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Synthetic studies towards ptilomycalin A: total synthesis of crambescidin 359

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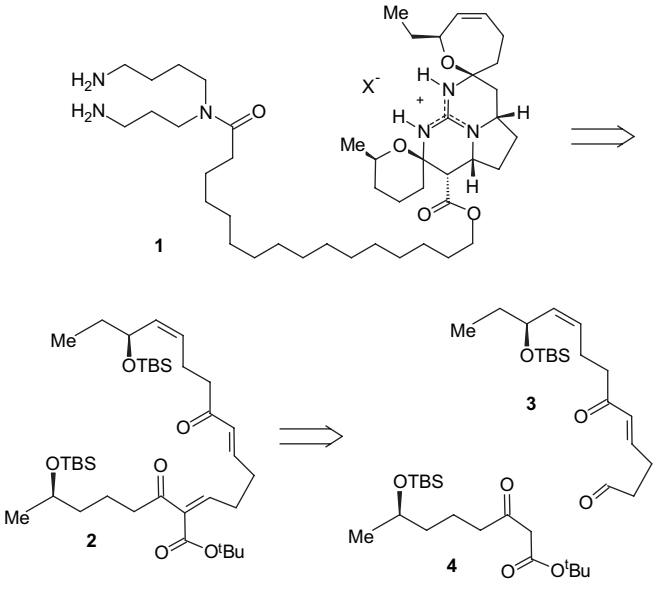
Abstract—A potentially biomimetic synthesis of the guanidine-containing marine natural product crambescidin 359 via a double Michael addition of guanidine to a suitably functionalised bis-enone is reported.

1. Introduction

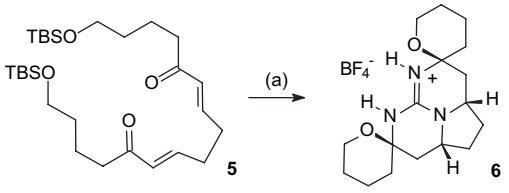
Molecules containing guanidinium sub-units are of considerable biological interest[1,2] and several of the most structurally complex have been isolated from marine organisms.[3] We have a continuing interest[4] in the synthesis of the marine natural product ptilomycalin A **1**, isolated by Kashman[5] in 1989, which is the parent member of a group of related metabolites including the crambescidins,[6] the crambines[7] and the batzelladines.[8] Ptilomycalin A possesses an intriguing structure consisting of a pentacyclic guanidine moiety linked by a long-chain ω-hydroxy acid to a spermidine unit; it shows cytotoxicity against a range of cell lines in addition to antifungal activity as well as very good antiviral activity (HSV).[9]

Our retrosynthetic analysis of the central polycyclic unit of ptilomycalin A illustrates the possibility of a rapid and potentially biomimetic construction of our target via a double Michael addition of guanidine to a bis-α,β-unsaturated ketone **2** to generate the central pyrrolidine ring. Subsequent bis-spirocyclisation would then lead to the required pentacycle. Disconnection of **2** leads to the unsaturated aldehyde **3** and the β-keto ester **4**. The *tert*-butyl ester was selected to inhibit irreversible amide formation during the guanidine addition step (Scheme 1).

We have reported previously[4] on the central double conjugate addition methodology and have shown it to be a successful strategy for the preparation of the pentacyclic moiety. For



Scheme 1.



Scheme 2. (a) (i) Guanidine, DMF, 3 h; (ii) MeOH, HCl, 0 °C–rt, 24 h; (iii) $NaBF_4$ (satd, aq), 25% overall.

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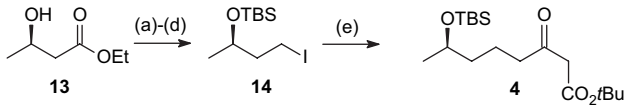
example, addition of guanidine to bis-α,β-unsaturated ketone **5** followed by deprotection and spirocyclisation gave the symmetrical pentacyclic model **6** in good overall yield (Scheme 2).

2. Results and discussion

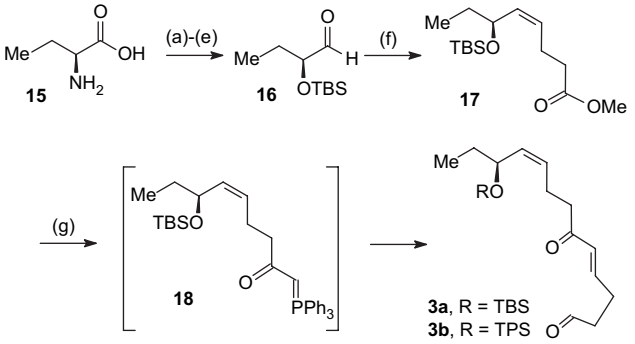
We initially attempted to prepare the ester substituted model compound **12** by reaction of guanidine with the diene **10**. Preparation of diene **10** required reaction of the dianion of *tert*-butyl acetoacetate with iodide **7**[10] to give **8**, which was condensed with the previously reported[4d] aldehyde **9** under Knoevenagel conditions.[11] Our initial attempts at this reaction using piperidine as the catalyst gave the required product **10** in low yield (14%), whilst the use of piperidine acetate gave slightly better results (26%). In both these reactions, cyclopentene **11** was obtained as a major by-product, which derived from a Baylis–Hillman type cyclisation of aldehyde **9**.[12] Attempts to further optimise these reactions using other bases and Lewis acids were unsuccessful. Despite this, reaction of **10** with guanidine followed by acidification led to the formation of a product in 20% yield, which gave the expected molecular weight in high resolution MS and from ^{13}C NMR spectroscopy appeared to be a mixture of four diastereoisomers as four signals were observed for both the guanidinium and ester quaternary carbons. Furthermore, the major signal for the proton H-6 appeared as a doublet at δ 2.8 ppm (J 5.6 Hz) suggesting an axial arrangement for the ester as found in ptilomycalin A. Whilst it was impossible to separate the major product from this mixture, the evidence for the formation of **12** was convincing and the retention of the *tert*-butyl ester under the reaction conditions was gratifying (Scheme 3).

Encouraged by this result we next sought to prepare the required fragments **3** and **4** and study their condensation. We prepared β-keto ester **4** in five steps from commercially available ethyl-(*R*)-3-hydroxybutyrate **13**. The hydroxyl group of **13** was silyl protected, then the ester function was reduced to the alcohol and converted into iodide **14** via the tosylate. Iodide **14** was then treated with the dianion of *tert*-butyl acetoacetate to afford **4** in 75% yield (Scheme 4).

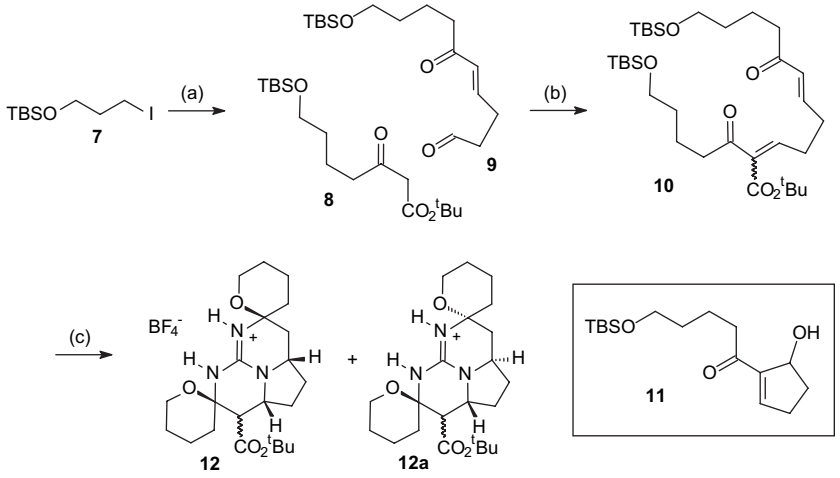


Scheme 4. (a) TBSCl, DMF, imid., 95%; (b) DIBAL-H, hexane, −78–20 °C, 8 h, 83%; (c) TosCl, Py. 0 °C–rt, 16 h, 62%; (d) NaI, acetone, reflux, 4 h, 95%; (e) *tert*-butyl acetoacetate, 2.2 equiv LDA, 0 °C–rt, 2 h, 75%.

The preparation of aldehyde **3a** proved to be a more significant challenge. Starting from commercially available (*S*)-2-aminobutyric acid **15**, the key intermediate aldehyde **16** was prepared in five steps. Thus **15** was diazotised in the presence of sodium nitrite and H_2SO_4 to give the corresponding α-hydroxy acid,[13] which was then esterified using HCl in methanol (23% over two steps). Silyl protection of the alcohol function (47%) was followed by DIBAL-H reduction (72%) and Swern oxidation of the resulting alcohol to give aldehyde **16** in 93% yield. Wittig reaction of **16** with the ylide generated from 3-carboxypropyltriphenylphosphonium bromide **19**, followed by esterification with diazomethane gave the *Z*-alkene **17** together with the *E*-isomer (minor) in 45% yield and in a 4:1 ratio.[14] After separation from the *E*-isomer, **17** was treated with 2 equiv of methylenetriphenylphosphorane to give the stabilised phosphorane **18**, which on reaction



Scheme 5. (a) $NaNO_2$, H_2SO_4 0 °C–rt, 24 h; (b) MeOH, HCl, 48 h, (23%, 2 steps); (c) TBSCl, imid., DMF, 0 °C–rt, 48 h, 47%; (d) DIBAL-H, −78 °C to rt, 5 h, 72%; (e) Swern oxidation, 93%; (f) (i) $MeO_2CCH_2CH_2CH_2PPh_3^+Br^-$ **19**, NaHMDS, THF, reflux, 30 min; (ii) **16**, rt, 30 min; (iii) CH_2N_2, Et_2O, 45%, 4:1, *Z*:*E*; (g) (i) 2 equiv $CH_2{=}PPh_3$, THF, −78 °C to rt, 2 h; (ii) succinaldehyde, THF, 42 h, (42%, 2 steps).

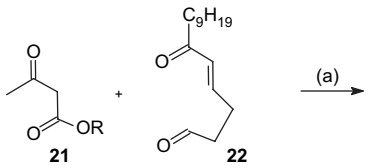


Scheme 3. (a) *tert*-Butyl acetoacetate, NaH, *n*-BuLi, −78 °C, then **7**, 66%; (b) piperidine acetate, CH_2Cl_2, −20 °C, 6 h, 26%; (c) (i) guanidine, DMF, 0 °C, 5 h; (ii) MeOH, HCl, 0 °C–rt, 16 h; (iii) satd $NaBF_4$, CH_2Cl_2, 4 h, 20%.

with an excess of freshly prepared succinaldehyde gave the desired aldehyde **3a** in 42% yield (Scheme 5).

Having prepared the key fragments **3a** and **4**, the stage was now set for their coupling via Knoevenagel condensation and as a very similar process had been reported,[11] we were confident of success. Initially, we employed piperidene (dichloromethane, −78 to −20 °C) as the catalyst but were disappointed to find that only a low yield (14%) of **2** was formed, which was contaminated with at least two unidentifiable side products. It was first thought that the starting materials had been recovered but on inspection of the NMR spectra of the recovered material we found that the Baylis–Hillman cyclisation product **20** had been formed in 41% yield and that all of aldehyde **3a** had been consumed. Similarly, piperidine acetate gave a low yield (15%) of contaminated **2** in addition to **20** in 14% yield. However, the use of morpholine gave contaminated **2** in 22% yield but did not lead to any cyclisation product **20**, but on this occasion aldehyde **3a** was recovered in 60% yield. Attempts to increase the yield of this process by extending the reaction time or varying the reaction temperature led to lower yields, further decomposition products and the formation of **20**. Morpholinium acetate under similar conditions, gave contaminated **2** in 17% yield and recovered aldehyde. To further test the condensation process, known aldehyde **3b** was prepared via a literature route,[11] however, similar results were obtained (Scheme 6).

Snider and Shi[11] have reported product yields of the order of 60–70% for similar Knoevenagel condensations together with the recovery of unreacted starting materials. In an attempt to determine the optimum conditions for the Knoevenagel reaction, a study was undertaken to ascertain whether electronic effects within the β-keto esters **21** have any effect on the outcome of the reaction. In a previous synthetic study towards the batzelladine alkaloids,[4g] aldehyde **22** was prepared, which was deemed to be suitable for use in this investigation (Scheme 7). Reaction of **22** with **21** (R=Me, Ph_2CH,[15] ^{t}Bu) in the presence of a range of cyclic amines, including a hindered base and also an amine salt, was attempted but with no success. The method of addition was also varied with premixing of the various reagents in different sequences and changes in reaction time and temperature were also employed but proved unproductive. In all cases the aldehyde **22** underwent decomposition or conversion to a Baylis–Hillman product under the reaction conditions and the β-keto ester **21** was recovered unchanged. We have no explanation as to the failure of this condensation reaction as literature reports suggest it to be an effective process with similar substrates.

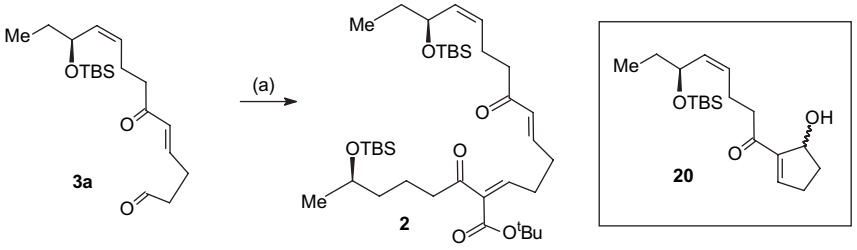


Scheme 7. (a) See text: piperidine, piperidine acetate, 2,6-dimethylpiperidine or morpholine, CH_2Cl_2, −78 to −20 °C. R=Me, Ph_2CH, ^{t}Bu.

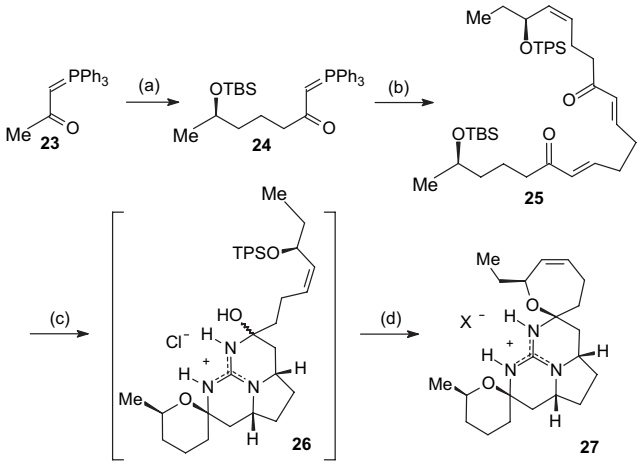
Despite this lack of success in our synthetic approach to ptilomycalin A, we wished to demonstrate the validity of our methodology and identified pentacycle **27**, which lacks the ester function, as a suitable target. Ylide **24** was prepared in 51% yield by treatment of iodide **14** with the lithium anion of acetylmethylene triphenylphosphorane **23**. Reaction of **24** with aldehyde **3b** in dichloromethane at 0 °C for 36 h gave the required bis-enone **25** in 72% yield. Addition of a DMF solution of guanidine to **25** at 0 °C followed by stirring at this temperature for 6 h resulted in the complete consumption of the starting bis-enone. After dilution with water and addition of a solution of methanolic HCl, a mixture of compounds was obtained in which the TBS protecting group had been removed, but the TPS group remained; NMR spectroscopic evidence strongly suggested the presence of the tetracycle **26**.[16–18] This mixture was treated with 5 equiv of TBAF in THF at 25–30 °C for 3 h and then at ambient temperature for a further 64 h. Finally, acid mediated cyclisation, counterion exchange and purification by column chromatography gave the desired pentacycle **27** (X=BF_4) in 18% yield from **25**. The yield is comparable with our previous work[4] in this area, as the guanidine addition step is not diastereoselective and half of the tricyclic bis-silylated guanidine adduct does not undergo cyclisation on deprotection (Scheme 8).

Interestingly, shortly after completing our synthesis[19] of **27**, Braekman[20] reported the isolation of crambescidin 359 **27** (X=Cl) from the marine sponge *Monanchora unguiculata* and the analytical data for synthetic **27** (X=BF_4) was found to be consistent with that reported. In particular, the optical rotation of **27** of −8.2 (X=BF_4, *c* 0.2, CH_2Cl_2) compared favourably with that of synthetic **27**[18] (X=Cl, −8.0, *c* 0.2, CH_2Cl_2) and also the natural product[20] (X=Cl, −9.0, *c* 0.2, CH_2Cl_2).

We also investigated the biological activity of synthetic crambescidin 359 **27** (X=BF_4) against four cancer cell lines in comparison with ptilomycalin A[5a,21] (Table 1). As can be seen, **27**·BF_4 was active against all the cell lines tested, however, the levels of activity were significantly lower than those reported for ptilomycalin A. This is in line with our previous



Scheme 6. (a) See text: **4**, morpholine, CH_2Cl_2, −20 °C, 6 h, 22%.



Scheme 8. (a) *n*-BuLi, −78 °C, then **14**, warm to rt, 51%; (b) **3b**, DCM, 36 h, 72%; (c) (i) guanidine, DMF, 0 °C, 6 h; (ii) H_2O, MeOH, HCl, 0 °C–rt, 16 h; (d) (i) THF, TBAF, 25–30 °C, 3 h, then rt, 64 h; (ii) MeOH, HCl, 0 °C, 4 h, then $NaBF_4$ (satd, aq), CH_2Cl_2, 18% overall.

Table 1

Compound	K562[a]	A2780[a]	H-460[a]	P388[a]
27·BF_4	12.30	24.44	10.36	2.93
Ptilomycalin A **1**	0.35	0.27	0.35	0.11[b]

[a] Cytotoxic activity (IC_{50}/μgmL^{-1}): K562: human chronic myelogenous leukaemia; A2780: human, ovarian carcinoma; H-460: human large cell carcinoma, lung. High DT-diaphorase; P388: mouse, lymphoid neoplasm.
[b] Data obtained from Ref. 5a.

studies in this area,[21] which suggest that the fatty acid chain and spermidine residue are essential for the high levels of activity in these types of compounds.

3. Conclusion

In conclusion, we have investigated the synthesis of ptilomycalin A with limited success and have found that a key Knovenagel condensation is problematic and in some cases impossible to effect. Despite this failure we have demonstrated the worth of the methodology and have completed a highly convergent and potentially biomimetic synthesis of crambescidin 359 **27**. We have also found that **27**·BF_4 displays much lower levels of biological activity than ptilomycalin A, demonstrating that the fatty acid chain and spermidine residue are required for high levels of activity.

4. Experimental

4.1. General

Column chromatography was carried out on silica gel (particle size 40–63 μm) and TLC were conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) with the eluent specified in each case. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Ether and THF were distilled from sodium and benzophenone. Methanol was dried by distillation from magnesium and iodine. Dry DMF was purchased from Aldrich. Dichloromethane was freshly distilled from calcium hydride. Chemical shifts are reported in δ values relative to tetramethylsilane as an internal standard. Proton (250 MHz) and carbon (62.5 MHz) NMR spectra were recorded in deuteriochloroform on a Bruker AC250 spectrometer unless otherwise stated. All mass spectra were run at the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea. Low resolution mass spectra were recorded on a VG Biotech Quattro II triple quadrupole mass spectrometer using chemical ionisation (CI), with ammonia as reagent gas, or by means of electron impact (EI). Accurate mass spectra (HRMS) were recorded on a VG ZAB-E mass spectrometer whereas fast atom bombardment (FAB) spectra were run on a VG Autospec mass spectrometer using caesium ion bombardment at 25 kV energy. Specific rotations were determined using a PolAAr 2001 polarimeter, (cell path length, l=1), with the temperature (t), concentration (*c*) and solvent recorded in each case. Infrared spectra were recorded as thin films (oils) or as chloroform solutions on a Perkin–Elmer 1600 series instrument. Melting points were recorded with a Gallenkamp MF370 apparatus.

4.2. 7-(*tert*-Butyl-dimethyl-silanyloxy)-3-oxo-heptanoic acid *tert*-butyl ester 8

Sodium hydride (0.27 g, 11.34 mmol) was suspended in dry THF (20 mL), cooled (0 °C) and treated with *tert*-butyl acetoacetate (0.9 g, 5.67 mmol). After stirring for 20 min at 0 °C, the resulting suspension was treated with *n*-butyllithium (4.36 mL, 5.67 mmol, 1.3 M) and stirred for 10 min. Iodide **7**[10] (1.7 g, 5.65 mmol) dissolved in THF (5 mL) was added and the resultant mixture stirred at rt over 20 min. Ammonium chloride solution (saturated, 1 mL) and water (50 mL) were added and the reaction mixture was extracted with diethyl ether (4×50 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated to give a crude oil. Column chromatography on silica gel (3% diethyl ether in petrol) gave **8** (1.23 g, 66%) as an oil. R_f 0.23 in 10% diethyl ether–petrol; δ_H 3.62 (2H, t, *J* 6.3 Hz, CH_2), 3.35 (2H, s, CH_2), 2.57 (2H, t, *J* 7.0 Hz, CH_2), 1.65–1.52 (4H, m, 2×CH_2), 1.48 (9H, s, ^{t}Bu), 0.90 (9H, s, ^{t}Bu), 0.06 (6H, s, 2×Me); δ_C 203.2 (C), 166.5 (C), 81.8 (C), 62.7 (CH_2), 50.6 (CH_2), 42.6 (CH_2), 32.1 (CH_2), 28.0 (3×CH_3), 25.9 (3×CH_3), 20.0 (CH_2), 18.3 (C), −5.3 (2×Me); ν_{max} 2934, 2860, 1736, 1716, 1643, 1368, 1252, 1147, 836, 776; *m/z* (CI) 348 (10% $[M+NH_4]^+$), 331 (40% $[M+H]^+$), 275 (100%), 231 (30%); HRMS found: 331.2305, $C_{17}H_{35}O_4Si$ ($[M+H]^+$) requires: 331.2305.

4.3. 12-(*tert*-Butyl-dimethyl-silanyloxy)-2-[5-(*tert*-butyl-dimethyl-silanyloxy)-pentanoyl]-8-oxo-dodeca-2,6-dienoic acid *tert*-butyl ester 10 and 5-(*tert*-butyl-dimethyl-silanyloxy)-1-(5-hydroxy-cyclopent-1-enyl)-pentan-1-one 11

A solution of aldehyde **9** (250 mg, 0.84 mmol) in dichloromethane (1 mL) was cooled (−78 °C) before being treated with a solution of **8** (277 mg, 0.84 mmol) in dichloromethane (2 mL). Subsequent treatment with piperidinium acetate (15 mg, 0.1 mmol) was followed by warming to −20 °C and stirring for 6 h. The resulting mixture was diluted with hexane (20 mL) before being washed with water (20 mL)

and brine (20 mL). The organic fraction was dried ($MgSO_4$) and evaporated to give a crude oil, which was purified by column chromatography (10–30% diethyl ether in petrol, gradient elution) to give **10** (132 mg, 26%) as a 2:1 mixture of geometric isomers, which were partially separable by careful chromatography. Minor isomer (*E*): R_f 0.41 in 40% diethyl ether–petrol; δ_H 6.75 (2H, m, 2×CH), 6.06 (1H, d, *J* 15.8 Hz, CH_2), 3.64 (4H, t, *J* 6.0 Hz, 2×CH_2), 2.65 (2H, t, *J* 7 Hz, CH_2), 2.57 (2H, t, *J* 6.6 Hz, CH_2), 2.35 (2H, m, CH_2), 2.25 (2H, m, CH_2), 1.67 (4H, m, 2×CH_2), 1.51 (9H, s, ^{t}Bu), 1.49 (4H, m, 2×CH_2), 0.90 (18H, s, 2×^{t}Bu), 0.0 (12H, s, 4×Me); δ_C 165.6 (ester C). Major isomer (*Z*): R_f 0.31 in 40% diethyl ether–petrol; δ_H 6.75 (1H, dt, *J* 15.8, 6.5 Hz, CH), 6.63 (1H, t, *J* 7.2 Hz, CH), 6.09 (1H, d, *J* 15.8 Hz, CH), 3.58 (2H, t, *J* 6.3 Hz, CH_2), 3.57 (2H, t, *J* 6.3 Hz, CH_2), 2.66 (2H, t, *J* 6.9 Hz, CH_2), 2.59 (2H, t, *J* 6.9 Hz, CH_2), 2.44 (4H, m, 2×CH_2), 1.68 (4H, m, 2×CH_2), 1.56 (9H, s, ^{t}Bu), 1.53 (4H, m, 2×CH_2), 0.91 (18H, s, 2×^{t}Bu), 0.00 (12H, s, 4×Me); δ_C 200.2 (C), 197.5 (C), 165.6 (ester C), 144.4 (CH), 143.5 (CH), 138.6 (C), 131.0 (CH), 82.6 (C), 62.8 (2×CH_2), 40.0 (CH_2), 39.2 (CH_2), 32.3 (CH_2), 32.2 (CH_2), 31.0 (CH_2), 28.1 (^{t}Bu), 28.0 (CH_2), 26.0 (6×Me), 20.6 (CH_2), 20.4 (CH_2), 18.3 (2×C), −5.3 (4×Me); ν_{max} 2929, 2856, 1736, 1699, 1670, 1627, 1385, 1255, 1102, 837, 776; *m/z* (CI) 611 (20% $[M+H]^+$), 563 (15%), 562 (40%), 536 (20% $[MH-{}^t BuO]^+$), 530 (30%), 516 (10%), 502 (15%), 479 (20% $[M-TBDMSO]^+$), 474 (20%), 462 (50%), 445 (30%), 430 (20%), 416 (25%), 398 (100%).

Similar reactions utilising piperidine gave the by-product **11** in 20–30% yield. R_f 0.49 in 40% ethyl acetate–petrol; δ_H 6.80 (1H, t, *J* 2.8 Hz, CH), 5.08 (1H, br t, *J* 5.3 Hz, CH), 3.59 (2H, t, *J* 6.4 Hz, CH_2), 2.68 (2H, t, *J* 6.7 Hz, CH_2), 2.20 (2H, m, CH_2), 1.75 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.50 (2H, m, CH_2), 0.89 (9H, s, 3×Me), 0.00 (6H, s, 2×Me); δ_C 200.4 (C), 145.8 (C), 145.6 (CH), 75.4 (CH), 62.7 (CH_2), 38.7 (CH_2), 32.2 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 25.9 (3×Me), 20.8 (CH_2), 18.2 (C), −4.9 (2×Me); *m/z* (CI) 299 (100% $[M+H]^+$), 281 (60% $[M-OH]^+$), 241 (5%), 223 (7%), 167 (18%), 149 (30%).

4.4. *tert*-Butyl dispiro[tetrahydropyran-2,4′-(1,2,3,4,7,8-hexahydro-5*H*-5,6,8b-triazaacenaphthylene-3′-carbonate)-7′-2″tetrahydropyran]-6′-ium tetrafluoroborate 12/12a

A solution of bis-enone **10** (174 mg, 0.29 mmol) in DMF (5 mL) was added dropwise to a cooled (0 °C) solution of guanidine (17 mg, 0.29 mmol) in DMF (5 mL). The reaction was slowly warmed to rt and stirred for 5 h. After evaporation to dryness under reduced pressure the residue was dissolved in dry methanol (10 mL), cooled (0 °C) and anhydrous HCl gas was bubbled into the solution for 2 min. After 16 h, the resulting mixture was evaporated to produce an oily residue, which was dissolved in dichloromethane (50 mL) and washed with water (2×50 mL) and brine (2×50 mL). Drying and evaporation gave an oily residue, which was dissolved in dichloromethane (10 mL) and treated with saturated aqueous sodium tetrafluoroborate solution (30 mL). After vigorous stirring for an hour, the resulting emulsion was extracted with dichloromethane (3×20 mL) before the combined organic fractions were dried and evaporated. The product was purified by column chromatography on silica gel (0.5% methanol–chloroform) and the combined product fractions dissolved in diethyl ether (5 mL) and diluted with petrol (10 mL). After 16 h the mother liquor was decanted leaving **12/12a** (29 mg, 20%) as a solid. R_f 0.31 in 5% methanol–chloroform; δ_H 8.50–7.50 (2H, m, 2×NH), 4.20–3.50 (6H, m, 2×CH_2), 2.90–0.70 (28H, m); selected δ_C 167.5, 166.9 (major), 166.6, 166.5 (C=O), 149.3, 148.9, 148.5, 147.8 (major) (C=N); ν_{max} 3283, 2947, 1728, 1660, 1604, 1044; *m/z* (CI) 406 (80% $[M]^+$), 388 (15%), 348 (15% $[M-{}^t Bu]^+$), 305 (15% $[MH-{}^t BuCO]^+$), 288 (50%), 286 (20%), 268 (10%), 208 (40%), 206 (30%), 182 (100%), 164 (70%); HRMS found: 406.2706, $C_{22}H_{36}N_3O_4$ ($[M]^+$) requires: 406.2706.

4.5. (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-iodobutane 14[22]

4.5.1. Ethyl (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]butanoate. Imidazole (5.36 g, 78.8 mmol) and ethyl (*R*)-3-hydroxybutyrate (4.0 g, 30.3 mmol) were dissolved in DMF (30 mL) and the resulting solution cooled (0 °C). *tert*-Butyldimethylsilyl chloride (6.00 g, 39.4 mmol) was then added and the reaction stirred at rt for 4 h. The reaction was extracted with hexane (3×40 mL) and the combined hexane layers washed with an aqueous acetic acid solution (2%, 40 mL) and water (3×40 mL). After drying ($MgSO_4$) and evaporation the crude oil was purified by column chromatography on silica gel (5% diethyl ether in petrol) to yield the ester (7.07 g, 94%) as an oil. R_f 0.57 in 10% diethyl ether/petrol; ν_{max} 2932, 2897, 1739, 1471, 1376, 1301, 1255, 1184, 1140, 1085, 1003, 940; δ_H 4.28 (1H, m, CH), 4.12 (2H, dq, *J* 7.1, 1.8 Hz, CH_2), 2.48 (1H, dd, *J* 14.4, 7.5 Hz, CH), 2.36 (1H, dd, *J* 14.5, 5.4 Hz, CH), 1.27 (3H, t, *J* 7.2 Hz, CH_3), 1.20 (3H, d, *J* 6.1 Hz, CH_3), 0.87 (9H, s, 3×CH_3), 0.07 (3H, s, CH_3), 0.05 (3H, s, CH_3); δ_C 171.7 (C), 65.9 (CH), 60.2 (CH_2), 45.0 (CH_2), 25.7 (3×CH_3), 23.9 (CH_3), 17.9 (C), 14.2 (CH_3), −4.5 (CH_3), −4.8 (CH_3); MS (CI) *m/z* 247 (100% $[M+H]^+$), 189 (10% $[M-({}^t Bu)]^+$); HRMS (CI) *m/z* found: 247.1729, $C_{12}H_{27}O_3Si$ ($[M+H]^+$) requires: 247.1729; $[\alpha]_D^{25}$ −27.0 (*c* 0.37, $CHCl_3$) [lit. $[\alpha]_D^{18}$ −26.9 (*c* 1.0, $CHCl_3$)].[22]

4.5.2. (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]butan-1-ol. A solution of the above compound (3.32 g, 13.4 mmol) in dry hexane (50 mL) was cooled (−78 °C) and treated with DIBAL-H (1 M, hexanes, 34.2 mL, 34.2 mmol) in a dropwise manner and stirred for 8 h at −20 °C. After warming (0 °C), methanol (2 mL) was added and the resulting mixture diluted with hexane (40 mL) followed by the addition of saturated ammonium chloride solution (30 mL). The resulting precipitated solid was filtered and washed with further hexane (200 mL in portions), the organic layer separated and washed with water (4×50 mL), dried ($MgSO_4$) and the solvent evaporated to give the title compound (2.26 g, 83%) as a yellow oil. R_f 0.15 in 10% diethyl ether–petrol; ν_{max} 3346, 2930, 2858, 1472, 1375, 1255, 1129, 1028, 940, 837, 775, 718, 658; δ_H 4.11 (1H, m, CH), 3.85 (1H, m, CH), 3.75 (1H, m, CH), 2.59 (1H, br t, *J* 5.0 Hz, OH), 1.86–1.80 (1H, m, CH), 1.79–1.57 (1H, m, CH), 1.21 (3H, d, *J* 6.2 Hz, CH_3), 0.90 (9H, s, 3×CH_3), 0.10 (3H, s, CH_3), 0.09 (3H, s, CH_3); δ_C 68.3 (CH), 60.4

(CH_2), 40.5 (CH_2), 25.8 (3×CH_3), 23.4 (CH_3), 17.9 (C), −4.4 (CH_3), −4.5 (CH_3); MS (CI) *m/z* 205 (100% $[M+H]^+$), 202 (2%), 132 (5%), 92 (12%), 91 (10%); HRMS (CI) *m/z* found: 205.1624, $C_{10}H_{25}O_2Si$ ($[M+H]^+$) requires: 205.1624. $[\alpha]_D^{30}$ −17.8 (*c* 0.41, $CHCl_3$) [lit. $[\alpha]_D^{18}$ −30.1 (*c* 1.1, $CHCl_3$)].[22]

4.5.3. (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]butan-1-*para*-toluene sulfonate.[23] *para*-Toluenesulfonyl chloride (2.27 g, 11.88 mmol) dissolved in dry pyridine (5 mL) was added dropwise to a cooled (0 °C) solution of the above alcohol (2.21 g, 10.8 mmol) in dry pyridine (5 mL). The resulting mixture was stirred at rt for 16 h, diluted with water (100 mL) and then extracted with hexane (3×40 mL). The combined organic layers were washed with sulfuric acid (2 M, 2×25 mL) and water (2×40 mL), dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (3% diethyl ether in petrol) gave the title compound (2.41 g, 62%) as a colourless oil. R_f 0.15 in 5% diethyl ether–petrol; ν_{max} 2955, 2856, 1598, 1471, 1362, 1255, 1178, 1097, 1047, 1006, 938, 891, 837, 776, 655; δ_H 7.80 (2H, d, *J* 8.3 Hz, CH), 7.35 (2H, d, *J* 8.3 Hz, CH), 4.11 (2H, t, *J* 6.2 Hz, CH_2), 3.91 (1H, m, CH), 2.46 (3H, s, CH_3), 1.74 (2H, m, CH_2), 1.11 (3H, d, *J* 6.2 Hz, CH_3), 0.82 (9H, s, CH_3), 0.03 (3H, s, CH_3), −0.02 (3H, s, CH_3); δ_C 144.7 (C), 133.0 (C), 129.8 (2×CH), 127.9 (2×CH), 67.9 (CH_2), 64.6 (CH), 38.5 (CH_2), 25.7 (3×CH_3), 23.9 (CH_3), 21.6 (CH_3), 17.9 (C), −4.4 (CH_3), −5.1 (CH_3); MS (CI) *m/z* 359 (100% $[M+H]^+$), 246 (8%), 227 (4% $[M-TBDMSO]^+$), 205 (40%), 52 (12%); HRMS (CI) *m/z* found: 359.1712, $C_{17}H_{31}O_4SiS$ ($[M+H]^+$) requires: 359.1712; $[\alpha]_D^{26}$ −22.6 (*c* 0.49, $CHCl_3$).

4.5.4. (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-iodobutane 14.[23] The above tosylate (2.23 g, 6.23 mmol) was dissolved in acetone (95 mL) and sodium iodide (5.20 g, 34.3 mmol) was added and the mixture heated to reflux for 4 h. After cooling, the resulting suspension was filtered and the solids thoroughly washed with diethyl ether (several portions ca. 100 mL). The filtrate was evaporated to give a crude oil, which was triturated with hexane (5×30 mL) and the combined triturates were dried ($MgSO_4$) and evaporated in vacuo to give **14** (1.87 g, 95%) as a clear oil. R_f 0.73 in 5% diethyl ether–petrol; ν_{max} 2955, 2929, 2892, 2856, 1472, 1374, 1255, 1178, 1147, 1127, 1063, 967, 871, 835, 775, 709; δ_H 3.90 (1H, m, CH), 3.24 (2H, m, CH_2), 1.97–1.88 (2H, m, CH_2), 1.17 (3H, d, *J* 6.1 Hz, CH_3), 0.90 (9H, s, 3×CH_3), 0.11 (3H, s, CH_3), 0.09 (3H, s, CH_3); δ_C 68.2 (CH), 43.2 (CH_2), 25.8 (3×CH_3), 23.5 (CH_3), 18.0 (C), 3.6 (CH_2), −4.2 (CH_3), −4.6 (CH_3); MS (CI) *m/z* 315 (45% $[M+H]^+$), 272 (10%), 189 (36%), 187 (64% $[M-I]^+$), 132 (100% $[TBDMSOH]^+$), 92 (42%), 91 (21%); HRMS (CI) *m/z* found: 315.0641, $C_{10}H_{24}IOSi$ ($[M+H]^+$) requires: 315.0641; $[\alpha]_D^{27}$ −46.3 (*c* 0.41, $CHCl_3$) [lit. $[\alpha]_D^{24}$ −49.6 (*c* 1.3, $CHCl_3$)].[23]

4.6. (*R*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-3-oxo-octanoic acid *tert*-butyl ester 4

n-Butyllithium (2.44 M in hexanes, 3.92 mL, 9.57 mmol) was added to a cooled (0 °C) solution of diisopropylamine (0.97 g, 9.57 mmol, 1.34 mL) in THF (50 mL) and the mixture stirred for 30 min. *tert*-Butyl acetoacetate (0.66 g, 4.15 mmol, 0.69 mL) was added and the mixture stirred for 1 h after which iodide **14** (1.0 g, 3.19 mmol) was added and the resulting mixture warmed to rt and stirred for a further 2 h. The solution was diluted with hexane (45 mL) followed by treatment with saturated aqueous ammonium chloride solution (15 mL) and water (45 mL). The organic layer was separated and washed with brine (2×45 mL) and the solvent dried and concentrated in vacuo to give a crude yellow oil, which was purified by chromatography on silica gel (3% diethyl ether–petrol) giving the desired product **4**, as a pale yellow oil (0.82 g, 75%). R_f 0.58 in 20% diethyl ether–petrol; ν_{max} 2930, 2856, 1735, 1717, 1642, 1462, 1406, 1369, 1318, 1253, 1147, 1032, 836, 775; δ_H 3.79 (1H, m, CH), 3.34 (2H, s, CH_2), 2.53 (2H, t, *J* 7.2 Hz, CH_2), 1.72–1.53 (2H, m, CH_2), 1.48 (9H, s, 3×CH_3), 1.45–1.22 (2H, m, CH_2), 1.12 (3H, d, *J* 6.1 Hz, CH_3), 0.89 (9H, s, 3×CH_3), 0.05 (6H, s, 2×CH_3) δ_C 203.2 (C), 166.4 (C), 81.8 (C), 68.2 (CH), 50.5 (CH_2), 42.9 (CH_2), 38.8 (CH_2), 27.9 (3×CH_3), 25.8 (3×CH_3), 23.7 (CH_3), 19.9 (CH_2), 18.0 (C), −4.5 (CH_3), −4.8 (CH_3); MS (CI) *m/z* 345 (14% $[M+H]^+$), 289 (39%), 245 (58%), 157 (17%), 132 (23% $[TBDMSOH]^+$), 113 (100%), 58 (24%), 52 (82%), 44 (65%), 36 (50%); HRMS (CI) *m/z* found: 345.2461, $C_{18}H_{37}O_4Si$ ($[M+H]^+$) requires: 345.2461; $[\alpha]_D^{27}$ −12.7 (*c* 0.37, $CHCl_3$).

4.7. (*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-butanal 16

4.7.1. Methyl (*S*)-2-hydroxybutanoate.[13] (*S*)-(+)-2-Aminobutyric acid **15** (10 g, 97 mmol) was dissolved in sulfuric acid (1 M, 200 mL), cooled (0 °C) and a solution of sodium nitrite (11 g, 159 mmol) in water (40 mL) added in a dropwise manner. After addition, the mixture was stirred at rt for 24 h before being saturated with sodium chloride (ca. 50 g). The resulting solution was extracted with ethyl acetate (4×80 mL) and the combined extracts dried ($MgSO_4$) and concentrated in vacuo to give crude (*S*)-2-hydroxybutanoic acid as a yellow oil. Acetyl chloride (11.2 g, 143 mmol, 10.2 mL) was added slowly (CAUTION! Exothermic reaction on mixing) to cooled (0 °C) methanol (100 mL) and the resulting solution stirred for 10 min. The crude α-hydroxy acid was dissolved in a small amount of dry methanol and added to the methanolic HCl and the mixture stirred at rt for 48 h. Careful evaporation of the solvent at atmospheric pressure (product is volatile) and column chromatography (dichloromethane) of the residue gave the ester (2.68 g, 23%) as a yellow oil. R_f 0.48 in 60% diethyl ether–petrol; ν_{max} 3453, 2925, 2850, 1734, 1654, 1230, 1136; δ_H 4.58 (1H, br s, OH), 4.20 (1H, dd, *J* 6.6, 4.5 Hz, CH), 3.82 (3H, s, CH_3), 1.86 (1H, m, CH), 1.73 (1H, m, CH), 0.97 (3H, t, *J* 7.4 Hz, CH_3); δ_C 175.5 (C), 71.5 (CH), 52.3 (CH_3), 27.3 (CH_2), 8.9 (CH_3); MS (CI) *m/z* 136 (45% $[M+NH_4]^+$), 104 (8%), 78 (21%), 74 (18%), 58 (14%), 46 (32%); HRMS (CI) *m/z* found: 136.0974, $C_5H_{14}NO_3$ ($[M+NH_4]^+$) requires: 136.0974.

4.7.2. Methyl (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-butanoate. Imidazole (6.33 g, 93 mmol) was added to a cooled (0 °C) solution of methyl (*S*)-2-hydroxybutanoate (3.44 g, 29 mmol) in DMF (60 mL) followed by the addition of *tert*-butyldimethylsilyl chloride (7.84 g, 52 mmol). After 48 h, the reaction was extracted with hexane (3×60 mL) and the combined hexane layers washed with aqueous acetic acid solution (2%, 50 mL) followed by water (2×40 mL),

then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude oil, which was purified by column chromatography (gradient elution, 0–10% diethyl ether in petrol) to give the title compound (3.17 g, 47%) as a colourless oil. R_f 0.63 in 10% diethyl ether–petrol; ν_{max} 2954, 2889, 2859, 1757, 1464, 1361, 1255, 1201, 1145, 1073, 1022, 935, 842, 780, 723; δ_H 4.06 (1H, dd, *J* 7.0, 5.1 Hz, CH), 3.64 (3H, s, CH_3), 1.65 (2H, m, CH_2), 0.89 (3H, t, *J* 7.4 Hz, CH_3), 0.88 (9H, s, 3×CH_3), 0.06 (3H, s, CH_3), −0.01 (3H, s, CH_3); δ_C 174.2 (C), 73.4 (CH), 51.7 (CH_3), 28.4 (CH_2), 25.7 (3×CH_3), 18.3 (C), 9.6 (CH_3), −5.0 (CH_3), −5.4 (CH_3); MS (CI) *m/z* 250 (100% $[M+NH_4]^+$), 233 (60% $[M+H]^+$), 217 (15%), 175 (21%), 132 (35%), 106 (16%), 74 (24%), 58 (30%), 52 (92%), 44 (43%), 36 (49%); HRMS (CI) *m/z* found: 233.1573, $C_{11}H_{25}O_3Si$ ($[M+H]^+$) requires: 233.1573; $[\alpha]_D^{24}$ −4.2 (*c* 0.3, $CHCl_3$).

4.7.3. (*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-butan-1-ol. The above silyl ester (2.12 g, 9 mmol) was dissolved in hexane (100 mL), cooled (−78 °C) and treated with a solution of DIBAL-H (1 M, hexanes, 20 mL, 20 mmol) in a dropwise manner. The solution was warmed (−20 °C) and stirred for 5 h before being treated with a mixture of 50% methanol–benzene (10 mL). The resulting mixture was diluted with hexane (50 mL) followed by an aqueous solution of saturated ammonium chloride (50 mL) and then filtered under vacuum. The organic phase was washed with water (3×50 mL), dried ($MgSO_4$) and evaporated to give a clear oil, which was purified by chromatography (10% diethyl ether–petrol) to give the title compound (1.34 g, 72%), as a clear oil. R_f 0.30 in 15% diethyl ether–petrol; ν_{max} 3358, 2955, 2858, 1464, 1361, 1256, 1050, 938, 836, 775, 665; δ_H 3.69 (1H, m, CH), 3.58 (1H, m, CH), 3.48 (1H, m, CH), 1.91 (1H, br t, *J* 7.8 Hz, OH), 1.54 (2H, dq, *J* 7.3, 6.3 Hz, CH_2), 0.93 (9H, s, 3×CH_3), 0.90 (3H, t, *J* 7.5 Hz, CH_3), 0.11 (6H, s, 2×CH_3); δ_C 74.1 (CH), 65.8 (CH_2), 26.7 (CH_2), 25.8 (3×CH_3), 18.1 (C), 9.7 (CH_3), −4.5 (CH_3), −4.6 (CH_3); MS (CI) *m/z* 222 (13% $[M+NH_4]^+$), 205 (30% $[M+H]^+$), 187 (7% $[M-OH]^+$), 132 (19%), 100 (12%), 98 (13%), 74 (28%), 72 (18%), 58 (28%), 52 (100%), 46 (29%), 44 (41%), 36 (53%); HRMS (CI) *m/z* found: 205.1624, $C_{10}H_{25}O_2Si$ ($[M+H]^+$) requires: 205.1624; $[\alpha]_D^{25}$ +6.2 (*c* 1.2, $CHCl_3$).

4.7.4. (*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-butanal 16. Oxalyl chloride (1.0 g, 7.85 mmol, 0.7 mL) in dry dichloromethane (100 mL) was cooled (−78 °C) and treated with dimethyl sulfoxide (1.1 g, 14.2 mmol, 1 mL) to give an effervescent mixture, which was stirred for 10 min. (*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-butan-1-ol (1.0 g, 4.9 mmol) dissolved in dichloromethane (5 mL) was added and the mixture stirred at −60 °C for 10 min. The solution was cooled (−78 °C) and triethylamine (2.97 g, 29.4 mmol, 4 mL) added. After stirring for 2 h at rt the mixture was diluted with water (100 mL) and extracted with hexane (2×50 mL) and the combined organic fractions washed with water (2×40 mL), aqueous acetic acid (7%, 2×40 mL) and brine (2×40 mL). Drying ($MgSO_4$) and evaporation in vacuo gave the title compound (0.92 g, 93%) as a yellow oil. R_f 0.60 in 5% diethyl ether–petrol; ν_{max} 2953, 2931, 2888, 2858, 2805, 2718, 1737, 1464, 1362, 1254, 1138, 1005, 939, 838, 778, 669; δ_H 9.62 (1H, d, *J* 1.7 Hz, CH), 3.93 (1H, ddd, *J* 7.0, 5.5, 1.7 Hz, CH), 1.77 (2H, m, CH_2), 0.98 (3H, t, *J* 7.4 Hz, CH_3), 0.95 (9H, s, CH_3), 0.11 (3H, s, CH_3), 0.10 (3H, s, CH_3); δ_C 204.4 (CH), 78.7 (CH), 25.8 (CH_2), 25.7 (3×CH_3), 18.1 (C), 9.0 (CH_3), −4.8 (CH_3), −5.0 (CH_3); MS (CI) *m/z* 220 (100% $[M+NH_4]^+$), 203 (40% $[M+H]^+$), 202 (45% $[M]^+$), 187 (27% $[M-CH_3]^+$), 173 (11% $[M-CHO]^+$), 145 (40% $[M-(^tBu)]^+$), 132 (40% $[M-TBDMSOH]^+$), 91 (13%), 74 (23%), 52 (17%), 46 (16%), 44 (10%); HRMS (CI) *m/z* found: 220.1732, $C_{10}H_{26}NO_2Si$ ($[M+NH_4]^+$) requires: 220.1733; $[\alpha]_D^{23}$ −11.5 (*c* 1.0, $CHCl_3$).

4.8. (*S*)-Methyl-(*E*),(*Z*)-6-[(*tert*-butyldimethylsilyl)-oxy]-oct-4-enoate 17

(3-Carboxypropyl)triphenylphosphonium bromide[24] (2.02 g, 4.7 mmol, 5 equiv) was suspended in THF (4.6 mL) and sodium bis(trimethylsilyl)amide (1.56 M solution in THF, 6.02 mL, 9.4 mmol) was added dropwise at rt to give a bright orange solution, which was then heated under reflux for 1 h. The solution was allowed to cool to rt then transferred (via syringe) to a solution of **16** (0.19 g, 0.94 mmol) in THF (3.2 mL). After stirring for 30 min the mixture was quenched with aqueous acetic acid solution (1%, 53 mL) and extracted with diethyl ether (5×35 mL). The combined organic fractions were then washed with brine (3×50 mL), dried ($MgSO_4$) and the solvent evaporated to give a yellow oil. This was dissolved in diethyl ether (5 mL), cooled (0 °C) and treated with excess ethereal diazomethane solution (1 M, ca. 6 mL). This solution was stirred then left to evaporate overnight to give a crude semi-crystalline product, which was purified by column chromatography (1–4% diethyl ether in petrol) yielding the title ester (0.12 g, 45%) as a 4:1 mixture of geometric isomers. Further chromatography (0.5% diethyl ether in petrol) gave pure **17** (80 mg, 28%). Data for the (*Z*) isomer: R_f 0.29 in 5% diethyl ether–petrol; ν_{max} 2956, 2930, 2856, 1743, 1462, 1437, 1361, 1253, 1166, 1082, 1048, 860, 836, 777; δ_H 5.42 (1H, dd, *J* 11.0, 9.1 Hz, CH), 5.30 (1H, m, CH), 4.35 (1H, dt, *J* 7.8, 6.4 Hz, CH), 3.69 (3H, s, CH_3), 2.45 (4H, m, 2×CH_2), 1.56–1.41 (2H, m, CH_2), 0.91 (9H, m, 3×CH_3), 0.90 (3H, t, *J* 7.4 Hz, CH_3), 0.06 (3H, s, CH_3), 0.03 (3H, s, CH_3); δ_C 173.3 (C), 135.4 (CH), 126.5 (CH), 70.0 (CH), 51.4 (CH_3), 34.0 (CH_2), 31.3 (CH_2), 25.8 (3×CH_3), 23.3 (CH_2), 18.1 (C), 9.5 (CH_3), −4.4 (CH_3), −4.8 (CH_3); *m/z* 304 (5% $[M+NH_4]^+$), 287 (8% $[M+H]^+$), 229 (48% $[M-(^tBu)]^+$), 155 (100% $[M-TBDMSO]^+$); HRMS (CI) *m/z* found: 287.2042, $C_{15}H_{31}O_3Si$ ($[M+H]^+$) requires: 287.2042; $[\alpha]_D^{25}$ +19.8 (*c* 0.4, $CHCl_3$). Selected data for the *E*-isomer: R_f 0.23 in 5% diethyl ether in petrol; δ_H 5.55 (2H, m, CH), 3.99 (1H, m, CH), 3.70 (3H, s, CH_3), 2.39 (4H, m, CH_2), 1.55–1.38 (2H, m, CH_2), 0.90 (9H, m, 3×CH_3), 0.89 (3H, t, *J* 7.4 Hz, CH_3), 0.07 (3H, s, CH_3), 0.05 (3H, s, CH_3); δ_C 173.3 (C), 134.8 (CH), 127.8 (CH), 74.5 (CH), 51.4 (CH_3), 33.9 (CH_2), 31.1 (CH_2), 27.4 (CH_2), 25.8 (3×CH_3), 18.1 (C), 9.6 (CH_3), −4.4 (CH_3), −4.8 (CH_3).

4.9. (*S*)-6-Oxo-11-[(*tert*-butyldimethylsilyl)-oxy]-(4*E*,9*Z*)-tridecadieneal 3a

Methyltriphenylphosphonium iodide (0.32 g, 0.78 mmol) was suspended in THF (10 mL), cooled (0 °C) and treated with *n*-butyllithium (2.0 M, 0.51 mL, 0.86 mmol) with stirring to give an orange coloured solution. After stirring at rt

for 30 min the solution was cooled (−78 °C) and **17** (0.11 g, 0.39 mmol) was added as a solution in THF (1 mL). The resulting pale yellow mixture was left to stir at rt for 2 h then quenched with water (20 mL) and extracted with ethyl acetate (4×25 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude yellow oil. This was then dissolved in THF (15 mL) and treated with freshly distilled succinaldehyde (0.53 g, 6.2 mmol). After stirring for 42 h the solvent was evaporated and the crude material purified by column chromatography on silica gel (25% diethyl ether–petrol) to give **3a** (0.06 g, 42%). R_f 0.23 in 35% diethyl ether/petrol; ν_{max} 2956, 2929, 2856, 1727, 1698, 1674, 1631, 1409, 1253, 1080, 1007, 979, 836, 727, 668; δ_H 9.82 (1H, s, CH), 6.83 (1H, dt, *J* 16.0, 6.5 Hz, CH), 6.14 (1H, dt, *J* 16.0, 2.1 Hz, CH), 5.42–5.26 (2H, m, 2×CH), 4.34 (1H, m, CH), 2.68–2.40 (6H, m, 3×CH_2), 2.34 (2H, m, CH_2), 1.51–1.27 (2H, m, CH_2), 0.89 (9H, s, 3×CH_3), 0.87 (3H, t, *J* 7.5 Hz, CH_3), 0.06 (3H, s, CH_3), 0.03 (3H, s, CH_3); δ_C 200.3 (C), 199.2 (C), 144.4 (CH), 135.1 (CH), 130.9 (CH), 126.9 (CH), 70.0 (CH), 41.9 (CH_2), 40.0 (CH_2), 31.3 (CH_2), 25.8 (3×CH_3), 24.6 (CH_2), 22.3 (CH_2), 18.2 (C), 9.8 (CH_3), −4.4 (CH_3), −4.8 (CH_3); MS (CI) *m/z* 356 (10% $[M+NH_4]^+$), 338 (5% $[M]^+$), 281 (10% $[M-(^tBu)]^+$), 207 (100% $[M-TBDMSO]^+$); HRMS (CI) *m/z* found: 356.2621, $C_{19}H_{38}NO_3Si$ ($[M+NH_4]^+$) requires: 356.2621; $[\alpha]_D^{25}$ +16.6 (*c* 1.1, $CHCl_3$).

4.10. *tert*-Butyl (13*S*,5′*R*),(2*E*/*Z*,6*E*,11*Z*)-2-{5′-[(*tert*-butyldimethylsilyl)oxy]-1′-oxo-hexanoyl}-[(13-*tert*-butyldimethylsilyl)oxy]-8-oxopentadeca-2,6,11-trienoate 2

Aldehyde **3a** (0.055 g, 0.16 mmol), β-keto ester **4** (0.071 g, 0.19 mmol) and sodium sulfate (0.05 g) were mixed together with stirring in dry dichloromethane (0.5 mL) for 10 min at −20 °C. Morpholine (6 mg, 0.064 mmol, 0.006 mL) was added and the reaction stirred for 6 h at −20 °C. The mixture was diluted with hexane (5 mL), washed with aqueous acetic acid solution (2%, 2×15 mL) and water (2×15 mL) then dried ($MgSO_4$) and evaporated to yield an orange oil. Purification on silica gel (gradient elution: 5–30% diethyl ether in petrol) gave the required enone **2** (0.023 g, 22%) as an oil with an estimated purity of 75%. Assignable data; R_f 0.63 in 40% diethyl ether–petrol. δ_H 6.89 (1H, m, CH), 6.67 (1H, t, *J* 7.4 Hz, CH), 6.09 (1H, dd, *J* 16.2, 4.0 Hz, CH), 5.33 (2H, m, 2×CH), 4.33 (1H, dt, *J* 7.1, 6.3 Hz, CH), 3.80 (1H, m, CH), 2.61 (2H, t, *J* 6.0 Hz, CH_2), 2.47 (2H, m, CH_2), 2.36 (2H, t, *J* 7.7 Hz, CH_2), 1.72–1.18 (19H, m, 5×CH_2, ^tBu), 1.13 (3H, d, *J* 6.1 Hz, CH_3), 0.88 (21H, m, CH_3, 2×^tBu), 0.05 (12H, s, 4×CH_3).

4.11. (*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-(triphenylphosphanylidene)-heptan-2-one 24

Acetylmethylene triphenylphosphorane (3.80 g, 11.94 mmol) was suspended in THF (70 mL), cooled to −78 °C and *n*-butyllithium (2.33 M, 11.94 mmol, 5.12 mL) slowly added. The deep red solution formed was warmed (−55 °C) and stirred for 1 h before re-cooling to −78 °C. Iodide **14** (2.50 g, 7.96 mmol) in THF (15 mL) was added and the mixture was stirred for 16 h whilst warming to rt. The solvent was removed under reduced pressure leaving a crude oily residue, which was purified by column chromatography on silica gel (70–85% ethyl acetate in petrol) to give the title compound (2.03 g, 51%) as a dense orange oil. R_f 0.13 in 70% ethyl acetate–petrol; ν_{max} 3059, 2956, 2855, 1727, 1525, 1482, 1438, 1400, 1254, 1107, 1028, 874, 836, 693; δ_H 7.72–7.42 (15H, m, 3×Ph), 4.13 (1H, m, CH), 3.66 (1H, br s, CH), 2.31 (2H, t, *J* 7.4 Hz, CH_2), 1.69 (2H, m, CH_2), 1.50 (2H, m, CH_2), 1.29 (3H, d, *J* 7.2 Hz, CH_3), 0.89 (9H, s, 3×CH_3), 0.05 (6H, s, 2×CH_3); δ_C 194.0 (C), 133.1, 133.0, 132.2, 132.0, 131.9, 128.9, 128.7, 128.6, 128.4 (15×CH), 128.1, 126.7 (3×C), 68.8 (CH), 51.0 (d, J_{C-P} 107 Hz, CH), 41.7 (d, J_{C-P} 14.4 Hz, CH_2), 39.8 (CH_2), 26.0 (3×CH_3), 23.8 (CH_3), 23.7 (CH_2), 18.2 (C), −4.4 (CH_3), −4.6 (CH_3); MS (CI) *m/z* 505 (11% $[M+H]^+$), 279 (24%), 263 (100%), 245 (44%), 187 (41%), 113 (45%); HRMS (CI) *m/z* found: 505.2691, $C_{31}H_{42}O_2PSi$ ($[M+H]^+$) requires: 505.2692; $[\alpha]_D^{22}$ −2.1 (*c* 1.0, $CHCl_3$).

4.12. (2*R*,18*S*),(7*E*,11*E*,16*Z*)-2-[(*tert*-Butyldimethylsilyl)oxy]-18-[(*tert*-butyldiphenylsilyl)oxy]-eicosa-7,11,16-triene-6,13-dione 25

A solution of phosphorane **24** (0.24 g, 0.47 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a cooled (0 °C) solution of aldehyde **3b** (0.15 g, 0.324 mmol) in CH_2Cl_2 (1 mL) and the reaction stirred for 36 h at rt. The solvent was evaporated and the remaining material purified by column chromatography on silica gel (gradient elution: 3–20% ethyl acetate–petrol) to give **25** (0.16 g, 72%) as a pale yellow oil. R_f 0.59 in 20% ethyl acetate–petrol; ν_{max} 3068, 3007, 2961, 2930, 2891, 2856, 1697, 1675, 1630, 1472, 1428, 1361, 1254, 1110, 1046, 983, 910, 836, 775, 735, 703; δ_H 7.69–7.66 (4H, m, 4×CH), 7.42–7.32 (6H, m, 6×CH), 6.81 (1H, m, CH), 6.67 (1H, m, CH), 6.14 (1H, d, *J* 15.8 Hz, CH), 6.01 (1H, d, *J* 15.8 Hz, CH), 5.44 (1H, dt, *J* 10.9, 1.6 Hz, CH), 5.18 (1H, dt, *J* 10.9, 7.4 Hz, CH), 4.38 (1H, m, CH), 4.14 (1H, m, CH), 2.54 (2H, t, *J* 7.2 Hz, CH_2), 2.38 (4H, m, 2×CH_2), 2.22 (2H, t, *J* 6.4 Hz, CH_2), 1.92 (2H, m, CH_2), 1.69–1.49 (4H, m, 2×CH_2), 1.48–1.36 (2H, m, CH_2), 1.13 (3H, d, *J* 6.1 Hz, CH_3), 1.05 (9H, s, 3×CH_3), 0.89 (9H, s, 3×CH_3), 0.80 (3H, t, *J* 7.4 Hz, CH_3), 0.06 (6H, s, 2×CH_3); δ_C 199.9 (C), 198.6 (C), 144.6 (CH), 144.5 (CH), 136.0 (2×CH), 135.9 (2×CH), 134.4 (C), 134.1 (C), 133.8 (CH), 130.8 (CH), 130.7 (CH), 129.5 (CH), 129.3 (CH), 127.7 (CH), 127.5 (2×CH), 127.7 (2×CH), 70.5 (CH), 68.4 (CH), 40.5 (CH_2), 39.8 (CH_2), 39.1 (CH_2), 31.1 (CH_2), 30.7 (2×CH_2), 26.9 (3×CH_3), 25.9 (3×CH_3), 23.7 (CH_3), 21.9 (CH_2), 20.4 (CH_2), 19.3 (C), 18.3 (C), 9.3 (CH_3), −4.4 (CH_3), −4.7 (CH_3); MS (CI) *m/z* 706 (75% $[M+NH_4]^+$), 438 (49%), 433 (100%), 297 (52%); HRMS (CI) *m/z* found: 706.4687, $C_{42}H_{68}NO_4Si_2$ ($[M+NH_4]^+$) requires: 706.4687; $[\alpha]_D^{26}$ −9.4 (*c* 0.9, $CHCl_3$).

4.13. (2*S*,7*S*,3a′*S*,7′*R*,8a′*R*,6″*R*)-Dispiro[7-ethyl-5*Z*-oxepene-2,4′-(1′,2′,3′,4′,7′,8′-hexahydro-5*H*-5′,6′,8b′-triazaacenaphthylene)-6″-methyl-7′,2″-tetrahydropyran]-6′-ium tetrafluoroborate 27

Guanidine (0.028 g, 0.48 mmol) dissolved in cooled (0 °C) DMF (1 mL) was added to a cooled (0 °C) solution of **25** (0.30 g, 0.435 mmol) in DMF (3 mL). The resulting green solution was stirred at 0 °C for 6 h eventually turning black. The reaction mixture was diluted with water (3.5 mL) and

a cold (0 °C) methanolic HCl solution (10 mL, from acetyl chloride (0.5 mL) and methanol (9.5 mL); CAUTION! exothermic reaction on mixing) and stirred for 16 h whilst warming to ambient temperature. Further water (40 mL) was added and the mixture extracted with CH_2Cl_2 (4×40 mL) and the combined organic fractions washed sequentially with water (2×50 mL), saturated lithium bromide solution (50 mL) and water (60 mL). After drying ($MgSO_4$) and concentration in vacuo, the resulting dense brown oil was dissolved in THF (1 mL) and treated with tetrabutylammonium fluoride (1 M in THF, 2.2 mmol, 2.2 mL) and stirred at 25–30 °C for 3 h and then at ambient temperature for a further 64 h. Water (10 mL) was added and the reaction extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were washed with water (25 mL), dried ($MgSO_4$) and concentrated in vacuo. The remaining brown oil was dissolved in methanol (1 mL) before being treated, at 0 °C with a solution of methanolic HCl (8 mL, from acetyl chloride (0.4 mL) and methanol (7.6 mL); CAUTION! exothermic reaction on mixing). After 4 h, water (10 mL) was added and the reaction extracted with CH_2Cl_2 (6×20 mL) and the combined organic fractions washed with water (50 mL). Concentration of the solvent gave a light brown oil, which was dissolved in CH_2Cl_2 (2 mL) and stirred vigorously for 3 h in the presence of an aqueous solution of saturated sodium tetrafluoroborate (3 mL). Dichloromethane (10 mL) was added and the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, which was purified by column chromatography on silica gel (gradient elution: 0–5% MeOH/CH_2Cl_2) to give **27**·HBF_4 (0.036 g, 18%) as a gum. R_f 0.10 in 3% methanol–dichloromethane; ν_{max} 3224, 2975, 2933, 2868, 1656, 1604, 1445, 1342, 1236, 1066, 1023; δ_H (500 MHz) 7.89 (1H, br s, NH), 7.83 (1H, br s, NH), 5.66 (1H, ddt, *J* 11.4, 7.7, 2.4 Hz, CH), 5.49 (1H, dt, *J* 11.0, 2.8 Hz, CH), 4.47 (1H, br d, *J* 9.8 Hz, CH), 4.06 (2H, m, 2×CH), 3.81 (1H, ddq, *J* 12.6, 6.5, 2.8 Hz, CH), 2.59 (1H, dd, *J* 12.7, 5.7 Hz, CH), 2.55 (1H, br t, *J* 13.7 Hz, CH), 2.32 (2H, m, 2×CH) 2.28 (1H, m, CH), 2.19 (1H, dd, *J* 14.0, 5.7 Hz, CH), 2.16 (1H, m, CH), 2.06 (1H, m, CH), 1.87 (1H, dd, *J* 14.3, 5.7 Hz, CH), 1.72 (3H, m, 3×CH), 1.70 (1H, m, CH), 1.69 (1H, m, CH), 1.62 (1H, m, CH), 1.52 (1H, m, CH), 1.49 (1H, t, *J* 12.7 Hz, CH), 1.42 (1H, m, CH), 1.36 (1H, t, *J* 12.4 Hz, CH), 1.20 (1H, m, CH), 1.06 (3H, *J* 6.4 Hz, CH_3), 0.83 (3H, t, *J* 7.2 Hz, CH_3); δ_C (125 MHz) 147.7 (C), 133.6 (CH), 129.8 (CH), 84.1 (C), 80.5 (C), 70.9 (C), 67.2 (C), 53.5 (CH), 52.0 (CH), 39.8 (CH_2), 37.1 (CH_2), 36.5 (CH_2), 33.6 (CH_2), 32.2 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 23.7 (CH_2), 21.7 (CH_3), 17.9 (CH_2), 10.2 (CH_3); MS (CI) *m/z* 360 (5% $[M+H]^+$); HRMS (EI) *m/z* found: 359.2566, $C_{21}H_{33}N_3O_2$ ($[M]^+$) requires: 359.2573; $[\alpha]_D^{26}$ −8.2 (*c* 0.2, CH_2Cl_2).

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