Investigation of a Unified Strategy for the Synthesis of Anatoxin Analogues: Scope and Limitations

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Abstract : Syntheses of the potent neurotoxins and biochemical probes anatoxin-a and homoanatoxin and several analogues by a combined two-directional synthesis–tandem reaction strategy are presented. Key steps include an oxidative desymmetrisation and a tandem Michael–intramolecular Mannich cyclisation.

Key words: anatoxin, homoanatoxin, two-directional, tandem, cascade, Michael, iminium, desymmetrisation

Anatoxin-a was initially isolated from the blue-green algae *Anabena flos aquae* in the 1970's,[1] after being first identified as the cause of incidents of fatal poisoning of wild and domestic animals by cyanobacterial blooms in North America and Europe,[2] leading to it being initially called VFDF (very fast death factor). Subsequently, anatoxin-a has been isolated from several other toxic strains of freshwater cyanobacteria.[3] Homoanatoxin (**2**) was first reported as a synthetic analogue of anatoxin-a by Gallagher in 1992,[4] and was later identified as a natural product from strains of *Oscillatoria formosa*[5] and *Rhabidopsis mediterranea*.[6] Anatoxin-a (**1**) and derivatives have been the subject of significant interest[7] due to their potent and selective activity as agonists at nicotinic acetylcholine receptors (nAChR), which has led to them being used as tools to investigate muscle and neuronal nAChR.[8] Due to their modulatory role in the brain, nAChRs have attracted attention as potential targets for therapeutic intervention in a range of disease states including neurodegenerative diseases, attention deficit disorder, pain, smoking cessation, schizophrenia and epilepsy.[9] Recently, we reported a concise and efficient total synthesis of anatoxin-a and homoanatoxin[10] using a combined two-directional synthesis and tandem reaction strategy which allowed both natural products to be accessed from a common intermediate. Herein, we report in full our investigations into an expansion of this work for the synthesis of several anatoxin analogues using the same common intermediate.

Our retrosynthetic analysis of the anatoxin framework is shown in Figure 1. We reasoned that a Mannich and a Horner–Wadsworth Emmons disconnective approach would allow the use of iminium synthon **3** as a precursor to both anatoxin-a and homologues through the choice of keto-phosphonate used. Iminium precursor **4** would be available through two-directional synthesis.

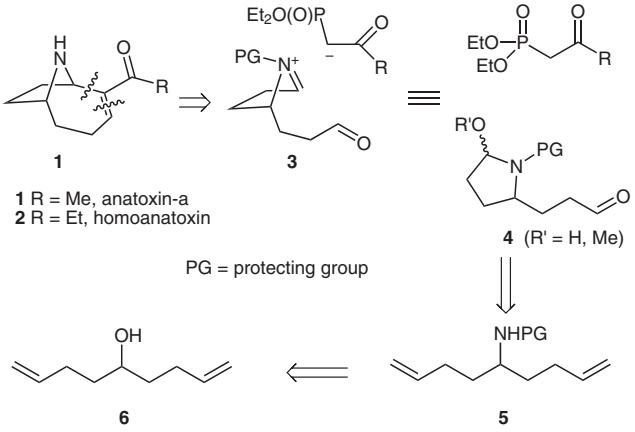
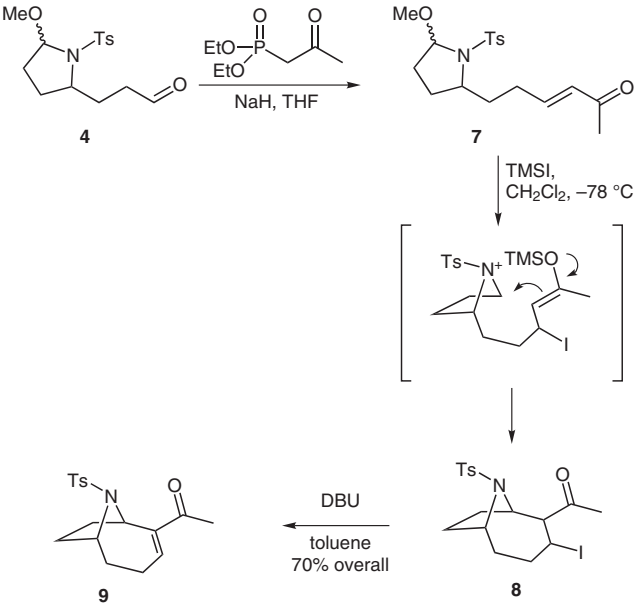


Figure 1 Retrosynthetic analysis

The key transformation in our synthesis of anatoxin-a and homoanatoxin was a iodotrimethylsilane (TMSI)-mediated tandem iminium formation–Bayliss–Hillman type cyclisation, developed from previously reported HCl-mediated cyclisations by Speckamp,[11] Somfai[12] and Tanner[13] on similar substrates for the formation of the anatoxin core structure (Scheme 1).



Scheme 1 Previously developed cyclisation to *N*-tosyl-protected anatoxin-a

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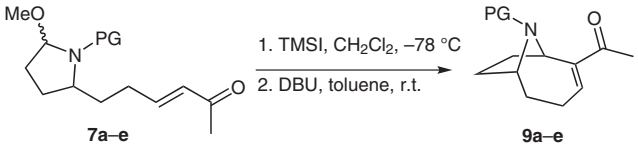
Table 1 Effect of Nitrogen Protecting Group on the Cyclisation to the Anatoxin Core Structure



Entry	Substrate **7**	PG	TMSI (equiv)	DBU (equiv)	Product **9**	Yield (%)[a]
1	**7a**	SES	1.2	–	**9a**	25[b]
2	**7a**	SES	2.4	1.4	**9a**	47
3	**7a**	SES	2.4	2.8	**9a**	66
4	**7b**[c]	Ts	2.0	2.8	**9b**[c]	70
5	**7b**[c]	Ts	2.0	2.8	**9b**[c]	50[d]
6	**7c**	2-NaphS	2.4	2.8	**9c**	78
7	**7d**	Ms	2.4	2.8	**9d**	15[e]
8	**7e**	Boc	2.4	2.8	**9e**	–

[a] Isolated yields.
[b] 51% yield of a single iodo-diastereoisomer **8** was also isolated.
[c] See Roe and Stockman.[10]
[d] Carried out on a 10.5 g scale with respect to starting material **7b**.
[e] This material is prone to facile polymerisation and the yield refers to product immediately isolated after column chromatography as a single spot by TLC. Concentration of this compound from solution leads to polymerisation.

The studies described herein investigate the substrate range for this cyclisation. In our work directed towards the synthesis of anatoxin-a,[10] we had screened around twenty conditions for the cyclisation reaction, of which TMSI–dichloromethane followed by treatment with DBU was found to be optimal.[14] Initially, we decided to investigate the effects of different nitrogen protecting groups on the yields of the cyclisation. The results of these studies are shown in Table 1.

An investigation into the effects of the number of equivalents of TMSI used suggested that more than one equivalent was necessary in order to attain good yields of product. Also, a separate dehydrohalogenation step was necessary. 2-Trimethylsilylethanesulfonyl (SES), tosyl (Ts) and 2-naphthalenesulfonyl groups (2-NaphS) were all found to give good yields of the cyclised products, although mesityl (Ms) and *tert*-butoxycarbonyl (Boc) protected products were found to degrade under the reaction conditions. As *N*-tosyl anatoxin-a had successfully been previously deprotected, we decided to conduct the analogue studies using this protecting group.

In order to undertake analogue syntheses,[15] and to probe the scope of the cyclisation, a series of phosphonates **11** were reacted with the *N*-sulfonyliminium ion cyclisation precursor **4**, to give a series of alkenes **7**. These were then subjected to the optimised cyclisation conditions, to give *N*-tosyl anatoxin-a analogues **9a–e** (Table 2).

The yields for the sequential ozonolytic desymmetrisation and olefination steps, providing the cyclisation precursors **7**, were consistently very good. However, as can be seen from Table 2, the yields for cyclisation and elimination steps providing the corresponding anatoxins **9** decreased as the alkyl chain substituent increased in size. Also, attempts at cyclisation with any functionality other than a ketone [R = -(CO)alkyl] resulted in only decomposition and no evidence of cyclisation (entries 6–10). In the penultimate example (entry 9) we hoped that the imide would be sufficiently similar to a ketone to enable cyclisation and also potentially facilitate a kinetic resolution. Unfortunately, since this imide substrate also failed to cyclise, this approach was not explored further. It is unclear why the cyclisation appears to be limited to ketone substrates. Indeed a few similar types of cyclisation in the literature have been shown to work on enal substrates but not on ketone substrates.[16] Thus, in this context, the current protocol does provide a complimentary protocol to these other methodologies. All but the longest alkyl chain analogue **9e** (entry 5) were crystallised so that their X-ray crystal structures could be collected (Figure 2).

Having explored the scope of the cyclisation and with a number of anatoxin analogues in hand, we looked into their deprotection. As in our initial work on anatoxin, we turned to a procedure developed by Bäckvall et al. who had successfully deprotected *N*-tosyl-protected ferruginine[17] via the dioxolane-protected ketone with magnesium in methanol under sonication.[18] Thus, dioxolane protection of the ketone functionality in the analogues **9** followed by treatment with 30 equivalents of magnesium powder in methanol under sonication for 40 minutes, followed by another 30 equivalents of magnesium and further sonication for 30 minutes, successfully

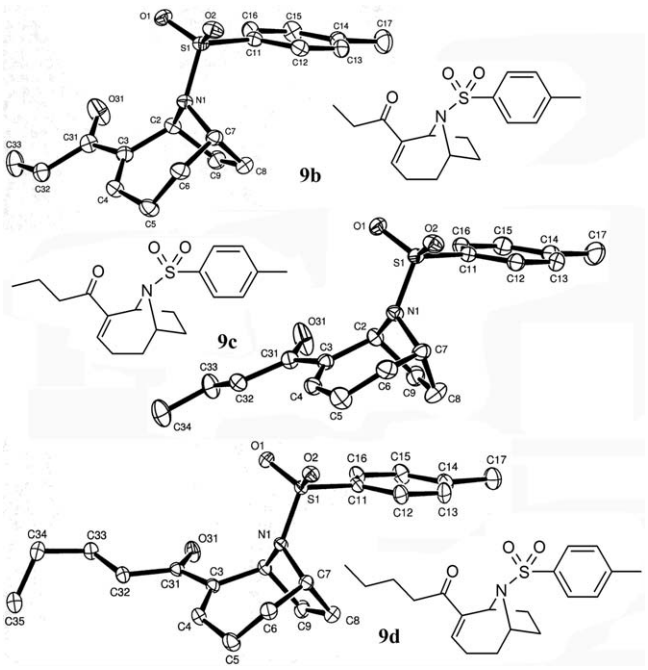


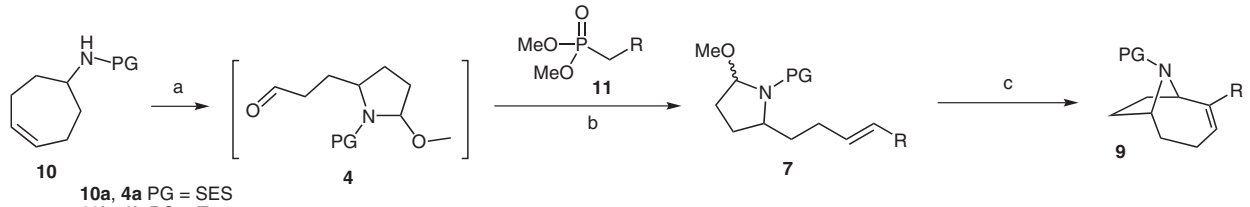
Figure 2 Tosyl anatoxin-a analogue crystal structures

cleaved the tosyl group giving the amine/dioxolane. The latter, fortuitously, swiftly deprotected on aqueous acidic workup affording the anatoxin analogues as shown in Table 3.

It was found that the determining factor that dictates the efficiency of the overall deprotection protocol was the initial ketone protection step, giving dioxolanes **12**. The best yield obtained for this step was obtained when the parent tosyl protected anatoxin-a was simply reacted under Dean–Stark conditions with ethylene glycol on a 1 g scale (Table 3, entry 1). However, since the classical Dean–Stark conditions could not be applied to the other analogues (entries 2–6) because of the small scale of the reactions, these analogues were reacted with ethylene glycol under catalytic Lewis acidic conditions with $BF_3{\cdot}Et_2O$ in the presence of triethyl orthoformate as a water scavenger.

In conclusion, we have developed a unified strategy for the synthesis of anatoxin analogues from a common intermediate using a TMSI-mediated tandem cyclisation. The scope and limitations of the cyclisation have been investigated and a robust procedure for the deprotection of *N*-arylsulfonyl anatoxin analogues has been developed.

Table 2 Synthesis of *N*-Tosyl-Protected Anatoxin Analogues[a]

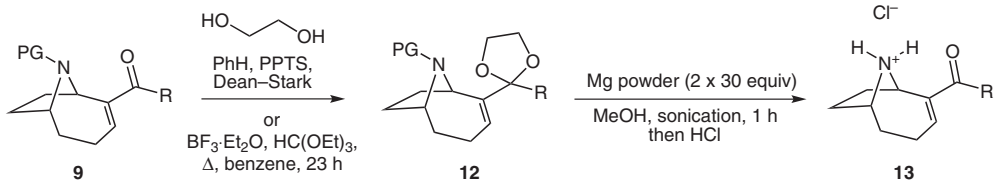


10a, **4a** PG = SES
10b, **4b** PG = Ts
10c, **4c** PG = 2-NaphS
10d, **4d** PG = Ms
10e, **4e** PG = Boc

Entry	Phosphonate **11**[c]	R	Yield (%)[b]			
1	**11a**[d]	-(CO)Me	**7b**[e]	76	**9b**[e]	70
2	**11b**	-(CO)Et	**7f**	65	**9f**[e]	55
3	**11c**	-(CO)*n*-Pr	**7g**	81	**9g**	52
4	**11d**	-(CO)*n*-Bu	**7h**	78	**9h**	50
5	**11e**	-(CO)*n*-Pent	**7i**	73	**9i**	20
6	**11f**	-CN	**7j**	64	–	–
7	**11g**	$-CO_2Et$	**7k**	64	–	–
8	**11h**	-(CO)-3-pyridyl	**7l**	66	–	–
9	**11i**	p087_t2-1a.eps	**7m**	76	–	–
10	–	CHO	**7n**	59[f]	–	–

[a] Reagents and conditions: (a) i. O_3, CH_2Cl_2–MeOH (5:1), –78 °C; ii. TsOH, r.t., 1.5 h; iii. $NaHCO_3$, r.t., 15 min; iv. Me_2S, r.t., 16 h; (b) NaH, phosphonate, THF, 0 °C → r.t., 18 h; (c) i. TMSI, CH_2Cl_2, –78 °C → r.t.; ii. DBU, r.t., toluene.
[b] Isolated yield after two steps.
[c] Phosphonates were prepared according to previous literature.[19]
[d] Commercially available diethyl (2-oxopropyl)phosphonate was used in this example.
[e] See Roe and Stockman.[10,]
[f] Compound **7n** was synthesised by reduction of nitrile **7j** with DIBAL-H in 50% yield.

Table 3 Deprotection of Anatoxin Analogues[a]



Entry	Substrate **9**	PG	R	Yield (%)[b]				
				12[c]		**13**		**13** (2 steps)
1	**9b**[d]	Ts	Me	**12a**	95[e]	**13a**	86[f]	82
2	**9f**[d]	Ts	Et	**12b**	71	**13b**	94	67
3	**9g**	Ts	*n*-Pr	**12c**	70	**13c**	87	61
4	**9h**	Ts	*n*-Bu	**12d**	52	**13d**	84	44
5	**9i**	Ts	*n*-Pent	**12e**	52	**13e**	–[g]	–
6	**9c**	2-NaphS	Me	**12f**	90[h]	**13a**	87	78

[a] Reagents and conditions for stage one: Ethylene glycol, cat. $BF_3{\cdot}Et_2O$, $HC(OEt)_3$, benzene, reflux, 23 h.
[b] Isolated yields.
[c] Two rotomers are seen in the NMR spectra for these compounds at r.t. due to hindered rotation around the C–C bond connecting the dioxolane ring to the bicycle.
[d] See Roe and Stockman.[10]
[e] Reagents and conditions for stage one: Ethylene glycol, cat. PPTS, benzene, Dean–Stark.
[f] A sample of this material was converted into its *N*-Boc derivative, the data for which matched those reported in the literature.[4]
[g] Reaction not performed due to insufficient amounts of material.
[h] Material taken directly into the next step after purification.

^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 101 MHz) spectra were recorded on Varian Gemini 300 or Varian 400 Lambda spectrometers. All NMR spectra were obtained from solutions of $CDCl_3$, unless otherwise stated. Signals are quoted in ppm as δ-shifts downfield from TMS (δ = 0.00 ppm) and coupling constants (*J*) are given in Hertz. Infrared spectra were recorded on a Perkin–Elmer 1720X FT-IR spectrophotometer as either thin films or Nujol mulls using KBr or NaCl plates. Elemental analyses were preformed by Mr Stephen Boyer at the London Metropolitan University with analytical data being quoted to the nearest 0.01%. Low resolution mass spectra EI, ES, CI and HRMS were obtained via the EPSRC National Mass Spectroscopy Service Centre at the University of Wales, Swansea. TLC analysis was carried out on Fluka glass-backed silica gel 60 F_{254} coated plates, or Merck aluminium-backed aluminium oxide 60 F_{254} coated plates, and were visualised by one or a combination of the following methods: (a) viewing under UV at 254 nm; (b) exposure to iodine vapour; (c) exposure to aq $KMnO_4$ solution containing: $KMnO_4$ (3 g), K_2CO_3 (20 g), aq NaOH (2 M, 5 mL), H_2O (300 mL); (d) exposure to an 8% ethanolic phosphomolybdic acid solution; (e) exposure to an ethanolic vanillin solution, containing: 4-hydroxy-3-methoxybenzaldehyde (6 g), EtOH (250 mL) and aq H_2SO_4 (12 M, 2.5 mL). Column chromatography was performed at r.t. using Merck silica gel 60 (0.063–0.200 mm) or BDH neutral aluminium oxide. Solvent systems are given as volume ratios. Melting points are uncorrected and were recorded using a Stuart Scientific SMP1 melting point apparatus.

Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. THF was freshly distilled from sodium and benzophenone; CH_2Cl_2 was freshly distilled from CaH_2; anhydrous MeCN, benzene, DMF, DCE, EtOH, MeOH and toluene were obtained commercially from Aldrich, in SureSeal™ grade packaging and stored over molecular sieves under argon. Other solvents were SLR-grade and used without further purification. H_2O refers to deionised water, and brine to sat. aq NaCl. The evaporation of solvents was carried out on a Buchi rotary evaporator at reduced pressure. Temperatures quoted in the reaction conditions refer to those of the cooling or heating bath, and all reactions were carried out under anhydrous argon or nitrogen using flame-dried glassware.

TMSI-Mediated Cyclisation of Hemi-aminal Ethers 7 to 9a–d and 9f–i; General Procedure

To a solution of the enone **7** (1.0 equiv) in CH_2Cl_2 (100 vols) at –78 °C, was added TMSI (2.4 equiv) dropwise. The reaction mixture was covered to exclude light, then allowed to warm to r.t. slowly in the cardice–acetone bath over 22 h. The reaction mixture was quenched with H_2O (20 vols) and extracted with CH_2Cl_2 (3 × 10 vols). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a brown oil which was then taken up in toluene (100 vols), and DBU (2.8 equiv) was added. The reaction mixture was stirred at r.t. for 2 h, then concentrated in vacuo, and purified by column chromatography over silica gel, affording the pure N-protected anatoxin **9**.

N-SES Anatoxin-a (9a); Method I

MeOH (3.9 mL) was saturated with HCl gas at –68 °C and a drying tube was fitted to the flask. A solution of **7a** (50.0 mg, 0.138 mmol) in MeOH (0.2 mL) was then added, and the reaction mixture was stirred at –61 °C for 1 h and then allowed to warm to r.t. slowly in the cardice–acetone bath over an additional 10 h. The reaction was poured into cold sat. aq $NaHCO_3$ (80 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, evaporated, and purified by column chromatography over silica gel (EtOAc–hexane, 1:2) to afford a mixture of stage one intermediate diastereoisomers (PG = SES) along with a small amount of product **9a** (51 mg). This mixture was dissolved in toluene (5 mL) and DBU (29 μL, 0.194 mmol) was

added. The reaction mixture was then stirred at reflux for 6.5 h, cooled, evaporated in vacuo, and purified by column chromatography over silica gel (EtOAc–hexane, 1:2) to afford **9a**.

Yield: 17.0 mg (37%); waxy white solid; mp 50–52 °C; R_f = 0.38 (EtOAc–hexane, 1:1).

IR ($CDCl_3$): 1664 (ketone), 1331 (sulfonamide) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.93 (dd, *J* = 7.0, 4.9 Hz, 1 H), 5.19 (d, *J* = 8.7 Hz, 1 H), 4.49 (dt, *J* = 7.4, 3.8 Hz, 1 H), 2.88 (t, *J* = 7.8 Hz, 2 H), 2.61 (m, 1 H), 2.45 (m, 1 H), 2.37–1.99 (m, 3 H), 2.29 (s, 3 H), 1.81–1.67 (m, 3 H), 0.96–0.90 (m, 2 H), 0.01 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.5, 148.4, 143.4, 58.5, 55.3, 48.6, 33.1, 32.5, 30.4, 25.3, 24.2, 10.4, –2.0.

MS (CI): *m*/*z* (%) = 347.2 (100) [M + NH_4^+], 330.2 (20).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{15}H_{31}N_2O_3S^{28}Si$: 347.1819; found: 347.1817.

Anal. Calcd for $C_{15}H_{27}NO_3SSi$: C, 54.67; H, 8.26; N, 4.25. Found: C, 54.65; H, 8.27; N, 4.32.

15 (PG = SES)

R_f = 0.32 and 0.23 (EtOAc–hexane, 1:2).

^1H NMR (400 MHz, $CDCl_3$): δ (Characteristic proton shifts for the intermediate chlorides; Major diastereoisomer) = 4.52 (ddd, *J* = 12.0, 9.8, 2.4 Hz, 1 H), 4.46 (dd, *J* = 10.1, 2.5 Hz, 1 H), 4.34 (m, 1 H), 3.66 (m, 1 H).

***N*-SES Anatoxin-a (9a); Method II**

Following the general procedure for TMSI-promoted cyclisation, **7a** (500 mg, 1.38 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:1) gave **9a** (303 mg, 66%) with identical spectral data to those produced via method I. Characteristic spectral data for the intermediate iodide (major diastereoisomer):

R_f = 0.55 (EtOAc–hexane, 1:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.60 (ddd, *J* = 12.1, 10.1, 1.9 Hz, 1 H), 4.48 (dd, *J* = 10.1, 2.6 Hz, 1 H), 4.36 (m, 1 H), 3.23 (d, *J* = 10.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 69.9, 59.6, 58.9, 26.1.

***N*-(2-Naphthalenesulfonyl) Anatoxin-a (9c)**

Following the general procedure for TMSI-promoted cyclisation, **7c** (0.48 g, 1.24 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:1) gave **9c**.

Yield: 342 mg (78%); colourless needles; mp 184–186 °C; R_f = 0.31 (EtOAc–hexane, 1:1).

IR (thin film): 1662 (carbonyl), 1341 and 1160 (sulfonamide) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 7.99–7.85 (m, 3 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 7.65–7.56 (m, 2 H), 6.86 (t, *J* = 5.9 Hz, 1 H), 5.33 (d, *J* = 8.5 Hz, 1 H), 4.52 (m, 1 H), 2.65 (m, 1 H), 2.37 (m, 1 H), 2.24 (s, 3 H), 2.23–2.14 (m, 1 H), 1.81–1.42 (m, 5 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.4, 147.4, 143.3, 137.1, 134.6, 132.1, 129.3, 129.2, 128.6, 128.0, 127.8, 127.4, 122.3, 58.9, 56.2, 33.3, 31.9, 29.8, 25.3, 24.3.

MS (CI): *m*/*z* (%) = 373.2 (31) [M + NH_4^+], 166.0 (100).

HRMS: *m*/*z* [M + H^+] calcd for $C_{20}H_{22}NO_3S$: 356.1315; found: 356.1318.

***N*-Mesyl Anatoxin-a (9d)**

Following the general procedure for TMSI-promoted cyclisation, **7d** (0.51 g, 1.86 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:1) gave **9d**.

Yield: 68.8 mg (15%); pale-yellow oil; R_f = 0.31 (EtOAc–hexane, 3:1).

IR (thin film): 1659 (carbonyl), 1323 and 1145 (sulfonamide) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.92 (t, *J* = 6.0 Hz, 1 H), 5.21 (d, *J* = 8.7 Hz, 1 H), 4.45 (m, 1 H), 2.83 (s, 3 H), 2.67–1.96 (m, 6 H), 2.28 (s, 3 H), 1.78–1.62 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.8, 147.7, 143.9, 58.8, 55.7, 39.7, 33.2, 32.5, 30.4, 25.6, 24.5.

MS (CI): *m*/*z* (%) = 261.1 (100) [M + NH_4^+], 244.1 (22).

HRMS: *m*/*z* [M + H^+] calcd for $C_{11}H_{18}NO_3S$: 244.1002; found: 244.1000.

1-(9′-Tosyl-9′-azabicyclo[4.2.1]non-2′-en-2′-yl)butan-1-one (9g)

Following the general procedure for TMSI-promoted cyclisation, **7g** (0.90 g, 2.37 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **9g**.

Yield: 0.43 g (52%); clear needles; mp 109–110 °C; R_f = 0.32 (EtOAc–hexane, 1:2).

IR ($CDCl_3$): 1663 (carbonyl), 1342 and 1161 (sulfonamide) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 6.86 (t, *J* = 5.9 Hz, 1 H), 5.19 (d, *J* = 8.7 Hz, 1 H), 4.43 (m, 1 H), 2.71–2.50 (m, 3 H), 2.40 (s, 3 H), 2.39–2.28 (m, 1 H), 2.21–2.09 (m, 1 H), 1.82–1.33 (m, 7 H), 0.91 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.8, 147.1, 143.2, 141.6, 137.2, 129.7, 127.0, 58.9, 56.6, 38.9, 33.5, 32.0, 29.8, 24.3, 21.5, 18.1, 13.8.

MS (CI): *m*/*z* (%) = 365.3 (52) [M + NH_4^+], 348.3 (39) [M + H^+], 194.2 (100).

HRMS: *m*/*z* [M + H^+] calcd for $C_{19}H_{26}NO_3S$: 348.1628; found: 348.1628.

1-(9′-Tosyl-9′-azabicyclo[4.2.1]non-2′-en-2′-yl)pentan-1-one (9h)

Following the general procedure for TMSI-promoted cyclisation, **7h** (0.95 g, 2.41 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **9h**.

Yield: 445 mg (50%); clear needles; mp 108–109 °C; R_f = 0.37 (EtOAc–hexane, 1:1).

IR (thin film): 1661 (carbonyl), 1342 and 1161 (sulfonamide) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.6 Hz, 2 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 6.84 (t, *J* = 5.9 Hz, 1 H), 5.18 (d, *J* = 8.5 Hz, 1 H), 4.43 (m, 1 H), 2.69–2.54 (m, 3 H), 2.39 (s, 3 H), 2.38–2.29 (m, 1 H), 2.20–2.10 (m, 1 H), 1.80–1.42 (m, 7 H), 1.30 (m, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.9, 147.1, 143.1, 141.6, 137.2, 129.6, 127.0, 58.9, 56.6, 36.7, 33.5, 32.0, 29.9, 26.8, 24.3, 22.4, 21.5, 13.9.

MS (CI): *m*/*z* (%) = 379.3 (100) [M + NH_4^+], 362.3 (64) [M + H^+], 208.2 (81).

HRMS: *m*/*z* [M + H^+] calcd for $C_{20}H_{28}NO_3S$: 362.1784; found: 362.1784.

1-(9′-Tosyl-9′-azabicyclo[4.2.1]non-2′-en-2′-yl)hexan-1-one (9i)

Following the general procedure for TMSI-promoted cyclisation, **7i** (0.64 g, 1.57 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **9i**.

Yield: 118 mg (20%); pale-yellow oil; R_f = 0.40 (EtOAc–hexane, 1:1).

IR (thin film): 1664 (carbonyl), 1342 and 1158 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 6.83 (t, *J* = 5.9 Hz, 1 H), 5.18 (d, *J* = 8.4 Hz, 1 H), 4.42 (m, 1 H), 2.67–2.57 (m, 1 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 2.38 (s, 3 H), 2.38–2.28 (m, 1 H), 2.18–2.08 (m, 1 H), 1.79–1.40 (m, 7 H), 1.34–1.16 (m, 4 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.9, 147.0, 143.1, 141.6, 137.2, 129.6, 126.9, 58.8, 56.5, 36.9, 33.4, 32.0, 31.4, 29.8, 24.3, 24.2, 22.4, 21.5, 13.9.

MS (CI): *m*/*z* (%) = 393.4 (100) [M + NH_4^+], 376.3 (63) [M + H^+], 222.2 (86).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{21}H_{33}N_2O_3S$: 393.2206; found: 393.2202.

Ozonolytic Desymmetrisation of Cycloheptenes and Subsequent Olefination; General Procedure

Ozone was bubbled through a solution of the cycloheptene derivative (1.0 equiv) in CH_2Cl_2–MeOH (5:1, 6 mL) at –78 °C until a deep-blue colouration persisted. Next, the solution was degassed with argon, and acidified with *p*-toluenesulfonic acid monohydrate (0.084 equiv), and stirred at r.t. for 1.5 h, after which the reaction was basified with anhydrous $NaHCO_3$ (0.34 equiv). The suspension was stirred for 15 min, then Me_2S (2.0 equiv) was added and the reaction was stirred for an additional 18 h. The reaction mixture was concentrated in vacuo and the crude residue was taken up in CH_2Cl_2 (2 × 3 mL), then washed with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the crude intermediate aldehyde **4**. To NaH (60% in mineral oil, 1.05 equiv) under an atmosphere of argon, was added *n*-pentane (3 mL). The slurry was mixed thoroughly, allowed to settle and the supernatant removed and the residue dried in vacuo. THF (2 mL) was added followed by the appropriate phosphonate (1.2 equiv) dropwise. Once hydrogen evolution had ceased, the reaction solution was cooled to 0 °C and a solution of the crude aldehyde **4** in THF (0.5 mL) was added dropwise over a period of 5 min. The reaction was stirred at r.t. for 16 h then quenched with H_2O (1 mL) and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (3 mL) and washed with H_2O (2 mL) and brine (2 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the crude product, which was purified by column chromatography over silica gel.

6-(5′-Methoxy-*N*-SES-pyrrolidin-2′-yl)hex-3-en-2-one (7a)

Following the general procedure for ozonolysis/olefination, **10a** (0.50 g, 1.82 mmol) and diethyl (2-oxopropyl)phosphonate (**11a**; 0.42 mL, 2.18 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:1) gave **7a** as a single diastereoisomer.

Yield: 519 mg (79%); clear oil; R_f = 0.40 (EtOAc–hexane, 1:1).

IR ($CDCl_3$): 1674 (ketone), 1626 (alkene), 1335 and 1145 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (dt, *J* = 15.9, 6.7 Hz, 1 H), 6.07 (d, *J* = 15.9 Hz, 1 H), 5.01 (d, *J* = 4.3 Hz, 1 H), 3.76 (m, 1 H), 3.33 (s, 3 H), 2.96–2.71 (m, 2 H), 2.33–1.57 (m, 8 H), 2.22 (s, 3 H), 1.10–0.92 (m, 2 H), 0.03 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.5, 147.2, 131.5, 92.0, 60.1, 54.9, 47.7, 35.2, 32.4, 29.4, 28.5, 26.8, 9.9, –2.0.

MS (CI): *m*/*z* (%) = 379.2 (48) [M + NH_4^+], 330.2 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{16}H_{35}N_2O_4S^{28}Si$: 379.2081; found: 379.2080.

Intermediate Aldehyde 4b

In an identical reaction, purification of the crude intermediate aldehyde **4b** by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **4b** as predominately a single diastereoisomer ≥90%.

Yield: 72.0 mg (62%); clear oil; R_f = 0.30 (EtOAc–hexane, 1:2).

IR ($CDCl_3$): 1724 (aldehyde), 1335 and 1146 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereoisomer) = 9.76 (m, 1 H), 5.02 (dd, *J* = 7.9, 4.6 Hz, 1 H), 3.81 (m, 1 H), 3.32 (s, 3 H), 2.94–2.71 (m, 2 H), 2.66–2.35 (m, 2 H), 2.19–1.41 (m, 6 H), 0.99 (m, 2 H), 0.02 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (major diastereoisomer) = 201.7, 92.2, 59.6, 54.9, 47.4, 39.8, 32.4, 29.4, 28.6, 9.9, –2.1.

6-[5′-Methoxy-*N*-(naphthalene-2′′-sulfonyl)pyrrolidin-2′-yl]hex-3-en-2-one (7c)

Following the general procedure for ozonolysis/olefination, **10c** (0.705 g, 2.339 mmol) and diethyl (2-oxopropyl)phosphonate (**11a**; 0.54 mL, 2.81 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:1) gave **7c** as a single diastereoisomer.

Yield: 0.658 g (73%); waxy white solid; mp 72–74 °C; R_f = 0.36 (EtOAc–hexane, 1:1).

IR ($CDCl_3$): 1672 (ketone), 1626 (alkene), 1346 and 1160 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 1.7 Hz, 1 H), 7.99–7.94 (m, 2 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.74 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.68–7.60 (m, 2 H), 6.83 (dt, *J* = 16.0, 6.7 Hz, 1 H), 6.10 (dt, *J* = 16.0, 1.4 Hz, 1 H), 5.17 (d, *J* = 5.0 Hz, 1 H), 3.57 (m, 1 H), 3.46 (s, 3 H), 2.40–2.08 (m, 2 H), 2.24 (s, 3 H), 1.87–1.64 (m, 5 H), 1.11 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.5, 147.4, 135.2, 134.7, 132.0, 131.5, 129.6, 129.2, 128.9, 128.7, 127.9, 127.7, 122.2, 92.8, 60.2, 55.0, 35.1, 32.1, 29.3, 28.4, 26.8.

MS (CI): *m*/*z* (%) = 405.2 (5) [M + NH_4^+], 356.2 (18), 166.0 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{21}H_{29}N_2O_4S$: 405.1843; found: 405.1843.

6-(5′-Methoxy-*N*-mesyl-pyrrolidin-2′-yl)hex-3-en-2-one (7d)

Following the general procedure for ozonolysis/olefination, **10d** (638 mg, 3.37 mmol) and diethyl (2-oxopropyl)phosphonate (**11a**; 0.78 mL, 4.04 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 3:1) gave **7d** as a single diastereoisomer.

Yield: 87 mg (63%); pale-yellow oil; R_f = 0.32 (EtOAc–hexane, 3:1).

IR ($CDCl_3$): 1672 (ketone), 1336 and 1154 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (dt, *J* = 16.0, 6.8 Hz, 1 H), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1 H), 4.96 (d, *J* = 4.7 Hz, 1 H), 3.69 (m, 1 H), 3.32 (s, 3 H), 2.82 (s, 3 H), 2.34–1.46 (m, 8 H), 2.21 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.5, 147.1, 131.5, 92.1, 60.4, 54.8, 38.0, 35.0, 32.3, 29.3, 28.4, 26.8.

MS (CI): *m*/*z* (%) = 293.2 (73) [M + NH_4^+], 261.1 (99), 244.1 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{12}H_{25}N_2O_4S$: 293.1530; found: 293.1529.

6-(5′-Methoxy-*N*-Boc-pyrrolidin-2-yl)hex-3-en-2-one (7e)

Following the general procedure for ozonolysis/olefination, **10e** (276 mg, 1.31 mmol) and diethyl (2-oxopropyl)phosphonate (**11a**) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7e** as an inseparable mixture of diastereoisomers.

Yield: 234 mg (60%); colourless oil; R_f = 0.50 (EtOAc–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (rotomers) = 6.73 (dt, *J* = 15.7, 7.5 Hz, 1 H), 5.99 (d, *J* = 15.7 Hz, 1 H), 5.17–5.00 (m, 1 H), 3.78–3.58 (m, 1 H), 3.21 (s, 3 H), 2.14 (s, 3 H), 2.10–1.41 (m, 8 H), 1.38 (s, 9 H).

7-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)oct-5-en-4-one (7g)

Following the general procedure for ozonolysis/olefination, **10b** (1.00 g, 3.77 mmol) and dimethyl (2-oxopentyl)phosphonate (**11c**; 1.02 g, 4.90 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7g** as a single diastereoisomer.

Yield: 1.16 g (81%); colourless oil; R_f = 0.33 (EtOAc–hexane, 1:2).

IR (thin film): 1670 (carbonyl), 1344 and 1159 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 6.77 (dt, *J* = 15.9, 6.8 Hz, 1 H), 6.05 (d, *J* = 15.9 Hz, 1 H), 4.97 (d, *J* = 5.2 Hz, 1 H), 3.47–3.36 (m, 1 H), 3.35 (s, 3 H), 2.46 (t, *J* = 7.3 Hz, 2 H), 2.35 (s, 3 H), 2.26–2.10 (m, 2 H), 2.08–1.97 (m, 1 H), 1.80–1.50 (m, 6 H), 1.09–0.96 (m, 1 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.6, 146.1, 143.6, 135.4, 130.5, 129.7, 127.1, 92.7, 60.1, 54.8, 41.8, 35.1, 32.0, 29.2, 28.3, 21.4, 17.6, 13.7.

MS (CI): *m*/*z* (%) = 397.3 (4) [M + NH_4^+], 348.2 (24), 194.1 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{20}H_{33}N_2O_4S$: 397.2156; found: 397.2156.

7-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)non-3-en-5-one (7h)

Following the general procedure for ozonolysis/olefination, **10b** (1.00 g, 3.77 mmol) and dimethyl (2-oxohexyl)phosphonate (**11d**; 1.02 g, 4.90 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7h** as a single diastereoisomer.

Yield: 1.16 g (78%); colourless oil; R_f = 0.35 (EtOAc–hexane, 1:2).

IR (thin film): 1668 (carbonyl), 1344 and 1159 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 6.79 (dt, *J* = 15.9, 6.8 Hz, 1 H), 6.07 (d, *J* = 15.9 Hz, 1 H), 4.98 (d, *J* = 5.2 Hz, 1 H), 3.48–3.38 (m, 1 H), 3.37 (s, 3 H), 2.49 (t, *J* = 7.6 Hz, 2 H), 2.37 (s, 3 H), 2.30–2.11 (m, 2 H), 2.10–1.98 (m, 1 H), 1.79–1.59 (m, 4 H), 1.59–1.45 (m, 2 H), 1.35–1.13 (m, 2 H), 1.11–0.96 (m, 1 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.7, 146.1, 143.6, 135.4, 130.5, 129.7, 127.1, 92.7, 60.2, 54.8, 39.7, 35.1, 32.0, 29.2, 28.3, 26.3, 22.3, 21.4, 13.8.

MS (CI): *m*/*z* (%) = 411.3 (9) [M + NH_4^+], 362.2 (41), 208.2 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{21}H_{35}N_2O_4S$: 411.2312; found: 411.2309.

7-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)dec-3-en-5-one (7i)

Following the general procedure for ozonolysis/olefination, **10b** (0.53 g, 1.99 mmol) and dimethyl (2-oxoheptyl)phosphonate (**11e**; 0.58 g, 2.59 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7i** as a single diastereoisomer.

Yield: 0.59 g (73%); colourless oil; R_f = 0.37 (EtOAc–hexane, 1:2).

IR (thin film): 1669 (carbonyl), 1344 and 1158 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 6.80 (dt, *J* = 15.9, 6.7 Hz, 1 H), 6.08 (dt, *J* = 15.9, 1.4 Hz, 1 H), 5.00 (d, *J* = 5.1 Hz, 1 H), 3.50–3.40 (m, 1 H), 3.38 (s, 3 H), 2.50 (t, *J* = 7.5 Hz, 2 H), 2.38 (s, 3 H), 2.31–2.12 (m, 2 H), 2.11–1.98 (m, 1 H), 1.82–1.62 (m, 4 H), 1.62–1.49 (m, 2 H), 1.35–1.14 (m, 4 H), 1.11–0.98 (m, 1 H), 0.85 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8, 146.1, 143.6, 135.4, 130.5, 129.7, 127.2, 92.7, 60.2, 54.8, 40.0, 35.1, 32.0, 31.4, 29.2, 28.4, 23.9, 22.4, 21.4, 13.9.

MS (CI): *m*/*z* (%) = 425.3 (20) [M + NH_4^+], 376.3 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{22}H_{37}N_2O_4S$: 425.2469; found: 425.2469.

5-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)pent-2-ene-nitrile (7j)

Following the general procedure for ozonolysis/olefination, **10b** (1.00 g, 3.77 mmol) and diethyl cyanomethylphosphonate (0.77 mL, 4.90 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7j** as a 1:1.3 mixture of *cis*/*trans* isomers and a single diastereoisomer.

Yield: 811 mg (64%); colourless oil; R_f = 0.47 (EtOAc–hexane, 1:2).

IR (thin film): 2221 (nitrile), 1343 and 1157 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 6.73 (dt, *J* = 16.3, 6.8 Hz, 0.56 H), 6.52 (dt, *J* = 10.9, 7.6 Hz, 0.44 H), 5.37 (dt, *J* = 16.3, 1.5 Hz, 0.56 H), 5.33 (dt, *J* = 10.9, 1.1 Hz, 0.44 H), 5.01 (d, *J* = 5.2 Hz, 1 H), 3.52–3.42 (m, 1 H), 3.40 (s, 3 H), 2.48–2.20 (m, 2 H), 2.41 (s, 3 H), 2.15–1.91 (m, 1 H), 1.88–1.56 (m, 4 H), 1.15–0.99 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1, 154.3, 143.8, 143.7, 135.3, 129.8, 127.1, 117.4, 115.8, 100.0, 99.8, 92.8, 92.7, 60.1, 59.8, 54.9, 54.8, 35.2, 34.4, 32.0, 31.9, 29.2, 29.1, 28.0, 21.4.

MS (CI): *m*/*z* (%) = 352.3 (12) [M + NH_4^+], 303.2 (100), 149.1 (98).

HRMS: *m*/*z* [M + NH_4^+] $C_{17}H_{26}N_3O_3S$: 352.1689; found: 352.1694.

Ethyl 5-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)pent-2-enoate (7k)

Following the general procedure for ozonolysis/olefination, **10b** (1.00 g, 3.77 mmol) and triethyl phosphonoacetate (0.97 g, 4.90 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7k** as a single diastereoisomer.

Yield: 913 mg (64%); colourless oil; R_f = 0.50 (EtOAc–hexane, 1:2).

IR (thin film): 1712 (carbonyl), 1340 and 1159 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 6.96 (dt, *J* = 15.6, 6.8 Hz, 1 H), 5.83 (dt, *J* = 15.6, 1.4 Hz, 1 H), 5.03 (d, *J* = 5.1 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.52–3.42 (m, 1 H), 3.40 (s, 3 H), 2.41 (s, 3 H), 2.32–2.14 (m, 2 H), 2.13–1.99 (m, 1 H), 1.84–1.63 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.15–1.02 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 148.2, 143.6, 135.5, 129.8, 127.2, 121.6, 92.7, 60.2, 60.1, 54.8, 35.1, 32.1, 29.3, 28.2, 21.5, 14.3.

MS (CI): *m*/*z* (%) = 399.3 (19) [M + NH_4^+], 350.3 (81), 196.2 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{19}H_{31}N_2O_5S$: 399.1948; found: 399.1949.

5-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)-1-pyridin-3″-yl-pent-2-en-1-one (7l)

Following the general procedure for ozonolysis/olefination, **10b** (1.00 g, 3.77 mmol) and dimethyl (2-oxo-2-pyridin-3-ylethyl)phosphonate (**11h**; 1.12 g, 4.90 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 5:1) gave **7l** as a single diastereoisomer.

Yield: 1.03 g (66%); colourless oil; R_f = 0.17 (EtOAc–hexane, 5:1).

IR (thin film): 1671 (carbonyl), 1342 and 1157 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (d, *J* = 1.5 Hz, 1 H), 8.75 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.20 (dt, *J* = 7.9, 1.5 Hz, 1 H), 7.64 (d, *J* = 8.3 Hz, 2 H), 7.41 (dd, *J* = 7.9, 4.9 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.10 (dt, *J* = 15.4, 6.7 Hz, 1 H), 6.90 (dt, *J* = 15.4, 1.3 Hz, 1 H), 5.02 (d, *J* = 5.2 Hz, 1 H), 3.53 (m, 1 H), 3.41 (s, 3 H), 2.47–2.30 (m, 2 H), 2.38 (s, 3 H), 2.13 (m, 1 H), 1.86–1.67 (m, 4 H), 1.16–1.03 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.3, 153.0, 150.3, 149.8, 143.7, 135.9, 135.4, 133.0, 129.8, 127.1, 125.7, 123.5, 92.8, 60.1, 54.9, 35.0, 32.0, 29.3, 28.7, 21.4.

MS (CI): *m*/*z* (%) = 415.3 (100) [M + H$^+$], 229.2 (70).

HRMS: *m*/*z* [M + NH$^+$] calcd for $C_{22}H_{27}N_2O_4S$: 415.1686; found: 415.1682.

4(*S*)-Benzyl-3-[5″-(5′-methoxy-*N*-tosyl-pyrrolidin-2′-yl)pent-2″-enoyl]oxazolidin-2-one (7m)

Following the general procedure for ozonolysis/olefination, **10b** (1.00 g, 3.77 mmol) and diethyl {2-[4(*S*)-benzyl-2-oxo-oxazolidin-3-yl]-2-oxo-ethyl}phosphonate (**11i**; 1.74 g, 4.90 mmol) were reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **7m** as a single diastereoisomer.

Yield: 1.47 g (76%); amorphous white foam; R_f = 0.22 (EtOAc–hexane, 1:2).

IR (thin film): 1778 (carbamate), 1688 (amide), 1354 and 1162 (sulfonamide) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 2 H), 7.36–7.17 (m, 9 H), 5.05 (d, *J* = 5.1 Hz, 1 H), 4.74 (m, 1 H), 4.24–4.14 (m, 2 H), 3.57–3.48 (m, 1 H), 3.42 (s, 3 H), 3.35–3.30 (m, 1 H), 2.80 (dd, *J* = 13.4, 9.5 Hz, 1 H), 2.43–2.31 (m, 5 H), 2.16–2.05 (m, 1 H), 1.88–1.67 (m, 4 H), 1.17–1.05 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4, 153.0, 150.0, 143.2, 135.1, 129.4, 129.0, 128.4, 126.8, 126.7, 126.0, 120.3, 92.4, 65.7, 59.9, 54.7, 54.3, 37.2, 34.7, 31.6, 28.8, 28.3, 21.0.

MS (ES): *m*/*z* (%) = 535.3 (8) [M + Na$^+$], 481.1 (22), 79.0 (100).

HRMS: *m*/*z* [M + NH_4^+] calcd for $C_{27}H_{36}N_3O_6S$: 530.2319; found: 530.2314.

5-(5′-Methoxy-*N*-tosyl-pyrrolidin-2′-yl)pent-2-enal (7n)

To a solution of nitrile **7j** (20 mg, 0.060 mmol) in anhydrous toluene (3 mL), was added DIBAL-H (1.5 M in toluene, 0.10 mL, 0.15 mmol) dropwise at –78 °C. The reaction mixture was stirred for 1.5 h under argon and then quenched with EtOAc (5 mL) and sat. aq NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by column chromatography over silica gel (EtOAc–petroleum ether, 20 → 50%) gave aldehyde **7n** as a single diastereoisomer.

Yield: 10 mg (50%); clear oil; R_f = 0.60 (EtOAc–petroleum ether, 1:1).

IR (thin film): 1689 (aldehyde), 1446, 1344, 1212, 1161, 1093, 1076 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (d, *J* = 7.9 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 6.88 (dt, *J* = 15.6, 6.7 Hz, 1 H), 6.14 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1 H), 5.04 (d, *J* = 5.1 Hz, 1 H), 3.53 (m, 1 H), 3.43 (s, 3 H), 2.46–2.35 (m, 1 H), 2.43 (s, 3 H), 2.16–2.03 (m, 1 H), 1.88–1.71 (m, 5 H), 1.19–1.07 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.0, 157.9, 143.8, 135.5, 133.2, 129.9, 127.3, 92.9, 60.1, 55.0, 34.8, 32.1, 29.3, 28.7, 21.5.

MS (ESI): *m*/*z* (%) = 360 (100) [M + Na$^+$], 306 (25), 355 (4).

HRMS: *m*/*z* [M + Na$^+$] calcd for $C_{17}H_{23}NO_4SNa$: 360.1240; found: 360.1247.

Preparation of Dioxolanes 12b–f; General Procedure

To a solution of the N-protected anatoxin derivative **9** (1.0 equiv) in benzene (5 mL), was added ethylene glycol (5.0 equiv), triethyl orthoformate (1.2 equiv) and 1 drop of $BF_3{\cdot}Et_2O$ and the resulting mixture was heated at reflux for 23 h. The reaction was washed with sat. aq $NaHCO_3$ (5 mL), H_2O (5 mL), then brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel.

2-(2′-Propyl[1,3]dioxolan-2′-yl)-9-tosyl-9-azabicyclo[4.2.1]non-2-ene (12c)

Following the general procedure for dioxolane preparation, **9g** (71.9 mg, 0.207 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:3) gave **12c**.

Yield: 57.0 mg (70%); colourless oil; R_f = 0.55 (EtOAc–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 5.73 (dd, *J* = 7.6, 3.7 Hz, 1 H), 4.53 (d, *J* = 8.6 Hz, 1 H), 4.38 (m, 1 H), 3.94–3.58 (m, 4 H), 2.35 (s, 3 H), 2.29–2.09 (m, 2 H), 1.89–1.16 (m, 10 H), 0.85 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.2, 143.1, 137.1, 129.6, 127.1, 125.9, 111.1, 64.4, 64.1, 60.1, 57.6, 38.9, 33.1, 32.9, 28.4, 23.1, 21.5, 16.9, 14.1.

MS (CI): *m*/*z* (%) = 392.3 (100) [M + H$^+$], 238.2 (56).

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{21}H_{30}NO_4S$: 392.1890; found: 392.1896.

2-(2′-Butyl[1,3]dioxolan-2′-yl)-9-tosyl-9-azabicyclo[4.2.1]non-2-ene (12d)

Following the general procedure for dioxolane preparation, **9h** (193 mg, 0.534 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:3) gave **12d**.

Yield: 113 mg (52%); colourless oil; R_f = 0.60 (EtOAc–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.73 (dd, *J* = 7.6, 3.7 Hz, 1 H), 4.53 (d, *J* = 8.6 Hz, 1 H), 4.37 (m, 1 H), 3.94–3.59 (m, 4 H), 2.34 (s, 3 H), 2.30–2.09 (m, 2 H), 1.90–1.12 (m, 12 H), 0.83 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.2, 143.1, 137.1, 129.6, 127.1, 125.9, 111.1, 64.4, 64.1, 60.1, 57.6, 36.5, 33.0, 32.9, 28.4, 25.6, 23.1, 22.7, 21.5, 14.1.

MS (CI): *m*/*z* (%) = 406.3 (100) [M + H$^+$], 252.2 (69).

HRMS: *m*/*z* [M + H$^+$] clacd for $C_{22}H_{32}NO_4S$: 406.2047; found: 406.2047.

2-(2′-Pentyl[1,3]dioxolan-2′-yl)-9-tosyl-9-azabicyclo[4.2.1]non-2-ene (12e)

Following the general procedure for dioxolane preparation, **9i** (61.2 mg, 0.163 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:3) gave **12e**.

Yield: 35.5 mg (52%); colourless oil; R_f = 0.63 (EtOAc–hexane, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.9 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 5.73 (dd, *J* = 7.6, 3.7 Hz, 1 H), 4.54 (d, *J* = 8.6 Hz, 1 H), 4.37 (m, 1 H), 3.93–3.60 (m, 4 H), 2.35 (s, 3 H), 2.29–2.09 (m, 2 H), 1.91–1.03 (m, 14 H), 0.81 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.3, 143.1, 137.2, 129.6, 127.2, 125.9, 111.1, 64.4, 64.2, 60.1, 57.6, 36.8, 33.1, 33.0, 31.9, 28.4, 23.2, 23.1, 22.7, 21.5, 14.1.

MS (CI): *m*/*z* (%) = 420.3 (100) [M + H$^+$], 266.2 (78).

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{23}H_{34}NO_4S$: 420.2203; found: 420.2201.

2-(2′-Methyl[1,3]dioxolan-2′-yl)-9-(naphthalene-2″-sulfonyl)-9-azabicyclo[4.2.1]non-2-ene (12f)

Following the general procedure for dioxolane preparation, **9c** (80.0 mg, 0.225 mmol) was reacted. Purification by column chromatography over silica gel (EtOAc–hexane, 1:2) gave **12f** which was taken directly into the preparation of **13a** without further analysis.

Yield: 80.8 mg (90%); colourless oil; R_f = 0.52 (EtOAc–hexane, 1:1).

Preparation of (±)-Anatoxin-a Hydrochlorides 13a–d; General Procedure

To a solution of the dioxolane **12** (1.0 equiv) in MeOH (5 mL) was added powdered magnesium (30 equiv) and the resulting suspension was sonicated at r.t. for 40 min. Additional powdered magnesium (30 equiv) was then added and sonicated for a further 30 min. The reaction was quenched with 3 N aq HCl until all solids had dissolved, then made basic (pH >12) by addition of solid K_2CO_3 and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in $CHCl_3$ (10 mL) and anhydrous HCl gas was bubbled through the solution for 10 s. Concentration in vacuo followed by purification by column chromatography over silica gel (MeOH–$CHCl_3$, 1:9) gave the product as its hydrochloride salt.

(±)-1-(9′-Azabicyclo[4.2.1]non-2′-en-2′-yl)butan-1-one Hydrochloride (13c)

Following the general procedure for preparation of anatoxin hydrochlorides, **12c** (27.0 mg, 69.0 μmol) was reacted and purified to give **13c**.

Yield: 13.8 mg (87%); colourless glass; R_f = 0.09–0.25 (MeOH–$CHCl_3$, 1:9).

IR (neat): 1674 (ketone), 1587 (alkene) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.12–9.95 (br s, 1 H), 9.43–9.28 (br s, 1 H), 7.18–7.09 (m, 1 H), 5.28–2.16 (m, 1 H), 4.38–4.28 (m, 1 H), 2.75–2.23 (m, 6 H), 1.98–1.71 (m, 4 H), 1.69–1.50 (m, 2 H), 0.90 (t, J = 6.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.7, 144.2, 143.5, 58.3, 52.3, 38.8, 30.3, 27.7, 27.5, 23.5, 17.9, 13.8.

MS (ES): m/z (%) = 194.0 (100) [M + H^+ – HCl].

HRMS: m/z [M + H^+ – HCl] calcd for $C_{12}H_{20}NO$: 194.1539; found: 194.1541.

(±)-1-(9′-Azabicyclo[4.2.1]non-2′-en-2′-yl)pentan-1-one Hydrochloride (13d)

Following the general procedure for preparation of anatoxin hydrochlorides, **12d** (50.0 mg, 0.138 mmol) was reacted and purified to give **13d**.

Yield: 28.3 mg (84%); colourless oil; R_f = 0.10–0.30 (MeOH–$CHCl_3$, 1:9).

IR (neat): 1668 (ketone), 1587 (alkene) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.13–9.96 (br s, 1 H), 9.42–9.25 (br s, 1 H), 7.18–7.09 (m, 1 H), 5.26–5.18 (m, 1 H), 4.37–4.29 (m, 1 H), 2.77–2.23 (m, 6 H), 1.99–1.75 (m, 4 H), 1.66–1.48 (m, 2 H), 1.39–1.23 (m, 2 H), 0.90 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.8, 144.2, 143.5, 58.2, 52.3, 36.5, 30.3, 27.7, 27.5, 26.5, 23.5, 22.4, 13.9.

MS (ES): m/z (%) = 208.0 (100) [M + H^+ – HCl].

HRMS: m/z [M + H^+ – HCl] calcd for $C_{13}H_{22}NO$: 208.1696; found: 208.1693.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Delvin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, *55*, 1367.
(2) Carmichael, W. W.; Biggs, D. F.; Gorham, P. R. *Science* **1975**, *187*, 542.
(3) (a) Gugger, M.; Lenoir, S.; Berger, C.; Ledreux, A.; Druart, J. C.; Humbert, J. F.; Guette, C.; Bernard, C. *Toxicon* **2005**, *45*, 919. (b) Edwards, C.; Beattie, K. A.; Scrimgeour, C. M.; Codd, G. A. *Toxicon* **1992**, *30*, 1165. (c) Sivonen, K.; Himberg, K.; Luukkainen, R.; Niemelae, S. I.; Poon, G. K.; Codd, G. A. *Toxicol. Assess.* **1989**, *4*, 339. (d) Wood, S. A.; Stirling, D. J.; Briggs, L. R.; Sprosen, J.; Holland, P. T.; Ruck, J. G.; Wear, R. G. *N. Z. J. Mar. Freshwater Res.* **2006**, *40*, 585. (e) Viaggiu, E.; Melchiorre, S.; Volpi, F.; Di Corcia, A.; Mancini, R.; Garibaldi, L.; Crichigno, G.; Bruno, M. *Environ. Toxicol.* **2004**, *19*, 191. (f) Namikoshi, M.; Murakami, T.; Watanabe, M. F.; Oda, T.; Yamada, J.; Tsujimura, S.; Nagai, H.; Oishi, S. *Toxicon* **2003**, *42*, 533. (g) Ballot, A.; Krienitz, L.; Kotut, K.; Wiegand, C.; Pflugmacher, S. *Harmful Algae* **2005**, *4*, 139.
(4) Wannacott, S.; Swanson, K. L.; Albuquerque, E. X.; Huby, N. J. S.; Thompson, P.; Gallagher, T. *Biochem. Pharmacol.* **1992**, *43*, 419.
(5) Skulberg, O. M.; Carmichael, W. W.; Andersen, R. A.; Matsunaga, S.; Moore, R. E.; Skulberg, R. *Environ. Toxicol. Chem.* **1992**, *11*, 321.
(6) Namikoshi, M.; Murakami, T.; Watanabe, M. F.; Oda, T.; Yamada, J.; Tsujimura, S.; Nagai, H.; Oishi, S. *Toxicon.* **2003**, *42*, 533.
(7) For reviews on synthetic approaches to anatoxin-a, see: (a) Mansell, H. L. *Tetrahedron* **1996**, *52*, 6025. (b) Rodriguez, V.; Pinto, S. M. e. E.; Pereira, C. M. P.; Braga, R. C. *Quim. Nova* **2006**, *29*, 1365.
(8) For a recent review on the pharmacology of anatoxin-a and analogues, see: Wannacott, S.; Gallagher, T. *Mar. Drugs* **2006**, *4*, 228.
(9) Cassels, C. B.; Bermudez, I.; Dajas, F.; Abin-Carriquiry, J. A.; Wannacott, S. *Drug Discovery Today* **2005**, *10*, 1657.
(10) Roe, S. J.; Stockman, R. A. *Chem. Commun.* **2008**, 3432.
(11) Melching, K. H.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986**, *27*, 4799.
(12) (a) Somfai, P.; Åhman, J. *Tetrahedron Lett.* **1992**, *33*, 3791. (b) Royer and Husson also used this type of cyclisation promoted by HCl in methanol in the synthesis of feruginine, see: Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 6704.
(13) Hjelmgaard, T.; Støtofte, I.; Tanner, D. *J. Org. Chem.* **2005**, *70*, 5688.
(14) A table of conditions screened is provided in the supporting information.

(15) For other syntheses of anatoxin analogues, see: (a) Magnus, N. A.; Ducry, L.; Rolland, V.; Wonnacott, S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2313. (b) Howard, M. H.; Sardina, F. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 2829. (c) Hernandez, A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 1058. (d) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654. (e) Huby, N. J. S.; Thompson, P.; Wonnacott, S.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1991**, 243. (f) Parsons, P. J.; Camp, N. P.; Edwards, N.; Sumoreeah, L. R. *Tetrahedron* **2000**, *56*, 309.

(16) (a) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Org. Lett.* **2009**, *11*, 1179. (b) Myers, E. L.; de Vries, J. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1893.

(17) Jonsson, S. Y.; Lofstrom, C. M. G.; Backvall, J. E. *J. Org. Chem.* **2000**, *65*, 8454.

(18) Nenajdenko, V. G.; Karpov, A. S.; Balenkova, E. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2517.

(19) (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931. (b) Coppola, G. M. *Synthesis* **1988**, 81. (c) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (d) Zurawinski, R.; Nakamura, K.; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3139. (e) Grieco, P. A.; Pogonows, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071. (f) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (g) Dias, L. C.; Melgar, G. Z.; Jardim, L. S. A. *Tetrahedron Lett.* **2005**, *46*, 4427.