Supporting Information

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Total Synthesis of Potent Antifungal Marine Bisoxazole Natural Products
Bengazoles A and B

James A. Bull, Emily P. Balskus, Richard A. J. Horan, Martin Langner and Steven V. Ley*[a]
For experimental procedures and characterisation data for known compounds 9, 37, 39, and 40, see Supporting Information.

**Diol 9:** To a suspension of Sharpless AD-mix β (36.8 g) in t-butanol (120 mL) and water (120 mL) was added methanesulfonamide (2.50 g, 26.3 mmol). The mixture was cooled to 0 °C and trans-ethyl crotonate (3.00 g, 26.3 mmol) was added. The reaction mixture was stirred at 0 °C for 24 h before adding sodium sulfite (39 g). The suspension was allowed to warm to rt. It was extracted with a 3:1 mixture of chloroform/isopropanol (4 x 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (30 to 50% ethyl acetate/hexanes) to give diol 9 (3.74 g, 96%) as a colorless oil: [α]D²⁵° = −12.3 (c 1.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 4.26 (q, J = 7.1 Hz, 1H; Et CH₂), 4.08 (dq, J = 2.5, 6.4, 8.5 Hz, 1H; 2-H), 4.00 (dd, J = 2.7, 5.5 Hz, 1H; 3-H), 3.05 (d, J = 5.5, 1H; 3-H OH), 2.06 (d, J = 8.3 Hz, 1H, 2-H CH₂), 1.33 (t, J = 7.1 Hz, 3H; Et CH₃), 1.31 (d, J = 5.6 Hz, 1H; 1-H); ¹³C NMR (100 MHz, CDCl₃): δ = 173.4 (C-1), 74.3 (C-3), 68.7 (C-2), 62.1 (ethyl CH₃), 19.7 (ethyl CH₂), 14.15 (C-1); IR (film): νₘₐₓ (cm⁻¹) = 3437 s, br, 2980, 1731 s; HRMS: m/z (+ESI) Found: 171.0636, C₆H₁₅O₄Na requires 171.0633. The observed data was consistent with that previously reported.[23]

![Oxazole-5-Carboxaldehyde 37: Hydrolysis of acetal 36](image)

**Oxazole-5-Carboxaldehyde 37:** Hydrolysis of acetal 36: Dimethylacetal 36 (3.8 g, 26.6 mmol) was dissolved in acetone (110 mL) and water (5.23 mL, 270 mmol) at rt. Amberlyst-15 (4.4 g) was added and the mixture was stirred for 2 h then filtered and concentrated to about 10 mL in volume. The remaining solution was purified by flash chromatography (50% ether/petrol 30-40) to afford aldehyde 37 as white crystalline needles (2.55 g, quant.);

**Swern oxidation of alcohol 40:** To a solution of oxalyl chloride (1.75 mL, 20.0 mmol) in dry CH₂Cl₂ (32 mL) under an argon atmosphere was added a solution of dry DMSO (3.6 mL, 50 mmol) in dry CH₂Cl₂ (8.5 mL) at −78 °C over 15 min. After stirring for 30 min, a solution of alcohol 40 (991 mg, 10 mmol) in dry CH₂Cl₂ (6.0 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 Et₃N (5.6 mL, 40 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 (50 mL), the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers were dried (MgSO₄). The solvent was evaporated under reduced pressure (t < 25 °C, p > 400 mbar) to a volume of 6 mL. The crude material was then purified by flash chromatography (50% ether/petrol 30-40) to yield aldehyde 37 (545 mg, 5.6 mmol, 56%) as a white solid.

Rₐ 0.17 (50% ether/petrol 30-40); mp = 30-32 °C; ¹H NMR (400 MHz, CDCl₃): δ = 9.86 (s, 1H; CHO), 8.11 (s, 1H; 13-H), 7.88 (s, 1H; 12-H); ¹³C NMR (100 MHz, CDCl₃): δ = 177.2 (CHO), 154.7 (C-13), 150.3 (C-11), 136.3 (C-12); IR (film): νₘₐₓ (cm⁻¹) = 3100, 1681, 1568, 1477; HRMS: m/z (EI⁺) Found: 97.0159, [M⁺] C₄H₇NO₂ requires 97.0164. The observed data was consistent with that previously reported.[45,15a]
Oxazol-5-yl-carboxylic acid ethyl ester 39: TosMIC (48.81 g, 250 mmol) was dissolved in dry CH₂Cl₂ (470 mL) under an argon atmosphere. At 0 °C, DBU (37.4 mL, 250 mmol) and a solution of ethyl glyoxylate (10) (66.36 ml, 325 mmol, 50% in toluene) in dry CH₂Cl₂ (230 ml) were added simultaneously over a period of 2.5 h. Further DBU (18.7 mL, 125 mmol) was added and the dark solution allowed to stir for 30 min. The organic layer was then washed with aqueous 1.5 N HCl (200 mL) and sat. aqueous Na₂CO₃ (200 mL), dried (MgSO₄) and evaporated under reduced pressure. The crude material was purified by flash chromatography (10:1 → 4:1 → 2:1 petrol/diethyl ether) to give oxazole 39 as a colourless liquid (28.4 g, 200 mmol, 80%). ¹H NMR (400 MHz, CDCl₃): δ = 7.99 (s, 1H; Ar-H), 7.74 (s, 1H; Ar-H), 4.37 (q, J = 7.2 Hz, 2H; CH₂), 1.36 (t, J = 7.1 Hz, 3H; CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 157.9, 153.6, 143.3, 133.6, 62.0, 14.6 ppm. elemental analysis calcd (%) for C₇H₉NO₃ (141.1): C 51.06, H 5.00, N 9.93; found: C 50.64, H 5.14, N 9.93. The observed data was consistent with that previously reported. [47,48,25]

Oxazol-5-yl-methyl alcohol 40: Ester 39 (7.06 g, 50.0 mmol) was dissolved in a mixture of dry THF (90 mL) and dry MeOH (190 mL) under an argon atmosphere. Lithium chloride (12.75 g, 300.0 mmol) was added and the suspension cooled to −10 °C. Subsequently, sodium borohydride (11.35 g, 300 mmol) was added in small portions over a period of 20 min with vigorous stirring and the temperature kept below −5 °C. After stirring for further 60 min at −5 °C, the suspension was slowly warmed to rt (a temperature of 20-25 °C was regulated with a water bath). The suspension was stirred for 21 h at rt and then quenched with water (500 ml). Sodium potassium tartrate (90 g) was added and the solution then extracted with ethyl acetate (1 x 300 mL, 4 x 200 mL and 5 x 150 mL). The combined organic extracts were washed with brine (100 mL) and dried with MgSO₄. The solvent was removed under reduced pressure and the resulting liquid dried in vacuo. The product (3.20 g, 32.3 mmol, 65%) was sufficiently clean by NMR but can be further purified by flash chromatography (diethyl ether). ¹H NMR (400 MHz, CDCl₃): δ = 7.83 (s, 1H; Ar-H), 6.97 (s, 1H; Ar-H), 4.66 (s, 2H; CH₂), 3.40 (br s, 1H; OH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 151.7, 151.6, 124.4, 55.4 ppm. The observed data was consistent with that previously reported. [47,48,25]
Alcohol 12: A solution of methyl-(4S)-trans-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate 14 (5.0 g, 28.7 mmol), trimethyl orthoformate (9.42 mL, 86.1 mmol), 2,3-butanedione (3.02 mL, 34.4 mmol) and camphorsulfonic acid (0.67 g, 2.87 mmol) in methanol (140 mL) was heated under reflux for 24 h. On cooling to rt solid sodium bicarbonate (4.28 g, 57.4 mmol) was added, the mixture was stirred for 2 h, filtered then concentrated in vacuo to give a 6:1 mixture of anomerically stabilised and non-anomerically stabilised esters.

The crude product was dissolved in CH₂Cl₂ (250 mL) and BF₃·OEt₂ (0.29 mL, 2.3 mmol) was added dropwise at rt. The brown solution was stirred for 13 days then the reaction was quenched by the dropwise addition of triethylamine (2 mL) and the mixture was concentrated under reduced pressure. The residue was dissolved in ether (80 mL) and cooled to 0 °C, then LiAlH₄ (1 M in THF, 27.6 mL, 45.92 mmol) was added dropwise over 25 min. The mixture was stirred for 30 min then quenched by the dropwise addition of methanol (25 mL). Saturated aqueous Rochelle’s salt (125 mL) and ether (125 mL) were added and the mixture stirred for 3 h then the phases were separated. The aqueous layer was extracted with ether (2 × 100 mL) then the combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo. The crude product was filtered through a plug of silica eluting with 50% ethyl acetate/petrol. Purification by flash chromatography (5% to 10% to 20% ethyl acetate/petrol) afforded alcohol 12 as a white solid (5.37 g, 84% over 3 steps); Rₐ 0.21 (50% ethyl acetate/petrol); mp = 55-56 °C; [α]D²⁵ +170.2 (c 1.0, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ = 3.81 (dq, J = 9.8, 6.4 Hz, 1H; 2-H), 3.66 (m, 1H; 3-H), 3.61-3.53 (m, 2H; 4-H₂), 3.26 (s, 3H; OCH₃), 3.25 (s, 3H; OCH₃), 2.18 (t, J = 6.3 Hz, 1H; OH), 1.31 (s, 3H; BDA CH₃), 1.29 (s, 3H; BDA CH₃), 1.13 (d, J = 6.4 Hz, 3H; 1-H₃); ¹³C NMR (150 MHz, CDCl₃): δ = 98.81 (BDA quaternary C), 98.75 (BDA quaternary C), 73.5 (C-3), 64.4 (C-2), 62.2 (C-4), 47.8 (OCH₃), 47.8 (OCH₃), 17.7 (BDA CH₃), 17.5 (BDA CH₃), 16.7 (C-1); IR (film): νmax (cm⁻¹) = 3456br, 2950, 2833, 1128s, 1040s; HRMS: m/z (ESI+) Found: 238.1648, [M+NH₄]⁺ C₆H₁₂NO₃ requires 238.1649.

Alcohol 13: Isolated as a byproduct in the LiAlH₄ reduction of unequilibrated esters 10 and 11. [α]D²⁵ –48 (c 0.30, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ = 4.07 (dq, J = 6.2, 10.2 Hz, 1H; 2-H), 3.78 (ddd, J = 2.9, 5.2, 10.2 Hz, 1H; 3-H), 3.69 (d, J = 11.5 Hz, 1H; 4-H), 3.53 (m, 1H; 4-H′), 3.36 (s, 3H; BDA OCH₃), 3.33 (s, 3H; BDA OCH₃), 1.90 (br s, 1H; OH), 1.42, (s, 3H; BDA CH₃), 1.39 (s, 3H; BDA CH₃), 1.14 (d, J = 6.2 Hz, 3H; 1-H₃); ¹³C NMR (150 MHz, CDCl₃): δ = 106.7 (BDA quaternary C), 100.4 (BDA quaternary C), 67.7 (C-3), 63.1 (C-2), 62.2 (C-4), 48.5 (BDA OCH₃), 48.3 (BDA OCH₃), 18.1 (C-1) 17.6 (BDA CH₃), 17.4 (BDA CH₃); IR (film): νmax (cm⁻¹) = 3486s,br, 2937, 1119s, 1043s; HRMS: m/z (ESI+) Found: 243.1216, C₆H₁₂O₃,Na requires 243.1208. Selected NOe data:
[32] See Supporting Information for characterisation of nitrile oxide dimer 17, which was confirmed by X-ray crystallography. CCDC 630712 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Nitrile oxide dimer 17: R, 0.72 (petrol/EtOAc, 1:1); mp = 132-133 °C; $[\alpha]_{D}^{25}$ +20.9 (c 1.0, CHCl$_3$); IR (film): $\nu_{\text{max}}$ (cm$^{-1}$) = 2991, 1712 (C=O), 1610s, 1408s, 1341s; HRMS: $m/z$ (ESI+) Found: 575.2097, [M+Na]$^+$, $C_{28}H_{32}N_{4}O_{8}$Na requires 575.2118; elemental analysis calcd (%) for $C_{28}H_{32}N_{4}O_{8}$ (552.6): C 60.86, H 5.84, N 10.14; found: C 60.77, H 5.80, N 10.05.
[34] See Supporting Information for further details of the coupling constant calculations for major and minor cycloadducts.

For 16 and 16a:

Coupling constant calculations: The diastereomers were assigned by correlating $^1$H-NMR data with predicted coupling constants generated by Macromodel MMFF calculations For each isomer, the three lowest conformations about the C3–C4 bond were predicted together with their relative energies and this information used to calculate a population-weighted average coupling constant between these two protons. These calculations were performed on the entire molecules but for clarity, only the relevant sections of the molecule are shown below

These predictions supported the assignment of the major product as the anti diastereoisomer.

For the fully functionalised system 3 and 3a:
[36] See Supporting Information for full characterisation of the minor cycloadduct diastereomer. CCDC 630709 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Minor isoxazoline 16a:** mp = 124 °C; [α]D25 + 95.3 (c 0.930, CHCl3); 1H NMR (400 MHz, d8-toluene, 70 °C): δ = 7.18 – 6.95 (m, 5H; Cbz Ph-H), 5.05 (d, J = 12.2 Hz, 1H; Cbz PhCH), 4.97 (d, J = 12.4 Hz, 1H; Cbz PhCH‘), 4.53 (m, 1H; 7-H), 4.31 (ddd, J = 2.9, 8.5, 11.2 Hz, 1H; 4-H), 4.07 (dq, J = 6.4, 9.5 Hz, 1H; 2-H), 3.75-3.68 (m, 1H; 8-H), 3.59 (dd, J = 6.4, 9.1 Hz, 1H; 8-H‘), 3.37 (dd, J = 2.9, 9.5 Hz, 1H; 3-H), 3.06 – 2.98 (m, 1H; 5-H), 3.01 (s, 3H; BDA OCH3), 2.97 (s, 3H; BDA OCH3), 2.51 (m, 1H; 5-H‘), 1.62 (s, 3H; acetal CH3), 1.38 (s, 3H; acetal CH3), 1.19 (s, 3H; BDA CH3), 1.18 (s, 3H; BDA CH3), 1.09 (d, J = 6.4 Hz, 3H; 1-H); 13C NMR (125 MHz, d8-toluene, 80 °C): δ = 156.8 (Cbz C=O), 152.2 (C-6), 136.5 (Ph quaternary C), PhH- obscured by toluene peaks, 99.3 (BDA quaternary C), 98.6 (BDA quaternary C), 94.5 (acetal quaternary C), 79.2 (C-4), 73.1 (C-3), 66.8 (PhCH2), 66.5 (C-8), 64.3 (C-2), 54.7 (C-7), 47.1 (BDA OCH3), 47.0 (BDA OCH3), 35.4 (C-5), 25.9 (acetal CH3), 23.3 (acetal CH3), 17.4 (BDA CH3), 17.2 (BDA CH3), 16.5 (C-1); IR (film): νmax (cm−1) = 2939, 1703s, 1122s; HRMS: m/z (ESI+) Found: 515.2364, C25H36N2O8Na requires 515.2369.
[38] Mosher’s esters of 19 were prepared, which showed that no epimerisation had occurred at the C10 centre during deprotection of the BDA group. See Supporting Information for full procedures and characterisation.

Ester 19b: To a solution of R-(-)-Mosher’s acid chloride (54 mg, 0.214 mmol) in anhydrous dichloromethane (0.25 mL) was added a solution of alcohol 19 (47 mg, 0.195 mmol) in dichloromethane (1.5 mL). This mixture was cooled to 0 °C and triethylamine (149 µL, 0.726 mmol) was added dropwise followed by DMAP (< 1 mg, cat.). The reaction mixture was stirred at 0 °C for 1 h and warmed to rt for an additional 2 h. Another portion of acide chloride (27 mg, 0.107 mmol) was added and the reaction stirred for another 15 min. Aqueous sodium bicarbonate (10 mL) was added to quench, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organics were dried (Na2SO4), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5% to 15% ethyl acetate/hexanes) to give the ester 19b (55 mg, 61%, >95:5 dr by 1H-NMR) as a colourless oil; [α]D25 +0.032 (c 0.8, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.87 (s, 1H; 13-H), 7.47 (d, J = 7.5 Hz, 2H; PhH), 7.39-7.34 (m, 3H; PhH), 7.18 (s, 1H; 12-H), 6.18 (dd, J = 5.6, 6.5 Hz, 1H; 10-H), 4.03 (dd, J = 6.9, 10.8 Hz, 1H; 9-H), 3.96 (dd, J = 5.6, 10.8 Hz, 1H; 9-H), 3.47 (q, J = 7.8 Hz, 9H; TES CH3), 0.88 (t, J = 7.8 Hz, 9H; TES CH3), 0.53 (q, J = 7.8 Hz, 6H; TES CH2); 13C NMR (100 MHz, CDCl3): δ = 165.8 (Mosher’s C=O), 151.2 (C-11), 146.8 (C-13), 132.0 (quaternary Ph C), 129.6 (Ph CH), 128.3 (Ph CH), 127.2 (Ph CH), 126.1 (C-12), 84.7 (q, J = 28 Hz, CF3), 69.7 (C-10), 62.3 (C-9), 55.6 (OCH3), 6.5 (TES CH3), 4.1 (TES CH2); IR (film): νmax (cm⁻¹) = 2956, 1758s, 1168s, 1107s; HRMS: m/z (ESI+) Found: 482.1588, C23H29F3NO5SiNa requires 482.1587.

Ester 19a: To a solution of alcohol 19 (62.2 mg, 0.256 mmol) in anhydrous dichloromethane (2.3 mL) was added dicyclohexylcarbodiimide (0.282 mL of a 1 M solution in dichloromethane, 0.282 mmol), DMAP (< 5 mg, cat), and R- (+)-Mosher’s acid (66.1 mg, 0.282 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was poured into a saturated ammonium chloride solution (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organics were dried over Na2SO4 and filtered. Silica gel was added and the suspension was concentrated in vacuo. The residue was purified by loading the solid directly onto a silica gel column and chromatographing (20% ethyl acetate/hexanes) to give ester 19a (110 mg, 94%, 98:2 dr by 1H-NMR) as a colourless oil; [α]D25 +59.9 (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.80 (s, 1H; C-13), 7.48 – 7.33 (m, 5H; Ph-H), 7.06 (s, 1H; 12-H), 6.20 (dd, J = 4.4, 7.6 Hz, 1H; 10-H), 4.09 (dd, J = 7.8, 10.9 Hz, 1H; 9-H), 4.00 (dd, J = 4.4, 11.0 Hz, 1H; 9-H), 3.58 (s, 3H; OCH3), 0.93 (t, J = 7.9 Hz, 9H; TES CH3), 0.61 (q, J = 7.9 Hz, 6H; TES CH2); 13C NMR (100 MHz, CDCl3): δ = 165.8 (Mosher’s C=O), 151.3 (C-11), 147.1 (C-13), 132.0 (quaternary Ph C), 129.6 (Ph CH), 128.4 (Ph CH), 127.3 (Ph CH), 126.6 (C-12), 84.6 (CF3), 69.1 (C-10), 62.1 (C-9), 6.5 (TES CH3), 4.3 (TES CH2); IR (film): νmax (cm⁻¹) = 2958, 1753s, 1168s, 1107s; HRMS: m/z (ESI+) Found: 482.1582, C23H29F3NO5SiNa requires 482.1587.
Addition of TMSCN to aldehyde 37 with chiral catalysis:

![Catalyst conditions](image)

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<th>entry</th>
<th>Catalyst reference</th>
<th>catalyst</th>
<th>conditions</th>
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<td>6</td>
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<td>TMSCN, 0 °C 0.1 mol% catalyst CH₂Cl₂, 0 °C, 2 h</td>
<td>93</td>
<td>48</td>
</tr>
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</table>

[a] Determined by Mosher’s ester analysis (see below).

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1 Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, 57, 805; We are grateful to Prof. Dr. Shibasaki and coworkers (University of Tokyo) for providing a sample of the chiral ligand.
In the case of Jacobsen’s thiourea catalyst (entry 2 above), modifying the reaction conditions to suppress the background reaction led to an improved enantioselectivity. Several variables were investigated, in particular the addition of TMS cyanide as a solution in CH₂Cl₂ to the aldehyde and catalyst solution at low temperature appeared to be very important and ee values up to 78% were obtained (see table below). However, on scale up the enantiomeric excess of compound 13 dropped steadily when the scale was raised to 1 mmol, 2 mmol and 10 mmol (entries 2-4). Since the temperature control is an issue when the TMS-cyanide solution is added quickly, it was attempted to re-optimise the process by extending the addition time but in this case the selectivity was not higher than 52% ee (entry 5).

### Table

<table>
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<th>ee [%]</th>
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<td>78</td>
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<td>2</td>
<td>1 mmol</td>
<td>CH₂Cl₂, catalyst (5 mol%), CF₃CH₂OH (1.0 equiv.), TMSCN (2.0 equiv.) in CH₂Cl₂ (0.5 M), added over 5 min, −78 °C, 2.5 h</td>
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<td>66</td>
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<td>3</td>
<td>2 mmol</td>
<td>CH₂Cl₂, catalyst (5 mol%), CF₃CH₂OH (1.0 equiv.), TMSCN (2.0 equiv.) in CH₂Cl₂ (0.5 M) added over 5 min, −78 °C, 2 h</td>
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<td>10 mmol</td>
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<tr>
<td>5</td>
<td>10 mmol</td>
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<td>70</td>
<td>52</td>
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[a] Determined by Mosher’s ester analysis (see below).

As alternative cyanation reagents, TBS-cyanide, ethyl cyanoformate, acetone cyanohydrin and tetrabutylammonium cyanide were also investigated but were unsuccessful.

These results clearly demonstrate the efficiency of our racemic route followed by the separation of diastereoisomers to provide stereochemically pure material reliably, allowing rapid access to large quantities.
[52] For cyanohydrin 41 and α-hydroxyester 42, the ee was assessed by formation of the Mosher’s esters. See Supporting Information for experimental procedures and full characterisation of the Mosher’s esters.

(R)-Mosher ester 41a: (S)-Cyanohydrin 41 (1.0 equiv.), DCC (2.0 equiv.), (R)-Mosher acid [(R)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid] (1.5 equiv.) and a catalytic amount of DMAP were mixed in dry THF (0.1 M). After stirring for 2 h at rt, the THF was removed, the residue suspended in diethyl ether and filtered. The solvent was removed in vacuo to give the crude Mosher ester 41a as a colourless oil. 1H NMR (400 MHz, CDCl3): δ = 7.99 (s, 1H; Ar-H\textsuperscript{maj}), 7.93 (s, 1H; Ar-H\textsuperscript{min}), 7.39-7.45 (m, 6H; Ar-H\textsuperscript{maj/min}), 6.74 (s, 1H; CH\textsuperscript{min}), 6.72 (s, 1H; CH\textsuperscript{maj}), 3.58 (s, 3H; OCH\textsubscript{3}\textsuperscript{min}), 3.51 (s, 3H; OCH\textsubscript{3}\textsuperscript{maj}) ppm. 13C NMR(100 MHz, CDCl3): δ = 164.93 (C=O\textsuperscript{maj}), 164.89 (C=O\textsuperscript{min}), 153.1 (C-13\textsuperscript{min}), 153.0 (C-13\textsuperscript{maj}), 141.3 (C-11\textsuperscript{maj}), 141.2 (C-11\textsuperscript{min}), 130.8 (Ph quaternary C\textsuperscript{maj}), 130.7 (Ph quaternary C\textsuperscript{min}), 130.21 (Ph-C\textsuperscript{maj}), 130.18 (Ph-C\textsuperscript{min}), 129.2 (Ph-C\textsuperscript{maj}), 129.1 (Ph-C\textsuperscript{min}), 128.8 (Ph-C\textsuperscript{maj}), 127.1 (Ph-C\textsuperscript{min}), 127.0 (C-12), 122.8 (q, J 290, CF\textsubscript{3}), 112.1 (CN\textsuperscript{maj}), 111.9 (CN\textsuperscript{min}), 85.0 (q, J 28, COCF\textsubscript{3}), 55.8 (C-10\textsuperscript{maj}), 55.7 (C-10\textsuperscript{min}), 55.1 (OCH\textsubscript{3}\textsuperscript{min}), 55.0 (OCH\textsubscript{3}\textsuperscript{maj}); IR (film): ν\textsubscript{max} (cm\textsuperscript{-1}) = 2953w, 1764, 1498, 1453, 1169s, 1107s, 996s, 716s; HRMS: m/z (ESI+) Found: 341.0757, [M+H]\textsuperscript{+} C\textsubscript{16}H\textsubscript{17}N\textsubscript{2}O\textsubscript{2}F\textsubscript{3} requires 341.0749.

(R)-Mosher ester 42a: α-Hydroxy ester 42 (1.0 equiv.), DCC (2.0 equiv.), (R)-Mosher acid [(R)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid] (2.0 equiv.) and a catalytic amount of DMAP were mixed in dry THF (0.1 M). After stirring for 2 h at rt, the THF was removed, the residue suspended in diethyl ether and filtered. The solvent was removed in vacuo to give the crude Mosher ester 42a as a colourless oil. 1H NMR (400 MHz, CDCl3): δ = 7.97 (s, 1H; Ar-H\textsuperscript{maj}), 7.92 (s, 1H; Ar-H\textsuperscript{min}), 7.57-7.62 (m, 2H; Ph-H\textsuperscript{maj/min}), 7.36-7.43 (m, 3H; Ph-H\textsuperscript{maj/min}), 7.28 (s, 1H; Ar-H\textsuperscript{min}), 7.22 (s, 1H; Ar-H\textsuperscript{maj}), 6.41 (s, 1H; CH\textsuperscript{min}), 6.38 (s, 1H; CH\textsuperscript{maj}), 3.85 (s, 3H; OCH\textsubscript{3}\textsuperscript{maj}), 3.82 (s, 3H; OCH\textsubscript{3}\textsuperscript{min}), 3.67 (s, 3H; OCH\textsubscript{3}\textsuperscript{maj}), 3.54 (s, 3H; OCH\textsubscript{3}\textsuperscript{min}) ppm. 13C NMR (100 MHz, CDCl3): δ = Only peaks for the major diastereoisomer are quoted: 168.1 (C-9), 165.1 (C=O), 152.5 (C-13), 144.1 (C-11), 131.1 (Ph quaternary C), 129.9 (Ph-C), 128.6 (Ph-C), 127.6 (Ph-C), 127.3 (C-12), 123.3 (q, J\textsubscript{C,F} 287, CF\textsubscript{3}), 84.8 (q, J\textsubscript{C,F} 28, COCF\textsubscript{3}, 66.5 (C-10), 55.5 (OCH\textsubscript{3}), 53.5 (ester OCH\textsubscript{3}); IR (film): ν\textsubscript{max} (cm\textsuperscript{-1}) = 2959, 1755br, 1498, 1452, 1169s; HRMS: m/z (ESI+) Found: 374.0860, [M+H]\textsuperscript{+} C\textsubscript{16}H\textsubscript{17}NO\textsubscript{2}F\textsubscript{3} requires 374.0851.
[58] Attempts to form the C-10 stereochemistry by an enantioselective reduction of the α-keto-ester formed by the oxidation of rac-48 gave low yields and ee. See Supporting Information for characterisation of the ketone intermediate.

Oxazol-5-yl-oxo-acetic acid methyl ester: To a solution of α-hydroxy ester rac-48 (808 mg, 5.14 mmol) in dry CH₂Cl₂ (20 mL) under an argon atmosphere was added Dess-Martin periodinane (2.55 g, 6.01 mmol) in one portion at rt (the temperature of the exothermic reaction was adjusted with a water bath). The mixture was allowed to stir for 80 min at rt and then quenched with sat. aqueous NaHCO₃ (20 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL), the combined organic layers dried (MgSO₄), and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (2:1 petrol/diethyl ether) to give the α-ketoester (128 mg, 0.83 mmol, 16%) as a solid. mp = 76-78 °C; ¹H NMR (400 MHz, CDCl₃): δ = 8.34 (s, 1H; Ar-H), 8.16 (s, 1H; Ar-H), 3.98 (s, 3H; OCH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 193.8, 160.4, 155.6, 147.7, 139.8, 53.9 ppm; IR (film): νₘₐₓ (cm⁻¹) = 3125, 1733, 1689, 1613, 1306, 1249, 1146, 1098, 1027, 954, 886, 796.
[69] See Supporting Information for selected results in the optimisation of the nitrile oxide cycloaddition between alkene 7 and the nitrile oxide derived from oxime 33.

Optimisation of cycloaddition conditions following chlorination:

<table>
<thead>
<tr>
<th>Cycloaddition conditions</th>
<th>C-4 ratio</th>
<th>Yield (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂Cl₂, slow addition of NEt₃, 0 °C, 3 h</td>
<td>2.7:1</td>
<td>23%</td>
</tr>
<tr>
<td>THF, Cs₂CO₃, trace water, rt, 4 h</td>
<td>4.1:1</td>
<td>29%</td>
</tr>
<tr>
<td>THF, Cs₂CO₃, anhydrous, rt, 22 h</td>
<td>3.0:1</td>
<td>66%</td>
</tr>
<tr>
<td>DME, Cs₂CO₃, trace water, rt, 4 h</td>
<td>4.5:1</td>
<td>50%</td>
</tr>
<tr>
<td>DME, Cs₂CO₃, anhydrous, 0 °C to rt, 22 h</td>
<td>3.5:1</td>
<td>77%</td>
</tr>
</tbody>
</table>
[70] The nitrile oxide dimer was also isolated in only 6%. Excess alkene employed in the reaction was recovered in excellent yields. See Supporting Information for characterisation data for minor cycloadduct diastereomer 3a and nitrile oxide dimer 3b.

![Diagram of molecular structure]

**Minor cycloadduct isoxazoline 3a**: R, 0.23 (50% ethyl acetate/petrol); [\(\alpha\)]\(_D\)\(^{25}\) +76.6 (c 1.05, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) = 7.94 (s, 1H; 8-H), 7.81 (s, 1H; 13-H), 7.61-7.55 (m, 4H; Ph-H), 7.47-7.31 (m, 6H; Ph-H), 6.97 (s, 1H; 12-H), 5.97 (s, 1H; 10-H), 4.75 (ddd, \(J = 11.1, 9.9, 2.4, 1\)H; 4-H), 4.11 (dq, \(J = 9.5, 6.4, 1\)H; 2-H'), 3.59 (dd, \(J = 9.5, 2.4, 1\)H; 3-H'), 3.43 (dd, \(J = 16.8, 9.9, 1\)H; 5-H), 3.25 (s, 3H; OCH\(_3\)), 3.22 (s, 3H; OCH\(_3\)), 3.17 (dd, \(J = 16.8, 11.1, 1\)H; 5-H'), 1.28 (s, 3H; BDA CH\(_3\)), 1.26 (s, 3H; BDA CH\(_3\)), 0.48 (50% ethyl acetate/petrol); \[\alpha\]\(_D\)\(^{25}\) -27.0 (c 0.25, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) = 8.05 (s, 2H; 8-H and 8-H'), 7.82 (2H; s, 13-H and 13-H'), 7.57 (8H; m, Ph-H), 7.49-7.35 (12H; m, Ph-H), 6.98 (2H; s, 12-H and 12-H'), 5.96 (2H; s, 10-H and 10-H'), 1.08 (18H; s, 2 \times C(CH\(_3\))\(_3\)); \(^13\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) = 162.4 (C-9 and C-9'), 151.6 (C-13 and C-13'), 148.2 (C-11 and C-11'), 137.5 (C-8 and C-8'), 135.6 (Ph-C), 135.6 (Ph-C), 131.6 (Ph quaternary C), 131.5 (Ph quaternary C), 131.5 (C-7 and C-7'), 130.4 (Ph-C), 130.4 (Ph-C), 127.9 (Ph-C), 127.9 (Ph-C), 125.4 (C-12 and C-12'), 115.3 (C-6), 111.1 (C-6'), 63.4 (C-10 and C-10'), 26.6 (C(CH\(_3\))\(_3\)), 19.3 (C(CH\(_3\))\(_3\)); IR (film): \(\nu_{\text{max}}\) (cm\(^{-1}\)) = 2932, 2858, 1724w, 1429, 1113s. 

**Nitrile oxide dimer 3b**: R, 0.48 (50% ethyl acetate/petrol); [\(\alpha\)]\(_D\)\(^{25}\) -27.0 (c 0.25, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) = 8.05 (s, 2H; 8-H and 8-H'), 7.82 (2H; s, 13-H and 13-H'), 7.57 (8H; m, Ph-H), 7.49-7.35 (12H; m, Ph-H), 6.98 (2H; s, 12-H and 12-H'), 5.96 (2H; s, 10-H and 10-H'), 1.08 (18H; s, 2 \times C(CH\(_3\))\(_3\)); \(^13\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) = 162.4 (C-9 and C-9'), 151.6 (C-13 and C-13'), 148.2 (C-11 and C-11'), 137.5 (C-8 and C-8'), 135.6 (Ph-C), 135.6 (Ph-C), 131.6 (Ph quaternary C), 131.5 (Ph quaternary C), 131.5 (C-7 and C-7'), 130.4 (Ph-C), 130.4 (Ph-C), 127.9 (Ph-C), 127.9 (Ph-C), 125.4 (C-12 and C-12'), 115.3 (C-6), 111.1 (C-6'), 63.4 (C-10 and C-10'), 26.6 (C(CH\(_3\))\(_3\)), 19.3 (C(CH\(_3\))\(_3\)); IR (film): \(\nu_{\text{max}}\) (cm\(^{-1}\)) = 2931, 2859, 1724w, 1428, 1113s.
See Supporting Information for characterisation of the minor cycloadduct isoxazoline 69a. The diastereoselectivity was consistently lower in the 10-epi-series (ent-33) than with oxime 33 (dr 2.5:1 vs. 3.5:1). Notwithstanding the distance of the chirality from the reacting centre, this was presumed to be due to a chirality match/mismatch between alkene 7 and the chiral oximes. A similar phenomenon was observed for the enantiomer of the nitrile oxide of Garner’s aldehyde oxime (d.r. 4.1:1 vs. 2.5:1) although in this case the chirality is closer to the reacting centres.

Minor cycloadduct isoxazoline 69a: Rf 0.35 (60% ethyl acetate/petrol); [α]D 25 +144.5 (c 1.05, CHCl₃);

1H NMR (400 MHz, CDCl₃): δ = 7.95 (s, 1H; 8-H), 7.80 (s, 1H; 13-H), 7.61-7.57 (m, 4H; Ph-H), 7.46-7.31 (m, 6H; Ph-H), 6.97 (s, 1H; 12-H), 5.98 (s, 1H; 10-H), 4.74 (ddd, J = 11.1, 10.0, 2.3 Hz, 1H; 4-H), 4.11 (dq, J = 9.5, 6.4 Hz, 1H; 2-H), 3.60 (dd, J = 9.5, 2.3 Hz, 1H; 3-H), 3.43 (dd, J = 16.8, 10.0 Hz, 1H; 5-H'), 3.26 (s, 3H; OCH₃), 3.24 (s, 3H; OCH₃), 3.19 (dd, J = 16.8, 11.1 Hz, 1H; 5-H'), 1.29 (s, 3H; BDA CH₃), 1.29 (s, 3H; BDA CH₃), 1.24 (d, J = 6.4 Hz, 3H; 1-H'), 1.08 (s, 9H; C(CH₃)₃); 13C NMR (400 MHz, CDCl₃): δ = 161.2 (C-9), 151.2 (C-13), 150.2 (C-6), 149.1 (C-11), 137.5 (C-8), 135.7 (Ph-C), 135.6 (Ph-C), 132.1 (C-7), 132.0 (Ph quaternary C), 131.9 (Ph quaternary C), 130.2 (Ph-C), 130.1 (Ph-C), 127.8 (Ph-C), 127.7 (Ph-C), 125.0 (C-12), 99.4 (BDA quaternary C), 98.7 (BDA quaternary C), 79.4 (C-4), 72.3 (C-3), 64.7 (C-2), 63.6 (C-10), 47.9 (OCH₃), 47.8 (OCH₃), 35.8 (C-5), 26.6 (C(CH₃)₃), 19.4 (C(CH₃)₃), 17.8 (BDA CH₃), 17.5 (BDA CH₃), 16.6 (C-1); IR (film): νmax (cm⁻¹) = 2935, 2860, 1429, 1114s; HRMS: m/z (ESI+) Found: 684.2710, [M+Na]+ C₃₅H₄₃N₃O₈SiNa requires 684.2717.
[75] See Supporting Information for spectra for bengazole A, 10-epi-bengazole A and bengazole B.
$^1$H NMR (600 MHz, CD$_3$OD)
$^1$H NMR (600 MHz, CD$_3$OD)
$^{13}$C NMR (150 MHz, CD$_3$OD)
10-epi-bengazole A

$^{13}$C NMR (150 MHz, CD$_3$CD)
Blue = Bengazole A
Red = 10-epi-Bengazole A
\[ ^1H \text{NMR (600 MHz, CD}_3\text{OD)} \]
$^{13}C$ NMR (150 MHz, CD$_3$OD)