Development and application of allyl, 2-sulfonylethyl and 2-thioethyl carbamate linkers for solid phase *N*-acyliminium ion chemistry

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Received (in Cambridge, UK) 29th January 2001, Accepted 8th March 2001
First published as an Advance Article on the web 4th April 2001

We have evaluated the allyl, 2-sulfonylethyl (SEC) and 2-thioethyl (TEC) carbamate linker systems for their application in solid supported *N*-acyliminium ion chemistry. As model reactions the syntheses of both homoallylic amines (*via* a three component protocol starting from an immobilised primary carbamate) and 2-substituted pyrrolidines (*via* carbamate bound 4,4-diethoxy-2-phenylbutylamine) were conducted. The required precursor *p*-nitrophenyl carbonate resins were prepared in high yields from cheap starting materials. All linkers proved to be stable under the required cationic reaction conditions. A serious drawback of the allyl carbamate linker is the tedious work up procedure which is required for the removal of the remains of the cleavage cocktail. The SEC linker is excellently stable to both Lewis and protic acidic conditions combined with a moderate base stability thus allowing the use of amines as reactants or bases in subsequent reactions. Cleavage of SEC linker bound amines was easily effected by treatment of the resins with a cocktail of 1 M NaOMe in THF–MeOH (2 : 1). The widest synthetic scope was found with the TEC linker which combined a sufficient stability against the cationic conditions required for *N*-acyliminium ion chemistry with complete stability under basic conditions. Cleavage of TEC linker bound amines could be effected by treatment with strong acid or by oxidation of the sulfide to the sulfone (to give the SEC linker) followed by addition of the basic cleavage cocktail.

Introduction

The majority of currently marketed drugs contain nitrogen atoms. Synthetic methodology for functionalisation of nitrogen atoms, such as amide formation, reductive amination or simple alkylation, is very important and, as a result, many solid phase synthetic approaches focus on diversification *via* such functionalisations.[1] We are especially interested in functionalisation of the nitrogen atom *via* *N*-acyliminium ion chemistry,[2] which allows the introduction of C-nucleophiles such as silyl enol ethers and allylsilanes. The resulting CO or CC double bond, respectively, is then amenable to additional diversification. These reasons underline the importance of translating *N*-acyliminium ion chemistry to the solid phase in order to facilitate its application in automated synthesis. A straightforward solid phase approach would involve immobilising the precursor amines as carbamate linkages, so that the activating acyl group is part of the linker system. Liberation of the functionalised amines should be easily accomplished by cleavage of the carbamate linkers. In solution phase *N*-acyliminium ion reactions a range of carbamates have been successfully used for functionalisation but most of these carbamates have drawbacks that render them incompatible for application on the solid phase.

In two previous papers we described the first applications of *N*-acyliminium ion chemistry on a solid support.[3] The first article described a one-pot three component reaction[4] to prepare homoallylic amines *via* the corresponding cations in moderate yields from an immobilised primary carbamate, aromatic aldehydes and allylsilanes by using $BF_3{\cdot}OEt_2$ as the Lewis acid (route A, Scheme 1).

The unsatisfactory yields were mainly attributed to the limited stability of the *p*-alkoxybenzyl carbamate linker **2** towards $BF_3{\cdot}OEt_2$ leading to premature cleavage of the product. The second application involved the preparation of 2-substituted *N*-methylpyrrolidines **9** in high yields *via* the immobilised 4-amino acetals **6** (L = C_2H_4) (route B, Scheme 1). Subjection of **6** to $BF_3{\cdot}OEt_2$ led to the cyclic *N*-acyliminium ion **7** which provided the adduct **8**. The 2-substituted pyrrolidine products were reductively cleaved by $LiAlH_4$ treatment resulting in the methylated amine **9**. Unfortunately, all attempts to cleave the carbamate *via* hydrolytic means failed.

The aforementioned drawbacks of both the *p*-alkoxybenzyl (Wang) and ethyl carbamate linkers prompted us to search for alternative carbamate linker systems.[5]

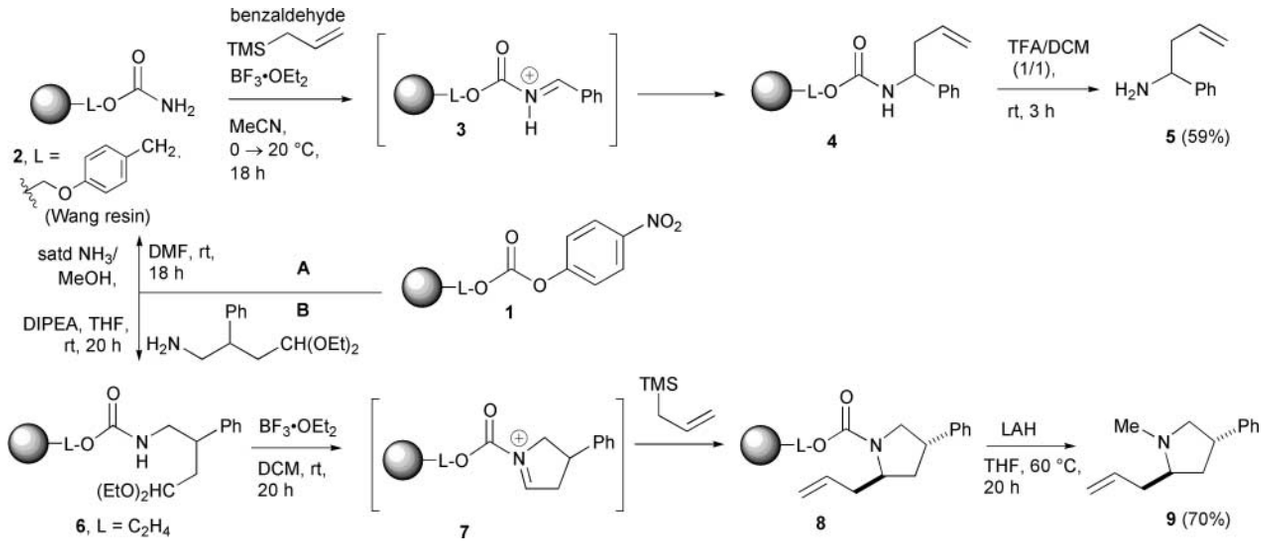
Due to their generally high stability under various conditions, carbamates which are based on the assisted cleavage principle particularly drew our attention.[6] In this paper, we describe the synthesis of the Pd(0) labile allyl carbamate **10**, the base labile 2-alkylsulfonylethyl carbamate (SEC) **11** and the SEC precursor 2-alkylthioethyl carbamate (TEC) **12** linkers and their application in solid supported *N*-acyliminium ion chemistry (Chart 1).

Results and discussion

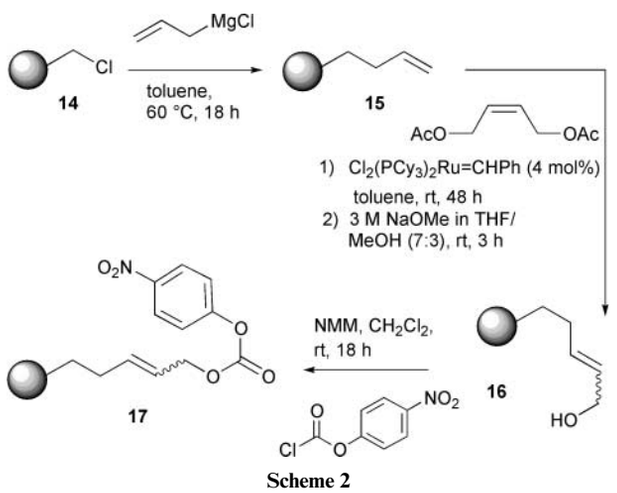
Synthesis of the *p*-nitrophenyl carbonate based carbamate precursor resins

Starting from Merrifield resin **14** the olefinic functionality was introduced using allylmagnesium chloride according to a litera-

 DOI: 10.1039/b100998m



Scheme 1



Scheme 2

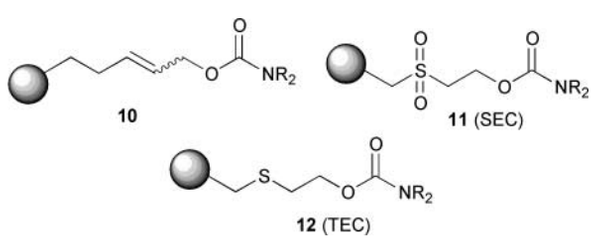
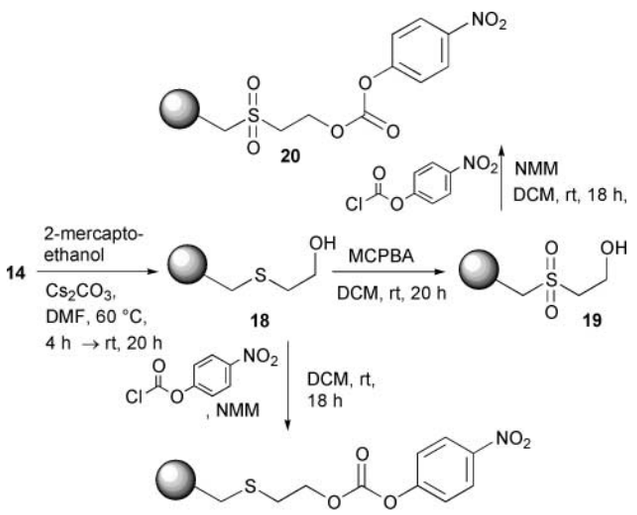


Chart 1



Scheme 3

ture procedure (Scheme 2).[7] The resulting olefin **15** was reacted with 1,4-diacetoxybut-2-ene *via* a ruthenium-catalysed cross-metathesis reaction,[8] followed by removal of the acetate protective group with NaOMe in THF–MeOH to provide the immobilised allylic alcohol **16**. Introduction of the carbonate functionality was effected using the previously described method by activation with *p*-nitrophenyl chloroformate to give resin **17** in an overall yield of 57%.[9]

The actual loading of resin **17** was 0.72 mmol g^{-1}, determined by elemental analysis of the nitrogen content on the resin.[10]

The synthesis of the SEC linker precursor started with the caesium carbonate-mediated coupling of 2-mercaptoethanol with the commercially available Merrifield resin **14** to furnish alcohol resin **18** (Scheme 3). Oxidation of the sulfide using an excess of MCPBA, followed by reaction with *p*-nitrophenyl chloroformate led to the mixed carbonate resin **20** (loading 91%).[11] The TEC linker was prepared by activation of the mercaptoethanol functionalised resin **18** with *p*-nitrophenyl chloroformate in a yield of 99%.[12]

Allyl carbamate linker

Because the Alloc protective group is both acid and base stable, and can be deprotected using mild and selective conditions, we decided to develop a similar allyl carbamate linker. Although several allyl ester linkers have been described[13] only one example of an allyl carbamate linker has been reported by Guibé and Undén, based on an amino acid spacer moiety and an allylic ether functionality (Chart 2).[14]

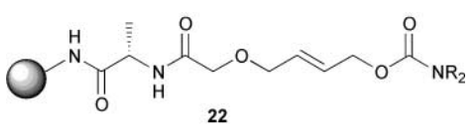
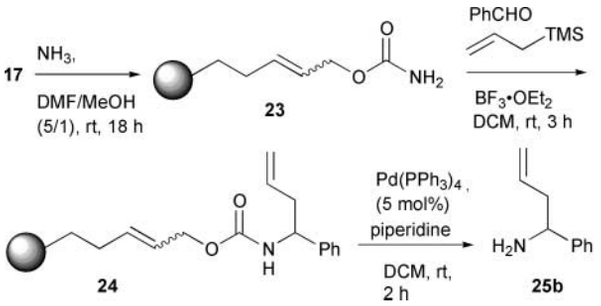


Chart 2

The incompatibility of the amino acid spacer with *N*-acyliminium ion chemistry led us to synthesise the all carbon-linker system **23**, which was prepared in quantitative yield by reaction of carbonate resin **17** with ammonia (Scheme 4). The usefulness of the primary allyl carbamate **23** for *N*-acyliminium ion chemistry was evaluated using the three-component *N*-acyliminium ion reaction. Carbamate **23** was reacted with benzaldehyde (20 equiv.), allyltrimethylsilane (10 equiv.) and BF_3·OEt_2 (1.1 equiv.) in MeCN, to provide the immobilised homoallylic carbamate **24**. Indeed, the Alloc linker was stable under the Lewis acidic reaction conditions and no premature



Scheme 4

cleavage of the product was observed during the *N*-acyliminium ion reaction.

The product was cleaved from the resin using palladium catalysis. Several nucleophiles (*i.e.* Et_3SiH, HCO_2H, dimedone (5,5-dimethylcyclohexane-1,3-dione), Bu_3SnH–AcOH and piperidine) were used to trap the immobilised π-allylpalladium species. By using Et_3SiH or HCO_2H no cleavage of the products was observed. Dimedone only gave partial removal of the immobilised amines, which was also found with similar solution phase experiments (data not shown). Although Bu_3SnH–AcOH efficiently effected the cleavage reaction, removal of the remains of this cocktail from the highly polar product could not be realized. The optimal cleavage conditions were 5 mol% $Pd(PPh_3)_4$ and 7 equiv. of piperidine as the nucleophile in DCM for 30 min at room temperature. IR analysis of the resin after cleavage and model studies in the solution phase showed that by using these conditions the homoallylic amine **25b** was liberated quantitatively. Purification of the product by column chromatography or preparative RP-HPLC was not reproducible due to tedious removal of the remains of the cleavage cocktail (especially triphenylphosphine oxide). Although we could obtain the products in good yields (39–85%) and purities, we abandoned this linker system because of the laborious procedure, which cannot be used for automated parallel synthesis. This drawback forced us to search on for yet another linker system that is orthogonal with *N*-acyliminium ion chemistry.

2-Sulfonylethyl carbamate (SEC) linker

To overcome the purification problems with the previous linker systems, a tailor-made linker that would be stable towards Lewis acids and would allow for cleavage under basic conditions using an easily removable base was synthesised. This linker system was based on the 2-(methylsulfonyl)ethoxycarbonyl (Msc) group, developed by Tesser and coworkers in the seventies as a cheap and readily available Fmoc equivalent.[16]

The scope of the SEC carbamate linker was determined by the synthesis of both 1-arylhomoallylamines and 2-substituted pyrrolidines using the same reactions as with the previously applied *p*-alkoxybenzyl (Wang) and ethyl carbamate linkers as depicted in Scheme 1.

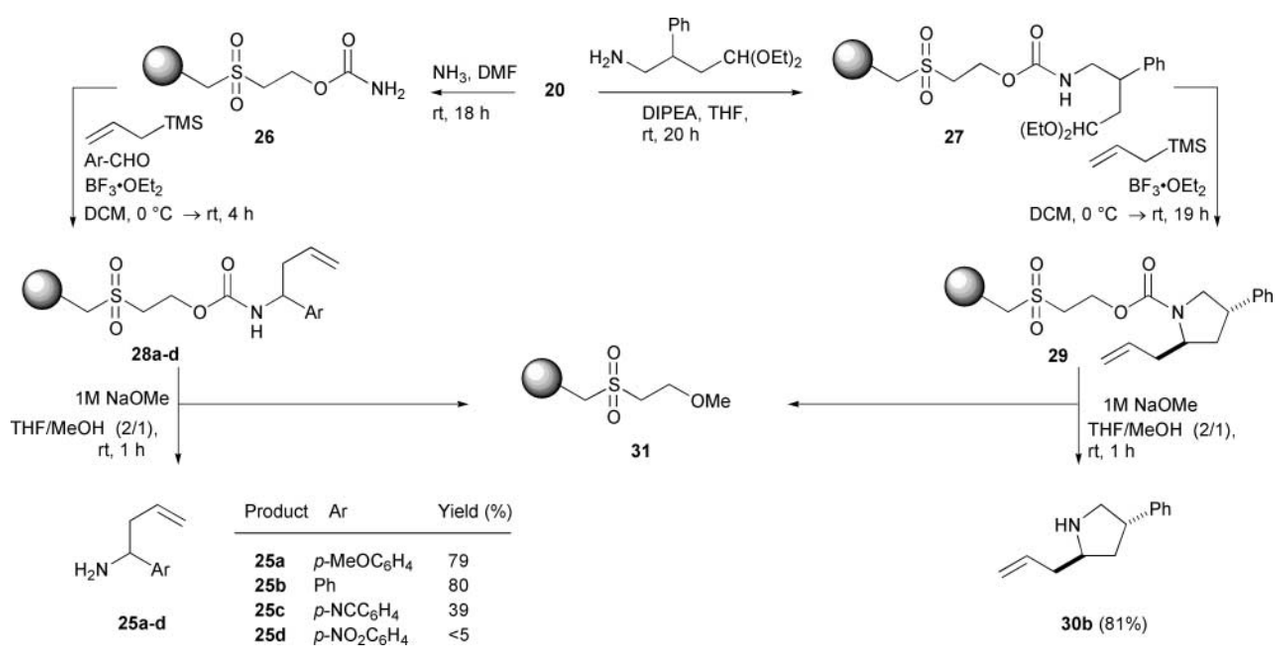
The precursor resins **26** and **27** were prepared by treatment of *p*-nitrophenyl carbonate resin **20** with ammonia or 4,4-diethoxy-2-phenylbutylamine.

Resin **26** was subjected to the three component reaction conditions with several aromatic aldehydes[15] and $BF_3{\cdot}OEt_2$, to give the corresponding transient *N*-acyliminium ions which were then trapped by allyltrimethylsilane. Cleavage was effected by stirring in a solution of 1 M NaOMe in THF–MeOH for one hour.[17] A simple partitioning between water and ethyl acetate, followed by filtration over a solid phase extraction (SPE) column gave the 1-arylhomoallylamines **25a**–**c** in yields of 79%, 80% and 39%, respectively, which was generally 20% higher than when the Wang resin was used. Only trace amounts of 1-(4-nitrophenyl)homoallylamine **25d** were isolated, most probably due to the low rate of formation of the intermediate *N*-acyliminium ion.

Using the SEC linker system, starting from resin **27** a number of 2-functionalised pyrrolidines were also synthesised.[3b] A representative example is shown in Scheme 5. Subjection of the immobilised amine **27** to the cyclisation–coupling conditions provided the immobilised pyrrolidine **29**, which was cleaved quantitatively by using 1 M NaOMe in a mixture of THF–MeOH. After workup, pyrrolidine **30b** was isolated in a yield of 81% (Scheme 5).

2-Thioethyl carbamate (TEC) linker

The anticipated orthogonal chemical behavior of the SEC linker in comparison with the TEC linker under basic conditions prompted us to study the compatibility with *N*-acyliminium ion chemistry. A very attractive feature of the TEC linker system is its application as a safety-catch linker. After performing basic reaction steps, oxidation of the sulfide to the sulfone will generate the SEC linker to enable facile cleavage of the product by NaOMe treatment. In addition, in reactions prior to the cleavage, moderately acidic reagents may be used

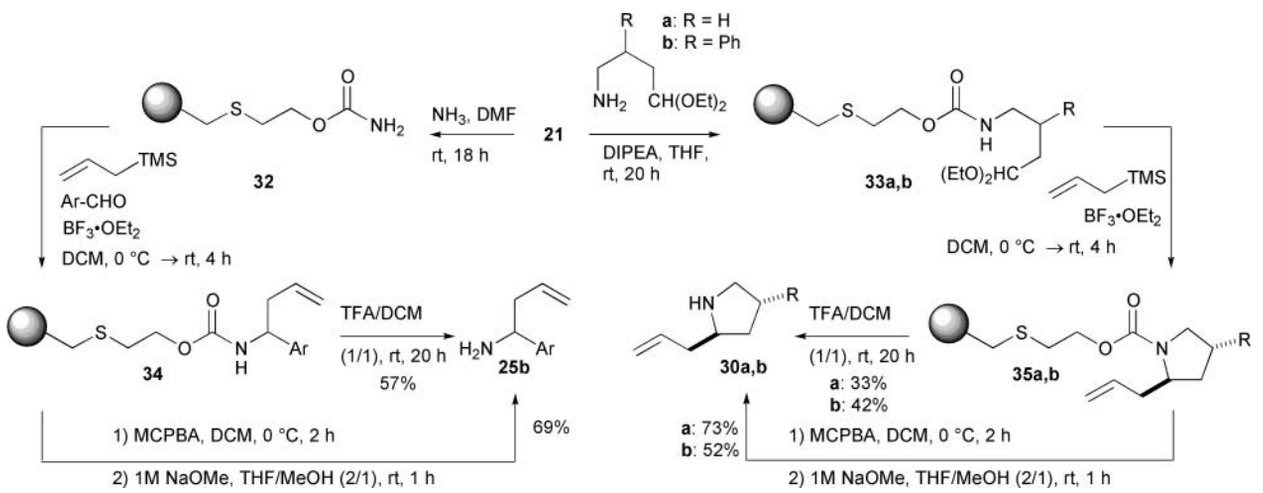


Product	Ar	Yield (%)
25a	*p*-$MeOC_6H_4$	79
25b	Ph	80
25c	*p*-NCC_6H_4	39
25d	*p*-$NO_2C_6H_4$	<5

Scheme 5

Table 1 Stability of the SEC and TEC linkers toward various acidic and basic conditions

Entry	Solvent	Reagent	Equiv.	Yield **25b** (%) from **28b**	Yield **25b** (%) from **34**	Yield **30b** (%) from **29**	Yield **30b** (%) from **35b**
1	DCM	$SnCl_4$	5	0	0	0	0
2	DCM	TFA (50%)	—	0	57	0	42
3	DCM	TfOH	5	0	53	0	39
4	DCM	TsOH	5	0	0	0	0
5	DCM	DIPEA	5	0	0	0	0
6	DCM	DMAP	5	0	0	0	0
7	DCM	Piperidine (20%)	—	<5	0	<5	0
8	DCM	DBU	5	57	0	67	0
9	THF	NaOMe (0.1 M)	—	47	0	71	0



Scheme 6

making the TEC linker even more versatile than the SEC linker as is demonstrated in Scheme 6.

Again, both approaches *via* acyclic and cyclic *N*-acyliminium ions have been evaluated. Reaction of **21** with ammonia, 4,4-diethoxybutylamine or 4,4-diethoxy-2-phenylbutylamine gave the *N*-acyliminium ion precursors **32** and **33a,b**, respectively.

Following the same procedures as with the SEC linker system, treatment with $BF_3{\cdot}OEt_2$ gave the transient *N*-acyliminium ions which were trapped with allylsilane to afford resins **34** and **35a,b**. Cleavage could now be effected *via* two different procedures. Firstly, treatment with TFA–DCM (1 : 1, v/v) directly liberated the amines **25b** or **30a,b** in yields of 57%, 33% and 42%, respectively. Alternatively, oxidation of resins **34** and **35a,b** with 2.2 equivalents of MCPBA in DCM gave the corresponding sulfone resin.[18] Subsequent cleavage under standard conditions provided the products **25b** and **30a,b** in somewhat lower (compared to starting from sulfone resin **20**), but still good overall yields of 69%, 73% and 52%, respectively (4 steps).

Stability of the SEC and TEC linkers towards Lewis and protic acidic and basic conditions

From the previous results, it was clear that the SEC and TEC linker systems were compatible with $BF_3{\cdot}OEt_2$, *N*,*N*-diisopropylethylamine (DIPEA) and *N*-methylmorpholine (NMM). To further test the stability of these linker systems the resin-bound products **28b**, **29** were subjected to a number of acids and bases in different solvents. After stirring for 24 hours at room temperature the filtrate was collected and checked (by TLC) for the presence of products. If present, the product was isolated to allow determination of the yield. The results are summarized in Table 1.

For the SEC linker it was found that the moderately strong Lewis acid $SnCl_4$ (entry 1) and strong protic acids TFA, TfOH and TsOH did not effect cleavage of the product. Stirring with DIPEA and the acylation catalyst DMAP (entries 5 and 6) did not cause any leaching of the product either. Even prolonged stirring with 20% of piperidine in DCM—conditions that one commonly uses for the cleavage of Fmoc-groups operating *via* a similar β-elimination mechanism—resulted in the formation of only trace amounts of products (entry 7). These observations clearly show the versatility of the SEC linker and set the scene for the use of carbamates as building blocks for the introduction of diversity *via* combinatorial chemistry. With a stronger base like DBU extensive cleavage of the products from the resin occurred (entry 8). Use of a tenfold lower concentration of NaOMe in THF–MeOH still resulted in extensive cleavage of the product (entry 9).

In conclusion, the SEC and TEC carbamate linker systems proved to be well suited for *N*-acyliminium ion chemistry. The SEC linker is completely stable to both Lewis and protic acidic conditions combined with moderate base stability. The widest synthetic scope was found with the TEC linker which combined a sufficient stability against the cationic conditions required for *N*-acyliminium ion chemistry with complete stability under basic conditions. Cleavage of TEC linker bound amines could be effected by oxidation of the sulfide to the sulfone (to give the SEC linker) followed by addition of the basic cleavage cocktail or by treatment with strong acid, albeit in lower yields.

Experimental

General

Reagents were purchased at highest commercial quality and used without further purification unless stated otherwise. Fluka Merrifield resin (200–400 mesh, 1% divinylbenzene, 1.7 mmol Cl g^{-1}) was used. R_f values were obtained by using thin-layer chromatography on silica gel-coated plastic sheets (Merck silica

gel 60 F_{245}) using UV light as visualizing agent or $KMnO_4$ solution and heat as developing agents. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and ACROS silica gel (particle size 35–70 μm). Infrared spectra were recorded using a Bruker IFS 28 spectrophotometer and absorptions are reported in units of cm^{-1}. Infrared spectra of resins were measured in KBr using a DRIFT module. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker ARX 400 instrument (400 MHz). Spectra are reported in units of ppm on the δ scale relative to an internal standard of residual chloroform (7.27 ppm for ^{1}H-NMR and 77.0 for ^{13}C-NMR). Mass spectra and accurate mass determination data are reported as *m*/*z* (relative intensity). Measurements were performed on a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a. d. Ruhr, Germany. The solid phase reactions were either gently stirred with a magnetic stirring bar or agitated by rotation of the reaction vessel under an angle of 45° at a rotary evaporator engine. The resins were washed according to the indicated sequence. The resin was allowed to swell/shrink for 1 minute before each filtration.

Resin 16

Resin **15**[7] (0.50 g, 0.84 mmol) was suspended in degassed toluene (5.0 ml), 1,4-diacetoxybut-2-ene (578 mg, 3.36 mmol) and $Cl_2(PCy_3)_2Ru$=CHPh (28 mg, 0.03 mmol) were added and the reaction mixture was stirred for 48 h under nitrogen atmosphere at rt. The suspension was filtered and the resin was washed with toluene (10 ml), CH_2Cl_2 (5 ml) and EtOH (5 ml, the last two steps were repeated four times) and Et_2O (2 × 5 ml). After drying *in vacuo* (50 °C), the immobilised acetate (0.53 g, 0.80 mmol, ν_{max}/cm^{-1} 1738) was suspended in THF (5 ml) and NaOMe (0.05 ml, 0.16 mmol of a 3 M solution in MeOH) was added. After stirring for 2 h at rt, the reaction mixture was filtered off, washed with THF (5 ml), CH_2Cl_2 (5 ml) and EtOH (5 ml, the last two steps were repeated four times) and Et_2O (2 × 5 ml). After drying *in vacuo* (50 °C) 0.43 g of resin **16** was obtained: ν_{max}/cm^{-1} 3573, 3432.

Resin 17

Immobilised alcohol **16** (1.50 g, 2.39 mmol) was suspended in 15 ml CH_2Cl_2 and cooled to 0 °C, 4-nitrophenyl chloroformate (1.45 g, 7.17 mmol) and *N*-methylmorpholine (791 μl, 7.17 mmol) were added, the reaction mixture was allowed to warm up to rt and was stirred for 18 h. The suspension was filtered, the resin was washed with CH_2Cl_2, EtOH (15 ml, the last two steps were repeated four times) and Et_2O (2 × 15 ml). After drying *in vacuo* (50 °C) 1.56 g of resin **17** were obtained: ν_{max}/cm^{-1} 1766, 1525, 1346; Elemental anal. Found: N 1.01% (0.72 mmol g^{-1} N, 57% from Merrifield resin).

Resin 18

A mixture of Merrifield resin **14** (25 g, 42.5 mmol), 2-mercaptoethanol (25 ml, 359 mmol) and Cs_2CO_3 (27.7 g, 85 mmol) in dry DMF (200 ml) was agitated for 4 h at 60 °C and then for 20 h at rt. The reaction mixture was filtered, washed with DMF, H_2O (200 ml, the last two steps were repeated two times), CH_2Cl_2, MeOH–H_2O (1 : 1, 200 ml, repeated two times), CH_2Cl_2, MeOH (200 ml, the last two steps were repeated two times), CH_2Cl_2 (200 ml) and dried in a vacuum oven (50 °C) to afford 26.1 g of white resin **18**: ν_{max}/cm^{-1} 3397.

Resin 19

To a suspension of resin **18** (10.1 g, 16.1 mmol) in CH_2Cl_2 (200 ml), MCPBA (85%, 20.3 g, 100 mmol) was added in portions at 0 °C. When addition was complete the mixture was agitated for 20 h at rt. Then the reaction mixture was filtered, washed with CH_2Cl_2, MeOH (100 ml, repeated three times), CH_2Cl_2 (100 ml) and dried in a vacuum oven (50 °C) to afford 10.8 g of white resin **19**: ν_{max}/cm^{-1} 3442, 1280, 1107.

Resin 20

To a suspension of resin **19** (10.6 g, 16 mmol) in CH_2Cl_2 (200 ml), *N*-methylmorpholine (4.4 ml, 40 mmol) and 4-nitrophenyl chloroformate (8.06 g, 40 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to room temperature and agitated for 18 h. Then the reaction mixture was filtered, washed with CH_2Cl_2, MeOH (100 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (100 ml, the last two steps were repeated two times), CH_2Cl_2 (100 ml) and dried in a vacuum oven (50 °C) to afford 13.4 g of resin **20**: ν_{max}/cm^{-1} 1765, 1524, 1346, 1320, 1110; Elemental anal. Found: N 1.55% (1.11 mmol g^{-1} N, 91% from Merrifield resin).

Resin 21

According to the same procedure as described for **20**, resin **18** (1.01 g, 1.61 mmol) was reacted with *N*-methylmorpholine (0.35 ml, 3.32 mmol) and 4-nitrophenyl chloroformate (649 mg, 3.32 mmol) to afford 1.29 g of resin **21**: ν_{max}/cm^{-1} 1767, 1526, 1347; Elemental anal. Found: N 1.75% (1.25 mmol g^{-1} N, 99% from Merrifield resin).

Resin 23

Resin **17** (0.42 g, 0.30 mmol) was suspended in DMF (4 ml) and a saturated NH_3–MeOH solution (1 ml) was added. After stirring for 18 h at rt, the resin was filtered off, washed with DMF (5 ml), CH_2Cl_2 (5 ml), EtOH (5 ml, the last two steps were repeated four times) and Et_2O (2 × 5 ml). After drying *in vacuo* (50 °C) 0.40 g of resin **23** was obtained in quantitative yield: ν_{max}/cm^{-1} 3498, 3403, 1731; Elemental anal. Found: N 1.05% (0.75 mmol g^{-1} N).

1-Phenylbut-3-enylamine, 25b (from 23)

Carbamate resin **23** (100 mg, 0.07 mmol) was suspended in CH_2Cl_2 (1 ml). Benzaldehyde (21 μl, 0.21 mmol), allyltrimethylsilane (34 μl, 0.21 mmol) and $BF_3{\cdot}OEt_2$ (13 μl, 0.11 mmol) were added. The reaction mixture was stirred under a nitrogen atmosphere for 3 h at rt, filtered off and washed with CH_2Cl_2 (2 ml), EtOH (2 ml, the last two steps were repeated four times) and Et_2O (2 × 2 ml). After drying *in vacuo* (50 °C) resin **24** was obtained: ν_{max}/cm^{-1} 3435, 1716 cm^{-1}. Resin **24** was then suspended in CH_2Cl_2 (1 ml), piperidine (48 μl, 0.49 mmol) and $Pd(PPh_3)_4$ (4 mg, 0.04 mmol) were added and the suspension was stirred under a nitrogen atmosphere for 2 h at rt. The reaction mixture was filtered, the resin was washed with CH_2Cl_2 (3 × 2 ml) and the collected filtrates were evaporated. The product was purified using flash chromatography (silica, 0⟶10% MeOH in CH_2Cl_2). Generally the product was still contaminated with the remains of the cleavage cocktail. Typical isolated yields of the pure product ranged from 39–85% (from resin **23**): R_f 0.20 (CH_2Cl_2–MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, Ar-H), 5.81–5.70 (1H, m, CH_2=C*H*CH_2), 5.15–5.07 (2H, m, CH_2=CHCH_2), 3.99 (1H, dd, J = 8.0, 5.4 Hz, NH_2C*H*), 2.51–2.33 (2H, m, CH_2=CHCH_2), 1.66 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6 (Ar-H), 133.6 (CH_2=*C*HCH_2), 128.6, 127.4, 126.6 (Ar-C), 118.6 (*C*H_2=CHCH_2), 55.4 (NH_2*C*H), 41.7 (CH_2=CH*C*H_2); ν_{max}/cm^{-1} 3385, 1642; *m*/*z* (EI) 147.1037 (M^+. $C_{10}H_{13}N$ requires 147.1048), 147 (M^+, 0.3%), 106 (100), 79 (72), 77 (40), 29 (95), 17 (26).

Resin 26

Resin **20** (6.10 g, 7.32 mmol) was suspended in DMF (50 ml) and a saturated NH_3–MeOH solution (10 ml) was added. After

stirring for 18 h at rt, the resin was filtered off, washed with DMF (50 ml), CH_2Cl_2 (50 ml), EtOH (50 ml, the last two steps were repeated four times) and Et_2O (2 × 50 ml). After drying *in vacuo* (50 °C) 5.52 g of resin **26** were obtained: ν_{max}/cm^{-1} 3474, 3327, 1727, 1343, 1121; Elemental anal. Found: N 1.37% (1.31 mmol g^{-1} N, 92% from Merrifield resin).

1-(4-Methoxyphenyl)but-3-enylamine, 25a

Carbamate resin **26** (150 mg, 0.17 mmol) was suspended in CH_2Cl_2 (1.5 ml). *p*-Anisaldehyde (62 µl, 0.51 mmol), allyltrimethylsilane (82 µl, 0.51 mmol) and $BF_3{\cdot}OEt_2$ (32 µl, 0.26 mmol) were added. The reaction mixture was stirred under a nitrogen atmosphere for 3 h at rt, filtered off and washed with CH_2Cl_2 (2 ml), EtOH (2 ml, the last two steps were repeated four times) and Et_2O (2 × 2 ml). After drying *in vacuo* (50 °C) resin **28a** was obtained: ν_{max}/cm^{-1} 3634, 3491, 1724. Resin **28a** was then suspended in THF (1.5 ml), NaOMe (0.75 ml of a 3 M solution in MeOH) was added and the suspension was stirred for 1 h at rt. The reaction mixture was filtered, the resin was washed with CH_2Cl_2 (3 × 2 ml) and the collected filtrates were washed with H_2O (2 ml), neutralized with conc. HCl and extracted with EtOAc (5 × 1 ml). The collected organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified using SPE chromatography (Isolute, silica, solvent system: 0⟶10% MeOH in CH_2Cl_2) to give compound **25a** (24 mg, 79%) as a colorless oil: R_f 0.13 (CH_2Cl_2–MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.7 Hz, Ar-H), 6.85 (2H, d, J = 8.5 Hz, Ar-H), 5.71–5.60 (1H, m, CH_2=C*H*CH_2), 5.11–5.03 (2H, m, C*H*$_2$=CHCH_2), 4.61 (2H, br s, N*H*$_2$), 3.99 (1H, dd, J = 14.2, 6.8 Hz, NH_2CH), 3.78 (3H, s, O*CH*$_3$), 2.51 (2H, t, J = 7.0 Hz, CH_2=CHC*H*$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2 (Ar-C), 133.6 (CH_2=*C*HCH_2), 127.8, 127.6 (Ar-C), 118.6 (*C*H$_2$=CHCH_2), 114.0, 113.7 (Ar-C), 55.1 (O*C*H$_3$, NH_2CH), 42.8 (CH_2=CH*C*H$_2$); ν_{max}/cm^{-1} 3374, 1612; *m*/*z* (EI) 136.0757 (M$^+$ − C_3H_5. $C_{11}H_{15}NO$ requires 136.0762), 136 (66), 31 (82), 17 (100).

1-Phenylbut-3-enylamine, 25b

According to the same procedure as described for **25a**, resin **26** (150 mg, 0.17 mmol) was reacted with benzaldehyde (52 µl, 0.51 mmol), allyltrimethylsilane (82 µl, 0.51 mmol) and $BF_3{\cdot}OEt_2$ (32 µl, 0.26 mmol) to afford resin **28b**: ν_{max}/cm^{-1} 3655, 3360, 1724. After subsequent cleavage and purification using SPE chromatography compound **25b** (20 mg, 80%) was obtained as a colorless oil which was identical to the compound obtained from the allyl carbamate resin **23**.

4-(1-Aminobut-3-enyl)benzonitrile, 25c

According to the same procedure as described for **25a**, resin **26** (150 mg, 0.17 mmol) was reacted with 4-cyanobenzaldehyde (67 mg, 0.51 mmol), allyltrimethylsilane (82 µl, 0.51 mmol) and $BF_3{\cdot}OEt_2$ (32 µl, 0.26 mmol) to afford resin **28c**: ν_{max}/cm^{-1} 3637, 3501, 2229, 1723. After subsequent cleavage and purification using SPE chromatography compound **25c** (12 mg, 39%) was obtained as a colorless oil: R_f 0.24 (CH_2Cl_2–MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, J = 8.3 Hz, Ar-H), 7.46 (2H, d, J = 8.2 Hz, Ar-H), 5.76–5.65 (1H, m, CH_2=C*H*CH_2), 5.13–5.01 (2H, m, C*H*$_2$=CHCH_2), 4.07 (1H, dd, J = 7.6, 5.6 Hz, NH_2CH), 2.47–2.29 (2H, m, CH_2=CHC*H*$_2$), 1.60 (2H, br s, N*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (Ar-C), 132.2 (CH_2=*C*HCH_2), 127.6, 127.1 (Ar-C), 119.1, 118.5 (*C*N, *C*H$_2$=CHCH_2), 111.2 (Ar-C), 55.6 (NH_2CH), 42.1 (CH_2=CH*C*H$_2$); ν_{max}/cm^{-1} 3339, 2228, 1641; *m*/*z* (EI) 156.0821 (M$^+$ − NH_3. $C_{11}H_{10}N$ requires 156.0813), 156 (3%), 132 (24), 17 (100).

1-(4-Nitrophenyl)but-3-enylamine, 25d

According to the same procedure as described for **25a**, resin **26** (150 mg, 0.17 mmol) was reacted with 4-nitrobenzaldehyde (78 mg, 0.51 mmol), allyltrimethylsilane (82 µl, 0.51 mmol) and $BF_3{\cdot}OEt_2$ (32 µl, 0.26 mmol) to afford resin **28d**: ν_{max}/cm^{-1} 3625, 3505, 1726, 1523, 1352. After cleavage a trace of **25d** was obtained as a light yellow oil: R_f 0.17 (CH_2Cl_2–MeOH 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (2H, d, J = 8.8 Hz, Ar-H), 7.52 (2H, d, J = 8.7 Hz, Ar-H), 5.75–5.67 (1H, m, CH_2=C*H*CH_2), 5.30–5.06 (2H, m, C*H*$_2$=CHCH_2), 4.14 (1H, dd, J = 5.3, 7.8 Hz, NH_2CH), 2.48–2.32 (2H, m, CH_2=CHC*H*$_2$), 1.75 (2H, br s, N*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 146.2 (Ar-C), 134.0 (CH_2=*C*HCH$_2$), 127.2, 123.6 (Ar-C), 118.6 (*C*H$_2$=CHCH$_2$), 54.7 (NH_2CH), 43.6 (CH_2=CH*C*H$_2$); ν_{max}/cm^{-1} 3356, 1598, 1520, 1345; *m*/*z* (EI) 193.0974 (M$^+$ − NH_3. $C_{10}H_{13}N_2O_2$ requires 193.0977), 193 (19%), 176 (56), 154 (100), 136 (92).

Resin 27

To a suspension of resin **20** (485 mg, 582 µmol) in THF (10 ml), 4,4-diethoxy-2-phenylbutylamine (414 mg, 1.75 mmol) and DIPEA (0.31 ml, 1.78 mmol) were added and the mixture was agitated at room temperature for 24 h. Then the reaction mixture was filtered, washed with CH_2Cl_2, MeOH (5 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (5 ml, the last two steps were repeated two times), CH_2Cl_2 (5 ml) and dried in a vacuum oven (50 °C) to afford 542 mg of resin **27**: ν_{max}/cm^{-1} 3342 (br), 1724, 1324, 1118.

Resin 29

To a suspension of resin **27** (450 mg, 482 µmol) in CH_2Cl_2 (5 ml) allyltrimethylsilane (0.76 ml, 4.78 mmol) and $BF_3{\cdot}OEt_2$ (0.18 ml, 1.42 mmol) were added at 0 °C. After 1 h the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. Then the reaction mixture was filtered, washed with CH_2Cl_2, MeOH (5 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (5 ml, the last two steps were repeated two times), CH_2Cl_2 (5 ml) and dried in a vacuum oven (50 °C) to afford 535 mg of resin **29**: ν_{max}/cm^{-1} 1708, 1324, 1118.

2-Allyl-4-phenylpyrrolidine, 30b

To a suspension of resin **29** (229 mg, 218 µmol) in THF (2 ml) a 3 M solution of NaOMe in MeOH (1 ml, 3 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. Then the reaction mixture was filtered and washed with CH_2Cl_2, MeOH (3 ml, the last two steps were repeated two times) and CH_2Cl_2 (3 ml). The filtrate was concentrated, taken up in 1 M NaOH (10 ml) and extracted twice with Et_2O (10 ml). The combined ether layers were concentrated and the residue was further purified using an SPE-column (Isolute, silica, solvent system: CH_2Cl_2–MeOH 100 : 0⟶90 : 10⟶0 : 100), to give 33 mg of **30b** (81%) as a clear oil: R_f 0.14 (CH_2Cl_2–MeOH = 9 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18–7.32 (5H, m, Ph), 5.79–5.90 (1H, m, CH_2CH=C*H*$_2$), 5.14 (1H, dd, J = 1.6, 17.1 Hz, CH_2CH=C*H*$_2$), 5.09 (1H, dd, J = 1.6, 10.2 Hz, CH_2CH=C*H*$_2$), 3.44–3.51 (2H, m, NHC*H*$_2$CH + NHC*H*-$(CH_2)_2$), 3.29–3.38 (1H, m, NHC*H*$_2$CH), 2.93 (1H, dd, J = 9.1, 10.5 Hz, CH_2CH(Ph)C*H*$_2$), 2.92 (1H, br s, N*H*), 2.30–2.40 (2H, m, C*H*$_2$CH=CH$_2$), 1.93–2.08 (2H, m, CHC*H*$_2$CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.7 (Ph), 135.5 (CH_2CH=CH$_2$), 128.7 (Ph), 127.4 (Ph), 126.6 (Ph), 117.4 (CH_2CH=*C*H$_2$), 58.7 (NH*C*H$(CH_2)_2$), 54.9 (NH*C*H$_2$CH), 44.6 (CH_2CH(Ph)CH$_2$), 40.6 (CH*C*H$_2$CH), 39.3 (*C*H$_2$CH=CH$_2$); ν_{max}(film)/cm^{-1} 3311 (br), 1406, 914; *m*/*z* (FAB) 188.1439 (M$^+$ + H. $C_{13}H_{18}N$ requires 188.1439), 188 (M$^+$ + H, 31%), 154 (100), 137 (72), 136 (71).

Resin 33a

According to the same procedure as described for **27**, resin **21** (548 mg, 685 µmol) was reacted with 4,4-diethoxybutylamine

(0.24 ml, 1.37 mmol) and DIPEA (0.24 ml, 1.37 mmol) to afford 552 mg of resin **33a**: ν_{max}/cm^{-1} 3378 (br), 1729.

Resin 33b

According to the same procedure as described for **27**, resin **21** (516 mg, 645 μmol) was reacted with 4,4-diethoxy-2-phenylbutylamine (459 mg, 1.94 mmol) and DIPEA (0.34 ml, 1.95 mmol) to afford 575 mg of resin **33b**: ν_{max}/cm^{-1} 3329 (br), 1726.

Resin 35a

According to the same procedure as described for **29**, resin **33a** (199 mg, 242 μmol) was reacted with allyltrimethylsilane (0.38 ml, 2.42 mmol) and $BF_3{\cdot}OEt_2$ (92 μl, 0.73 mmol) to afford 185 mg of resin **35a**: ν_{max}/cm^{-1} 1700.

Resin 35b

According to the same procedure as described for **29**, resin **33b** (543 mg, 586 μmol) was reacted with allyltrimethylsilane (0.9 ml, 5.9 mmol) and $BF_3{\cdot}OEt_2$ (0.22 ml, 1.76 mmol) to afford 188 mg of resin **35b**: ν_{max}/cm^{-1} 1713.

Activation and basic cleavage of 35a. Resin **35a** (99 mg, 129 μmol) was suspended in 5 ml of CH_2Cl_2 and cooled to 0 °C. Then MCPBA (54 mg, 92%, 288 μmol) was added and the reaction mixture was stirred at 0 °C for 2 h, filtered, washed with CH_2Cl_2, MeOH (5 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (5 ml, the last two steps were repeated two times), CH_2Cl_2 (5 ml) and dried in a vacuum oven (50 °C) to give 103 mg of resin. To a suspension of this resin (90 mg, 113 μmol) in THF (2 ml) a 3 M solution of NaOMe in MeOH (1 ml, 3 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. Then the reaction mixture was filtered and washed with CH_2Cl_2, MeOH (3 ml, the last two steps were repeated two times) and CH_2Cl_2 (3 ml). The filtrate was concentrated, taken up in 1 M NaOH (10 ml) and extracted twice with Et_2O (10 ml). The combined ether layers were extracted twice with 1 M HCl (10 ml) and concentrated to give 12.2 mg of 2-allylpyrrolidine **30a** (73%) as the HCl salt: ^1H NMR (D_2O, 400 MHz) δ 5.86–5.96 (1H, m, $CH_2CH{=}CH_2$), 5.26–5.34 (2H, m, $CH_2CH{=}CH_2$), 3.68–3.74 (1H, m, $NHCH(CH_2)_2$), 3.31–3.43 (2H, m, $NHCH_2CH_2$), 2.58–2.65 (1H, m, $CH_2CH{=}CH_2$), 2.48–2.55 (1H, m, $CH_2CH{=}CH_2$), 2.24–2.30 (1H, m, $CHCH_2CH_2$), 2.03–2.16 (2H, m, $CH_2CH_2CH_2$), 1.72–1.82 (1H, m, $CHCH_2CH_2$); ^{13}C NMR (D_2O, 100.6 MHz) δ 137.7 ($CH_2CH{=}CH_2$), 121.9 ($CH_2CH{=}CH_2$), 62.8 ($NHCH(CH_2)_2$), 48.0 ($NHCH_2CH_2$), 38.6 ($CH_2CH{=}CH_2$), 32.1 ($CHCH_2CH_2$), 25.8 ($CH_2CH_2CH_2$); ν_{max}(KBr)/cm^{-1} 2746, 1642; *m/z* (FAB) 112.1112 ($M^+ + H$. $C_7H_{14}N$ requires 112.1126), 112 ($M^+ + H$, 100%), 107 (17), 89 (16), 77 (12), 70 (12).

Acidic cleavage of 35a. Resin **35a** (198 mg, 257 μmol) was suspended in 2 ml of TFA–CH_2Cl_2 (1:1, v/v) and stirred at room temperature for 20 h. Then the reaction mixture was filtered, washed with CH_2Cl_2, MeOH (5 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (5 ml, the last two steps were repeated two times), CH_2Cl_2 (5 ml) and dried in a vacuum oven (50 °C). The filtrate was concentrated to give 19.2 mg of **30a** (33%) as the TFA salt.

Activation and basic cleavage of 35b. Resin **35b** (96 mg, 129 μmol) was suspended in 5 ml of CH_2Cl_2 and cooled to 0 °C. Then MCPBA (54 mg, 92%, 288 μmol) was added and the reaction mixture was stirred at 0 °C for 2 h, filtered, washed with CH_2Cl_2, MeOH (5 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (5 ml, the last two steps were repeated two times), CH_2Cl_2 (5 ml) and dried in a vacuum oven (50 °C) to give 103 mg of resin **29**. To a suspension of this resin (92 mg, 105 μmol) in THF (1 ml) a 3 M solution of NaOMe in MeOH (0.5 ml, 1.5 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was worked up as usual to give 10.2 mg of **30b** (52%).

Acidic cleavage of 35b. Resin **35b** (110 mg, 130 μmol) was suspended in 3 ml of TFA–CH_2Cl_2 (1:1, v/v) and stirred at room temperature for 20 h. Then the reaction mixture was filtered, washed with CH_2Cl_2, MeOH (5 ml, the last two steps were repeated two times), CH_2Cl_2, Et_2O (5 ml, the last two steps were repeated two times), CH_2Cl_2 (5 ml) and dried in a vacuum oven (50 °C). Concentration of the filtrate followed by SPE column chromatography gave 10.2 mg of **30b** (42%).

Acknowledgements

This research has been financially supported by the Council for Chemical Sciences (C. W.) and the Netherlands Technology Foundation (S. T. W.) of the Netherlands Organisation for Scientific Research (N. W. O.). Dr R. Verhage (Solvay Pharmaceuticals) is acknowledged for carefully reading the manuscript.

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