.6 mmol), in the presence of AcOH (1%) for 24 h. The obtained resins were filtered, washed consecutively with DMF (5×0.5 min), DMF/MeOH (1:1, 5×0.5 min) and DCM (5×0.5 min), and dried under vacuum.

Incorporation of the Chloroalkanoyl Group (Resins 9–12)

Method A: Resins **5–8** (0.2 mmol) were swollen in DCM (5×0.5 min) and THF (2×0.5 min). Then, THF was added and the resin was treated with (*S*)-2-chloropropionic acid (1 mmol), and a mixture of PyBroP (1 mmol) and DIEA (0.9 mmol) in THF was added, and the reaction was continued at room temperature for 5 h. The resins were filtered and washed consecutively with THF/DMF/DCM/THF (5×0.5 min).The reaction was repeated once and left overnight. Finally, resins **9–12** were filtered, washed with THF/DMF:MeOH (1:1)/DMF/DCM:MeOH (1:1)/DCM (5×0.5 min), and dried under vacuum.

Method B: Resins **5–8** (0.2 mmol) were swollen in DCM (5×0.5 min) and THF (2×0.5 min). Then, THF was added and the resin was treated with propylene oxide (3 mmol) and cooled to 0 °C. Then, chloropropionyl chloride (1 mmol) was added and the reaction continued at room temperature for 5 h. The resins were filtered and washed consecutively with THF/DMF/DCM/THF (5×0.5 min).The reaction was repeated once and left overnight. The following work-up was as indicated in method A.

Method C: Resins **5–8** (0.2 mmol) were swollen in DCM (5×0.5 min) and THF (2×0.5 min). Then, THF was added and the resin was treated with (*S*)-2-chloropropionic acid (1 mmol), Cl_3CCN (2.25 mmol) and DIEA (2.25 mmol), and cooled to 0 °C. Then, Ph_3P (2.4 mmol) was added and the reaction was continued at room temperature for 5 h. The resins were filtered and washed consecutively with THF/DMF/DCM/THF (5×0.5 min).The reaction was repeated once and left overnight. The following work-up was as indicated in method A.

Method D: Resins **5–8** (0.2 mmol) were swollen in DCM (5×0.5 min) and THF (2×0.5 min). Then, THF was added and the resin was treated with (*S*)-2-chloropropionic acid (1 mmol), Cl_3CCN (2.25 mmol) and propylene oxide (3 mmol), and cooled to 0 °C. Then, Ph_3P (2.4 mmol) was added and the reaction was continued at room temperature for 5 h. The resin was filtered and washed consecutively with THF/DMF:MeOH (1:1)/DMF/DCM/MeOH (1:1)/DCM/THF (5×0.5 min). The reaction was repeated once and left overnight. The following work-up was as indicated in method A.

Base-Promoted Cyclization to Resin-Bound β-Lactams 13–16

The corresponding resins **9–12** (0.2 mmol) were washed with DCM/DMF/DCM/DMF (5×0.5 min), swollen in DMF and treated at room temperature with BTPP (1 mmol), under an argon atmosphere. Reactions were continued overnight, filtered and washed with DMF/DCM/DMF/DCM (5×0.5 min). The resins were swollen in DMF and the reactions were repeated again. Finally, resin-bound β-lactams **13–16** were filtered, washed with DMF/DCM/DMF/DCM (5×0.5 min), and dried under vacuum.

Cleavage from the Resin to 1,3,4,4-Tetrasubstituted β-Lactams 17–20

Resins **13–16** (0.2 mmol) were treated with TFA/H_2O (95:5, 1.5 mL) at room temperature for 4 h. After filtration and washing with DCM, the combined filtrates were concentrated to give a residue which was dissolved in mixtures of MeCN/H_2O and lyophilized. The resulting residues were purified on silica gel cartridges (for Ala, Phe and Glu derivatives) or reverse-phase cartridges (for Lys-derived compounds), evaporated and lyophilized from H_2O or MeCN/H_2O mixtures.

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