Synthesis of New Polycyclic β-Lactams via One-Pot Enyne Metathesis and Diels–Alder Reactions

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Abstract: One-pot ring-closing enyne metathesis and Diels–Alder reactions led to efficient synthesis of tricyclic and tetracyclic β-lactams.

Key words: metathesis, Diels–Alder cycloaddition, one-pot reactions, polycycles, lactams

One-pot processes are of considerable interest for the synthetic chemist due to the convenient experimental procedure, which does not require the isolation and purification of intermediates. Such processes have been widely investigated in the last decade due to their ecological and economic advantages when compared to stepwise procedures.[1] Consecutive ring-closing enyne metathesis and Diels–Alder reactions provide an attractive route to polycyclic compounds.[2] Variation of the size of the ring formed by enyne metathesis[3] and appropriate choice of dienophiles for the Diels–Alder cycloaddition[4] allow for the synthesis of a broad diversity of molecules. In this article we describe the synthesis of new polycyclic β-lactams via one-pot enyne metathesis and Diels–Alder reactions.

Although Penicillin G (**1**) and Cephalosporin C (**2**) were discovered more than fifty years ago, β-lactams still play a major role in current antibiotherapy.[5]

Whereas the early antibiotics were from natural sources, synthetic compounds with enhanced stability and activity against resistant bacteria have been developed in the last two decades. In 1984 researchers at Merck discovered 1β-methylcarbapenem (**3**) and in 1988 scientists at Glaxo introduced the class of trinems (tricyclic carbapenems), of which sanfetrinem (GV104326) (**4**) and sanfetrinem cilexetil (GV118819) (**5**) were until recently undergoing phase II clinical trials (Figure 1). Many research groups, both academic and industrial, have then devoted efforts towards the synthesis of polycyclic β-lactams.[6,7]

As part of our ongoing program dedicated to the synthesis of biologically relevant molecules,[8] we reported a few years ago our efforts towards the synthesis of 1β-methylcarbapenems using π-allylpalladium ring-closure strategy

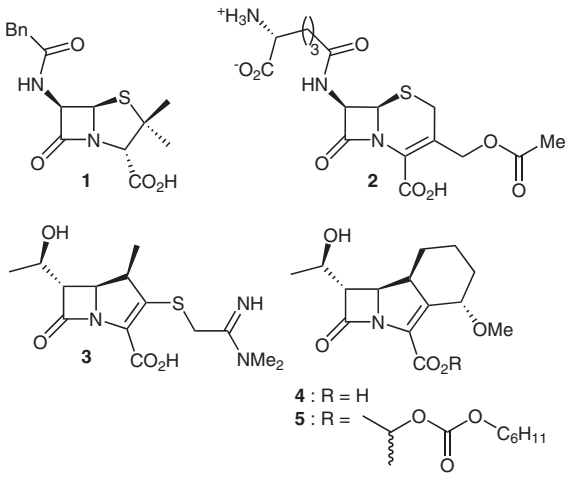
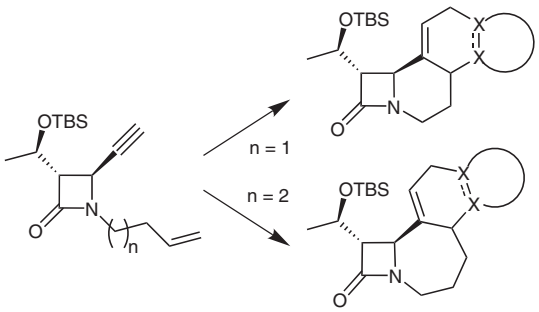


Figure 1

to form the functionalized carbapenem skeleton.[9] More recently a preliminary report described our strategy for the synthesis of polycyclic 4/5/6 β-lactams based on enyne metathesis and Diels–Alder reactions.[10] Herein we report an extension of this strategy applied to the synthesis of new 4/6/6 and 4/7/6 polycyclic β-lactams via one-pot enyne metathesis and Diels–Alder reactions (Scheme 1). For comparison, metathesis and cycloaddition were first realised in separate steps.

Starting from the commercially available acetoxyazetidinone **6**,[11] condensation of the anion of trimethylsilylacetylene was performed in 85% yield with retention of configuration (Scheme 2). Alkylation of **7** with suitable bromide under phase transfer conditions also led to desi-



Scheme 1

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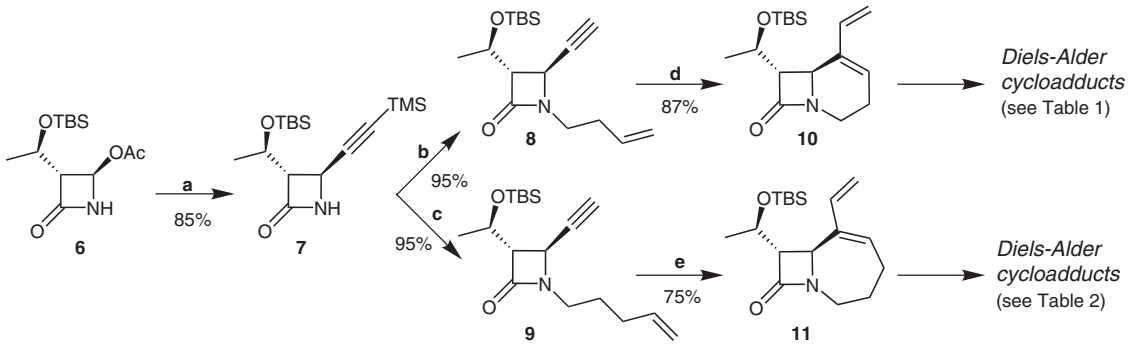


Scheme 2 *Reagents and conditions*: a) trimethylsilylacetylene, BuLi, THF, –10 °C, then **6**, –50 °C→ –30 °C; b) 4-bromobut-1-ene, Bu_4NHSO_4, NaI, KOH, THF, r.t.; c) 5-bromopent-1-ene, Bu_4NHSO_4, NaI, KOH, THF, r.t.; d) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 50 °C, 22 h; e) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 80 °C, 24 h

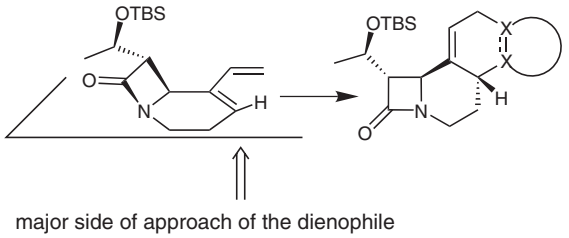
lylation of the alkyne to give the desired enynes **8** and **9** in high yields. Ring-closing enyne metathesis with 5% of Grubbs' first generation catalyst[12] (**A**) afforded the bicyclic compounds 4/6 **10** and 4/7 **11** in 87% and 75% yields, respectively. These dienes were next engaged in Diels–Alder reactions with various dienophiles. Cycloadditions of diene **10** in dichloromethane at 80 °C with dimethylacetylene dicarboxylate (DMAD), *para*-benzoquinone and maleimide led to high yields (90–99%) of the cycloadducts **12**–**14** (Table 1). Due to the high reactivity of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), the cycloaddition with this dienophile had to be performed at room temperature to prevent decomposition of the product **15**. A single diastereomer was obtained with *para*-benzoquinone and PTAD, whereas reactions with DMAD and maleimide yielded a mixture of diastereomers.

The stereochemistry of the products was elucidated by NOESY. In all cases, the adduct or major product arose from an approach of the dienophile on the opposite side of the β-lactam ring in order to avoid the steric hindrance of the bent structure of the fused bicyclic system (Scheme 3). Cycloadditions with diene **11** were performed with DMAD, maleic anhydride and PTAD as dienophiles in dichloromethane (Table 2). Moderate to excellent yields (57–95%) of the cycloadducts **16**–**18** were obtained. As in

Table 1 Diels–Alder Reactions with Diene **10**

Entry	Dienophile	Temp (°C)[a] (equiv)	Yield (%)[b]	Products
1	CO_2Me, CO_2Me	80 (4 equiv)	92	OTBS, CO_2Me, CO_2Me, N, O **12a** + (1.8 : 1) OTBS, CO_2Me, CO_2Me, N, O **12b**
2	O, O	80 (4 equiv)	90	OTBS, OH, OH, N, O **13**
3	NH, O, O	80 (3 equiv)	99	OTBS, NH, O, O, N, O **14a** + (5.6 : 1) OTBS, NH, O, O, N, O **14b**
4	N, N, N, O, O, Ph	25 (2 equiv)	90	OTBS, N, N, N–Ph, O, O, N, O **15**

[a] Reactions run in CH_2Cl_2 for 20 h in screw-cap tubes.
[b] Isolated yields.

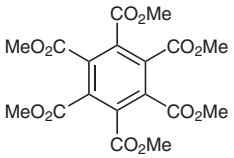


Scheme 3

the case of diene **10**, a preferential approach of the dienophile on the opposite side of the β-lactam ring was observed.

However, in order to avoid the isolation and purification of dienes **10** and **11**, one-pot ring-closing enyne metathesis and subsequent Diels–Alder reactions were carried out consecutively (Schemes 4 and 5). Experimentally, reactions between enynes **8** and **9** and Grubbs' catalyst were first run in dichloromethane at 50 or 80 °C, respectively, for 20 h. The dienophile was then added and the temperature was set to perform the cycloaddition.

Interestingly, one-pot metathesis–cycloaddition of enyne **8** with maleimide and PTAD gave better yields of the 4/6/6 cycloadducts **14**, **15** than the stepwise procedure, with a remarkable 97% yield in **14** (Scheme 4). On the contrary, better yields were obtained via the stepwise sequence with *para*-benzoquinone and DMAD due to the formation of side-products resulting from the side-reactions of the Grubbs' catalyst with the cycloadducts or the dienophile. In one example, one-pot sequence with DMAD afforded by-product **19** in approximately 10% yield (Figure 2). Formation of hexamethyl mellitate **19** might involve enyne metathesis or [2 + 2 + 2] cycloaddition catalyzed by the ruthenium complex as possible mechanistic pathways.[13,14]



19

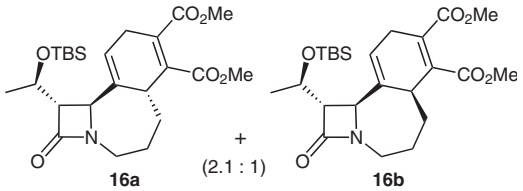
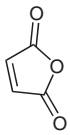
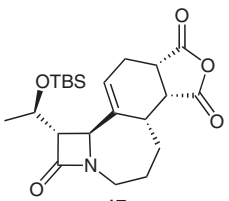
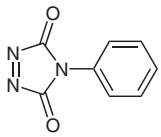
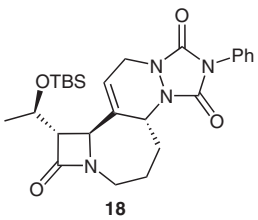
Figure 2

One-pot metathesis–Diels–Alder reactions of enyne **9** gave better yields of the 4/7/6 products **16–18** (Scheme 5). Surprisingly, and in contrast with the result obtained with diene **8** and DMAD, the one-pot sequence of **9** with DMAD was more efficient than the stepwise procedure, although the formation of hexamethyl mellitate **19** was again observed.

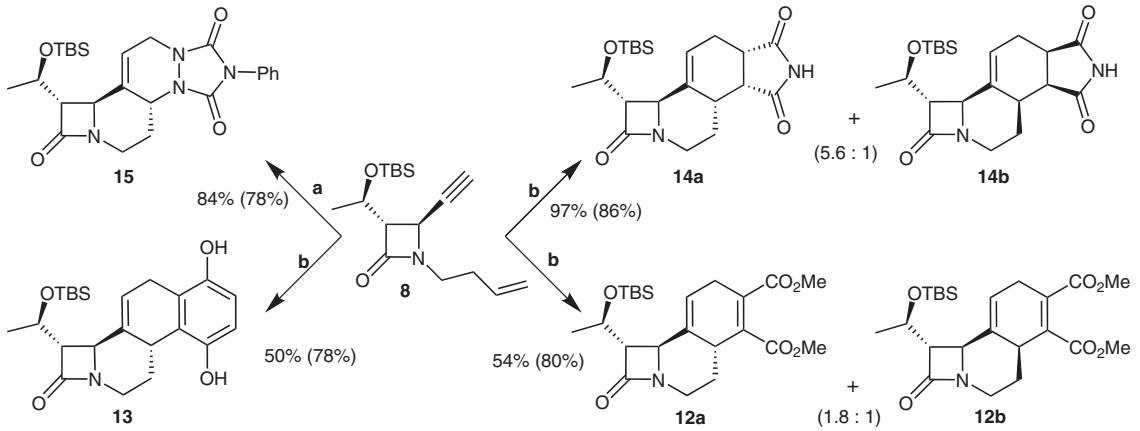
The selectivity of the Diels–Alder reactions with enyne **8** and **9** in the one-pot sequence was the same as with dienes **10** and **11** in the stepwise procedure.

In conclusion, we have devised an atom economical route to new polycyclic 4/6/6 and 4/6/7 β-lactams via enyne metathesis and Diels–Alder reactions. These two key steps could be performed consecutively in a one-pot fashion. In most cases this one-pot procedure not only avoided the isolation of intermediate dienes, but also gave in-

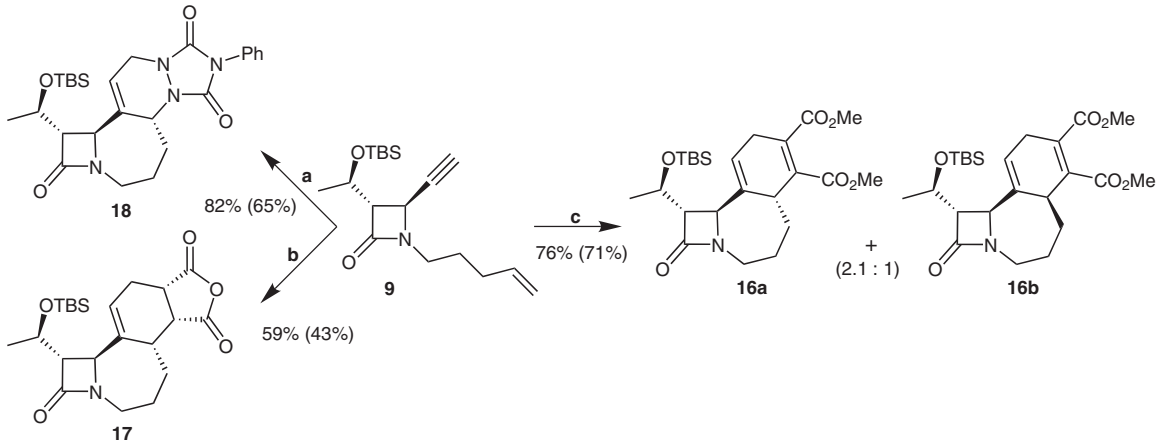
Table 2 Diels–Alder Reactions with Diene **11**

Entry	Dienophile	Temp (°C)[a] (equiv)	Yield (%)[b]	Products
1		80 (4 equiv)	95	 **16a** (2.1 : 1) **16b**
2		65 (4 equiv)	57	 **17**
3		25 (2 equiv)	86	 **18**

[a] Reactions run in CH_2Cl_2 for 20 h in screw-cap tubes.
[b] Isolated yields.



Scheme 4 *For comparison, overall yields for the reactions run in separate steps are indicated in brackets. Reagents and conditions*: a) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 50 °C, 20 h, then PTAD, r.t., 20 h; b) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 50 °C, 20 h, then dienophile, 80 °C, 20 h



Scheme 5 *For comparison, overall yields for the reactions run in separate steps are indicated in brackets. Reagents and conditions*: a) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 80 °C, 20 h, then PTAD, r.t., 20 h; b) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 80 °C, 20 h, then maleic anhydride, 65 °C, 20 h; c) $RuCl_2(=CHPh)(PCy_3)_2$ (**A**), CH_2Cl_2, 80 °C, 20 h, then DMAD, 80 °C, 20 h

creased overall yields of polycyclic compounds. Extension of this methodology and biological evaluation of these new compounds is envisaged in our laboratory. These results will be presented in due course.

All the reactions were performed in oven-dried glassware under an atmosphere of argon. THF was freshly distilled from sodium and benzophenone, and CH_2Cl_2 was distilled over calcium hydride prior to use. All other reagents and solvents were used as supplied. 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 using a thin film supported on NaCl plates or KBr discs where stated. Details are reported as ν_{max} 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 = quartet, 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. Mps are uncorrected and were measured on a Stuart Scientific or on Kofler apparatus. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

(3*S*,4*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-trimethylsilanylethynylazetidin-2-one (7)

Under argon, to a solution of trimethylsilylacetylene (8.83 mL, 62.5 mmol, M = 98.22, d = 0.695, 2.5 equiv) in THF (150 mL) at –15 °C was added dropwise a solution of BuLi in hexane (2.14 M; 29.2 mL, 62.5 mmol, 2.5 equiv). The solution was stirred for 1 h, then cooled to –50 °C, and a solution of acetoxyazetidinone **6** (7.181 g, 25 mmol, M = 287.24, 1 equiv) in THF (50 mL) was slowly added via cannula. The reaction mixture was allowed to warm up slowly to –30 °C (5 h) and was then quenched with sat. aq NH_4Cl. Extraction with Et_2O and EtOAc followed by drying (Na_2SO_4), concentration in vacuo and purification by flash chromatography (500 g of silica gel; cyclohexane–EtOAc, 9:1) gave **7**.

Yield: 6.932 g (85%); white solid; mp 137 °C (Lit.[15] not reported); $[\alpha]_D^{29}$ +37 (*c* 1.05, $CHCl_3$) {Lit.[15] $[\alpha]_D^{21}$ +39.0 (*c* 1.016, $CHCl_3$)}.

IR (KBr): 3165, 2953, 2927, 2857, 2182, 1765, 1251 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.15 (s, 9 H), 0.85 (s, 9 H), 1.23 (d, 3 H, *J* = 6.3 Hz), 3.24–3.28 (m, 1 H), 4.21 (qd, 1 H, *J* = 6.2, 3.8 Hz), 4.33 (d, 1 H, *J* = 2.4 Hz).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = –5.3, –4.4, –0.4, 17.8, 22.1, 25.5, 39.4, 64.5, 67.6, 89.9, 103.2, 167.7.

MS (CI, NH_3): *m*/*z* = 343 $[M + NH_4]^+$, 326 $[M + H]^+$, 268 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{16}H_{31}NO_2Si_2$ (325.59): C, 59.02; H, 9.60; N, 4.30. Found: C, 59.02; H, 9.55; N, 4.30.

(3*S*,4*S*)-1-(3-Butenyl)-3-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)ethyl]-4-ethynylazetidin-2-one (8)

Under argon, to a solution of **7** (2.28 g, 7 mmol, M = 325.59, 1 equiv) in THF (70 mL) at r.t., were successively added 4-bromobut-1-ene (1.42 mL, 14 mmol, M = 135.0, d = 1.33, 2 equiv), tetrabutylammonium hydrogen sulfate (950.7 mg, 2.8 mmol, M = 339.54, 0.4 equiv), sodium iodide (105 mg, 0.7 mmol, M = 150, 0.1 equiv) and freshly crushed potassium hydroxide (982 mg, 17.5 mmol, M = 56.11, 2.5 equiv). The solution was stirred vigorously for 3 h and then quenched with sat. aq NH_4Cl. The aq layer was extracted several times with Et_2O, the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (45 g of silica gel; cyclohexane–EtOAc, 9:1) afforded **8**.

Yield: 2.049 g (95%); pale yellow oil; $[\alpha]_D^{25}$ –20 (*c* 1.00, $CHCl_3$).

IR (NaCl film): 3311, 3084, 2954, 2929, 2857, 2117, 1766, 1645, 1259 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.86 (s, 9 H), 1.21 (d, 3 H, *J* = 6.3 Hz), 2.31–2.37 (m, 2 H), 2.44 (d, 1 H, *J* = 2.0 Hz), 3.13–3.20 (m, 2 H), 3.38–3.45 (m, 1 H), 4.19 (m, 1 H), 4.23 (dd, 1 H, *J* = 2.2, 2.0 Hz), 5.05 (dd, 1 H, *J* = 10.3, 1.4 Hz), 5.12 (dd, 1 H, *J* = 17.1, 1.4 Hz), 5.79 (ddt, 1 H, *J* = 17.0, 10.2, 6.7 Hz).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = –5.0, –4.5, 17.8, 22.2, 25.6, 32.0, 40.1, 42.5, 64.5, 65.9, 74.2, 80.4, 116.8, 134.8, 166.8.

MS (CI, NH_3): *m*/*z* = 325 $[M + NH_4]^+$, 308 $[M + H]^+$, 250 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{17}H_{29}NO_2Si$ (307.50): C, 66.40; H, 9.51; N, 4.55. Found: C, 66.50; H, 9.45; N, 4.42.

(3*S*,4*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-ethynyl-1-pent-4-enylazetidin-2-one (9)

Under argon, to a solution of **7** (1.63 g, 5 mmol, M = 325.59, 1 equiv) in THF (50 mL) at r.t., were successively added 5-bromopent-1-ene (97%, 1.07 mL, 9 mmol, M = 149.04, d = 1.259, 1.8 equiv), tetrabutylammonium hydrogen sulfate (679 mg, 2 mmol, M = 339.54, 0.4 equiv), sodium iodide (75 mg, 0.5 mmol, M = 150, 0.1 equiv) and freshly crushed potassium hydroxide (701 mg, 12.5 mmol, M = 56.11, 2.5 equiv). The solution was stirred vigorously for 3 h and then quenched with sat. aq NH_4Cl. The aq layer was extracted several times with Et_2O, the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (50 g of silica gel; cyclohexane–EtOAc, 9:1) afforded **9**.

Yield: 1.530 g (95%); pale yellow oil; $[\alpha]_D^{25}$ –24.5 (*c* 1.26, $CHCl_3$).

IR (NaCl film): 3310, 3078, 2954, 2929, 2857, 2117, 1762, 1641, 1257, 1142, 1061, 837, 779 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.86 (s, 9 H), 1.22 (d, 3 H, *J* = 6.2 Hz), 1.65–1.74 (m, 2 H), 2.04–2.17 (m, 2 H), 2.44 (d, 1 H, *J* = 1.9 Hz), 3.07–3.20 (m, 1 H), 3.19 (t, 1 H, *J* = 2.6 Hz), 3.28–3.44 (m, 1 H), 4.15–4.26 (m, 2 H), 4.99 (d, 1 H, *J* = 10.4 Hz), 5.04 (dd, 1 H, *J* = 16.8, 1.5 Hz), 5.75 (dddd, 1 H, *J* = 16.8, 10.4, 6.6, 6.4 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –4.9, –4.5, 17.9, 22.3, 25.7, 26.8, 31.1, 40.3, 42.2, 64.3, 65.8, 74.2, 80.6, 115.3, 137.3, 167.0.

MS (CI, NH_3): *m*/*z* = 339 $[M + NH_4]^+$, 322 $[M + H]^+$, 264 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{18}H_{31}NO_2Si$ (321.53): C, 67.24; H, 9.72; N, 4.36. Found: C, 67.20; H, 9.76; N, 4.39.

Diene 10

In a screw-cap tube flushed with argon, enyne **8** (315 mg, 1.02 mmol, M = 307.50, 1 equiv), degassed CH_2Cl_2 (20 mL), and Grubbs' first generation catalyst **A** (42.2 mg, 51.3 μmol, M = 822.96, 0.05 equiv) were successively introduced. The solution was heated at 50 °C (oil bath temperature) for 22 h, then concentrated in vacuo. Purification by flash chromatography (15 g of silica gel; cyclohexane–EtOAc, 9:1) gave **10**.

Yield: 274.8 mg (87%); brownish–yellow oil which crystallised (mp 20–30 °C) when kept below 0 °C; $[\alpha]_D^{25}$ –180 (*c* 1.05, $CHCl_3$).

IR (NaCl film): 2954, 2930, 2857, 1757, 1257 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.32 (d, 3 H, *J* = 6.2 Hz), 2.05–2.18 (m, 1 H), 2.45–2.62 (m, 1 H), 2.73 (dd, 1 H, *J* = 13.4, 5.2 Hz), 2.77–2.86 (m, 1 H), 3.88 (dd, 1 H, *J* = 13.4, 7.4 Hz), 3.97 (br s, 1 H), 4.12–4.25 (m, 1 H), 5.03 (d, 1 H, *J* = 11.0 Hz), 5.48 (d, 1 H, *J* = 17.9 Hz), 5.83–5.85 (m, 1 H), 6.23 (dd, 1 H, *J* = 17.9, 11.0 Hz).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = –4.6, 18.0, 23.2, 24.2, 25.7, 35.3, 49.2, 64.3, 67.7, 114.0, 127.6, 135.9, 136.3, 170.3.

MS (CI, NH_3): *m*/*z* = 325 $[M + NH_4]^+$, 308 $(M + H)^+$.

Anal. Calcd for $C_{17}H_{29}NO_2Si$ (307.50): C, 66.40; H, 9.51; N, 4.55. Found: C, 66.31; H, 9.60; N, 4.56.

Diene 11

In a screw-cap tube flushed with argon, enyne **9** (165.8 mg, 0.52 mmol, M = 321.53, 1 equiv), degassed CH_2Cl_2 (10 mL), and Grubbs' first generation catalyst **A** (20.6 mg, 25 μmol, M = 822.96, 0.05 equiv) were successively introduced. The solution was heated at 80 °C (oil bath temperature) for 24 h, then concentrated in vacuo. Purification by flash chromatography (10 g of silica gel; cyclohexane–EtOAc, 85:15) gave **11**.

Yield: 124.6 mg (75%); yellow oil; $[\alpha]_D^{25}$ –133.6 (*c* 1.14, $CHCl_3$).

IR (NaCl film): 2952, 2928, 2856, 1755, 1634, 1255, 1142, 1063, 835, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.28 (d, 3 H, *J* = 6.4 Hz), 1.81–1.86 (m, 2 H), 2.23–2.32 (m, 2 H), 2.89 (d, 1 H, *J* = 4.0 Hz), 3.12 (dt, 1 H, *J* = 13.0, 4.4 Hz), 3.79 (ddd, 1 H, *J* = 13.0, 8.7, 8.3 Hz), 4.15–4.23 (m, 1 H), 4.34 (br s, 1 H), 4.97 (d, 1 H, *J* = 11.0 Hz), 5.37 (d, 1 H, *J* = 17.5 Hz), 5.87–5.91 (m, 1 H), 6.18 (dd, 1 H, *J* = 17.5, 11.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –4.7, –4.4, 17.9, 23.2, 25.8, 26.0, 26.6, 41.4, 55.8, 65.1, 66.3, 113.6, 129.7, 137.1, 139.1, 167.9.

MS (CI, NH_3): *m*/*z* = 339 $[M + NH_4]^+$, 322 $[M + H]^+$, 264 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{18}H_{31}NO_2Si$ (321.53): C, 67.24; H, 9.72; N, 4.36. Found: C, 67.29; H, 9.61; N, 4.28.

Diels–Alder Cycloadduct 12a

White solid; mp 105 °C; $[\alpha]_D^{25}$ – 43.5 (*c* 0.85, $CHCl_3$).

IR (NaCl film): 2974, 2954, 2934, 2896, 2882, 2853, 1751, 1726, 1649, 1269, 1153, 1065, 841, 830, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.87 (s, 9 H), 1.23 (d, 3 H, *J* = 6.2 Hz), 1.58–1.67 (m, 1 H), 2.08–2.15 (m, 1 H), 2.90–3.00 (m, 1 H), 2.94 (dd, 1 H, *J* = 4.6, 1.9 Hz), 3.08–3.21 (m, 3 H), 3.76 (s, 3 H), 3.77–3.87 (m, 1 H), 3.79 (s, 3 H), 4.18–4.23 (m, 2 H), 5.63 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.8, –4.2, 18.0, 22.8, 25.8, 27.8, 29.1, 34.2, 38.0, 52.5, 52.8, 65.2, 65.9, 117.6, 131.1, 136.0, 136.6, 167.5, 168.3, 170.0.

MS (CI, NH_3): *m/z* = 467 $[M + NH_4]^+$, 450 $[M + H]^+$, 392 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{23}H_{35}NO_6Si$ (449.61): C, 61.44; H, 7.85; N, 3.12. Found: C, 61.37; H, 8.03; N, 2.98.

Diels–Alder Cycloadduct 12b

White solid; mp 131 °C; $[\alpha]_D^{25}$ +84.5 (*c* 2.155, $CHCl_3$).

IR (NaCl film): 2952, 2928, 2934, 2893, 2856, 1747, 1732, 1651, 1258, 1140, 1072, 836, 777 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.86 (s, 9 H), 1.26 (d, 3 H, *J* = 6.3 Hz), 1.53 (qd, 1 H, *J* = 12.5, 5.5 Hz), 1.88 (dt, 1 H, *J* = 12.5, 2.9 Hz), 2.89–2.99 (m, 2 H), 3.13 (ddd, 1 H, *J* = 7.4, 3.0, 2.0 Hz), 3.19 (dd, 1 H, *J* = 5.5, 1.9 Hz), 3.19–3.28 (m, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.88–3.93 (m, 1 H), 3.91 (br s, 1 H), 4.19 (quint, 1 H, *J* = 5.9 Hz), 5.60 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.0, –4.1, 18.0, 23.0, 25.7, 27.3, 32.8, 36.9, 38.8, 52.5, 53.6, 64.6, 65.6, 117.0, 130.8, 133.9, 136.4, 167.0, 167.5, 168.5.

MS (CI, NH_3): *m/z* = 467 $[M + NH_4]^+$, 450 $[M + H]^+$, 392 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{23}H_{35}NO_6Si$ (449.61): C, 61.44; H, 7.85; N, 3.12. Found: C, 61.34; H, 7.90; N, 3.30.

Diels–Alder Cycloadduct 13

White solid; mp 249–254 °C; $[\alpha]_D^{25}$ –62.0 (*c* 0.71, $CHCl_3$).

IR (KBr): 3324, 2956, 2928, 2887, 2857, 1726, 1704, 1686, 1654, 1251, 1146, 1059, 832, 776 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.12 (s, 6 H), 0.91 (s, 9 H), 1.26 (d, 3 H, *J* = 6.2 Hz), 1.45–1.52 (m, 1 H), 2.66–2.74 (m, 1 H), 3.02–3.08 (m, 2 H), 3.28–3.30 (m, 2 H), 3.40–3.46 (m, 1 H), 3.85 (dt, 1 H, *J* = 12.9, 9.6 Hz), 4.24–4.29 (m, 1 H), 4.29 (br s, 1 H), 5.88–5.89 (m, 1 H), 6.56 (s, 2 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = –4.8, –4.3, 18.4, 22.7, 25.7, 26.0, 31.9, 32.7, 38.6, 55.3, 65.7, 66.3, 113.2, 113.4, 118.9, 122.4, 124.5, 138.4, 148.2, 148.4, 170.8.

MS (CI, NH_3): *m/z* = 433 $[M + NH_4]^+$, 416 $[M + H]^+$, 358 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{23}H_{33}NO_4Si$ (415.60): C, 66.47; H, 8.00; N, 3.37. Found: C, 66.32; H, 8.18; N, 3.49.

Diels–Alder Cycloadduct 14a

White solid; mp 85 °C; $[\alpha]_D^{25}$ –46.6 (*c* 1.03, $CHCl_3$).

IR (KBr): 3224, 3077, 2956, 2930, 2885, 2856, 1777, 1724, 1655, 1352, 1321, 1257, 1142, 1056, 835, 810, 777 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 1.23 (d, 3 H, *J* = 6.2 Hz), 1.95–2.06 (m, 1 H), 2.09–2.21 (m, 1 H), 2.29–2.40 (m, 1 H), 2.59 (qd, 1 H, *J* = 13.8, 5.5 Hz), 2.76–2.82 (m, 2 H), 3.19–3.24 (m, 2 H), 3.25–3.35 (m, 1 H), 3.41–3.48 (m, 1 H), 3.94 (br s, 1 H), 4.13 (quint, 1 H, *J* = 5.9 Hz), 5.74–5.80 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.1, –5.1, 18.0, 22.7, 22.9, 24.1, 25.7, 35.1, 39.0, 41.4, 44.5, 49.4, 65.0, 65.4, 121.1, 141.2, 168.7, 177.6, 179.3.

MS (CI, NH_3): *m/z* = 422 $[M + NH_4]^+$, 405 $[M + H]^+$, 347 $[M - C(CH_3)_3]^+$.

HRMS: *m/z* calcd for $C_{21}H_{33}N_2O_4Si$ (M + H): 405.2210; found: 405.2213.

Diels–Alder Cycloadduct 14b

White solid; mp 163 °C; $[\alpha]_D^{25}$ +35.3 (*c* 0.85, $CHCl_3$).

IR (KBr): 3171, 3075, 2955, 2929, 2887, 2856, 1741, 1714, 1647, 1352, 1250, 1144, 1057, 835, 811, 778 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.86 (s, 9 H), 1.24 (d, 3 H, *J* = 6.2 Hz), 1.90–2.10 (m, 2 H), 2.22–2.34 (m, 1 H), 2.58–2.81 (m, 2 H), 2.88–2.94 (m, 1 H), 3.00 (dd, 1 H, *J* = 5.1, 2.0 Hz), 3.15 (td, 1 H, *J* = 8.2, 2.7 Hz), 3.24 (t, 1 H, *J* = 8.2 Hz), 3.88 (dt, 1 H, *J* = 13.3, 5.1 Hz), 4.01 (br s, 1 H), 4.17 (quint, 1 H, *J* = 5.9 Hz), 5.72–5.79 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.4, –5.1, 17.8, 21.8, 22.8, 26.0, 27.0, 32.2, 38.0, 40.1, 43.4, 52.2, 65.2, 65.4, 120.5, 137.0, 167.8, 177.9, 178.9.

MS (CI, NH_3): *m/z* = 422 $[M + NH_4]^+$, 405 $[M + H]^+$, 347 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{21}H_{32}N_2O_4Si$ (404.58): C, 62.34; H, 7.97; N, 6.92. Found: C, 62.32; H, 7.98; N, 6.76.

Diels–Alder Cycloadduct 15

White solid; mp 245 °C; $[\alpha]_D^{25}$ –19.4 (*c* 0.89, $CHCl_3$).

IR (KBr): 2954, 2929, 2895, 2856, 1769, 1753, 1713, 1420, 1139, 839, 779, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.89 (s, 9 H), 1.27 (d, 3 H, *J* = 6.2 Hz), 1.76–1.88 (m, 1 H), 2.99–3.05 (m, 1 H), 3.02 (dd, 1 H, *J* = 4.5, 2.0 Hz), 3.18 (ddd, 1 H, *J* = 13.1, 8.4, 1.3 Hz), 3.97 (ddd, 1 H, *J* = 13.1, 10.7, 8.9 Hz), 4.17–4.20 (m, 2 H), 4.22–4.28 (m, 1 H), 4.34–4.40 (m, 1 H), 4.39 (br s, 1 H), 5.85–5.87 (m, 1 H), 7.36–7.40 (m, 1 H), 7.45–7.50 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.8, –4.2, 18.0, 22.8, 25.8, 26.4, 36.4, 42.8, 52.2, 52.7, 65.1, 66.4, 115.5, 125.5, 128.4, 129.3, 131.0, 136.3, 152.2, 152.5, 168.9.

MS (CI, NH_3): *m/z* = 500 $[M + NH_4]^+$, 483 $[M + H]^+$, 426 $[M - C(CH_3)_3]^+$.

HRMS: *m/z* calcd for $C_{25}H_{35}N_4O_4Si$ (M + H): 483.2428; found: 483.2434.

Diels–Alder Cycloadduct 16a

White solid; mp 94 °C; $[\alpha]_D^{25}$ –67.0 (*c* 1.01, $CHCl_3$).

IR (NaCl film): 2999, 2956, 2929, 2897, 2885, 1738, 1721, 1648, 1256, 1154, 1073, 835, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.86 (s, 9 H), 1.19 (d, 3 H, *J* = 6.3 Hz), 1.14–1.26 (m, 1 H), 1.60–1.80 (m, 2 H), 2.05–2.12 (m, 1 H), 2.55–2.62 (m, 1 H), 2.83 (dd, 1 H, *J* = 4.2, 2.1 Hz), 2.90–3.15 (m, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.84–3.90 (m, 1 H), 4.22–4.27 (m, 2 H), 5.75–5.76 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.9, –4.2, 18.0, 22.6, 25.8, 28.4, 28.6, 36.0, 37.4, 41.7, 52.5, 52.6, 58.2, 63.7, 65.2, 120.6, 133.5, 137.2, 139.0, 167.6, 167.8, 168.4.

MS (Electrospray, CI): *m/z* = 486 $[M + Na]^+$, 481 $[M + NH_4]^+$, 464 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{37}NO_6Si$ (463.64): C, 62.17; H, 8.04; N, 3.02. Found: C, 62.03; H, 8.22; N, 2.86.

Diels–Alder Cycloadduct 16b

White solid; mp 92 °C; $[\alpha]_D^{25}$ +147.9 (*c* 0.545, $CHCl_3$).

IR (NaCl film): 2951, 2928, 2855, 1738, 1721, 1650, 1258, 1143, 1066, 836 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.84 (s, 9 H), 1.16 (d, 3 H, *J* = 6.3 Hz), 1.15–1.32 (m, 1 H), 1.65–1.82 (m, 1 H), 1.94–2.03 (m, 1 H), 2.11–2.18 (m, 1 H), 2.91–3.15 (m, 3 H), 3.19–3.28 (m, 1 H), 3.22 (br s, 1 H), 3.41 (dt, 1 H, *J* = 13.0, 4.3 Hz), 3.77 (s, 3 H), 3.87 (s, 3 H), 4.09 (br s, 1 H), 4.25 (qd, 1 H, *J* = 6.3, 3.7 Hz), 5.73 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.0, –4.1, 17.9, 22.7, 25.7, 25.8, 27.9, 34.0, 41.8, 43.3, 52.4, 52.5, 56.2, 57.6, 64.8, 118.7, 131.0, 135.5, 138.1, 167.3, 167.7, 168.7.

MS (Electrospray, CI): *m/z* = 486 $[M + Na]^+$, 481 $[M + NH_4]^+$, 464 $[M + H]^+$.

HRMS: *m/z* calcd for $C_{24}H_{38}NO_6Si$ (M + H): 483.2468; found: 464.2470.

Diels–Alder Cycloadduct 17

White solid; mp 58–65 °C; $[\alpha]_D^{25}$ –7.3 (*c* 1.745, $CHCl_3$).

IR (KBr): 2955, 2930, 2897, 2856, 1847, 1751, 1777, 1750, 1631, 1251, 1139, 1085, 965, 834, 777 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.05 (s, 3 H), 0.82 (s, 9 H), 1.20 (d, 3 H, *J* = 6.2 Hz), 1.47–1.72 (m, 1 H), 1.91–2.04 (m, 3 H), 2.30–2.36 (m, 1 H), 2.50–2.53 (m, 1 H), 2.70–2.81 (m, 2 H), 2.99 (dd, 1 H, *J* = 5.6, 1.0 Hz), 3.36 (dd, 1 H, *J* = 9.8, 5.4 Hz), 3.42–3.47 (m, 1 H), 3.85–3.89 (m, 1 H), 4.06 (br s, 1 H), 4.11–4.19 (m, 1 H), 5.84–5.86 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.0, –4.2, 17.8, 22.9, 23.7, 25.7, 28.3, 29.1, 39.7, 40.3, 41.9, 46.7, 57.3, 63.3, 65.7, 123.8, 142.4, 167.3, 172.0, 173.8.

MS (CI, NH_3): *m/z* = 437 $[M + NH_4]^+$, 420 $[M + H]^+$, 362 $[M - C(CH_3)_3]^+$.

HRMS: *m/z* calcd for $C_{22}H_{34}NO_5Si$ (M + H): 420.2206; found: 420.2208.

Diels–Alder Cycloadduct 18

White solid; mp 192–194 °C; $[\alpha]_D^{25}$ –180.0 (*c* 1.03, $CHCl_3$).

IR (KBr): 2952, 2928, 2934, 2895, 2882, 2855, 1777, 1746, 1732, 1708, 1652, 1504, 1455, 1429, 1140, 1060, 989, 830, 776, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.88 (s, 9 H), 1.24 (d, 3 H, *J* = 6.3 Hz), 1.61–1.71 (m, 1 H), 1.71–1.80 (m, 1 H), 1.85–1.95 (m, 1 H), 2.19–2.25 (m, 1 H), 2.65 (ddd, 1 H, *J* = 14.1, 11.0, 2.9 Hz), 2.95 (dd, 1 H, *J* = 4.0, 2.0 Hz), 3.89 (dt, 1 H, *J* = 14.1, 4.0 Hz), 4.00–4.04 (m, 1 H), 4.29 (qd, 1 H, *J* = 6.3, 4.0 Hz), 4.37 (br s, 1 H), 4.44 (dd, 1 H, *J* = 16.9, 4.2 Hz), 4.54–4.56 (m, 1 H), 5.91–5.92 (m, 1 H), 7.35–7.39 (m, 1 H), 7.45–7.53 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.9, –4.1, 18.0, 22.7, 25.8, 26.3, 33.0, 41.5, 43.9, 53.5, 55.8, 64.8, 65.0, 117.9, 125.4, 128.3, 129.3, 131.1, 138.1, 151.3, 153.4, 166.7.

MS (CI, NH_3): *m/z* = 514 $[M + NH_4]^+$, 497 $[M + H]^+$, 439 $[M - C(CH_3)_3]^+$.

Anal. Calcd for $C_{26}H_{36}N_4O_4Si$ (496.67): C, 62.87; H, 7.31; N, 11.28. Found: C, 62.97; H, 7.26; N, 11.04.

Hexamethyl Mellitate (19)

White solid; mp 179–184 °C (Lit.[16] 180–184 °C).

IR (KBr): 2958, 2928, 2855, 1729, 1575 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 18 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 51.1, 131.5, 162.7.

MS (CI, NH_3): *m/z* = 461 $[M + N_2H_7]^+$, 444 $[M + NH_4]^+$.

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