TOTAL SYNTHESIS OF THE POTENT ANTIFUNGAL AGENTS BENGAZOLE C AND E

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Dedicated to Dr. Alfred Bader on the occasion of his 85th birthday.

The bengazoles are marine natural products with unique structure, containing two oxazole rings flanking a single carbon. They show very potent antifungal activity. The total syntheses of bengazole C and E are described following a convergent route which involves diastereoselective cycloaddition of an appropriately substituted nitrile oxide with a butane-1,2-diacetal-protected alkenediol as the key step.
Keywords: Antifungal agents; Cycloaddition; Oxazoles; Natural products; Total synthesis; Bengazoles; Marine compounds.

The bengazoles are potent antifungal compounds isolated from various marine sources[1]. To date 22 members of this family are known and their structures and biological profiles have been well documented[2]. Total syntheses of bengazole A and B [3] together with a deacylated derivative have also been reported[4]. Nevertheless, the synthesis in this area has been complicated by the lability and ease of epimerisation of the C-10 stereogenic centre located between the oxazole rings. For example, a previous synthesis of bengazole A and its C-10 epimer was previously described by Molinski et al. as an inseparable mixture of diastereoisomeres[5]. During our work on bengazoles A and B we defined a route that allowed control on this important stereogenic centre and provided access to key building blocks for analogue preparation. Here we describe the extension and further optimisation of this process to synthesise two additional members of the series bengazole C (**1**) and bengazole E (**2**) (Chart 1).

While the new synthesis reported here closely follows our previous studies, we have now optimised a large number of the steps with the aim of pro-

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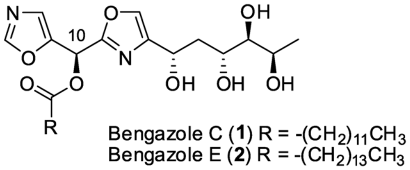
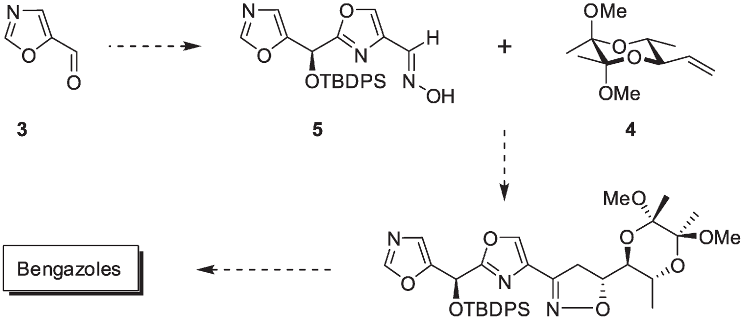


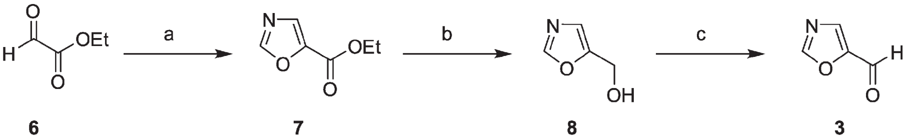
CHART 1

viding larger quantities of material. In very general terms the synthesis requires efficient preparation of two important fragments namely the oxazole aldehyde **3** and the butane-1,2-diacetal (BDA)-protected pent-4-ene-2,3-diol (**4**). Following elaboration of **3** to a suitable precursor **5** for nitrile oxide generation and subsequent stereoselective coupling of this with **4** rapidly assembles the carbon containing backbone of all the bengazole natural products (Scheme 1).



SCHEME 1

Oxazole-5-carbaldehyde (**3**) can be most easily obtained from ethyl glyoxylate (**6**) through initial reaction with tosyl methylisocyanide (TosMIC) using DBU as a base to afford the ester **7**. This can be reduced on scale, using sodium borohydride in the presence of lithium chloride in a mixture of THF/MeOH at 0 °C to provide the alcohol **8**. The product can be stored or



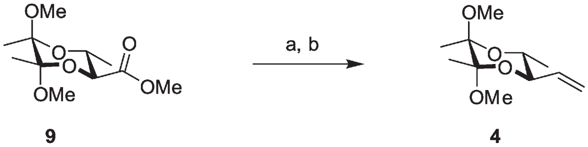
SCHEME 2

Synthesis of oxazole-5-carbaldehyde (**3**)

Reagents and conditions: (a) TosMIC, DBU, CH_2Cl_2, 0 °C, 92%; (b) $NaBH_4$, LiCl, THF, MeOH, 0 °C to r.t., 71%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to 0 °C, 64%

converted by oxidation under Swern conditions to provide the aldehyde **3** (Scheme 2). The new optimised conditions give **3** in 42% overall yield which compares favourably with our previous route (29%).

Next the BDA alkenediol **4** was obtained from the previously synthesised building block **9** via direct reduction with DIBAL-H in CH_2Cl_2 to afford an intermediate aldehyde which undergoes essentially a quantitative conversion to the protected alkenediol **4** using a Wittig coupling process (Scheme 3). Again this route proceeds with a 7% improvement over our previous route.

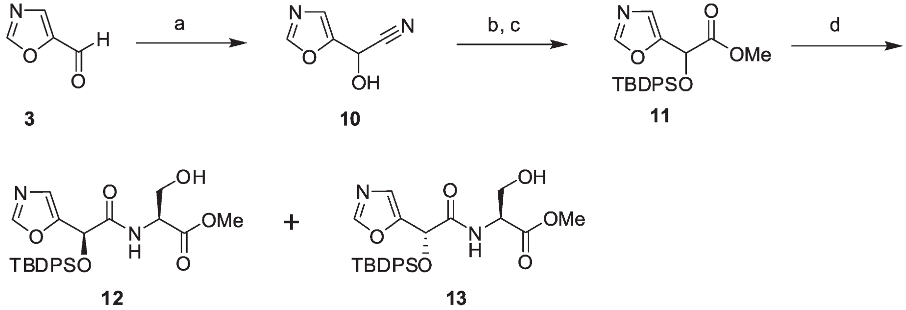


SCHEME 3

Synthesis of BDA alkenediol **4**

Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 78 °C, 93%; (b) $NaBH_4$, LiCl, THF, MeOH, 0 °C to r.t., 71%; (c) $MePPh_3Br$, KHMDS, Et_2O, –78 °C to r.t., 99%

For the next steps of the synthesis again several improvements to the yield were realised upon scaling-up of the reaction process. Firstly upon treatment of the aldehyde **3** with trimethylsilyl cyanide the cyanohydrin **10** can be obtained in an excellent 98% yield. This can be further transformed in two steps to the *tert*-butyldiphenylsilyl-protected ester **11** in 99% yield on batches over 8 g. Following ester hydrolysis and coupling with L-Ser-OMe a readily separated mixture of diastereomeric products **12** and **13** was obtained (Scheme 4).



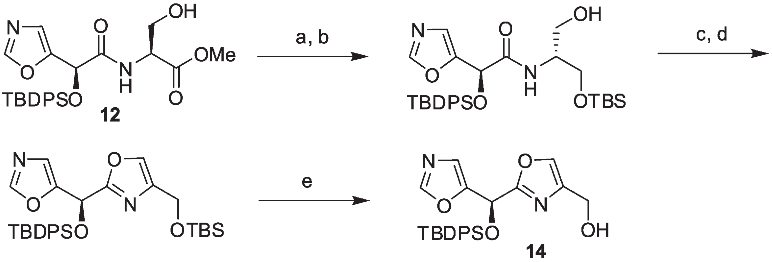
SCHEME 4

Synthesis of amides **12** and **13**

Reagents and conditions: (a) TMSCN, Et_3N, CH_2Cl_2, 0 °C, then 2 M HCl aqueous, 98%; (b) 2 M HCl in MeOH, reflux to r.t., 89%; (c) TBDPSCl, Et_3N, DMAP, DMF, r.t., 99%; (d) 1. LiOH, H_2O, THF, 0 °C to r.t.; 2. TBTU, H-L-Ser-OMe, i-Pr_2NEt, DMF

The unwanted diastereoisomer **13** is not wasted as this can be used for analogue programmes and by inversion of the C-10 stereogenic centre, to other bengazoles.

Compound **12** was then processed following our previously established route and progresses uneventfully to the alcohol **14** in the yields and conditions shown in Scheme 5.

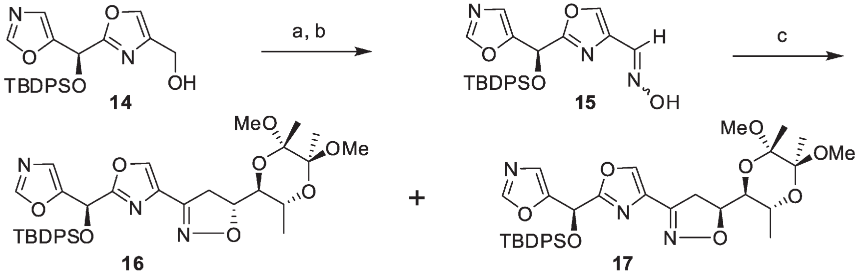


SCHEME 5

Synthesis of alcohol **14**

Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, r.t., 92%; (b) $NaBH_4$, LiCl, THF, MeOH, 0 °C to r.t., 80%; (c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C; (d) PPh_3, $C_2Br_2Cl_4$, CH_2Cl_2, 2,6-di-*tert*-butylpyridine, 0 °C, then Et_3N, MeCN, 0 °C to r.t., 89% over 2 steps, >98% ee; (e) PPTS, MeOH, r.t., 93%

Similarly this alcohol **14** serves as the precursor for the oxime **15** which upon treatment with *N*-chlorosuccinimide and then Cs_2CO_3 provides the corresponding nitrile oxide which undergoes stereoselective cycloaddition with **4** to give the readily separated diastereoisomers **16** and **17** in 7:2 ratio (Scheme 6). These steps are reproducible and mimic our previously reported yields and observations.

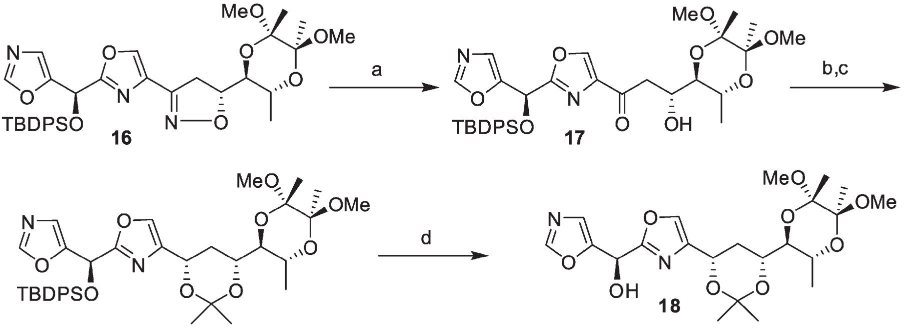


SCHEME 6

Synthesis of the bengazole backbone **16**

Reagents and conditions: (a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C; (b) $NH_2OH\cdot HCl$, K_2CO_3, MeOH, H_2O, r.t., 93% over 2 steps; (c) alkenediol **4**, Cs_2CO_3, DME, r.t., 77%

Next we were able to cleave the N–O bond in **16** and affect a hydrolysis to give ketone **17** in 71% yield which also constitutes a 10% improvement over our original studies. However, this reaction is still capricious and we are still seeking alternative solutions. Nevertheless it was suitable to progress to the next and final steps of the synthesis towards the two bengazoles C and E. Diastereoselective reduction of β-hydroxy ketone **17** gave alcohol **18** after acetal protection using 2,2-dimethoxybutane and cleavage of the silyl ether (Scheme 7).

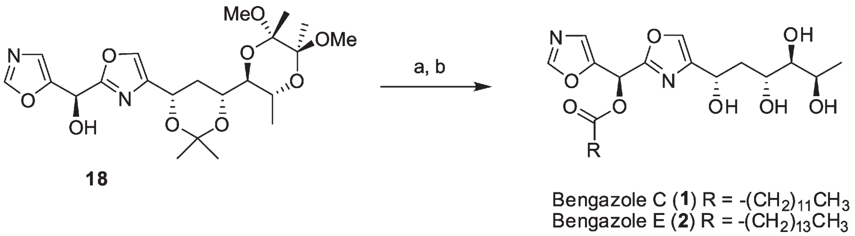


SCHEME 7

Synthesis of alcohol **18**

Reagents and conditions: (a) Raney nickel, H_2, $B(OH)_3$, EtOH, H_2O, r.t., 71%; (b) Et_2BOMe, $NaBH_4$, THF, –78 °C (dr 14:1); (c) 2,2-dimethoxypropane, TsOH, 89% over 2 steps; (d) TBAF, THF, 0 °C, 99%

To complete the total synthesis, alcohol **18** was treated with the corresponding acid chloride to afford the immediate bengazole precursors. Cleavage of both acetonide and BDA groups under acidic conditions afforded bengazole C (**1**) and bengazole E (**2**) whose spectral data agreed with the literature values[1a,5] (Scheme 8).



SCHEME 8

Synthesis of bengazole C (**1**) and bengazole E (**2**)

Reagents and conditions: (a) RCOCl, Et_3N, CH_2Cl_2, 0 °C, R = $-(CH_2)_{11}CH_3$ 88% and R = $-(CH_2)_{13}CH_3$ 75%; (b) TFA, H_2O, r.t., R = $-(CH_2)_{11}CH_3$ 91% and R = $-(CH_2)_{13}CH_3$ 69%

In summary, we have completed a stereocontrolled total synthesis of bengazole C and E by an optimised synthesis route which potentially could also provide access to many other members of the bengazole family and other analogue components.

EXPERIMENTAL

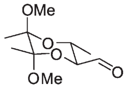
General

Solvents were purified by filtration on drying columns using Solvtek system. Anhydrous *N*,*N*-dimethylformamide, dimethoxyethane and pyridine were used as supplied. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over 4Å molecular sieves. All non-aqueous reactions were performed under an atmosphere of argon and carried out using oven-dried glassware. Reagents were used as supplied or purified using standard procedures as necessary.

Flash column chromatography was carried out using silica gel (Merck or Breckland (230–400 mesh)) under pressure. Collection was monitored by UV absorption at 220 and 254 nm. Analytical thin layer chromatography (TLC) was performed using precoated glass-backed plates and visualised by ultraviolet radiation (254 nm) and/or by oxidative staining with aqueous acidic ammonium molybdate(VII) solution.

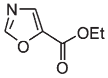
Optical rotations were measured using a Perkin–Elmer Polarimeter 343 over a path length of 10 cm with the sample temperature maintained at 25 °C. $[\alpha]_D^{25}$ values are given in 10^{-1} cm^2 g^{-1}, concentration (*c*) in g per 100 ml. Melting points were performed on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded as thin films on a Perkin–Elmer Spectrum One FT-IR spectrometer. Only selected absorbances (ν_{max} in cm^{-1}) are reported and peak shape indicated (s, strong; br, broad; w, weak) followed by assignment. ^1H NMR spectra were recorded at 25 °C (unless stated otherwise) on Bruker DPX-400, Bruker DRX-500 (VT or Cryoprobe) and Bruker DPX-600 spectrometers and are reported as follows: chemical shift δ in ppm (number of protons, multiplicity, coupling constant *J* in Hz, assignment). Residual protic solvent was used as the internal reference ($CHCl_3$ δ_H 7.27 ppm). ^{13}C NMR spectra were recorded at 100, 125 and 150 MHz on Bruker DPX-400, Bruker DRX-500 Cryoprobe and Bruker DPX-600 spectrometers, respectively. The resonance $CDCl_3$ (δ_C 77.0 ppm, t) was used as the internal reference. Assignments were made using a range of NMR experiments and these assignments are made according to the natural product numbering of bengazole A 1 to allow direct comparison of NMR data between compounds. Mass spectra were recorded on Waters LCT Premier, Bruker Daltronics Bioapex II or Kratos Concept spectrometers at the Department of Chemistry, University of Cambridge. Chiral HPLC was performed on an Agilent 1100 series HPLC using Chiralcel columns, HPLC grade solvents and UV detection (λ = 215 and 254 nm) at room temperature. Chiral SFC (supercritical fluid chromatography) was performed on a Berger Minigram, using a Chiralcel AS column with 7% methanol/carbon dioxide, 3 ml min^{-1} at 100 bar and UV detection (λ = 210 nm) at 35 °C.

(2*S*,3*R*,5*S*,6*S*)-5,6-Dimethoxy-3,5,6-trimethyl-[1,4]dioxane-2-carbaldehyde



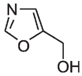
DIBAL-H (1 M in hexanes, 7.46 ml, 7.46 mmol) was added dropwise to a solution of ester **9** (1.30 g, 5.30 mmol) in CH_2Cl_2 (43 ml) at –78 °C, via syringe pump over 2 h 30 min. The mixture was stirred for further 1 h 30 min, then methanol (1.24 ml) was added dropwise at –78 °C. The reaction mixture was warmed to room temperature, then saturated aqueous Rochelle's salt (12 ml) and ether (10 ml) were added and the mixture stirred overnight. Water (12 ml) was added and the layers separated. The aqueous layer was extracted with ether (2–20 ml) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (10 to 20 to 40% ethyl acetate/petrol ether, 30–40 °C) afforded title compound as a white solid (1.08 g, 93%); m.p. 72–74 °C; R_F 0.63 (50% ethyl acetate/petrol ether, 30–40 °C); $[\alpha]_D^{25}$ +107.2 (*c* 1.6, $CHCl_3$). IR: 2951, 1738 (C=O), 1120 s, 1036, 908 s, 727 s. ^{1}H NMR (400 MHz, $CDCl_3$): 9.64 (1 H, s, 4-H), 3.87 (2 H, m, 2-H and 3-H), 3.29 (3 H, s, OCH_3), 3.27 (3 H, s, OCH_3), 1.38 (3 H, s, BDA CH_3), 1.30 (3 H, s, BDA CH_3), 1.26 (3 H, d, *J* = 5.8, 1-H_3). ^{13}C NMR (100 MHz, $CDCl_3$): 199.8 (C-4), 98.9 (BDA quaternary C), 98.6 (BDA quaternary C), 77.7 (C-3), 63.1 (C-2), 48.2 (OCH_3), 48.1 (OCH_3), 17.7 (BDA CH_3), 17.3 (BDA CH_3), 16.4 (C-1). MS (ESI+), *m/z*: found 241.1048, $[M + Na]^+$ $C_{10}H_{18}NaO_5$ requires 241.1046.

Oxazol-5-ylcarboxylic Acid Ethyl Ester (**7**)



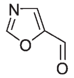
TosMIC (73.2 g, 375 mmol) was dissolved in dry CH_2Cl_2 (700 ml) under an argon atmosphere. At 0 °C, DBU (56.1 ml, 375 mmoL) and a solution of ethyl glyoxylate (**10**) (99.54 ml, 487 mmol, 50% in toluene) in dry CH_2Cl_2 (345 ml) were added simultaneously over a period of 2.5 h. Further DBU (28.1 ml, 187 mmol) was added and the dark solution was allowed to stir for further 30 min. The organic layer was then washed with aqueous 1.5 M HCl (300 ml) and saturated aqueous Na_2CO_3 (300 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluent: 10 to 25 to 33% diethyl ether/petrol ether, 30–40 °C) to give the desired compound as a colourless liquid (48.7 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.99 (1 H, s, Ar-H), 7.74 (1 H, s, Ar-H), 4.37 (2 H, q, *J* = 7.2, CH_2), 1.36 (3 H, t, *J* = 7.1, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 157.9, 153.6, 143.3, 133.6, 62.0, 14.6. The analytical data are consistent with those reported in the literature[6].

Oxazol-5-ylmethyl Alcohol (**8**)



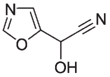
Ester **7** (14.0 g, 100.0 mmol) was dissolved in a mixture of dry THF (180 ml) and dry MeOH (380 ml) under an argon atmosphere. Lithium chloride (25.5 g, 600.0 mmol) was added and the suspension cooled to –10 °C. Subsequently, sodium borohydride (22.7 g, 600 mmol) was added in small portions over a period of 20 min under vigorous stirring and the temperature kept below –5 °C. After stirring for further 60 min at –5 °C, the suspension was slowly warmed to room temperature. If necessary, the temperature was adjusted with a water bath to 20–25 °C (*caution: due to the strong* H_2 *evolution at room temperature, a thermal runaway is possible*). The suspension was stirred for 21 h at room temperature and then quenched with water (1 l). Sodium potassium tartrate (180 g) was added and the solution then extracted with ethyl acetate (1 × 600 ml, 4 × 400 ml and 5 × 300 ml). The combined organic extracts were washed with brine (200 ml) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting liquid dried in vacuo. The product (7.4 g, 71%) was sufficiently clean by NMR but can be further purified by flash chromatography (eluent: diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (1 H, s, Ar-H), 6.97 (1 H, s, Ar-H), 4.66 (2 H, s, CH_2), 3.40 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$): 151.7, 151.6, 124.4, 55.4. The analytical data are consistent with those reported in the literature[6].

Oxazole-5-carbaldehyde (**3**)



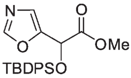
To a solution of oxalyl chloride (3.5 ml, 40.0 mmol) in dry CH_2Cl_2 (64 ml) under an argon atmosphere was added a solution of dry DMSO (7.2 ml, 100 mmol) in dry CH_2Cl_2 (17 ml) at –78 °C over 15 min. After stirring for 30 min, a solution of alcohol **8** (2.00 g, 20 mmol) in dry CH_2Cl_2 (12 ml) was added over a period of 15 min. The mixture was allowed to stir for further 30 min and was then treated with dry Et_3N (12.2 ml, 80 mmol). Stirring was continued for 30 min at –78 °C, then the mixture was warmed up to 0 °C and allowed to stir for 65 min. After hydrolysis with pH 7 buffer solution (100 ml), the aqueous layer was extracted with CH_2Cl_2 (3 × 40 ml) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated under reduced pressure ($t < 25$ °C, $p > 400$ mbar) to a volume of 12 ml. The crude material was then purified by flash chromatography (eluent: 50% diethyl ether/petrol ether, 30–40 °C) to yield aldehyde **3** (1.3 g, 56%) as colourless solid; m.p. 30–32 °C; R_F 0.17 (50% ether/petrol ether, 30–40 °C). IR: 3100 (C–H), 1681 (C=O), 1568 (oxazole), 1477 (oxazole). ^{1}H NMR (400 MHz, $CDCl_3$): 9.86 (1 H, s, C=O), 8.11 (1 H, s, 13-H), 7.88 (1 H, s, 12-H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.2 (CHO), 154.7 (C-13), 150.3 (C-11), 136.3 (C-12). MS (ESI+), *m/z*: found 97.0159, $[M]^+$ $C_4H_3NO_2$ requires 97.0164. The analytical data are consistent with those reported in the literature[5a,7].

Hydroxyoxazol-5-yl Acetonitrile *rac*-**10**



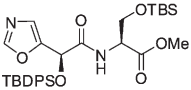
Triethylamine (1.00 ml, 7.16 mmol) was added to a solution of aldehyde **3** (7.00 g, 72.11 mmol) in CH_2Cl_2 (290 ml) at 0 °C. Trimethylsilyl cyanide (7.14 g, 51.50 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h 30 min. Aqueous 2 M HCl (70 ml) was added dropwise to the vented flask with vigorous stirring. After 30 min, further aqueous 2 M HCl (70 ml) was added, stirred for 30 min and the layers separated. The organic layer was washed with aqueous 2 M HCl (70 ml) and the combined aqueous layers extracted with ethyl acetate (7 × 150 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to give cyanohydrin *rac*-**10** as a yellow solid (8.81 g, 98%); m.p. 106–107 °C; R_F 0.40 (80% ethyl acetate/petrol ether, 30–40 °C). IR: 3134, 3043 br (O–H), 2839, 2716, 1507, 1123 s, 1056 s, 971 s. ^{1}H NMR (400 MHz, CD_3OD): 8.30 (1 H, s, 13-H), 7.31 (1 H, s, 12-H), 5.87 (1 H, s, 10-H). ^{13}C NMR (100 MHz, CD_3OD): 154.8 (C-13), 149.4 (C-11), 126.1 (C-12), 118.6 (CN), 56.2 (C-10). MS (ESI+), *m/z*: found 124.0271, $[M]^+$ $C_5H_4N_2O_2$ requires 124.0273.

2-[(*tert*-Butyldiphenylsilyloxy)-2-oxazol-5-yl]acetic Acid Methyl Ester (**11**)



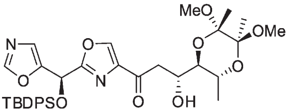
Imidazole (7.01 g, 103 mmol) was added to a solution of methyl 2-hydroxy-2-(oxazol-5-yl)-acetate (8.10 g, 65.3 mmol) in DMF (28 ml) at room temperature, followed by the addition of TBDPSCl (16.9 ml, 64.9 mmol) and DMAP (79.2 mg, 0.65 mmol) at room temperature. After 1 h 45 min, water (260 ml) was added to the stirred solution and the aqueous mixture extracted with ether (3 × 200 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (25% diethyl ether/petrol ether) afforded silyl-protected **11** as a colourless oil (24.6 g, 99%); R_F 0.58 (50% ethyl acetate/petrol ether (30–40 °C)). IR: 2955, 2859, 1764 s (C=O), 1112 s. ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (1 H, s, 13-H), 7.71 (2 H, d, $J = 7.2$, Ph-H), 7.65 (2 H, d, $J = 6.8$, Ph-H), 7.47–7.33 (6 H, m, Ph-H), 6.88 (1 H, s, 12-H), 5.25 (1 H, s, 10-H), 3.63 (3 H, s, OCH_3), 1.10 (9 H, s, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 169.2 (C-9), 151.0 (C-13), 148.8 (C-11), 135.9 (Ph-C), 135.6 (Ph-C), 132.3 (Ph quaternary C), 132.2 (Ph quaternary C), 130.13 (Ph-C), 130.06 (Ph-C), 127.75 (Ph-C), 127.72 (Ph-C), 125.1 (C-12), 67.0 (C-10), 52.4 (OCH_3), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$). MS (ESI+), *m/z*: found 396.1624, $[M + H]^+$ $C_{22}H_{26}NO_4Si$ requires 396.1624.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-[(*S*)-2-(*tert*-butyldiphenylsilyloxy)-2-oxazol-5-ylacetylamino]propionic Acid Methyl Ester



Imidazole (1.30 g, 18.98 mmol) was added to a solution of serine amide **12** (4.60 g, 9.48 mmol) in DMF (28 ml), followed by the addition of TBSCl (1.72 g, 11.38 mmol) and a catalytic amount of DMAP (30 mg, 0.25 mmol) at room temperature. The mixture was stirred for 45 min and then quenched by the addition of saturated aqueous sodium bicarbonate (75 ml) and water (40 ml). The aqueous solution was extracted with ether (2 × 110 ml) and the combined organic extracts washed with 10% w/v aqueous LiCl (75 ml), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (40 to 50% ethyl acetate/petrol ether, 30–40 °C) afforded the title compound as a colourless gum (5.21 g, 92%); R_F 0.30 (50% ethyl acetate/petrol ether, 30–40 °C); $[\alpha]_D^{25}$ +63.7 (*c* 1.3, $CHCl_3$). IR: 3430 (N–H), 2955, 2859, 1751 (C=O ester), 1694 s (C=O amide), 1509, 1107 s, 837 s, 702 s. ^1H NMR (400 MHz, $CDCl_3$): 8.06 (1 H, d, *J* = 8.8, N-H), 7.69 (2 H, d, *J* = 7.3, Ph-H), 7.65 (1 H, s, 13-H), 7.48 (3 H, m, Ph-H), 7.41 (3 H, t, *J* = 7.4, Ph-H), 7.30 (2 H, t, *J* = 7.4, Ph-H), 6.53 (1 H, s, 12-H), 5.21 (1 H, s, 10-H), 4.76 (1 H, ddd, *J* = 8.8, 2.8, 2.4, 7-H), 4.17 (1 H, dd, *J* = 10.1, 2.4, 8-H), 3.89 (1 H, dd, *J* = 10.1, 2.8, 8-H′), 3.80 (3 H, s, OCH_3), 1.13 (9 H, s, TBDPS $C(CH_3)_3$), 0.91 (9 H, s, TBS $C(CH_3)_3$), 0.10 (3 H, s, TBS CH_3), 0.07 (3 H, s, TBS CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 170.2 (C-6), 168.2 (C-9), 150.6 (C-13), 148.8 (C-11), 135.8 (Ph-C), 135.4 (Ph-C), 131.8 (Ph quaternary C), 131.8 (Ph quaternary C), 131.2 (Ph-C), 130.4 (Ph-C), 128.1 (Ph-C), 127.7 (Ph-C), 125.8 (C-12), 68.1 (C-10), 63.8 (C-8), 54.2 (C-7), 52.4 (OCH_3), 26.8 (TBDPS $C(CH_3)_3$), 25.7 (TBS $C(CH_3)_3$), 19.2 (TBDPS $C(CH_3)_3$), 18.2 (TBS $C(CH_3)_3$), –5.6 (TBS CH_3), –5.7 (TBS CH_3). MS (ESI+), *m/z*: found 597.2816, $[M + H]^+$ $C_{31}H_{45}N_2O_6Si_2$ requires 597.2814.

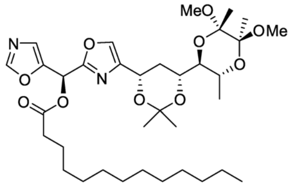
(*R*)-1-{2-[(*S*)-(*tert*-Butyldiphenylsilyloxy)oxazol-5-ylmethyl]oxazol-4-yl}-3-[(2*R*,3*R*,5*S*,6*S*)-5,6-dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-yl]-3-hydroxypropan-1-one (**17**)



Boric acid (264 mg, 4.26 mmol) was added to a solution of isoxazoline **16** (55 mg, 0.084 mmol) in ethanol (5.5 ml) and water (0.55 ml) at room temperature. Raney nickel (~1 ml as an aqueous slurry) was added and the mixture stirred under an atmosphere of hydrogen. After 3 h the mixture was filtered through a plug of celite and the solvent removed in vacuo, azetroping with toluene. The crude product was purified by flash chromatography (20 to 80% ethyl acetate/petrol ether, 30–40 °C) to afford β-hydroxy ketone **17** as a colourless oil (39 mg, 71%); R_F 0.26 (60% ethyl acetate/petrol ether); $[\alpha]_D^{25}$ +56.6 (*c* 0.6, $CHCl_3$). IR: 3420 br (O–H), 2935, 2860, 1691 (C=O), 1127 s. ^1H NMR (400 MHz, $CDCl_3$): 8.14 (1 H, s, 8-H), 7.80

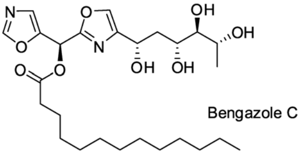
(1 H, s, 13-H), 7.59 (4 H, t, *J* = 7.8, Ph-H), 7.48–7.41 (2 H, m, Ph-H), 7.39–7.32 (4 H, m, Ph-H), 6.97 (1 H, s, 12-H), 5.97 (1 H, s, 10-H), 4.19 (1 H, m, 4-H), 3.70 (1 H, m, 2-H), 3.62 (1 H, dd, *J* = 9.6, 4.6, 3-H), 3.23 (3 H, s, OCH_3), 3.23 (3 H, s, OCH_3), 3.10 (2 H, m, 5-H_2), 1.28 (3 H, s, BDA CH_3), 1.24 (3 H, s, BDA CH_3), 1.22 (3 H, d, *J* = 6.2, 1-H_3), 1.08 (9 H, s, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 194.8 (C-6), 161.0 (C-9), 151.3 (C-13), 148.7 (C-11), 142.7 (C-8), 140.6 (C-7), 135.67 (Ph-C), 135.61 (Ph-C), 131.8 (Ph quaternary C), 131.8 (Ph quaternary C), 130.25 (Ph-C), 130.23 (Ph-C), 127.86 (Ph-C), 127.82 (Ph-C), 125.2 (C-12), 98.8 (BDA quaternary C), 98.6 (BDA quaternary C), 75.1 (C-3), 68.0 (C-4), 65.9 (C-2), 63.7 (C-10), 47.9 (OCH_3), 47.8 (OCH_3), 42.1 (C-5), 26.6 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 17.7 (BDA CH_3), 17.4 (BDA CH_3), 17.1 (C-1). MS (ESI+), *m/z*: found 687.2710, $[M + Na]^+$ $C_{35}H_{44}N_2NaO_9Si$ requires 687.2714.

Tridecanoic Acid (*S*)-{4-[(4*S*,6*R*)-6-((2*S*,3*R*,5*S*,6*S*)-5,6-Dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-yl)-2,2-dimethyl-[1,3]dioxan-4-yl]oxazol-2-yl}oxazol-5-ylmethyl Ester



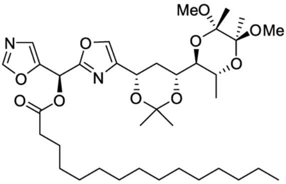
Triethylamine (339 µl, 2.43 mmol) was added to a solution of the bisoxazole alcohol **18** (38 mg, 0.081 mmol) in CH_2Cl_2 (4.3 ml) at 0 °C. Tridecanoyl chloride (31 µl, 0.12 mmol) was added dropwise to the stirred solution and after 20 min methanol (85 µl) was added and the mixture stirred for further 5 min. Saturated aqueous sodium bicarbonate (35 ml) was added and the mixture extracted with ether (5 × 35 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (35 ml), then dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (20 to 40% ethyl acetate/petrol ether, 30–40 °C) afforded acetal-protected bengazole C as a colourless oil (47 mg, 88%); R_F 0.47 (40% ethyl acetate/petrol ether, 30–40 °C); $[\alpha]_D^{25}$ +56 (*c* 1.73, $CHCl_3$). IR: 2923 s (C–H), 2854, 1751 (C=O), 1461, 1378, 1156 s. ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (1 H, s, 13-H), 7.60 (1 H, s, 8-H), 7.21 (1 H, s, 12-H), 7.07 (1 H, s, 10-H), 4.92 (1 H, dd, *J* = 11.9, 2.01, 6-H), 3.98 (1 H, ddd, *J* = 9.4, 7.2, 4.9, 4-H), 3.71 (1 H, dq, *J* = 9.5, 6.4, 2-H), 3.39 (1 H, dd, *J* = 9.5, 7.2, 3-H), 3.26 (3 H, s, OCH_3), 3.20 (3 H, s, OCH_3), 2.38 (2 H, t, 7.0, 15-H_2), 2.16 (1 H, ddd, *J* = 12.2, 2.5, 1.9, 5-H^{eq}), 1.63–1.58 (3 H, m, 16-H_2 and 5-H^{ax}), 1.48 (3 H, s, acetonide $CH_3{}^{eq}$), 1.41 (3 H, s, acetonide $CH_3{}^{ax}$), 1.29 (3 H, s, BDA CH_3), 1.27 (3 H, s, BDA CH_3), 1.28–1.20 (18 H, m, 17-H_2 to 25-H_2), 1.19 (3 H, d, *J* = 5.9, 1-H_3), 0.86 (3 H, t, *J* = 6.8, 26-H_3). ^{13}C NMR (125 MHz, $CDCl_3$): 171.9 (C-14), 157.5 (C-9), 151.8 (C-13), 145.9 (C-11), 142.9 (C-7), 136.2 (C-8), 126.9 (C-12), 99.0 (acetonide quaternary C), 98.4 (BDA quaternary C), 98.3 (BDA quaternary C), 74.5 (C-3), 69.6 (C-4), 67.5 (C-2), 65.5 (C-6), 61.3 (C-10), 47.93 (OCH_3), 47.88 (OCH_3), 33.8 (C-15), 32.6 (C-5), 31.9 (C-17), 29.9 (acetonide $CH_3{}^{eq}$), 29.59, 29.58, 29.54, 29.38, 29.31, 29.14, 28.94 (C-18 to C-24), 24.8 (C-15), 22.7 (C-25), 19.7 (acetonide $CH_3{}^{ax}$), 17.9 (C-1), 17.7 (BDA CH_3), 17.5 (BDA CH_3), 14.1 (C-26). MS (ESI+), *m/z*: found 687.3833, $[M + Na]^+$ $C_{35}H_{56}N_2NaO_{10}$ requires 687.3833.

Bengazole C (**1**)



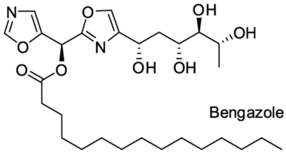
Acetal-protected bengazole C (46 mg, 0.069 mmol) was dissolved in TFA/water (1:1 mixture, 2.2 ml) and stirred for 10 min at room temperature, then water was added (1.1 ml, to give a 1:2 TFA/water mixture). The reaction mixture was stirred for 30 min at room temperature, then stirred under reduced pressure for 15 min (reducing the reaction volume by about half). Saturated aqueous sodium bicarbonate (55 ml) was added dropwise and the mixture extracted with ethyl acetate (4 × 55 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (5% methanol/CH_2Cl_2) afforded bengazole C (**1**) as a colourless oil (32 mg, 91%); R_F 0.23 (10% methanol/CH_2Cl_2); $[\alpha]_D^{25}$ +7 (*c* 0.83, MeOH). IR: 3351 br (O–H), 2923, 2853, 1750 (C=O). ^1H NMR (600 MHz, CD_3OD): 8.25 (1 H, s, 13-H), 7.85 (1 H, s, 8-H), 7.30 (1 H, s, 12-H), 7.10 (1 H, s, 10-H), 4.90 (1 H, t, *J* = 6.9, 6-H), 3.92 (1 H, dq, *J* = 6.4, 3.4, 2-H), 3.66 (1 H, ddd, *J* = 9.2, 6.8, 2.5, 4-H), 3.17 (1 H, dd, *J* = 6.7, 3.3, 3-H), 2.42 (2 H, t, *J* = 7.4, 15-H_2), 2.22 (1 H, ddd, *J* = 14.1, 6.9, 2.7, 5-H), 1.89 (1 H, ddd, *J* = 14.1, 9.5, 7.0, 5-H′), 1.61 (2 H, t, *J* = 7.0, 16-H_2), 1.33–1.24 (18 H, br m, 17-H_2 to 25-H_2), 1.14 (3 H, d, *J* = 6.8, 1-H_3), 0.88 (3 H, t, *J* = 6.7, 26-H_3). ^{13}C NMR (150 MHz, CD_3OD): 173.3 (C-14), 159.7 (C-9), 154.4 (C-13), 147.7 (C-11), 145.6 (C-7), 138.0 (C-8), 127.6 (C-12), 78.8 (C-3), 71.2 (C-4), 67.7 (C-2), 66.3 (C-6), 62.8 (C-10), 40.4 (C-5), 34.5 (C-15), 33.1, 30.77, 30.76, 30.71, 30.59, 30.49, 30.34, 30.0 (C-17 to C-24), 25.8 (C-16), 23.7 (C-25), 19.9 (C-1), 14.5 (C-26). MS (ESI+), *m/z*: found 533.2863, $[M + H]^+$ $C_{26}H_{42}N_2NaO_8$ requires 533.2839. The observed data was consistent with that previously reported[1a,5].

Pentadecanoic Acid (*S*)-{4-[(4*S*,6*R*)-6-((2*S*,3*R*,5*S*,6*S*)-5,6-dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-yl)-2,2-dimethyl-[1,3]dioxan-4-yl]oxazol-2-yl}oxazol-5-ylmethyl Ester



Triethylamine (196 µl, 1.41 mmol) was added to a solution of the bisoxazole alcohol **18** (22 mg, 0.047 mmol) in CH_2Cl_2 (2.5 ml) at 0 °C. Pentadecanoyl chloride (20 µl, 0.07 mmol) was added dropwise to the stirred solution and after 20 min methanol (0.05 ml) was added and the mixture stirred for further 5 min. Saturated aqueous sodium bicarbonate (20 ml) was added and the mixture extracted with ether (5 × 20 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (20 ml), then dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (20 to 40% ethyl acetate/petrol ether, 30–40 °C) afforded acetal-protected bengazole A as a colourless oil (24 mg, 75%); R_F 0.55 (50% ethyl acetate/petrol ether, 30–40 °C); $[\alpha]_D^{25}$ +52 (*c* 1.13, $CHCl_3$). IR: 2923 s (C–H), 2853, 1752 (C=O), 1464, 1379, 1124 s. ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (1 H, s, 13-H), 7.61 (1 H, s, 8-H), 7.22 (1 H, s, 12-H), 7.07 (1 H, s, 10-H), 4.93 (1 H, dd, *J* = 11.9, 2.1, 6-H), 3.98 (1 H, ddd, *J* = 11.4, 7.3, 2.3, 4-H), 3.72 (1 H, dq, *J* = 9.5, 6.4, 2-H), 3.39 (1 H, dd, *J* = 9.4, 7.2, 3-H), 3.23 (3 H, s, OCH_3), 3.21 (3 H, s, OCH_3), 2.41 (2 H, t, 7.6, 15-H_2), 2.18 (1 H, ddd, *J* = 13.2, 2.3, 1.9, 5-H^{eq}), 1.66–1.57 (3 H, m, 16-H_2 and 5-H^{ax}), 1.49 (3 H, s, acetonide CH_3^{eq}), 1.41 (3 H, s, acetonide CH_3^{ax}), 1.28 (3 H, s, BDA CH_3), 1.26 (3 H, s, BDA CH_3), 1.26–1.19 (22 H, m, 17-H_2 to 27-H_2), 1.21 (3 H, d, *J* = 6.4, 1-H_3), 0.86 (3 H, t, *J* = 6.7, 28-H_3). ^{13}C NMR (125 MHz, $CDCl_3$): 172.0 (H-14), 157.5 (C-9), 151.8 (C-13), 146.0 (C-11), 142.9 (C-7), 136.2 (C-8), 127.1 (C-12), 99.0 (acetonide quaternary C), 98.4 (BDA quaternary C), 98.4 (BDA quaternary C), 74.6 (C-3), 69.6 (C-4), 67.5 (C-2), 65.6 (C-6), 61.4 (C-10), 47.91 (OCH_3), 47.86 (OCH_3), 33.8 (C-15), 32.6 (C-5), 31.9 (C-17), 29.9 (acetonide CH_3^{eq}), 29.67, 29.65, 29.63, 29.61, 29.55, 29.4, 29.3, 29.2, 28.9 (C-18 to C-25), 24.7 (C-16), 22.7 (C-27), 19.7 (acetonide CH_3^{ax}), 17.9 (C-1), 17.7 (BDA CH_3), 17.5 (BDA CH_3), 14.1 (C-28). MS (ESI+), *m/z*: found 715.4147, $[M + Na]^+$ $C_{37}H_{60}N_2NaO_{10}$ requires 715.4146.

Bengazole E (**2**)



Acetal-protected bengazole E (23 mg, 0.033 mmol) was dissolved in TFA/water (1:1 mixture, 1 ml) and stirred for 10 min at room temperature, then water was added (0.5 ml, to give a 1:2 TFA/water mixture). The reaction mixture was stirred for 30 min at room temperature, then stirred under reduced pressure for 15 min (reducing the reaction volume by about half). Saturated aqueous sodium bicarbonate (25 ml) was added dropwise and the mixture extracted with ethyl acetate (4 × 25 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (5% methanol/CH_2Cl_2) afforded bengazole C (**2**) as a colourless oil (12 mg, 69%); R_F 0.17 (10% methanol/CH_2Cl_2); $[\alpha]_D^{25}$ +8 (*c* 0.25, MeOH). IR: 3377 br (O–H), 2918, 2851, 1751 (C=O), 1468. ^{1}H NMR (500 MHz, CD_3OD): 8.25 (1 H, s, 13-H), 7.85 (1 H, s, 8-H), 7.31 (1 H, s, 12-H), 7.11 (1 H, s, 10-H), 4.90 (1 H, t, *J* = 6.9, 6-H), 3.91 (1 H, dq, *J* = 6.4, 3.4, 2-H), 3.65 (1 H, ddd, *J* = 9.2, 6.8, 2.5, 4-H), 3.17 (1 H, dd, *J* = 6.8, 3.3, 3-H), 2.43 (2 H, t, *J* = 7.4, 15-H_2), 2.22 (1 H, ddd, *J* = 14.1, 11.4, 7.0, 5-H), 1.89 (1 H, ddd, *J* = 16.5, 9.6, 6.9, 5-H′), 1.62 (2 H, t, *J* = 7.1, 16-H_2), 1.32–1.22 (22 H, br m, 17-H_2 to 27-H_2), 1.15 (3 H, d, *J* = 6.5, 1-H_3), 0.88 (3 H, t, *J* = 6.7, 28-H_3). ^{13}C NMR (125 MHz, CD_3OD): 173.3 (C-14), 159.6 (C-9), 154.4 (C-13), 147.7 (C-11), 145.6 (C-7), 138.0 (C-8), 127.5 (C-12), 78.8 (C-3), 71.2 (C-4), 67.7 (C-2), 66.3 (C-6), 62.8 (C-10), 40.4 (C-5), 34.5 (C-15), 33.1, 30.85, 30.83, 30.81, 30.79, 30.75, 30.63, 30.5, 30.4, 30.8 (C-17 to C-26), 25.8 (C-16), 23.7 (C-27), 19.9 (C-1), 14.4 (C-28). MS (ESI+), *m/z*: found 561.3145, $[M + H]^+$ $C_{28}H_{46}N_2NaO_8$ requires 561.3152. The observed data was consistent with that previously reported[1a,5].

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