# Soluble-Polymer-Supported Synthesis of β-Lactams on a Modified Poly(ethylene glycol)

**Rita Annunziata, Maurizio Benaglia, Mauro Cinquini, and Franco Cozzi*[a]**

**Abstract:** A modified poly(ethylene glycol) (PEG) has been developed for the soluble-polymer-supported synthesis of β-lactams. The monomethylether of PEG (MeOPEG) with an average $M_W$ of 5000 was used as the support, a 4-(3-propyl)phenyl residue as the spacer, and a 4-oxyphenylamino group as the moiety with the reactive functionality. From this modified PEG representative aromatic, heteroaromatic, unsaturated, and aliphatic imines were obtained in high yields by different procedures. The polymer-supported imines were then employed to prepare several β-lactams by enolate/imine condensation and ketene/imine cycloaddition. Examples of the control of the absolute stereochemistry during the azetidinone ring formation are also reported. The reactions carried out on the polymer-bound imines showed a remarkable similarity to those performed on nonimmobilized imines, both in terms of yields and stereoselectivities. Removal of the β-lactams from the polymer has also been accomplished to directly deliver the *N*-unsubstituted azetidinones.

**Keywords:** imines · lactams · polymers · polymer-supported synthesis

## Introduction

The polymer-supported synthesis of small organic molecules is a subject of intense research activity.[1] In this context, soluble polymers,[2] in comparison to other supports, recently emerged as suitable for use in such reactions, since they profit from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena,[3] analytical simplicity) and of solid-phase methods (ready isolation and easy purification of the products).[1, 2] Last, but not least, soluble polymers generally cost much less than insoluble ones.

Modified poly(ethylene glycol)s (PEGs)[2a, 4] are very popular soluble supports. They are inexpensive,[5] readily functionalized with different spacers and linkers,[6] and, provided that their $M_W$ is greater than 2000 Da, are insoluble in nonpolar solvents (hexanes, diethylether, *tert*-butylmethylether) and simply purified by precipitation. As a consequence, the synthesis and the immobilization of several organic molecules on PEG supports have been reported over the last few years.[2, 4, 7, 8] The extension to the field of combinatorial chemistry is particularly attractive, since biological evaluation can be carried out directly on the PEG-anchored molecules.[2, 4] Some of the problems associated with the use of PEGs, such as the low number of functional groups per gram of polymer (loading)[9] and the difficult removal of poorly soluble by-products in the purification step[10] have been solved.

We have recently reported[7d] a soluble-polymer-supported synthesis of imines and β-lactams by using the monomethylether of PEG with a $M_W$ of 5000 (MeOPEG) as the support, a succinate spacer, and a 4-oxyaniline as the group bearing the nitrogen moiety for imine and β-lactam construction.[7d, 11] Since the use of this modified PEG had some limitations (for instance in the synthesis of aliphatic imines, or in the two-step procedure required for β-lactam removal from the polymer), we decided to develop a new PEG support for β-lactam synthesis that would ideally reproduce the results observed under "nonpolymeric" conditions. Here we report the results of this work.

## Results and Discussion

Reaction of MeOPEG mesylate **1**[10b] with the Cs salt of the commercially available 3-(4-hydroxyphenyl)-1-propanol (3 mol equiv, dimethylformamide (DMF), 48 h) afforded **2** (Scheme 1). This was mesylated and converted by reaction with the Cs salt of 4-aminophenol (5 mol equiv) into PEG **3** in 91 % overall yield from **1** (see the Experimental Section for the determination of the yields of reactions that involve polymer-supported substrates and the purity criteria for polymer-supported products).

[a] Prof. R. Annunziata, Dr. M. Benaglia
Prof. M. Cinquini, Prof. F. Cozzi
Centro C.N.R. and Dipartimento di Chimica Organica e Industriale
Universita' di Milano via Golgi, 19-20133 Milano (Italy)
Fax: (+39) 02-2364369
E-mail: franco.cozzi@unimi.it

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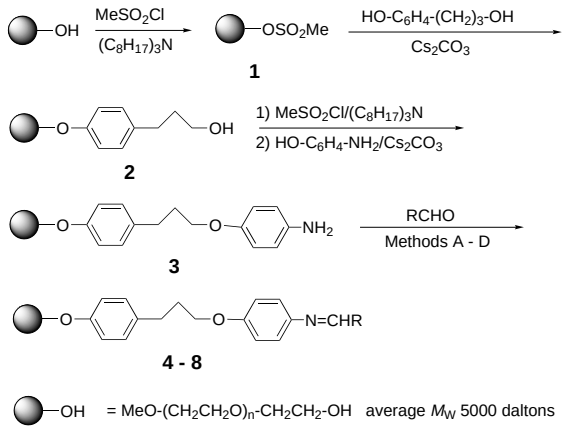



Scheme 1. Synthesis of PEG-supported imines **4–8**.

The conversion of amine **3** into representative imines **4–8** was carried out under different conditions (Table 1). The first

Table 1. Synthesis of imines **4–8** from PEG **3** by methods A–D (see text).

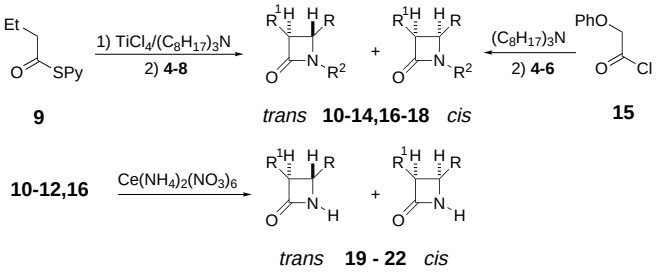
| | Method | Imine | Yield [%] |
|---|---|---|---|
| Ph | A | **4** | 91 |
| Ph | B | **4** | 90 |
| 2-thienyl | A | **5** | 91 |
| (*E*)-Ph–CH=CH | A | **6** | 92 |
| (*E*)-Ph–CH=CH | C | **6** | 91 |
| *c*-$C_6H_{11}$ | A | **7** | 83 |
| *c*-$C_6H_{11}$ | C | **7** | 91 |
| COOEt | D | **8** | 90 |

method (A) involved the addition of the aldehyde (2 mol equiv) to the melted amine (90 °C), and the thick oily mixture was then stirred for 1 h. Finally, the unreacted aldehyde and any water released were removed under vacuum, and the cooled mixture was precipitated with $Et_2O$.[7d] This procedure gave imines **4–7** in 91, 91, 92, and 83 % yield, respectively.

The second method (B) was under milder conditions and involved stirring a solution of amine and aldehyde in $CH_2Cl_2$ (4 mol equiv) in the presence of anhydrous $MgSO_4$ for 18 h at room temperature, and this was followed by filtration and precipitation with $Et_2O$. However, this procedure worked, in comparison with method A, only for the preparation of imine **4** (90 % yield).

Another mild alternative to method A was found when the protocol for the solid-phase synthesis of imines, recently reported by Gallop et al,[12] was extended to the present case. This method (C) involved the reaction of **3** with aldehyde (3 mol equiv) in a 2:1 mixture of $CH_2Cl_2$ and trimethylorthoformate for 18 h at room temperature, and the reaction gave imines **6** and **7** in 92 and 91 % yield, respectively. Surprisingly method C was ineffective for the preparation of **4**.

Finally, imine **8** was best obtained (90 % yield) by heating a solution of amine **3** and ethyl glyoxalate (3 mol equiv) in toluene at 100 °C for 18 h in the presence of anhydrous $MgSO_4$ (Method D). Imines **4–8** were then used in the synthesis of $\beta$-lactams. To this end, the two more popular reactions employed for their preparation, namely the enolate/imine condensation[13] and the [2+2] cycloaddition,[14] were selected (Scheme 2).




Scheme 2. Synthesis of PEG-supported $\beta$-lactams **10–14** and **16–18**. **10**, **19** R = Ph, $R^1$ = Et; **11**, **20** R = 2-thienyl, $R^1$ = Et; **12**, **21** R = (*E*)-Ph–CH=CH, $R^1$ = Et; **13** R = *c*-$C_6H_{11}$, $R^1$ = Et; **14** R = COOEt, $R^1$ = Et; **16**, **22** R = Ph, $R^1$ = PhO; **17** R = 2-thienyl, $R^1$ = PhO; **18** R = (*E*)-Ph–CH=CH, $R^1$ = PhO. $R^2$ = –$C_6H_4$–O–$(CH_2)_3$–$C_6H_4$–O–●.

Reaction of **4–8** with the titanium enolate[15] of *S*-2-pyridylthiobutanoate **9** (2–4 mol equiv)[16] in $CH_2Cl_2$ afforded $\beta$-lactams **10–14** in fair to high yields (Table 2). The compounds were obtained as mixtures of *trans* (**t**) and *cis* (**c**) isomers; this was determined directly from the products bound to the polymer and was based on the HC-3/HC-4 coupling constant values ($J_{trans}$ = 1.5–2.5 Hz; $J_{cis}$ = 4.5–6.0 Hz). The *trans*/*cis* ratios were similar to those observed

Table 2. Synthesis of $\beta$-lactams **10–14** and **16–18** by reaction of imines **4–8** with **9** or **15**.

| | Reagent | $\beta$-Lactam | Yield [%] | *trans*/*cis* ratio |
|---|---|---|---|---|
| **4** | **9** | **10t,c** | 95 | 70/30 |
| **5** | **9** | **11t,c** | 80 | ≤5/95 |
| **6** | **9** | **12t,c** | 95 | 80/20 |
| **7** | **9** | **13t,c** | 43 | ≤5/95 |
| **8** | **9** | **14t,c** | 64 | 50/50 |
| **4** | **15** | **16t,c** | 70 | ≤5/95[a] |
| **4** | **15** | **16t,c** | 72 | 70/30[b] |
| **5** | **15** | **17t,c** | 67 | ≤5/95[a] |
| **6** | **15** | **18t,c** | 40 | ≤5/95[a] |
| **6** | **15** | **18t,c** | 75 | 83/17[b] |

[a] In $CH_2Cl_2$ at RT. [b] In toluene at 100 °C.

**Abstract in Italian:** *E' stato sviluppato un polietilenglicole (PEG) modificato che permette una sintesi di β-lattami ancorati ad un polimero solubile, usando come supporto il monometiletere del PEG di peso molecolare medio 5000, uno spaziatore 4-(3-propil)benzenico, ed un gruppo 4-ossifenilamminico come residuo che fornisce la funzione reattiva. Dal PEG cosi' modificato sono state preparate con rese elevate ed attraverso procedure diverse immine aromatiche, eteroaromatiche, insature ed alifatiche, e da queste i corrispondenti β-lattami o per condensazione enolato/immina o per cicloaddizione chetene/immina. Le reazioni condotte sulle immine supportate sono molto simili, sia come rese che come stereoselezione, alle reazioni condotte su immine non immobilizzate. La rimozione dal supporto polimerico per trattamento ossidativo fornisce direttamente β-lattami non sostituiti all' atomo di azoto.*



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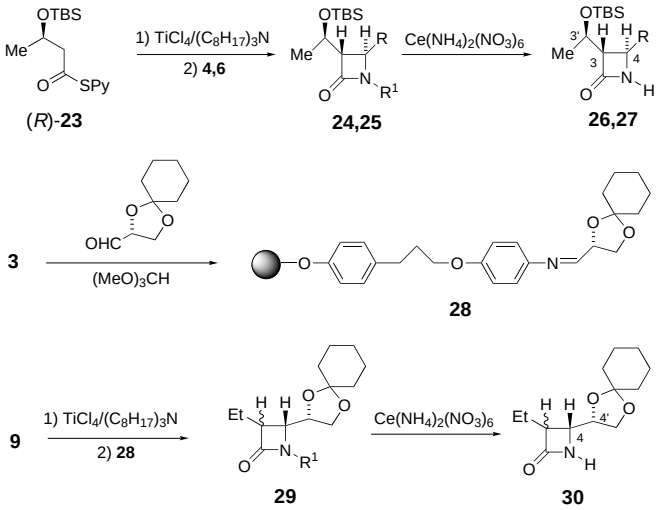
when thioester **9** was condensed with the PMP-substituted imines (PMP = *N*-4-methoxyphenyl) corresponding to **4–8**.[16]

Reaction of imines **4–6** with phenoxyacetylchloride **15** (20 mol equiv) in the presence of trioctylamine (22 mol equiv)[10b] carried out at room temperature in $CH_2Cl_2$ afforded *cis* β-lactams **16c–18c** as the only detected isomers in fair to good yields. If the reactions were carried out in refluxing toluene, the expected[17] switch of stereoselectivity in favor of the *trans* compounds **16t** and **18t** was observed. These were obtained in 72 and 75% yield, respectively.

The removal of the β-lactams from the polymer was then studied with the aim of developing a method that would directly yield a *N*-unsubstituted azetidinone. We were pleased to find that by deprotection of compounds **10–12** and **16** with $[Ce(NH_4)_2(NO_3)_6]$ (CAN, 4 mol equiv) under the usual reaction conditions,[18] β-lactams **19–22** were obtained in 57, 51, 42, and 40% yield, respectively (Scheme 2). This reaction was mild enough not to alter the *trans*/*cis* ratios of these β-lactams.

To further expand the scope of this polymer-supported synthesis of β-lactams, the use of enantiomerically pure reagents was investigated (Scheme 3). Reaction of imine **4** with the titanium enolate derived from *S*-2-pyridyl (*R*)-3-*tert*-butyldimethylsilyloxybutanoate **23** (7 mol equiv, $CH_2Cl_2$, −78 °C to RT)[16a] afforded azetidinone **24**, which was




Scheme 3. Stereoselective synthesis of PEG-supported β-lactams **24**, **25**, and **29**. **24**, **26** R = Ph; **25**, **27** R = (*E*)-Ph−CH=CH $R^1$ = $-C_6H_4-O-(CH_2)_3-C_6H_4-O-\bullet$.

obtained as a 90:10 mixture of two *trans* isomers in 78% yield. Their absolute configuration was established as 3,3′-*anti*-3,4-*trans* (**24ta**) and 3,3′-*syn*-3,4-*trans* (**24ts**) by converting them into the *N*-unprotected β-lactam **26** (39% yield, diastereoisomeric ratio = 90:10) of known stereochemistry.[16a] The reaction of **23** with imine **6** gave azetidinone **25**, which had a very complex $^1$H NMR spectrum. However, reaction of **25** with CAN gave **27**,[16a] which was obtained as a single 3,3′-*anti*-3,4-*trans* compound in 21% overall yield from imine **6**. When β-lactams **26** and **27** were prepared by the same reaction sequence that started from the corresponding *N*-PMP imines,[16a] the observed diastereoisomeric ratios were 91:9 and 84:16, respectively.

To anchor an enantiomerically pure imine to the polymer, PEG **3** was treated with *O*,*O*-cyclohexylidene (*R*)-glyceraldehyde (method C at 45 °C) to afford imine **28** in 90% yield. Condensation with the titanium enolate of **9** (7 mol equiv, $CH_2Cl_2$, −78 °C to RT) gave β-lactam **29**. Reaction with CAN led to the *N*-unprotected azetidinone **30**, which was isolated as a 50:50 mixture of one *trans* and one *cis* isomer (24% overall yield). These two β-lactams were identical, when analyzed by $^1$H NMR spectroscopy, to the 3,4-*trans*-4,4′-*syn* and 3,4-*cis*-4,4′-*syn* isomers that were obtained by the same reaction sequence that started from **9** and the *N*-PMP imine derived from *O*,*O*-cyclohexylidene (*R*)-glyceraldehyde.[16a] In this case, a 54:46 *trans*:*cis* diastereoisomeric ratio was observed.

## Conclusion

In conclusion, a modified PEG has been developed for the soluble-polymer-supported synthesis of β-lactams by enolate/imine condensation and [2+2] cycloaddition. Azetidinones with alkyl and phenoxy groups at C-3, and aryl, heteroaryl, unsaturated, aliphatic, and carbethoxy substituents at C-4 were obtained. The reaction was extended to the use of an enantiomerically pure enolate and an enantiomerically pure immobilized imine. In all the cases examined, a remarkable similarity was observed between the reactions carried out on polymer-bound and nonimmobilized imines, and thus the ability of the modified PEG to mimic "nonpolymeric" reaction conditions was shown. Finally, it is also worth mentioning that this "liquid-phase" synthesis of β-lactams has some advantages over the solid-phase methods reported so far.[11a–c] In particular, this procedure has the following advantages: i) it allows the use of the versatile enolate/imine condensation reaction for the first time; ii) it allows the production of C4-alkyl-substituted azetidinones; and iii) it delivers polymer-free *N*-unsubstituted β-lactams under mild conditions.

## Experimental Section

**General**: All PEG samples were melted at 80 °C in vacuum for 30 min before use to remove traces of moisture. After reaction, product purification involved evaporation of the reaction solvent in vacuum and addition of the residue dissolved in a few mL of $CH_2Cl_2$ to diethylether (50 mL g$^{-1}$ of polymer), which was stirred and cooled at 0 °C. After 20–30 min stirring at 0 °C, the obtained suspension was filtered through a sintered glass filter, and the solid was repeatedly washed on the filter with diethylether (up to 100 mL g$^{-1}$ of polymer, overall). $^1$H NMR spectra were recorded at 300 MHz as solutions in $CDCl_3$ at 25 °C; $\delta$ were in ppm downfield from TMS; IR spectra were recorded on thin film or as solutions in $CH_2Cl_2$.

**Yield and purity determination of PEG-supported compounds**: The yields of the PEG-supported compounds were determined by weight with the assumption that $M_W$ is 5000 Da for the PEG fragment. The $M_W$ actually ranged from 4500 to 5500. The indicated yields were for pure compounds. The purity of these compounds was determined by $^1$H NMR analysis in $CDCl_3$ at 300 MHz with pre-saturation of the methylene signals of the polymer at $\delta = 3.63$. In recording the NMR spectra, a relaxation delay of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of integration. The relaxation delay was selected after $T_1$

measurements. The integrations of the signals of the PEG $CH_3OCH_2$ fragment at $\delta = 3.30$ and 3.36 were used as internal standards. The estimated integration error was ±5%.

**Synthesis of alcohol 2 and amine 3**

*Alcohol* ***2***: $Cs_2CO_3$ (3.3 mol equiv) and 3-(4-hydroxyphenyl)-1-propanol (3.0 mol equiv) were added to a solution of **1**[2, 4] (0.05 M, 10–50 g, previously dried at 100 °C under vacuum) in DMF. The mixture was stirred for 18 h at RT and concentrated under vacuum to half of the original volume. Purification by precipitation in $Et_2O$ gave PEG **2** in 96% yield. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.07$ (A part of AB system, $^3J(H,H) = 8.5$ Hz, 2H; H *meta* to O in aromatic ring), 6.82 (B part of AB system, $^3J(H,H) = 8.5$ Hz, 2H; H *ortho* to O in aromatic ring), 4.10 (t, $^3J(H,H) = 5.0$ Hz, 2H; $PEGCH_2CH_2OAr$), 2.67 (t, $^3J(H,H) = 7.4$ Hz, 2H; $ArCH_2$), 1.83 (m, 2H; $CH_2$–$CH_2$–$CH_2$). Compound **2** was converted into its mesylate by reaction with mesyl chloride (3.0 mol equiv) and trioctylamine (3.3 mol equiv) in $CH_2Cl_2$ as described in reference [10b]. The $MeSO_2$ signal resonated at $\delta = 3.07$.

*Amine* ***3***: $Cs_2CO_3$ (5.5 mol equiv) and 4-aminophenol (5.0 mol equiv) were added to a solution of the mesylate of **2** (0.05 M) in DMF. The mixture was stirred for 18 h at RT and concentrated under vacuum to half of the original volume. Purification by precipitation in $Et_2O$ gave PEG **3** in 95% overall yield from **2**. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.07$ (A part of AB system, $^3J(H,H) = 8.5$ Hz, 2H; H *meta* to O in O–*Ar*–$CH_2$), 6.80 (B part of AB system, $^3J(H,H) = 8.5$ Hz, 2H; H *ortho* to O in O–*Ar*–$CH_2$), 6.76 (A part of AB system, $^3J(H,H) = 9.0$ Hz, 2H; H *ortho* to O in O–*Ar*–N), 6.60 (A part of AB system, $^3J(H,H) = 9.0$ Hz, 2H; H *meta* to O in O–*Ar*–N), 4.07 (t, $^3J(H,H) = 5.2$ Hz, 2H; $PEGCH_2CH_2OAr$), 2.67 (t, $^3J(H,H) = 7.4$ Hz, 2H; $ArCH_2$), 2.60 (br s, 2H; $NH_2$), 2.03 (m, 2H; $CH_2$–$CH_2$–$CH_2$).

**Synthesis of imines 4–8 and 28**: These compounds were obtained by different methods (A–D); yields have been reported in the text and in Table 1; $^1$H NMR data in Table 3.

*Method A* (*compounds* ***4–7***): The aldehyde (2 mol equiv) was added to the polymer-supported amine (1–10 g) kept at 90 °C, and the thick oily mixture was stirred for 1 h. The unreacted aldehyde and any water released were removed under vacuum. The cooled mixture was purified by precipitation in $Et_2O$, and the product was isolated by filtration.

*Method B* (*compound* ***4***): Benzaldehyde (4 mol equiv) was added to a solution of the polymer-supported amine (0.05 M, 1–10 g) in $CH_2Cl_2$, followed by anhydrous $MgSO_4$ (1 mol equiv). The resulting mixture was stirred for 18 h at RT. $MgSO_4$ was filtered off, and half of the solvent was removed under vacuum. The product was isolated by the usual procedure.

*Method C* (*compounds* ***6***, ***7***, *and* ***28***): The aldehyde (3 mol equiv) was added to a solution of the polymer-supported amine (0.05 M, 1–10 g) in a 2:1 mixture of $CH_2Cl_2$ and $(MeO)_3CH$ stirred at RT. The resulting mixture was stirred for 18 h at RT (or at 45 °C in the case of **28**). After evaporation of most of the solvent removed under vacuum, the product was isolated by the usual procedure.

*Method D* (*compound 8*): The commercially available solution (50%, *w*/*w*) of ethylglyoxalate in toluene (3 mol equiv) was added to a refluxing solution of the polymer-supported amine (0.05 M, 1–5 g) in toluene, followed by anhydrous $MgSO_4$ (1 mol equiv). The resulting mixture was stirred for 18 h at 100 °C, and the solvent was evaporated under vacuum. $CH_2Cl_2$ was added to the residue, and $MgSO_4$ was filtered off. The product was isolated by the usual procedure.

**General procedures for the synthesis of β-lactams**: These compounds were obtained as described below; yields have been reported in the text and in Table 2; $^1$H NMR data in Table 4.

*Enolate/imine condensation*: The appropriate titanium enolate, generated as described in reference [10b] (see text for the employed enolate/imine ratios), was added to a solution of the polymer-supported imine (0.05 M, 1–5 g) in $CH_2Cl_2$ (cooled at −78 °C) by means of a cannula. The mixture was stirred at −78 °C for 1 to 2 h and then allowed to warm up to RT. After stirring overnight at RT, a small amount of a saturated aqueous solution of $NaHCO_3$ (0.5–2 mL) was added, and the resulting mixture was filtered through a Celite cake. The filter was washed several times with $CH_2Cl_2$, and the filtrate was dried over $MgSO_4$. This was filtered off, and the filtrate was concentrated under vacuum to one third of its original volume. The product was isolated by the usual purification procedure.

*Ketene/imine cycloaddition*: Phenoxyacetylchloride (20 mol equiv) and trioctylamine (22 mol equiv) were added to a solution of the polymer-supported imine (0.05 M, 1–5 g) in $CH_2Cl_2$ (or in toluene), and the mixture was stirred at RT (or under reflux) for 18 h. The solvent was then evaporated to one third of its original volume. The product was isolated by the usual purification procedure.

**General procedure for the removal of the β-lactams from the polymer**: A solution of CAN (4 mol equiv) in water (final MeCN/water ratio 4:1) was added to a solution of the supported β-lactam (0.03 M, 0.1–1 g) in MeCN that had been cooled to −30 °C, and the mixture was stirred for 1 to 2 h at −20/−30 °C. Saturated aqueous solutions of $NaHSO_3$ and $NaHCO_3$ were then added in this order (2–10 mL each), and the mixture was warmed up to RT and then filtered through a Celite cake. The residue was washed several times with $CH_2Cl_2$, and the filtrate was transferred into a separating funnel. The organic phase was separated, dried, and concentrated under vacuum. The residue was poured into $Et_2O$ to separate the polymeric materials, which were removed by filtration. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography with a 50:50 hexanes/$Et_2O$ mixture as eluant. β-lactams **19**,[19] **20**,[20] **21**,[20] **22**,[21] and **27**[16a] were known compounds.

**3-{1-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl}-4-phenylazetidin-2-one (26)**: This compound was obtained as a 90:10 3,3′-*anti*-3,4-*trans*:3,3′-*syn*-3,4-*trans* mixture of isomers. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.30$–$7.45$ (m, 5H; $C_6H_5$), 6.02 (br s, 1H; NH), 4.80 (d, $^3J(H,H) = 2.1$ Hz, 0.9H; H-C4 *anti* isomer), 4.67 (d, $^3J(H,H) = 2.0$ Hz, 0.1H; H-C4 *syn* isomer), 4.25–4.33 (m, 1H; H-C3′), 3.12 (dd, $^3J(H,H) = 6.0$, 2.0 Hz, 0.1H; H-C3 *syn* isomer), 3.02 (dd, $^3J(H,H) = 6.0$, 2.1 Hz, 0.9H; H-C3 *trans* isomer), 1.31 (d, $^3J(H,H) = 6.5$ Hz, 0.3H; $CH_3$–CH *syn* isomer), 1.27 (d, $^3J(H,H) = 6.5$ Hz, 2.7H; $CH_3$–CH *anti* isomer), 0.93 (s, 9H; $C(CH_3)_3$), 0.15 and 0.13 (2s, 5.4H; $(CH_3)_2Si$ *anti* isomer), 0.09 and 0.07 (2s, 0.6H; $(CH_3)_2Si$ *syn* isomer); $^{13}$C NMR data of the *anti* isomer (75 MHz, $CDCl_3$, 25 °C): $\delta = 168.0$, 140.8, 128.7, 127.9, 125.9, 68.7, 65.3, 52.8, 25.8, 22.6, 18.0, −5.0. This compound was also obtained as a 91:9 mixture of the same two isomers by deprotection with CAN of the corresponding *N*-PMP substituted β-lactam, which was obtained as described.[16a] This mixture had $[\alpha]_D^{23} = -30.0$ ($c = 0.3$ in $CH_2Cl_2$); m.p. 137–139 °C; IR: $\tilde{\nu} = 3295$ (N–H), 1757 $cm^{-1}$ (C=O);

Table 3. $^1$H NMR data for imines **4–8** and **28**.

| Imine[a] | A[b] | B[c] | *HC*=N | R |
|---|---|---|---|---|
| **4** | 7.13 | 6.82 | 8.47 (s) | 7.43–7.90 (m, 5H) |
| **5** | 7.20 | 6.88 | 8.57 (s) | 7.12 (d, $J = 8.5$ Hz, 1H; H-5), 7.40–7.50 (m, 2H) |
| **6** | 7.17 | 6.88 | 8.27 (d, $J = 2.0$ Hz) | 7.00–7.08 (m, 2H; CH=CH), 7.33–7.80 (m, 5H) |
| **7**[d] | 7.10 | 6.80 | 7.50 (d, $J = 5.2$ Hz) | 1.30–1.90 (m, 11H; $C_6H_{11}$) |
| **8** | 7.08 | 6.85 | 7.93 (s) | 4.36 (q, $J = 7.0$ Hz, 2H), 1.35 (t, 3H) |
| **28** | 7.08 | 6.84 | 7.83 (d, $J = 6.0$ Hz) | 4.75 (q, $J = 6.0$ Hz, 1H; CH–O), 4.25 (dd, $J = 7.0$, 6.0 Hz, 1H; one H of $CH_2O$), 3.97 (dd, 1H; one H of $CH_2O$), 1.50–2.00 (m, 10H; $C_6H_{10}$) |

[a] For all of these compounds the following protons resonate at constant values: $\delta = 7.08$ (A part of AB system, $J = 8.0$–$9.0$ Hz, 2H; H *meta* to O in PEG–O–*Ar*), 6.83 (B part of AB system, $J = 8.0$–$9.0$ Hz, 2H; H *ortho* to O in PEG–O–*Ar*), 4.08 (t, $J = 5.2$–$5.5$ Hz, 2H; $PEGCH_2CH_2$–OAr), 2.70 (t, $J = 7.2$–$7.5$ Hz, 2H; Ar–$CH_2$), 2.05 (m, 2H; $CH_2$–$CH_2$–$CH_2$). [b] A part of the AB system, $^3J(H,H) = 7.5$–$8.0$ Hz, 2H; H *ortho* to N in Ar–N. [c] A part of the AB system, $^3J(H,H) = 7.5$–$8.0$ Hz, 2H; H *meta* to N in Ar–N. [d] Another imine isomer was detected with different signals at 7.00 (A) and 7.70 (CH=N, $J = 2.5$ Hz); isomer ratio = 70:30



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Table 4. $^1$H NMR data of β-lactams **10–14**, **16–18**, and **24**.

| β-Lactam[a] | A[b] | B[c] | *H*C-4 | *H*C-3[d] | $J(H_3,H_4)$ | *R*C-3[e–g] | *R*C-4 |
|---|---|---|---|---|---|---|---|
| **10t** | 7.17 | 6.73 | 4.60(d) | 3.03 | 2.0 | 1.07 | 7.20–7.30 (m, 5H) |
| **10c** | 7.17 | 6.73 | 5.13 (d) | [h] | 4.5 | 0.82 | 7.20–7.30 (m, 5H) |
| **11t** | 7.23 | 6.80 | 4.87 (d) | 3.33 | 1.8 | 1.05 | 6.80 (m, 2H), 7.00 (d, $J$ = 3.5 Hz, 1H) |
| **11c** | 7.23 | 6.80 | 5.36 (d) | [h] | 5.0 | 0.80 | 6.80 (m, 2H), 7.00 (d, $J$ = 3.5 Hz, 1H) |
| **12t** | 7.17 | 6.88 | 4.27 (dd, $J$ = 8.0 Hz) | 2.84 | 2.2 | 1.07 | 6.30 (dd, $J$ = 15 Hz, 1H), 7.20–7.33 (m, 6H) |
| **12c** | 7.17 | 6.88 | 4.20 (dd, $J$ = 6.0 Hz) | [h] | 4.7 | 0.89 | 6.25 (dd, $J$ = 15 Hz, 1H), 7.20–7.33 (m, 6H) |
| **13c** | 7.19 | 6.85 | 3.93 (dd, $J$ = 9.0 Hz) | 3.17 | 5.0 | 1.20 | 1.67–2.33 (m, 11H) |
| **14t** | 7.24 | 6.84 | 4.15 (d) | 3.88 | 2.4 | 1.12 | 4.27 (m, 2H), 1.26 (t, $J$ = 7.0 Hz, 3H) |
| **14c** | 7.24 | 6.84 | 4.57 (d) | 3.20 | 6.0 | 1.10 | 4.27 (m, 2H), 1.26 (t, $J$ = 7.0 Hz, 3H) |
| **16t** | 7.13 | 6.77 | 5.09 (d) | 4.97 | 1.5 | – | 7.20–7.30 (m, 5H) |
| **16c** | 7.13 | 6.77 | 5.55 (d) | 5.33 | 4.8 | – | 7.20–7.30 (m, 5H) |
| **17c** | 7.01 | 6.87 | 5.58 (d) | 5.67 | 4.7 | – | 6.80–7.00 (m, 3H) |
| **18t** | 7.03 | 6.84 | 4.68 (dd, $J$ = 7.0 Hz) | 5.16 | 1.5 | – | 6.40 (dd, $J$ = 15 Hz, 1H), 7.00–7.40 (m, 6H) |
| **18c** | 7.03 | 6.84 | 5.00 (dd, $J$ = 8.0 Hz) | 5.49 | 4.8 | – | 6.34 (dd, $J$ = 15 Hz, 1H), 7.00–7.40 (m, 6H) |
| **24ta** | 7.17 | 6.71 | 5.03 (d) | 3.03 | 2.0 | – | 7.20–7.30 (m, 5H) |
| **24ts** | 7.17 | 6.71 | 4.83 (d) | 3.13 | 2.0 | – | 7.20–7.30 (m, 5H) |

[a] For all of these compounds the following protons resonate at constant values: $\delta$ = 7.10 (A part of AB system, $J$ = 8.5–9.0 Hz, 2H; H *meta* to O in PEG–O–*Ar*), 6.83 (B part of AB system, $J$ = 8.5–9.0 Hz, 2H; H *ortho* to O in PEG–O–*Ar*), 4.10 (t, $J$ = 5.2–5.5 Hz, 2H; PEG$CH_2CH_2$–OAr), 2.73 (t, $J$ = 7.2–7.5 Hz, 2H; Ar–$CH_2$), 2.03 (m, 2H; $CH_2$–$CH_2$–$CH_2$). [b] A part of the AB system, $J$ = 8.0–9.0 Hz, 2H; H *ortho* to N in Ar–N. [c] A part of AB system, $J$ = 8.0–9.0 Hz, 2H; H *meta* to N in Ar–N. [d] In **10–14** this proton gives a doublet of triplets, $J$ = 6.5 Hz; in **16–18** gives a doublet. In **24** gives a doublet of doublets ($J$ = 3.0 Hz). [e] In **10–14** the $CH_2$ group gives a multiplet at 1.70–2.00, the $CH_3$ group gives a triplet, $^3J$(H,H) = 7.0 Hz. [f] In **16–18** these protons resonate at 6.90–7.01. [g] In **24** HC-3′ gives a multiplet at 4.26–4.36; $CH_3$-C3′ gives a doublet, $J$ = 6.3 Hz, at 1.24 (ta) and 1.33 (ts); the *t*BuSi signal is a singlet at 0.77; the $(CH_3)_2$Si signals are singlets at 0.06 and 0.03. [h] Undetected.

$C_{17}H_{27}NO_2Si$ (305.5): calcd C 66.84, H 8.91, N 4.58; found C 66.63, H 8.83, N 4.51.

**3-Ethyl-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one (30)**: A thick oil was obtained as a 50:50 3,4-*trans*-4,4′-*syn*:3,4-*cis*-4,4′-*syn* mixture of isomers. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 6.20 (br s, 1H; NH), 4.06–4.21 (m, 2H; CHO, one H of $CH_2O$), 3.63–3.68 (m, 1H; one H of $CH_2O$), 3.60 (dd, $^3J$(H,H) = 5.0, 8.5 Hz, 0.5H; HC-4 *cis* isomer), 3.33 (dd, $^3J$(H,H) = 2.3, 7.0 Hz, 0.5H; HC-4 *trans* isomer), 3.17 (dt, $^3J$(H,H) = 5.0, 7.0 Hz, 0.5H; HC-3 *cis* isomer), 2.83 (dt, $^3J$(H,H) = 2.3, 6.7 Hz, 0.5H; HC-3 *trans* isomer), 1.70–2.00 (m, 2H; $CH_2CH_3$), 1.20–1.65 (m, 10H; $C_6H_{10}$), 1.11 (t, $^3J$(H,H) = 7.3 Hz, 1.5H; $CH_3$ *cis* isomer), 1.05 (t, $^3J$(H,H) = 7.5 Hz, 1.5H; $CH_3$ *trans* isomer); $^{13}$C NMR data of the *cis* isomer (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 173.0, 111.0, 75.6, 66.2, 56.1, 53.8, 36.3, 34.6, 25.0, 23.9, 23.7, 18.4, 12.5; $^{13}$C NMR data of the *trans* isomer: $\delta$ = 172.0, 111.5, 77.2, 65.8, 54.7, 54.2, 36.3, 34.6, 25.0, 23.9, 23.7, 21.2, 11.4. This compound was also obtained as a 54:46 mixture of the same two isomers by deprotection with CAN of the corresponding *N*-PMP substituted β-lactam, which was obtained as described.[16a] A 60:40 *cis*:*trans* mixture of this compound had $[\alpha]_D^{23} = -22.8$ ($c$ = 0.6 in $CHCl_3$); IR: $\tilde{\nu}$ = 3293 (N–H), 1757 cm$^{-1}$ (C=O); $C_{13}H_{21}NO_3$ (239.3): calcd C 65.25, H 8.84, N 5.85; found C 65.36, H 8.91, N 5.78.

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