An Efficient Route to 4/5/6 Polycyclic β-Lactams

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The synthesis of 4/5/6 polycyclic β-lactams by enyne metathesis and Diels–Alder reactions is described. Compared to the synthesis of 4/6/6 and 4/7/6 polycyclic β-lactams previously reported by our laboratory, formation of the strained 4/5/6 compounds requires alternative reaction conditions. Indeed, the synthesis of the 4/5 bicyclic diene **12** was more difficult than those of the 4/6 (**13**) and 4/7 (**14**) dienes. The strain of the 4/5 system could be observed by NMR spectroscopy and molecular modelling. Moreover, the reactivity of 4/5 diene **12** towards Diels–Alder cycloaddition was also different from that of the 4/6 (**13**) and 4/7 (**14**) dienes. Cycloadditions with 4/5 diene **12** therefore had to be performed in lithium perchlorate/diethyl ether (LPDE) or in an ionic liquid in order to proceed in good yields with various dienophiles.

Introduction

Many classes of β-lactam antibiotics have appeared since the discovery of Penicillin by Fleming in 1928. Whereas the early antibiotics were from natural sources, synthetic compounds with enhanced stability and activity against resistant bacteria have been developed in the last three decades.[1−5] The class of trinems (tricyclic carbapenems) was introduced by scientists at Glaxo in 1988. Sanfetrinem (GV104326; **1**) and sanfetrinem cilexetil (GV118819; **2**) were until recently undergoing phase-II clinical trials (Figure 1).[6−9]

Many research groups, both academic and industrial, have devoted efforts towards the synthesis of polycyclic β-lactams.[10−24] Recently, the new tricyclic carbapenems **3**−**5** were patented by Hoffmann-La Roche (**3**),[18] and Lek (**4**, **5**).[19,20] These compounds exhibit potential antibacterial properties and inhibitory activities against β-lactamases (Figure 1).

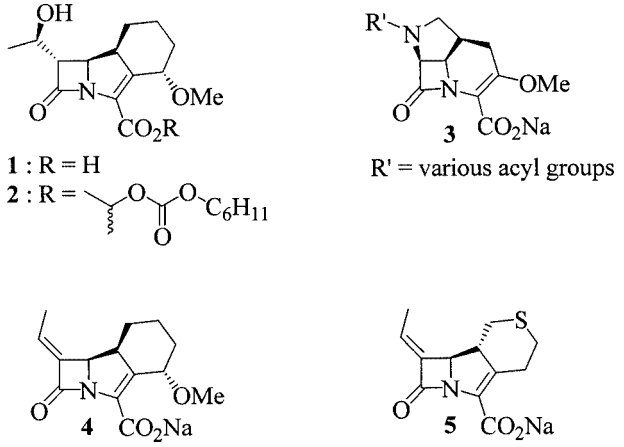

Figure 1. Tricyclic β-lactams

As a result of the introduction of well-defined and highly active metathesis catalysts such as **A**−**C** (Figure 2), ring-closing metathesis has recently emerged as a powerful and versatile tool for the construction of natural and non-natural molecules.[25]

Barrett's group first used ring-closing metathesis to synthesise fused bicyclic β-lactams in 1996.[21] Closure of 6- to 10-membered-rings was achieved by alkene or alkyne metathesis with catalysts **A** or **C**. In 2000, further transformations were envisaged to afford the functionalised polycyclic compound **6** (Scheme 1).[21c] However, ring-closing metathesis with a terminal alkyne or to form the 4/5 fused-bicyclic framework was not successful.

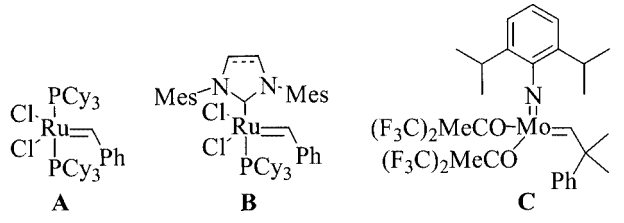

Figure 2. Examples of alkene and alkyne metathesis catalysts

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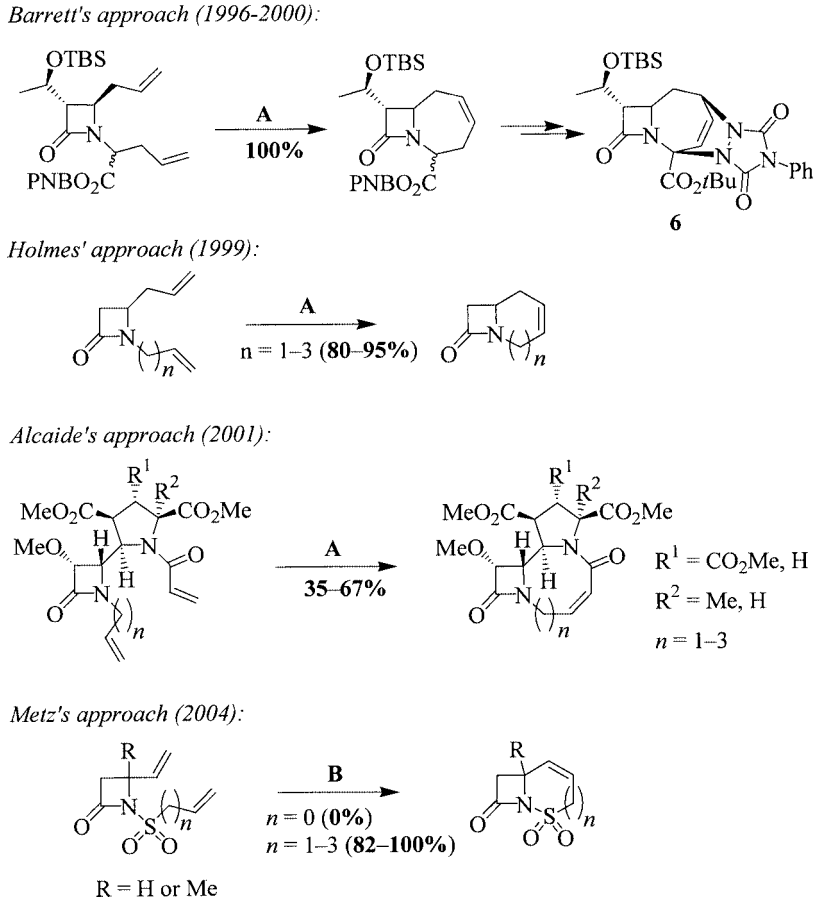
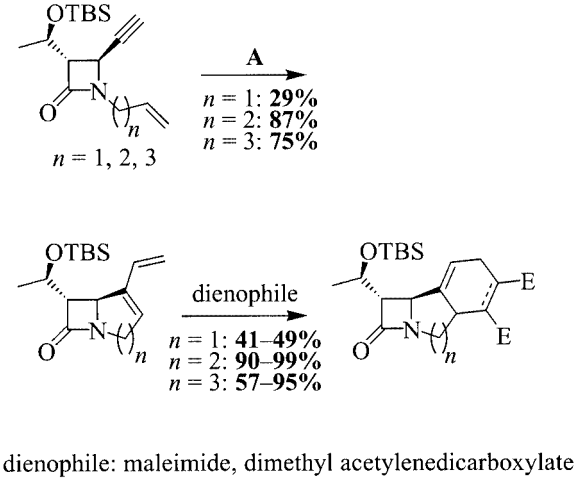


Scheme 1. Selected examples from the groups of Barrett, Holmes, Alcaide and Metz

In 1999, Holmes also described the synthesis of 4/6 to 4/8 fused bicyclic β-lactams using ring-closing metathesis with Grubbs' first-generation catalyst **A** (Scheme 1).[22]

As part of our ongoing program dedicated to the synthesis of biologically relevant molecules,[26−30] we reported in 2001 our strategy for the synthesis of polycyclic 4/5/6 and 4/6/6 β-lactams based on enyne metathesis and Diels−Alder reactions (Scheme 2).[31] In our case metathesis with a terminal alkyne was possible, as was the construction of the 4/5 fused bicyclic system, albeit in low yield. This strategy was recently extended to the synthesis of 4/6/6 and 4/7/6 polycyclic molecules by one-pot metathesis and Diels−Alder reactions.[32]



Scheme 2. Synthesis of polycyclic β-lactams from our group

In 2001, Alcaide's group also published an approach towards polycyclic β-lactams using ring-closing metathesis to elaborate the medium-sized ring of tricyclic β-lactams (Scheme 1),[23] and in 2004 Metz's group reported the use of ring-closing metathesis to synthesise β-lactams fused to a sultam moiety of variable ring size (Scheme 1).[24] Whereas metathesis led to high yields of the 4/6 to 4/8 bicyclic compounds, formation of the 4/5 bicyclic system was not observed.

The elaboration of the 4/5 fused bicyclic system is the most attractive since it is part of the framework of biologically active trinems such as Sanfetrinem. Our approach towards polycyclic β-lactams previously led to low yield of this 4/5 bicyclic system and moderate yields of the cycloadducts, whereas, in comparison, good yields of the 4/6 and 4/7 bicyclic systems and the corresponding Diels−Alder cycloadducts could be obtained (Scheme 2).[31,32]

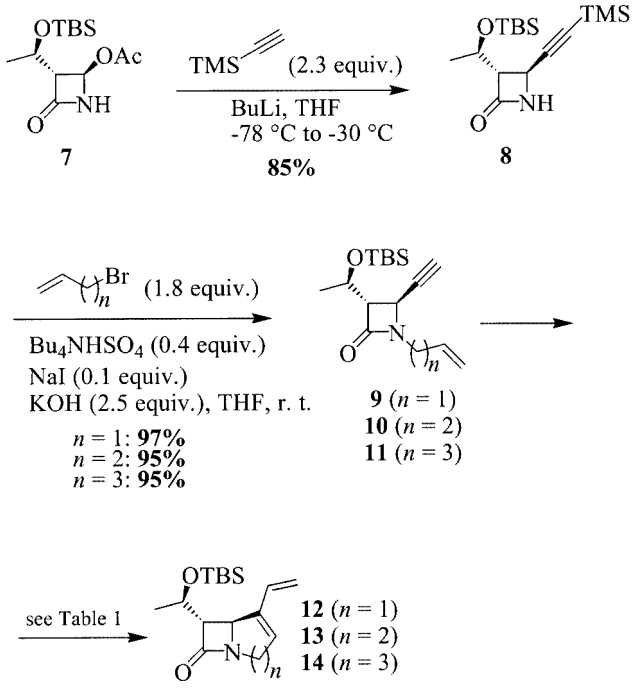
Herein we report our efforts to overcome these difficulties and synthesise efficiently these attractive 4/5/6 polycyclic β-lactams. We also present our observations and investigations concerning the influence of the size of the central

ring on the reactivity of the different classes of compounds towards ring-closing enyne metathesis and Diels−Alder reactions.

Results and Discussion

Synthesis of Dienes by Enyne Metathesis

Our synthetic approach started from commercially available (3*R*,4*R*)-4-acetoxy-3-{(*R*)-1′-[(*tert*-butyldimethylsilyl)-oxy]ethyl}-2-azetidinone (**7**).[33−35] Condensation of the anion of trimethylsilylacetylene with the azetidinone **7** at low temperature was performed in 85% yield with retention of configuration (Scheme 3). Alkylation of **8** under phase-transfer conditions also led to desilylation of the alkyne to furnish the desired enynes **9**−**11** in high yields (95−97%). Ring-closing enyne metathesis[36,37] was next achieved with Grubbs' first- and second-generation catalysts **A** and **B** (Figure 2).[38,39] In the presence of Grubbs' first-generation catalyst **A**, 4/6 and 4/7 fused bicyclic dienes **13** and **14** were readily obtained in 87% and 75% yield, respectively



Scheme 3. Synthesis of enynes **9**−**11**

(Table 1, entries 3 and 5). In contrast, enyne metathesis of **9** gave only 29% of the 4/5 bicyclic compound **12** and recovered starting material (Table 1, entry 1).

The difficulty to form the 4/5 fused bicyclic system was overcome by the use of Grubbs' more active second-generation catalyst to provide **12** in 86% yield (Table 1, entry 2). Use of this catalyst also afforded slightly increased yields of **13** (89%) and **14** (87%) (Table 1, entries 4 and 6).

This difference in reactivity might be interpreted as the result of the formation of a highly strained system and a partial loss of resonance in the lactam function, which is thermodynamically unfavourable.[40] This could be observed by ^{13}C NMR spectroscopy and molecular modelling. The ^{13}C NMR chemical shift of the carbonyl group of diene **12**, at δ = 180.1 ppm, appears at a much higher value than that of enyne **9** (δ = 166.7 ppm) or those of dienes **13** and **14** (δ = 170.3 ppm and 167.8 ppm respectively). This shift is consistent with a partial loss of resonance in the amide function in the formation of the 4/5 fused bicyclic diene **12** (Figure 3).

The planar environment necessary for a complete resonance in the amide function is not compatible with the β-lactam strained system. Molecular modelling (Spartan Pro, semi-empirical method PM3) of these compounds allowed the measurement of the angle between the C−N bond of the ring formed by metathesis and the plane defined by the C−N bonds of the β-lactam core (Figure 3).

Thus, the deformation angle of 29° observed for enyne **9** indicates a partial resonance in this compound. The measured angle of 42° for dienes **13** and **14** shows that formation of these bicycles leads to a slight loss of resonance compared to the enyne **9**. In the case of the 4/5 fused bicyclic system **12**, the angle of 54° indicates a high loss of resonance in this compound compared to enyne **9**.

We were therefore able to observe that the formation of the 4/5 fused bicyclic diene **12** leads to more important distortion and loss of resonance in the amide function than the formation of the related 4/6 and 4/7 dienes **13** and **14**. These phenomena are thermodynamically unfavourable, hence synthesis of highly strained diene **12** in high yield requires the use of the more active second-generation catalyst **B**.

Diels−Alder Cycloadditions

With dienes **12**−**14** in hand, we next investigated the Diels−Alder reactions[41−43] with various dienophiles in di-

Table 1. Ring-closing metathesis of enynes **9**−**11**

Entry	Enyne	Catalyst[a]	Experimental conditions[b]	Product (yield)[c]
1	**9**	**A**	CH_2Cl_2 (0.02 M),[d] 80 °C, 24 h	**12** (29%)
2	**9**	**B**	CH_2Cl_2 (0.02 M),[d] 50 °C, 24 h	**12** (86%)
3	**10**	**A**	CH_2Cl_2 (0.05 M),[d] 50 °C, 22 h	**13** (87%)
4	**10**	**B**	CH_2Cl_2 (0.05 M),[d] 50 °C, 22 h	**13** (89%)
5	**11**	**A**	CH_2Cl_2 (0.05 M),[d] 80 °C, 24 h	**14** (75%)
6	**11**	**B**	CH_2Cl_2 (0.05 M),[d] 80 °C, 21 h	**14** (84%)

[a] Reactions run in screw-cap tubes. [b] 5 mol % of catalyst was used for each reaction. [c] Isolated yields. [d] Enyne concentration.

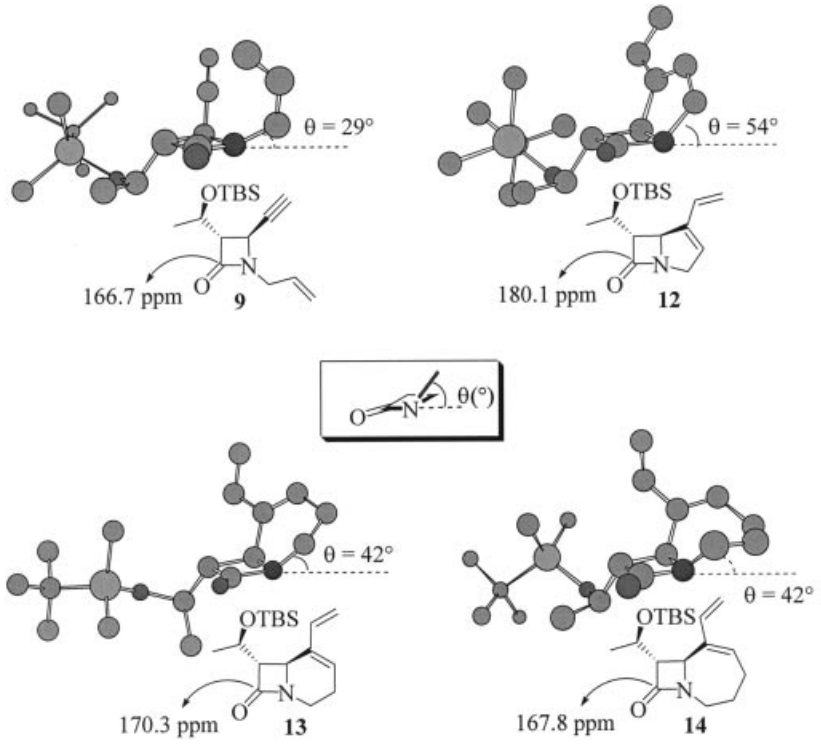


Figure 3. ^{13}C NMR chemical shifts (in $CDCl_3$) of carbonyl groups and molecular modelling of enyne **9** and **12**−**14**

chloromethane at 80 °C or at room temperature (Table 2). As can be seen from Table 2, cycloadditions with 4/6 and 4/7 dienes **13** and **14** proceeded efficiently to yield the expected cycloadducts **15**−**21** in high yields (Table 2, entries 1−4).[32] The selectivity of the reaction was moderate with dimethyl acetylenedicarboxylate (DMAD) and maleimide (Table 2, entry 1−3), but high with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), since a single diastereomer **21** was obtained (Table 2, entry 4). With the latter dienophile, the reaction had to be performed at room temperature to prevent decomposition of the product.

In contrast, the 4/5-fused bicyclic diene **12** reacted efficiently only with highly reactive 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to give **22** in 91% yield (entry 5). With dimethyl acetylenedicarboxylate (DMAD) and maleimide, low to moderate yields of cycloadducts **23**−**26** were obtained even when using a large excess of dienophile (entries 6 and 7).

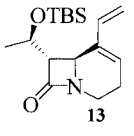
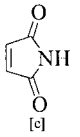
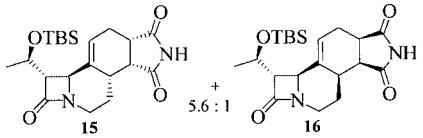
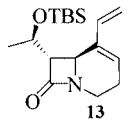
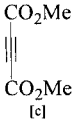
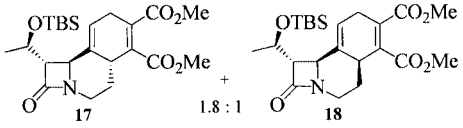
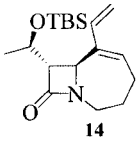
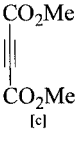
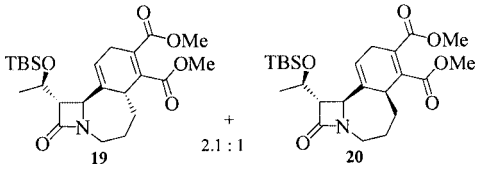
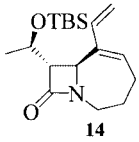
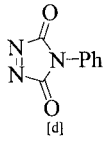
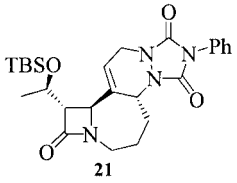
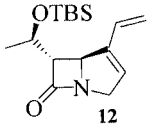
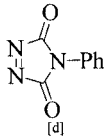
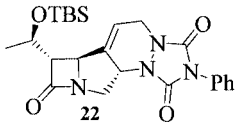
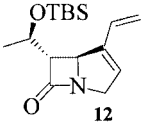
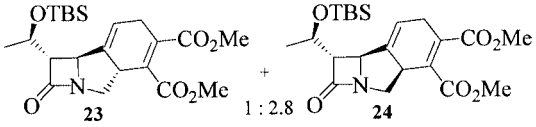
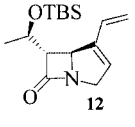
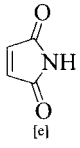
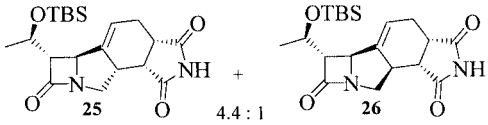
Again, the difference in reactivity between the 4/5 and the 4/6 or 4/7 classes of compounds is apparent. Synthesis of the 4/5/6 compounds is probably hampered by the formation of a double bond exocyclic to the already strained 4/5 bicyclic system. Therefore it was necessary to establish better conditions for the Diels−Alder cycloaddition with 4/5 bicyclic diene **12**. Reaction with DMAD, which led to **23** and **24** as an inseparable mixture, was chosen to set up the conditions (Table 3). Reaction with a large excess of dienophile in refluxing dichloromethane afforded a slight increase of the yield from 29% to 44% (Table 3, entries 1 and 2). In the absence of solvent, cycloadducts **23** and **24** were obtained in 86% yield along with 1% of aromatized product **29** (Figure 4, Table 3, entry 3). However, these experimental conditions were not suitable with solid dienophiles.

In the presence of Lewis acids (BF_3, BCl_3), disappointing results were obtained since no product or decomposition of the starting material was observed. In water or LiCl aqueous solution,[44] low yields of **23** and **24** were obtained, accompanied by substantial amounts of **29** (6%), decomposition products and recovered starting material (Table 3, entry 4). Interestingly, the best procedure was to perform the reaction either in LPDE (lithium perchlorate/diethyl ether)[45−47] or in an ionic liquid[48,49] [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate) at 80 °C. The reaction was sluggish at room temperature, since only 54% yield was obtained after one week (starting diene **12** was recovered, Table 3, entry 5). However, at 80 °C for 23 h good yields of 89% and 84%, respectively, were obtained (Table 3, entries 6 and 7).

These reaction conditions were applied to the Diels−Alder cycloadditions of dienes **12** with other dienophiles to afford good yields (73−92%) of the expected adducts (Table 4). Reaction with methyl vinyl ketone yielded an inseparable mixture of three diastereomers in both reaction media (Table 4, entries 3 and 4). Cycloaddition with maleimide gave a separable mixture of the same two diastereomers in both media (Table 4, entries 5 and 6). In the case of *N*-phenylmaleimide only the major diastereomer **27** could be partially separated (Table 4, entry 7).

Although the exact role of LPDE and ionic liquid still remains unclear, it is likely that a combination of the different suggested effects (high internal pressure, Lewis acidity...) allows the reactions to proceed in good yields.[50]

Table 2. Diels−Alder cycloadditions in dichloromethane

Entry	Diene[a]	Dienophile	Products (selectivity)	Yield[b]
1	 13	 [c]	 15 : 16 = 5.6 : 1	99%
2	 13	 [c]	 17 : 18 = 1.8 : 1	92%
3	 14	 [c]	 19 : 20 = 2.1 : 1	95%
4	 14	 [d]	 21	86%
5	 12	 [d]	 22	91%
6	 12	 [c]	 23 : 24 = 1 : 2.8	29%
7	 12	 [e]	 25 : 26 = 4.4 : 1	49%

[a] For each reaction the concentration of the diene was 0.05 M in dichloromethane. [b] Isolated yields. [c] Reactions performed with 4 equiv. of dienophile in screw-cap tubes at 80 °C for 20−24 h. [d] Reactions performed with 2 equiv. of dienophile at room temperature for 20 h. [e] Reaction performed with 20 equiv. of dienophile in a screw-cap tube at 80 °C for 20 h.

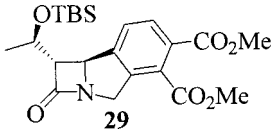
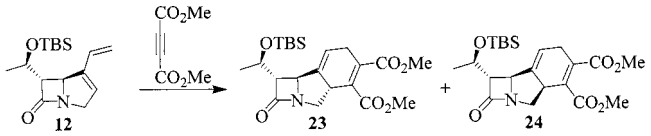

29

Figure 4. Aromatized product **29**

The diastereoselectivity of the cycloadditions was better, and sometimes different, in ionic liquid or dichloromethane than in LPDE. The major side of approach of the dienophiles varies depending on the structure of the dienophile and on the nature of the reaction medium (Table 2−4, Figure 5). With DMAD, only variations of the ratio of diastereomers **23**:**24** were observed since the major cycloadduct arises from addition of the dienophile on the same side as the β-lactam ring of diene **12** in dichloromethane, [bmim]PF_6, and LPDE (Table 3, entries 2, 6, 7). With maleimide, the major product derives from an *endo* approach at the face opposite to the β-lactam ring of diene **12** in dichloromethane and [bmim]PF_6 (Table 2, entry 7 and Table 4, entry 6). However, in LPDE an *exo* approach of maleimide at the same side as the β-lactam ring of **12** is slightly favoured (Table 4, entry 5). Surprisingly, changing maleimide for *N*-phenylmaleimide reversed the selectivity in LPDE so that the major product arises from an *endo* approach at the face opposite to the β-lactam ring of **12** (Table 4, entry 7).

The selectivity of the cycloaddition was also different in some cases between 4/5 diene **12** and the 4/6 (**13**) and 4/7 (**14**) dienes. The product or major product arises from an

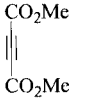
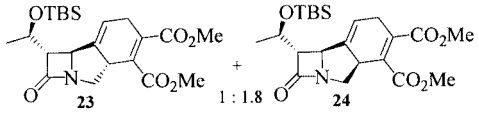
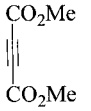
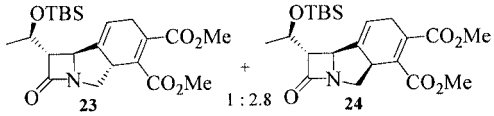
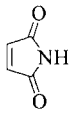
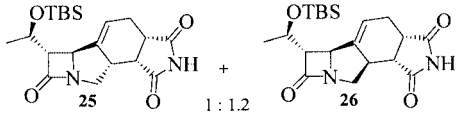
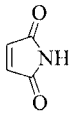
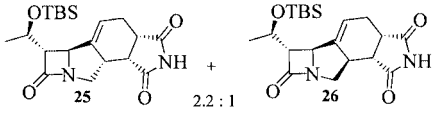
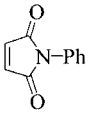
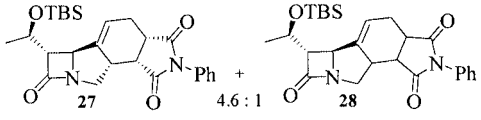
Table 3. Diels–Alder cycloaddition between diene **12** and DMAD



Entry	Experimental conditions	Yield[a]	Ratio of diastereomers[b] **23**:**24**
1	DMAD (4 equiv.), CH_2Cl_2, 80 °C, 22 h[c]	29%	1:2.8
2	DMAD (20 equiv.), CH_2Cl_2, 80 °C, 22 h[c]	44%	1:2.8
3	DMAD (0.5 mL), 80 °C, 20 h	86%	1:2.8
4	DMAD (4 equiv.), H_2O, LiCl (4.86 M), 80 °C, 20 h[c]	36%	1:2.1
5	DMAD (4 equiv.), Et_2O, $LiClO_4$ (5 M), 25 °C, 7 d	54%	1:1.6
6	DMAD (4 equiv.), Et_2O, $LiClO_4$ (5 M), 80 °C, 23 h[c]	89%	1:1.8
7	DMAD (4 equiv.), [bmim]PF_6, 80 °C, 23 h	84%	1:2.8

[a] Isolated yields. [b] Ratio of diastereomers determined by NMR spectroscopy. [c] Reactions performed in screw-cap tubes.

Table 4. Diels–Alder cycloadditions with diene **12** in LPDE or ionic liquid

Entry	Dienophile	Method[a]	Products (selectivity)	Yield[b]
1		A	 1 : 1.8 [c]	89%
2		B	 1 : 2.8 [c]	84%
3		A[d]	Inseparable mixture of 3 diastereomers	74%
4		B[d]	Inseparable mixture of 3 diastereomers	81%
5		A	 1 : 1.2	92%
6		B	 2.2 : 1	73%
7		A	 4.6 : 1 [c]	82%

[a] Method A: dienophile (4 equiv.), Et_2O, $LiClO_4$ (5 M), in a screw-cap tube, 80 °C, 23 h; Method B: dienophile (4 equiv.), [bmim]PF_6, 80 °C, 23 h. [b] Isolated yields. [c] Ratio of diastereomers determined by NMR spectroscopy. [d] Reaction performed at 65 °C.

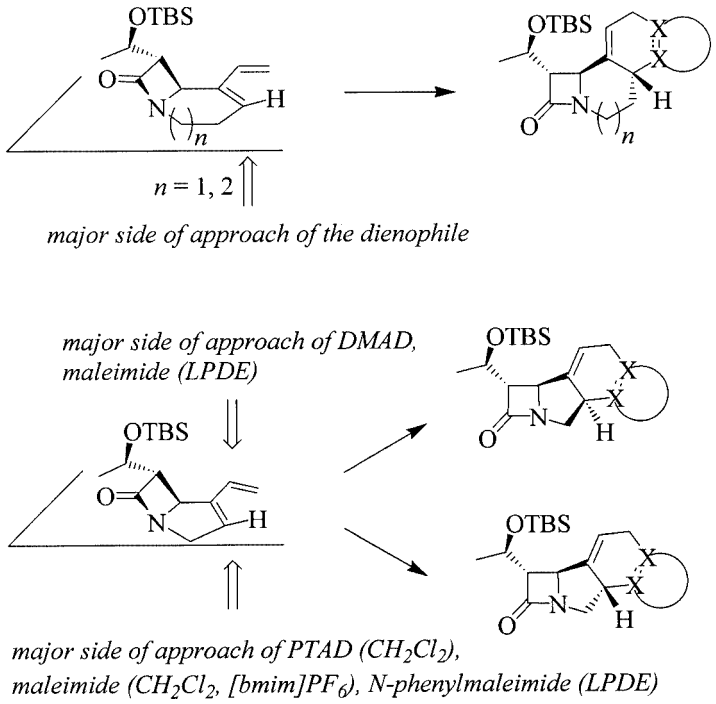


Figure 5. Selectivity of the Diels–Alder cycloaddition depending on the diene and dienophile (reaction media indicated in brackets where necessary)

approach of the dienophiles on the face opposite to the β-lactam ring of dienes **13** and **14** (Figure 5).[32] With dienes **12** and **14**, *endo* addition of PTAD takes place on the face opposite to the β-lactam ring to yield a single diastereomer in each case (Table 2, entries 4 and 5). With maleimide, preferential *endo* approach of the dienophile at the face opposite to the β-lactam ring of the diene was observed with diene **13** in dichloromethane and with diene **12** in dichloromethane and [bmim]PF_6 (Table 2, entries 1 and 7; Table 4, entry 6). However, as mentioned previously, preferential *exo* approach of maleimide at the same side as the β-lactam ring of **12** occurs in LPDE (Table 4, entry 5). In contrast with the cycloadditions between DMAD and dienes **13** and **14** in dichloromethane, preferential addition of DMAD takes place on the same side as the β-lactam ring of diene **12** in dichloromethane, [bmim]PF_6, and LPDE (Table 3).

The stereochemistry of the Diels–Alder cycloadducts was determined by NMR NOESY experiments. Interactions between H_h, H_j, H_k, $H_{k'}$ and H_c and H_d of known stereochemistries allowed us to establish the new stereocenters (Figure 6). In most cases the stereochemistry of H_j could be determined from its NOE interactions with H_c (**23**, **25**, **27**) or H_d (**24**, **26**). However, in the case of **22** no NOE interaction between H_j and H_c or H_d was present. The presence of interactions between H_d and $H_{k'}$, H_j and H_k, and the absence of an interaction between $H_{k'}$ and H_j established that H_j and $H_{k'}$ are on opposite sides of the molecule. H_h and H_i are on the same side of the molecule due to the concerted nature of the cycloaddition, and their stereochemistries were determined from the NOE interactions between H_h and H_j (**25**, **27**) or between H_h and H_k (**26**).

Conclusion

In summary, we have developed an efficient synthesis of 4/5/6 polycyclic β-lactams. NMR observations and molecular modelling have provided evidence that formation of these 4/5/6 compounds leads to more-strained systems than the related 4/6/6 and 4/7/6 compounds, and therefore requires alternative reaction conditions. The use of Grubbs' second-generation catalyst instead of the first-generation catalyst allowed the formation of the 4/5 bicyclic diene **12** with a good yield (86%). Diels–Alder cycloadditions with diene **12** had to be performed in LPDE or ionic liquid media instead of dichloromethane to obtain good yields (73–92%) of the 4/5/6 cycloadducts. The diastereoselectivity of the cycloadditions with diene 4/5 **12** depended on the dienophile and the reaction media, and in some cases was also different from the diastereoselectivity with 4/6 (**13**) and 4/7 (**14**) dienes. The stereochemistry of the cycloadducts was established by NMR NOESY experiments.

The antibacterial activities of the polycyclic β-lactams still containing the TBS protecting group were measured in vitro on sensitive strains of *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922. Whereas no activity was observed for most 4/6/6 and 4/7/6 compounds (minimal inhibitory concentration, MIC > 100 μg/mL), some 4/5/6 molecules displayed slight activity (MIC = 100 μg/mL) on *Staphylococcus aureus.* These activities are encouraging since these compounds are readily synthesised. Further extension of this methodology and biological evaluations of the new compounds are envisaged in our laboratory. These results will be presented in due course.

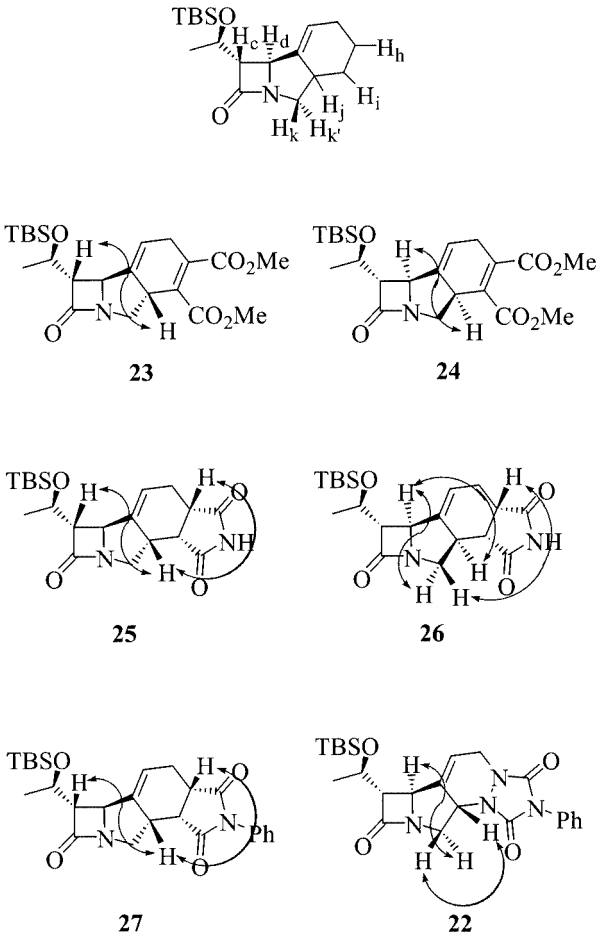


Figure 6. Determination of the stereochemistry of the 4/5/6 cycloadducts by NOESY; arrows indicate NOE interactions

Experimental Section

General Remarks: All reactions were performed in oven-dried glassware under an atmosphere of argon. Tetrahydrofuran was freshly distilled from sodium and benzophenone, and dichloromethane was distilled from calcium hydride prior to use. All commercially available reagents and solvents were used without further purification unless otherwise indicated. Column chromatography and TLC were performed on Merck silica gel 60 (0.040−0.063 mm) and 60 F_{254}, respectively. IR spectra were recorded using a Nicolet 210 spectrophotometer from a thin film supported on NaCl plates or KBr disks. Absorptions are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400, Avance 300 or AC 200 apparatus. The chemical shift in ppm is quoted relative to the residual signals of non-deuterated NMR solvent. Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. Mass spectra were recorded on a Nermag R10−10C or on a API 3000 PE Sciex apparatus. Melting points are uncorrected and were measured on a Stuart Scientific or on Kofler apparatus. Optical rotations were measured on a Perkin−Elmer 241 polarimeter.

Compounds **7**, **8**, **10**, **11** and **13**−**21** have already been fully described in a previous article.[32]

4/5 Enyne 9: Allyl bromide (1.25 mL, 14.4 mmol, 1.8 equiv.), tetrabutylammonium hydrogen sulfate (1.10 g, 3.2 mmol, 0.4 equiv.), sodium iodide (121 mg, 0.8 mmol, 0.1 equiv.) and freshly crushed potassium hydroxide (1.14 g, 20 mmol, 2.5 equiv.) were successively added to a solution of **8** (2.64 g, 8.1 mmol, M = 325.59, 1 equiv.) in THF (100 mL) at room temperature. The solution was stirred vigorously for 3 h and then quenched with saturated NH_4Cl. The aqueous layer was extracted several times with diethyl ether, and the combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by flash chromatography (120 g of silica gel, cyclohexane/ethyl acetate, 9:1) afforded 2.31 g of **9** (97% yield) as a pale-yellow oil. $[\alpha]_D^{25} = +16$ (*c* = 1.42, $CHCl_3$). IR (NaCl film): $\tilde{\nu}$ = 3309, 3084, 2954, 2928, 2885, 2856, 2118, 1762, 1645, 1257, 837, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 1.20 (d, *J* = 7.3 Hz, 3 H), 2.43 (d, *J* = 2.0 Hz, 1 H), 3.20 (d, *J* = 2.7 Hz, 1 H), 3.59 (dd, *J* = 15.4, 7.6 Hz, 1 H), 4.06 (dd, *J* = 15.4, 3.8 Hz, 1 H), 4.22−4.25 (m, 2 H), 5.19 (dd, *J* = 10.1, 1.1 Hz, 1 H), 5.26 (dd, *J* = 16.9, 1.1 Hz, 1 H), 5.72−5.82 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.0, −4.6, 17.8, 22.2, 25.6, 41.7, 43.1, 64.2, 65.9, 74.2, 80.2, 118.8, 131.3, 166.7 ppm. MS (DCI/NH_3): *m*/*z* = 311 $[M + NH_4]^+$, 294 $[M + H]^+$, 236 $[M - C(CH_3)_3]^+$. $C_{16}H_{27}NO_2Si$ (293.48): calcd. C 65.48, H 9.27, N 4.77; found C 65.16, H 9.44, N 4.65.

4/5 Diene 12: Enyne **9** (98 mg, 0.33 mmol, 1 equiv.), degassed CH_2Cl_2 (16 mL), and Grubbs' second-generation catalyst (14.1 mg, 14.9 μmol, 0.05 equiv.) were successively introduced into a screw-cap tube flushed with argon. The tube was heated at 50 °C for 24 h, then the reaction mixture was concentrated in vacuo. Purification by flash chromatography (6 g of silica gel, cyclohexane/ethyl acetate, 9:1) afforded 84 mg of **12** (86% yield) as a yellow oil. $[\alpha]_D^{25} = -55.8$ (*c* = 1.29, $CHCl_3$). IR (NaCl film): $\tilde{\nu}$ = 2957, 2930, 2896, 2885, 2859, 1777, 1770, 1634, 1257, 836, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.90 (s, 9 H), 1.31 (d, *J* = 6.2 Hz, 3 H), 3.03 (dd, *J* = 7.2, 2.2 Hz, 1 H), 3.58 (dd, *J* = 17.0, 4.1 Hz, 1 H), 4.18−4.31 (m, 1 H), 4.35−4.45 (m, 2 H), 5.18 (d, *J* = 10.8 Hz, 1 H), 5.38 (d, *J* = 17.6 Hz, 1 H), 5.84 (br. s, 1 H), 6.51 (dd, *J* = 17.6, 10.8 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.8, −4.6, 17.8, 22.8, 25.6, 53.0, 60.4, 65.5, 66.9, 117.3, 129.5, 130.6, 141.8, 180.1 ppm. MS (DCI/NH_3): *m*/*z* = 311 $[M + NH_4]^+$, 294 $[M + H]^+$, 236 $[M - C(CH_3)_3]^+$. $C_{16}H_{27}NO_2Si$ (293.48): calcd. C 65.48, H 9.27, N 4.77; found C 65.35, H 9.29, N 4.69.

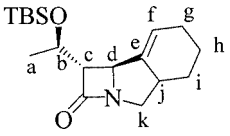
General Procedure for Diels−Alder Cycloadditions in Dichloromethane: A mixture of diene **12** (73.4 mg, 0.25 mmol) and dienophile (2−20 equiv., see Table 2 and 3) in 5 mL of dichloromethane was warmed at the desired temperature for 20−24 h in a screw-cap tube. The solvent was concentrated and purification by flash chromatography on a silica-gel column (cyclohexane/ethyl acetate) afforded the Diels−Alder adducts.

General Procedure for Diels−Alder Cycloadditions in LPDE: A mixture of diene **12** (73.4 mg, 0.25 mmol) and dienophile (4 equiv.) in 5 mL of 5 M LPDE (2.66 g, 25 mmol of $LiClO_4$ in 5 mL of diethyl ether) was heated at the required temperature (see Table 3 and 4) for 23 h in a screw-cap tube. The diethyl ether was then removed and water was added to the crude product (***Caution! Exothermic***). Extraction with dichloromethane followed by purification by flash chromatography on a silica-gel column (cyclohexane/ethyl acetate) afforded the Diels−Alder adducts.

General Procedure for Diels−Alder Cycloadditions in [bmim]PF_6: A mixture of diene **12** (73.4 mg, 0.25 mmol) and dienophile (4 equiv.) in 300μL of [bmim]PF_6 was heated at the required temperature (see Table 3 and 4) for 23 h in a small reaction vessel. Thorough extrac-

tion with diethyl ether followed by purification by flash chromatography on a silica-gel column (cyclohexane/ethyl acetate) afforded the Diels–Alder adducts.

The following backbone numbering is used to describe the NMR spectra of 4/5/6 polycyclic compounds:



Diels–Alder Cycloadduct with PTAD (22): White solid, m.p. 236 °C. $[\alpha]_D^{25}$ = +150.5 (*c* = 1.12, $CHCl_3$). IR (KBr disk): $\tilde{\nu}$ = 2957, 2929, 2896, 2894, 2886, 2855, 1767, 1713, 1634, 1456, 1258, 988, 836, 768, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6 H, Si–CH_3), 0.91 [s, 9 H, Si–C(CH_3)], 1.25 (d, *J* = 6.0 Hz, 3 H, H_a), 3.01 (dd, *J* = 12.1, 9.8 Hz, 1 H, $H_{k'}$), 3.12 (dd, *J* = 4.4, 3.0 Hz, 1 H, H_c), 4.07 (br. d, *J* = 17.5 Hz, 1 H, H_g), 4.22–4.33 (m, 1 H, H_j), 4.25 (quint, 1 H, *J* = 5.7 Hz, H_b), 4.33 (br. s, 1 H, H_d), 4.45 (br. d, *J* = 17.5 Hz, 1 H, $H_{g'}$), 4.62 (dd, *J* = 12.1, 7.3 Hz, 1 H, H_k), 6.05 (br. s, 1 H, H_f), 7.37–7.40 (m, 1 H, $^{Ar}H_{para}$), 7.44–7.50 (m, 4 H, $^{Ar}H_{ortho}$, $^{Ar}H_{meta}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9 (Si–*C*H_3), −4.2 (Si–*C*H_3), 18.0 [Si–*C*(CH$_3$)], 22.6 (C_a), 25.8 [Si–C(*C*H$_3$)], 43.0 (C_g), 50.9 (C_k), 54.6 (C_d), 57.8 (C_j), 65.3 (C_b), 67.6 (C_c), 117.5 (C_f), 125.4 ($^{Ar}C_{ortho}$), 128.4 ($^{Ar}C_{para}$), 129.3 ($^{Ar}C_{meta}$), 130.9 ($^{Ar}C_{ipso}$), 137.7 (C_e), 151.6 and 153.8 (*C*=O), 178.3 (*C*=O_{lactam}) ppm. MS (DCI/NH_3): *m*/*z* = 486 $[M + NH_4]^+$, 469 $[M + H]^+$, 411 $[M - C(CH_3)_3]^+$. $C_{24}H_{32}N_4O_4Si$ (468.62): calcd. C 61.51, H 6.88, N 11.96; found C 61.79, H 7.01, N 11.63.

Diels–Alder Cycloadducts with DMAD (Inseparable Mixture of 23 and 24): Pale-yellow oil. IR (NaCl film): $\tilde{\nu}$ = 2954, 2930, 2896, 2895, 2857, 1754, 1740, 1725, 1716, 1643, 1279, 1264, 1145, 1063, 1051, 833, 781 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6 H^{24}, Si–CH_3), 0.07 (s, 6 H^{23}, Si–CH_3), 0.87 [s, 9 H^{23}, 9 H^{24}, Si–C(CH_3)], 1.22 (d, *J* = 6.2 Hz, 3 H^{23}, H_a), 1.25 (d, *J* = 6.2 Hz, 3 H^{24}, H_a), 2.67 (dd, *J* = 11.7, 10.5 Hz, 1 H^{23}, $H_{k'}$), 2.90 (dd, *J* = 5.8, 2.0 Hz, 1 H^{24}, H_c), 3.00 (dd, *J* = 5.3, 2.9 Hz, 1 H^{23}, H_c), 3.02–3.07 (m, 1 H^{23}, H_g), 3.07–3.15 (m, 2 H^{24}, H_g), 3.13–3.23 (m, 1 H^{23}, $H_{g'}$), 3.28 (dd, *J* = 10.5, 9.4 Hz, 1 H^{24}, H_k), 3.39–3.46 (m, 1 H^{24}, $H_{k'}$), 3.75–3.85 (m, 1 H^{24}, H_j), 3.76 (s, 3 H^{24}, CO_2CH_3), 3.77 (s, 6 H^{23}, CO_2CH_3), 3.78 (s, 3 H^{24}, CO_2CH_3), 4.01 (br. s, 1 H^{24}, H_d), 4.15–4.22 (m, 3 H^{23}, 1 H^{24}, $^{23}H_b$, $^{23}H_d$, $^{23}H_k$, $^{24}H_b$), 5.66–5.68 (m, 1 H^{24}, H_f), 5.86–5.87 (m, 1 H^{23}, H_f) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9 (**23**, **24**, Si–*C*H_3), −4.2 (**23**, **24**, Si–*C*H_3), 18.0 [**23**, **24**, Si–*C*(CH$_3$)], 22.6 (**23**, C_a), 22.9 (**24**, C_a), 25.8 [**23**, **24**, Si–C(*C*H$_3$)], 29.5 (**24**, C_g), 29.7 (**23**, C_g), 42.2 (**23**, C_j), 42.5 (**24**, C_j), 48.2 (**24**, C_k), 50.8 (**23**, C_k), 52.4 (**23**, **24**, CO_2CH_3), 52.5 (**23**, **24**, CO_2CH_3), 55.6 (**23**, C_d), 55.7 (**24**, C_d), 64.3 (**24**, C_c), 65.5 (**23**, C_b), 65.7 (**24**, C_b), 67.5 (**23**, C_c), 116.2 (**24**, C_f), 118.6 (**23**, C_f), 132.1 (**24**, C_i), 133.2 (**23**, C_i), 134.5 (**24**, C_h), 134.7 (**23**, C_h), 136.4 (**24**, C_e), 138.2 (**23**, C_e), 167.0 (**24**, *C*O_2CH_3), 167.2 (**23**, *C*O_2CH_3), 167.9 (**23**, *C*O_2CH_3), 168.3 (**24**, *C*O_2CH_3), 176.9 (**24**, *C*=O_{lactam}), 179.2 (**23**, *C*=O_{lactam}) ppm. MS (DCI/NH_3): *m*/*z* = 453 $[M + NH_4]^+$, 436 $[M + H]^+$, 378 $[M - C(CH_3)_3]^+$. $C_{22}H_{33}NO_6Si$ (435.59): calcd. C 60.66, H 7.64, N 3.22; found C 60.71, H 7.74, N 3.11.

Diels–Alder Cycloadduct with Maleimide (25): White solid, m.p. 158–162 °C. $[\alpha]_D^{25}$ = +46.4 (*c* = 0.70, $CHCl_3$). IR (KBr disk): $\tilde{\nu}$ = 3256, 1768, 1719, 1646, 1258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H, Si–CH_3), 0.88 [s, 9 H, Si–C(CH_3)], 1.22 (d, *J* = 6.2 Hz, 3 H, H_a), 2.12–2.19 (m, 1 H, H_g), 2.84–2.90 (m, 2 H, H_c, $H_{g'}$), 2.93–3.01 (m, 1 H, H_j), 3.17–3.21 (m, 1 H, H_h), 3.31 (t, *J* = 8.6 Hz, 1 H, H_i), 3.65 (dd, *J* = 12.5, 8.6 Hz, 1 H, $H_{k'}$), 4.10–4.15 (m, 2 H, H_d, H_k), 4.18 (quint, *J* = 6.0 Hz, 1 H, H_b), 5.88–5.90 (m, 1 H, H_f) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8 (Si–*C*H_3), −4.2 (Si–*C*H_3), 18.0 [Si–*C*(CH$_3$)], 22.7 (C_a), 25.1 (C_g), 25.8 [Si–C(*C*H$_3$)], 41.1 (C_h), 42.2 (C_i), 42.3 (C_j), 46.5 (C_k), 55.7 (C_d), 65.7 (C_b), 68.8 (C_c), 119.8 (C_f), 143.8 (C_e), 177.2 (*C*=O_{lactam}), 177.6 and 179.6 (*C*=O) ppm. MS (DCI/NH_3): *m*/*z* = 408 $[M + NH_4]^+$, 391 $[M + H]^+$, 333 $[M - C(CH_3)_3]^+$. $C_{20}H_{30}N_2O_4Si$ (390.55): calcd. C 61.51, H 7.74, N 7.17; found C 61.82, H 7.93, N 6.96.

Diels–Alder Cycloadduct with Maleimide (26): White solid, m.p. 130 °C. $[\alpha]_D^{25}$ = +19.7 (*c* = 1.09, $CHCl_3$). IR (KBr disk): $\tilde{\nu}$ = 3250, 1768, 1717, 1643, 1257 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, Si–CH_3), 0.87 [s, 9 H, Si–C(CH_3)], 1.22 (d, *J* = 6.2 Hz, 3 H, H_a), 2.07–2.15 (m, 1 H, H_g), 2.74 (dd, *J* = 6.4, 2.3 Hz, 1 H, H_c), 2.82 (ddd, *J* = 15.4, 7.3, 1.4 Hz, 1 H, $H_{g'}$), 2.98–3.05 (m, 1 H, H_j), 3.16 (td, *J* = 7.5, 1.4 Hz, 1 H, H_h), 3.24 (dd, *J* = 12.4, 9.4 Hz, 1 H, $H_{k'}$), 3.34 (dd, *J* = 8.8, 7.5 Hz, 1 H, H_i), 4.08–4.15 (m, 1 H, H_b), 4.13 (br. s, 1 H, H_d), 4.72 (dd, *J* = 12.4, 3.7 Hz, 1 H, H_k), 5.85–5.89 (m, 1 H, H_f) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9 (Si–*C*H_3), −4.2 (Si–*C*H_3), 18.0 [Si–*C*(CH$_3$)], 22.8 (C_a), 25.2 (C_g), 25.8 [Si–C(*C*H$_3$)], 40.6 (C_h), 43.0 (C_i), 44.7 (C_j), 45.8 (C_k), 56.6 (C_d), 66.0 (C_b), 67.1 (C_c), 119.4 (C_f), 144.3 (C_e), 175.0 (*C*=O_{lactam}), 177.3 and 179.1 (*C*=O) ppm. MS (DCI/NH_3): *m*/*z* = 408 $[M + NH_4]^+$, 391 $[M + H]^+$, 333 $[M - C(CH_3)_3]^+$. $C_{20}H_{30}N_2O_4Si$ (390.55): calcd. C 61.51, H 7.74, N 7.17; found C 61.78, H 8.04, N 6.96.

Diels–Alder Cycloadduct with *N*-phenylmaleimide (27): White solid, m.p. 165 °C. $[\alpha]_D^{25}$ = +24.0 (*c* = 1.00, $CHCl_3$). IR (KBr disk): $\tilde{\nu}$ = 2958, 2932, 2856, 1747, 1697, 1630, 1383, 840, 777, 692 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]acetone): δ = 0.09 (s, 6 H, Si–CH_3), 0.89 [s, 9 H, Si–C(CH_3)], 1.25 (d, *J* = 6.2 Hz, 3 H, H_a), 2.30–2.39 (m, 1 H, H_g), 2.82–2.89 (m, 1 H, $H_{g'}$), 2.93 (dd, *J* = 5.6, 2.5 Hz, 1 H, H_c), 3.18–3.27 (m, 1 H, H_j), 3.42–3.47 (m, 1 H, H_h), 3.62 (dd, *J* = 9.0, 7.6 Hz, 1 H, H_i), 3.71 (dd, *J* = 12.2, 8.3 Hz, 1 H, $H_{k'}$), 4.05 (dd, *J* = 12.2, 9.0 Hz, 1 H, H_k), 4.14–4.16 (m, 1 H, H_d), 4.22 (quint, *J* = 6.0 Hz, 1 H, H_b), 5.97–6.01 (m, 1 H, H_f), 7.20–7.22 (m, 2 H, $^{Ar}H_{ortho}$), 7.37–7.41 (m, 1 H, $^{Ar}H_{para}$), 7.43–7.48 (m, 2 H, $^{Ar}H_{meta}$) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = −4.9 (Si–*C*H_3), −4.3 (Si–*C*H_3), 18.4 [Si–*C*(CH$_3$)], 22.7 (C_a), 26.0 [Si–C(*C*H$_3$)], 26.1 (C_g), 40.8 (C_h), 42.0 (C_i), 43.2 (C_j), 47.2 (C_k), 56.3 (C_d), 66.5 (C_b), 69.5 (C_c), 120.1 (C_f), 127.7 ($^{Ar}C_{ortho}$), 128.9 ($^{Ar}C_{para}$), 129.5 ($^{Ar}C_{meta}$), 133.5 ($^{Ar}C_{ipso}$), 145.3 (C_e), 176.9, 177.6 and 179.1 (*C*=O) ppm. MS (DCI/NH_3): *m*/*z* = 484 $[M + NH_4]^+$, 467 $[M + H]^+$, 409 $[M - C(CH_3)_3]^+$. HRMS (DCI) for $C_{26}H_{34}N_2O_4Si$ (466.64) $[M + H^+]$: calcd. 467.2366; found 467.2372.

Aromatized Compound 29: White solid, m.p. 126 °C. $[\alpha]_D^{29}$ = −81.0 (*c* = 1.01, $CHCl_3$). IR (KBr disk): $\tilde{\nu}$ = 2954, 2936, 2896, 2858, 1755, 1737, 1725, 1617, 1276, 1134, 1056, 837, 824, 785 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, Si–CH_3), 0.13 (s, 3 H, Si–CH_3), 0.93 [s, 9 H, Si–C(CH_3)], 1.33 (d, *J* = 6.2 Hz, 3 H, H_a), 3.13 (dd, *J* = 5.6, 2.6 Hz, 1 H, H_c), 3.90 (s, 3 H, CO_2CH_3), 3.91 (s, 3 H, CO_2CH_3), 4.18 (dd, *J* = 15.9, 1.6 Hz, 1 H, H_k or $H_{k'}$), 4.31 (quint, 1 H, *J* = 6.0 Hz, H_b), 4.87 (br. s, 1 H, H_d), 5.02 (dd, *J* = 15.9, 1.1 Hz, 1 H, H_k or $H_{k'}$), 7.44 (d, *J* = 7.8 Hz, 1 H, H_f), 7.77 (d, *J* = 7.8 Hz, 1 H, H_g) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8 (Si–*C*H_3), −4.1 (Si–*C*H_3), 18.1 [Si–*C*(CH$_3$)], 22.9 (C_a), 25.8 [Si–C(*C*H$_3$)], 51.5 (C_k), 52.8 (CO_2CH_3), 52.9 (CO_2CH_3), 59.9 (C_d), 65.8 (C_b), 68.4 (C_c), 125.6 (C_f), 128.5 (C_e), 129.6 (C_g), 131.1 (C_j), 142.7 (C_h), 144.7 (C_i), 167.1 (*C*O_2CH_3), 167.3 (*C*O_2CH_3), 178.3 (*C*=O_{lactam}) ppm. MS (DCI/NH_3): *m*/*z* = 451 $[M + NH_4]^+$,

434 $[M + H]^+$, 376 $[M - C(CH_3)_3]^+$. $C_{22}H_{31}NO_6Si$ (433.57): calcd. C 60.94, H 7.21, N 3.23; found C 61.26, H 7.40, N 2.96.

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