A Short Synthesis of an Enantiopure Benzo[*e*]isoindolinone

Mark D. Andrews,[a] Andrew G. Brewster,[c] John Chuhan,[b] Ashley J. Ibbett,[b] Mark G. Moloney,* Keith Prout,[b] David Watkin[b]

[a] The Dyson Perrins Laboratory, University of Oxford, South Parks Rd, Oxford OX1 3QY, UK
Fax +44(1865)275674; E-mail mark.moloney@dpl.ox.ac.uk

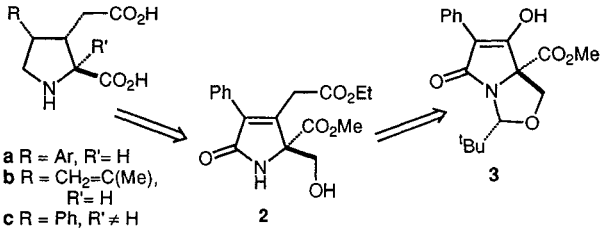
[b] Chemical Crystallography Laboratory, University of Oxford, 9 Parks Rd, Oxford OX1 3PD, UK

[c] Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, SK10 4TG, UK

Received 20 September 1996; revised 14 October 1996

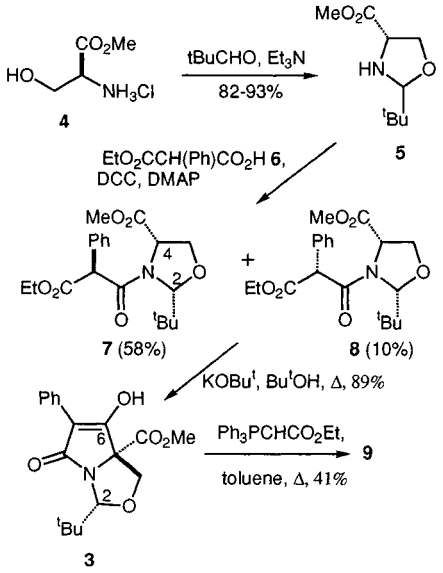
An enantiopure benzo[*e*]isoindolinone is available by a sequence involving the reaction of a phenyl substituted tetramic acid with two equivalents of a stabilised phosphorane $Ph_3P{=}CHCO_2R$ (R = Et or *t*-Bu).

The synthesis of the kainoid group of amino acids has been of considerable recent interest, principally because of the biological activity of these compounds as excitatory amino acids. The aryl analogues **1a** of kainic acid **1b** have recently become readily accessible using various elegant methodologies starting with 4-hydroxyproline;[1-5] this is significant because this class of analogues possesses highly potent neuroexcitatory activity. We were interested in making use of enantiopure tetramic acids, the synthesis of which we have recently developed using Dieckmann cyclisations of substituted oxazolidines,[6] for the construction of more highly substituted analogues **1c**. To this end, we envisaged that these compounds would be available via the quaternary alcohol **2**, which in turn would come from the tetramic acid **3** (Scheme 1).



Scheme 1

The required tetramic acid was obtained as follows (Scheme 2). Oxazolidine **5**, readily prepared from serine methyl ester hydrochloride according to the literature procedure,[7,8] upon acylation with acid **6**,[9] gave the products **7** and **8** after careful column chromatography in 58 and 10% yield, respectively. The structure of oxazolidine **7** was determined by single crystal X-ray crystallography (Figure 1a)[11] and found to be (*S*)-configured at the new stereogenic centre of the acyl side chain. This structure also confirmed the keto-tautomeric nature of the dicarbonyl unit, the *cis*-relationship of the C(2) and C(4) substituents of the oxazolidine ring, and also indicated that the nitrogen is partially pyramidalised, as has been observed in related systems.[10] The minor isomer **8** was found to epimerise readily on silica. Dieckmann cyclisation of oxazolidine **7** or **8** under standard conditions (*t*-BuOK, *t*-BuOH at reflux) gave the product tetramic acid **3** in 89% yield. However, subsequent reaction of this compound with the stabilised phosphorane $Ph_3P{=}CHCO_2Et$ did not give the simple Wittig homologation product, but rather an unknown in 41% yield.



Scheme 2

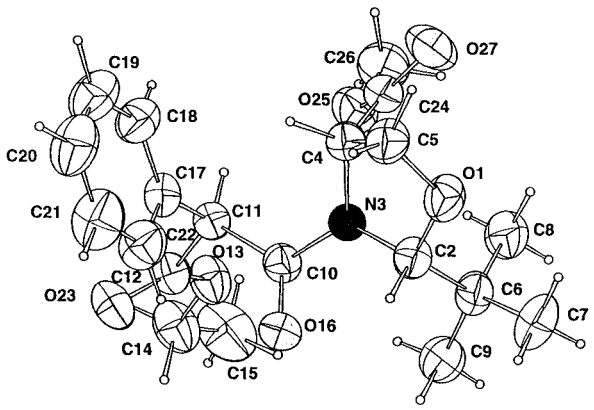


Figure 1a. Structure of **7**

The mass spectrum of the unknown indicated that its mass was 425 a.m.u., 24 greater than the mass of the expected product, while the ^{13}C NMR spectrum had ten peaks between $\delta = 120$ and $\delta = 145$, five singly protonated and five non-protonated. The ^1H NMR spectrum had the correct number of protons for the anticipated product but the five aromatic protons were unusually split, with a single proton singlet at $\delta = 7.38$, the other four protons being spread from $\delta = 7.70$ to $\delta = 9.17$. It was clear that tetramic acid **3** had reacted with two equivalents of Wittig reagent, but unequivocal structural assignment as the isoindolinone **9** only came after single crystal X-ray analysis (Figure 1b).[11]

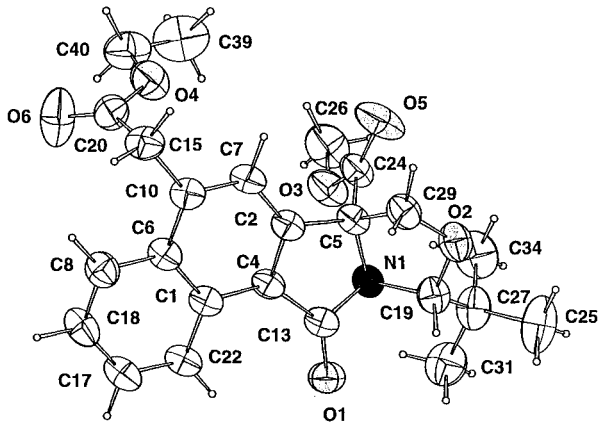
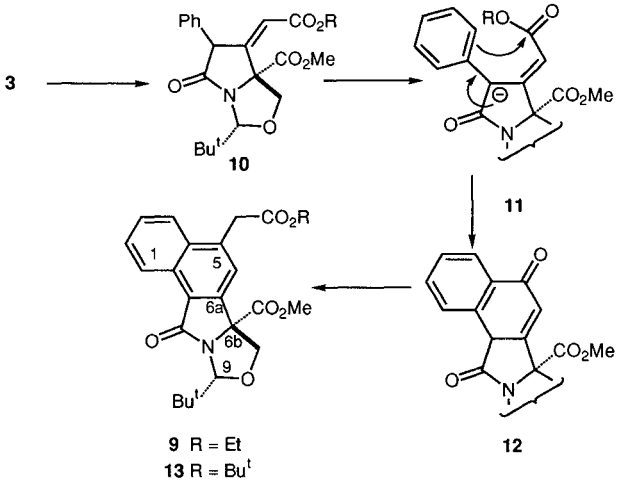


Figure 1b. Structure of **9**

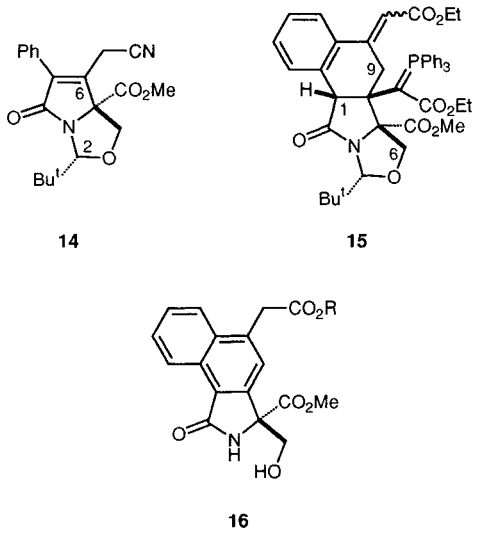
A postulated mechanism by which this unusual tetracyclic product **9** could have arisen is shown in Scheme 3. Initial condensation of tetramic acid **3** with the stabilised ylid generates the expected alkene **10** which, under the reaction conditions, is deprotonated to generate the highly resonance stabilised anion **11**. Intramolecular acylation of the aromatic ring by the ethyl ester gives ketone **12**, which on condensation with another equivalent of Wittig reagent and further tautomerisation gives the observed product **9**.



Scheme 3

The analogous isoindolinone system **13** was also obtained with the more hindered phosphorane $Ph_3P{=}CHCO_2t$-Bu[12] in 23% yield, but application of the nitrile-substituted ylid $Ph_3P{=}CHCN$ gave the direct Wittig homologated product **14** in 32% yield, since the intramolecular cyclisation is blocked in this case.

Attempts to increase the yield of isoindolinone **9** by the use of excess Wittig reagent led to the isolation of an additional product from the reaction. Using six equivalents of Wittig reagent the yield of the desired product **9** dropped to only 7% while the ylid **15** was isolated in 14% yield. Ylid **15** was tentatively identified on the basis of its spectroscopic properties. The chemical ionisation mass spectrum showed a peak at 774 a.m.u. indicating that the mass of the compound was 773 a.m.u., corresponding formally to the addition of a molecule of Wittig reagent to isoindolinone **9**. Structure **15** was most consistent with the observed ^1H and ^{13}C NMR spectra. Extensive ^{31}P–^{13}C coupling in the ^{13}C NMR spectrum confirmed that phosphorus was present in the compound. In agreement with the proposed structure, those carbons assigned as being C(1), C(7) and C(9) [δ = 113.6 (CH), 77.1 (4°C) and 38.0 (CH_2) respectively] all appeared as doublets in the ^{13}C NMR spectrum. The C(1) and C(8) stereochemistry of ylid **15** was assigned with the aid of observed NOE enhancements. Irradiation of the C(1) proton gave a 12% enhancement of the 5 proton multiplet at δ = 7.76–7.80 in the ^1H NMR spectrum assigned to the triphenylphosphonium unit, thus indicating the C(1)–C(8) ring junction to be *cis*. A 3.2% enhancement was also observed at one of the C(6) protons indicating that the stereochemistry at C(1) was *R* as shown. Adduct **15** can, in a formal sense, be considered to have arisen from a further conjugate addition of the ylid to C(6a) of isoindolinone **9**.



Finally, the tetracycle **9** was treated with propane-1,3-dithiol in acidic trifluoroethanol (1.5% w/v HCl) in order to cleave the oxazolidine ring. This gave the free amido alcohol **16** in 86% yield. Alcohol **16** is, to our knowledge, the only example of an enantiopure benz[*e*]isoindolinone in the literature, although some unsubstituted examples have been reported.[13–15]

Methyl (2*R*,4*S*,2′*S*)-2-(*tert*-Butyl)-3-(2′-ethoxycarbonyl-2′-phenyl)-ethanoyloxazolidine-4-carboxylate (7) and Methyl (2*R*,4*S*,2′*R*)-2-(*tert*-Butyl)-3-(2′-ethoxycarbonyl-2′-phenyl)ethanoyloxazolidine-4-carboxylate (8):

To a solution of oxazolidine **5**[7,8] (6.13 g, 32.7 mmol), DMAP (0.30 g, 2.4 mmol) and DCC (7.43 g, 36.0 mmol) in CH_2Cl_2 (125 mL) at 0°C was added dropwise a solution of acid **6**[9] (7.50 g, 36.0 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at 0°C for 15 min, and at r.t. for 4 h. The mixture was filtered, the residue washed with CH_2Cl_2 (2 × 50 mL), and the filtrate was evaporated in vacuo. Recrystallisation from hexane gave oxazolidine **7** (6.61 g, 53.5%) as colourless crystals; mp 119–122°C (from hexane); R_f = 0.16 (CH_2Cl_2); $[\alpha]_D^{20}$ + 48.8 (*c* = 3.05 in $CHCl_3$).

Found: C, 63.4; H, 7.3; N, 3.5. $C_{20}H_{27}NO_6$ requires: C, 63.6; H, 7.2; N, 3.7%.

IR ($CHCl_3$): ν = 2990m, 2960m, 1745s, 1670s cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.95 [9H, s, $C(CH_3)_3$], 1.29 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 3.60 (1H, m) and 4.42 (2H, m) [C(4)HC(5)H_2], 3.87 (3H, s, CO_2CH_3), 4.26 (2H, m, $CO_2CH_2CH_3$), 5.03 and 5.34 (2H, 2 × s, t-BuCH and PhCH), 7.38 (5H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.7 and 25.3 (2 × CH_3), 37.2 (4°C), 52.7 (CH_3), 58.0 and 58.5 (2 × CH), 61.5 and 67.4 (2 × CH_2), 96.6, 128.5, 128.8 and 129.1 (4 × CH), 132.0, 168.5, 169.0 and 170.0 (4 × 4°C).

MS(DCI): m/z = 378 (MH^+, 59%), 320 (15), 292 (62) and 130 (100).

Purification of the mother liquor by careful column chromatography [EtOAc/petroleum ether (bp 30–40°C), 1:4] gave further oxazolidine **7** (0.58 g, 4.7%), and oxazolidine **8** (1.28 g, 10.4%) as a colourless, viscous oil; R_f = 0.26 (EtOAc/hexane, 3:7); $[\alpha]_D^{22}$ + 9.0 (c = 0.97 in $CHCl_3$).

IR (film): ν = 2960m, 1750s, 1675s, 1220s, 1175s, 725m, 700m cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80 [9H, s, $C(CH_3)_3$], 1.24 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 3.75 (3H, s, CO_2CH_3, major rotamer), 3.87 (3H, s, CO_2CH_3, minor rotamer), 4.21 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.47–4.65 (1H, m), 3.99 (1H, t, J = 8.0 Hz), 4.78 (1H, d, J = 6.5 Hz, minor rotamer) and 4.89 (1H, d, J = 6.5 Hz, major rotamer) [C(4)HC(5)H_2], 5.05 (1H, s), 5.37 (1H, s, major rotamer) and 5.50 (1H, s, minor rotamer) (t-BuCH and CHPh) and 7.28–7.45 (5H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 25.4 (CH_3, major rotamer), 26.3 (CH_3, minor rotamer), 37.0 (4°C), 52.6 (CH_3), 57.2 and 59.5 (2 × CH), 61.8 and 67.5 (2 × CH_2), 96.4, 127.8, 128.2 and 129.5 (4 × CH), 133.5, 168.3, 169.4 and 169.7 (4 × 4°C).

MS(CI): m/z = 395 (MNH_4^+, 4%), 378 (MH^+, 100), 320 (23), 292 (52).

HRMS: 378.1918, $C_{20}H_{28}NO_6$ (MH^+) requires 378.1917.

(2*R*,5*R*)-2-(*tert*-Butyl)-6-hydroxy-5-methoxycarbonyl-8-oxo-7-phenyl-3-oxa-1-azabicyclo[3.3.0]oct-6-ene (3):

A solution of oxazolidine **7/8** (6.06 g, 16.1 mmol) and t-BuOK (1.89 g, 16.9 mmol) in t-BuOH (100 mL) was heated at reflux for 3 h then cooled to r.t. and partitioned between Et_2O (100 mL) and H_2O (2 × 75 mL). The aqueous layer was acidified with 2 M HCl and extracted with EtOAc (2 × 100 mL), the organic extracts being washed with brine (150 mL), dried ($MgSO_4$) and evaporated in vacuo to give dicarbonyl **3** (4.74 g, 89%) as a white foam; mp 72–77°C; R_f = 0.19 (EtOAc/MeOH, 9:1); $[\alpha]_D^{20}$ + 140 (c = 1.17 in $CHCl_3$).

Found: C, 64.95; H, 6.5; N, 3.9. $C_{18}H_{21}NO_5$ requires: C, 65.2; H, 6.4; N, 4.2%.

IR ($CHCl_3$): ν = 3520w, 1785w, 1750s, 1710s, 1665s cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.95 [9H, s, $C(CH_3)_3$], 3.43 (1H, d, J = 8.5 Hz, C(4)HH'), 3.81 (3H, s, CO_2CH_3), 4.71 (1H, s, t-BuCH), 4.76 [1H, d, J = 8.5, C(4)HH'], 7.4 (3H, m, ArH), 7.6 (2H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 24.5 (CH_3), 34.9 (4°C), 53.1 (CH_3), 69.4 (CH_2), 73.8 (4°C), 96.7 (CH), 108.2 (4°C), 127.8 and 128.4 (2 × CH), 129.0, 168.0, 169.0 and 179.2 (4 × 4°C).

MS(DCI): m/z = 349 (MNH_4^+, 16%), 332 (MH^+, 95), 274 (100).

(6b*S*,9*R*)-9-*tert*-Butyl-5-(ethoxycarbonylmethyl)-6b-methoxycarbonyl-11-oxo-8-oxabenzo[*e*]pyrrolo[2,1-*a*]isoindole (9):

To a solution of compound **3** (200 mg, 0.60 mmol) in toluene (10 mL) was added ethoxycarbonylmethylenetriphenylphosphorane (420 mg, 1.21 mmol). The mixture was heated at reflux for 16 h, cooled to r.t. and washed with 2.5 M NaOH (10 mL). The aqueous layer was acidified with conc. HCl and partitioned with Et_2O (2 × 10 mL). The Et_2O extracts were dried ($MgSO_4$) and evaporated in vacuo to give starting material (26 mg, 13%) as a white foam. The toluene layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography (CH_2Cl_2) gave the title compound **9** (105 mg, 41%) as a white foam. Recrystallisation from hexane/EtOAc gave pale yellow crystals; mp 107–110°C (from EtOAc/hexane); R_f = 0.24 (CH_2Cl_2); $[\alpha]_D^{20}$ + 87.7 (c = 2.00 in $CHCl_3$).

Found: C, 67.5; H, 6.4; N, 3.2. $C_{24}H_{27}NO_6$ requires: C, 67.75; H, 6.4; N, 3.3%.

IR ($CHCl_3$): ν = 1735s, 1710s, 1630w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.07 [9H, s, $C(CH_3)_3$], 1.23 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 3.39 [1H, d, J = 8.5 Hz, C(7)HH'], 3.73 (3H, s, CO_2CH_3), 4.15 (4H, m, $CO_2CH_2CH_3$, CH_2CO_2Et), 4.98 (1H, s, t-BuCH), 5.07 [1H, d, J = 8.5 Hz, C(7)HH'], 7.38 (1H, s, ArH), 7.7 (2H, m, ArH), 8.07 (1H, m, ArH), 9.17 (1H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.8 and 24.7 (2 × CH_3), 35.2 (4°C), 39.5 (CH_2), 52.9 (CH_3), 61.1 and 71.1 (2 × CH_2), 74.6 (4°C), 97.2, 120.7, 124.3, 124.5, 127.7 and 128.6 (6 × CH), 125.7, 129.7, 132.8, 138.0, 143.7, 170.4 and 175.6 (7 × 4°C).

MS(CI): m/z = 443 (MNH_4^+, 4%), 426 (MH^+, 100), 368 (32).

(6b*S*,9*R*)-5-*tert*-Butoxycarbonylmethyl-9-*tert*-butyl-6b-methoxycarbonyl-11-oxo-8-oxabenzo[*e*]pyrrolo[2,1-*a*]isoindole (13):

To a solution of compound **3** (200 mg, 0.60 mmol) in toluene (10 mL) was added *tert*-butoxycarbonylmethylenetriphenylphosphorane[12] (227 mg, 0.60 mmol). The mixture was heated at reflux for 16.25 h, cooled to r.t. and washed with 2.5 M NaOH (10 mL). The aqueous layer was acidified with conc. HCl and partitioned with Et_2O (2 × 10 mL). The Et_2O extracts were dried ($MgSO_4$) and evaporated in vacuo to give starting material (51 mg, 26%) as a white foam. The toluene layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography (CH_2Cl_2) gave the title compound **13** (63 mg, 23%) as a pale brown glass; R_f = 0.22 (CH_2Cl_2); $[\alpha]_D^{21}$ + 86.6 (c = 2.69 in $CHCl_3$).

IR ($CHCl_3$): ν = 1735s, 1710s cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.07 [9H, s, $C(CH_3)_3$], 1.40 [9H, s, $CO_2C(CH_3)_3$], 3.38 [1H, d, J = 8.5 Hz, C(7)HH'], 3.72 (3H, s, CO_2CH_3), 3.98 (1H, d, J = 15.5 Hz, CHH'CO_2-t-Bu), 4.08 (1H, d, J = 15.5 Hz, CHH'CO_2-t-Bu), 4.97 (1H, s, t-BuCH), 5.07 [1H, d, J = 8.5 Hz, C(7)HH'], 7.36 (1H, s, ArH), 7.68 (2H, m, ArH), 8.07 (1H, m, ArH), 9.15 (1H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 24.8 and 27.7 (2 × CH_3), 35.3 (4°C), 41.1 (CH_2), 53.0 (CH_3), 71.2 (CH_2), 74.8 and 81.7 (2 × 4°C), 97.3, 120.7, 124.5, 124.7, 127.8 and 128.7 (6 × CH), 125.6, 129.9, 133.0, 138.8, 143.9, 169.9, 170.9 and 175.9 (8 × 4°C).

MS(DCI): m/z = 454 (MH^+, 100%), 368 (MH^+-^{t}BuH, 33).

HRMS: 454.2230, $C_{26}H_{32}NO_6$ (MH^+) requires 454.2230.

(2*R*,5*S*)-2-(*tert*-Butyl)-6-cyanomethyl-5-methoxycarbonyl-8-oxo-7-phenyl-3-oxa-1-azabicyclo[3.3.0]oct-6-ene (14):

To a solution of compound **3** (434 mg, 1.31 mmol) in toluene (10 mL) was added cyanomethylenetriphenylphosphorane (592 mg, 1.96 mmol). The mixture was heated at reflux for 20 h, cooled to r.t. and washed with 2.5 M NaOH (10 mL). The aqueous layer was acidified with conc. HCl and partitioned with Et_2O (2 × 10 mL). The Et_2O extracts were dried ($MgSO_4$) and evaporated in vacuo to give starting material (113 mg, 26%) as a white foam. The toluene layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography (CH_2Cl_2) gave the title compound **14** (150 mg, 32%) as a yellowish glass; R_f = 0.27 (CH_2Cl_2); $[\alpha]_D^{21}$ + 197 (c = 1.31 in $CHCl_3$).

IR ($CHCl_3$): ν = 2250w, 1740m, 1720s cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.99 [9H, s, $C(CH_3)_3$], 3.30 (1H, d, J = 17.5 Hz, CHH'CN), 3.53 [1H, d, J = 8.5 Hz, C(4)HH'], 3.60 (1H, d, J = 17.5 Hz, CHH'CN), 3.86 (3H, s, CO_2CH_3), 4.80 [1H, s, C(2)], 5.03 [1H, d, J = 8.5 Hz, C(4)HH'], 7.47 (5H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 16.0 (CH_2), 24.6 (CH_3), 35.1 (4°C), 53.4 (CH_3), 70.7 (CH_2), 76.6 (4°C), 97.2 (CH), 114.4 (4°C), 129.0, 129.1 and 129.9 (3 × CH), 128.4, 138.9, 141.7, 169.0 and 175.2 (5 × 4°C).

GCMS: m/z = 372 (MNH_4^+, 8%), 355 (MH^+, 100), 297 (14).

HRMS: 355.1665, $C_{20}H_{23}N_2O_4$ (MH^+) requires 355.1658.

Ylid 15:

To a solution of compound **3** (605 mg, 1.83 mmol) in toluene (10 mL) was added ethoxycarbonylmethylenetriphenylphosphorane

(3.82 g, 11.9 mmol). The mixture was heated at reflux for 15 h, cooled to r.t. and washed with 2.5 M NaOH (10 mL). The aqueous layer was acidified with conc. HCl and partitioned with Et_2O (2 × 10 mL). The Et_2O extracts were dried ($MgSO_4$) and evaporated in vacuo to give starting material **3** (97 mg, 16%) as a white foam. The toluene layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography (EtOAc/petroleum ether, 1:9 increasing polarity to EtOAc/petroleum ether, 2:3) gave diester **9** (58 mg, 7%) and the ylid **15** (197 mg, 14%) as an orange foam. Recrystallisation from hexane/$CHCl_3$ gave orange crystals; mp 128–134°C (from $CHCl_3$/hexane); $R_f = 0.10$ (EtOAc/petroleum ether, 3:7); $[\alpha]_D^{21} + 373$ ($c = 0.98$ in $CHCl_3$).

IR ($CHCl_3$): ν = 3050w, 1740s, 1700s, 1640m, 695s cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 0.58$ (3H, t, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 0.89 [9H, s, $C(CH_3)_3$], 1.10 (3H, t, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.99 [1H, d, $J = 8.4$ Hz, C(6),*H*H'], 3.28 (1H, dd, $J = 1.5$, 17.8 Hz, C(9)*H*H'), 3.57–3.88 (4H, m, $2 \times CO_2CH_2CH_3$), 3.64 (3H, s, CO_2CH_3), 3.71 [1H, d, $J = 17.8$ Hz, C(9)H*H'*], 4.47 [1H, d, $J = 8.4$ Hz, C(6)H*H'*], 4.65 (1H, s, *t*-BuC*H*), 4.91 [1H, d, $J = 1.9$ Hz, C(1)*H*], 7.01–7.03 (2H, m, ArH), 7.20–7.22 (3H, m, ArH and vinylic), 7.51–7.58 (10H, m, ArH) and 7.76–7.80 (5H, m, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.8, 13.9 and 24.7 ($3 \times CH_3$), 35.2 (4°C), 38.0 (d, $J = 7$ Hz, CH_2), 52.8 (CH_3), 55.7 (d, $J = 120$ Hz, 4°C), 57.9, 60.1 and 70.5 ($3 \times CH_2$), 77.1 (d, $J = 16$ Hz, 4°C), 97.2 (CH), 113.6 (d, $J = 9$ Hz, CH), 125.7, 126.5 and 127.5 (3×4°C), 127.6, 128.1, 128.5, 128.7, 129.0, 131.9, 133.7 and 133.9 ($8 \times CH$), 144.0 (d, $J = 11$ Hz, 4°C), 150.1 (4°C), 167.7 (d, $J = 14$ Hz, 4°C) and 170.0, 170.5 and 178.1 (3×4°C).

MS(DCI): m/z = 774 (MH^+, 3%), 263 (100).

NOE experiment (500 MHz, $CDCl_3$) irradiation at $\delta_H = 2.99$ gave enhancements at δ = 4.47 (27%), 4.65 (4) and 4.91 (1.3); irradiation at $\delta_H = 3.28$ gave enhancements at δ = 3.71 (26%) and 7.02 (1); irradiation at $\delta_H = 4.47$ gave enhancements at $\delta = 2.99$ (24.8%) and 4.91 (1.7); irradiation at $\delta_H = 4.65$ gave enhancements at δ = 0.89 (6%) and 2.99 (3.7); irradiation at $\delta_H = 4.91$ gave enhancements at δ = 4.47 (3.2%), 7.02 (2.8) and 7.78 (12).

(3*S*)-2*H*-5-Ethoxycarbonylmethyl-3-hydroxymethyl-3-methoxycarbonylbenz[*e*]isoindol-1-one (16):

To a solution of diester **9** (135 mg, 0.32 mmol) in acidic trifluoroethanol (1.5% w/v HCl) (3 mL) was added propane-1,3-dithiol (35 μL, 38 mg, 0.35 mmol). The mixture was stirred at r.t. for 15 h and solvent was then removed in vacuo at r.t. Purification by column chromatography (EtOAc/petroleum ether, 1:1 increasing polarity to MeOH/EtOAc, 1:19) gave alcohol **16** (97 mg, 86%) as a crystalline solid; mp 122–123°C (from EtOAc/petroleum ether); $R_f = 0.38$ (EtOAc); $[\alpha]_D^{21} = +126$ ($c = 0.68$ in $CHCl_3$).

Found: C, 63.6; H, 5.2; N, 3.9. $C_{19}H_{19}NO_6$ requires: C, 63.9; H, 5.4; N, 3.9%.

IR (KBr): ν = 3350m, 3270m, 1735s, 1685s cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 1.22$ (3H, t, $J = 7.0$ Hz, $CO_2CH_2CH_3$), 3.72 (3H, s, CO_2CH_3), 3.81 (1H, dd, $J = 6.0$, 11.0 Hz, CH*H'*OH), 4.10–4.25 (4H, m, $CH_2CO_2CH_2CH_3$), 4.64 (1H, dd, $J = 6.5$, 11.0 Hz, CH*H'*OH), 5.16 (1H, t, $J = 6.0$ Hz, O*H*), 7.56–7.72 (3H, m, ArH), 8.02 (1H, d, $J = 7.5$ Hz, ArH), 8.52 (1H, br s, N*H*), 9.21 (1H, d, $J = 8.5$ Hz, ArH).

^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (CH_3), 39.8 (CH_2), 53.3 (CH_3), 61.2 and 68.0 ($2 \times CH_2$), 70.0 (4°C), 121.7, 124.1, 124.5, 127.4 and 128.0 ($5 \times CH$), 125.2, 129.5, 132.4, 136.8, 141.9, 170.2, 170.7 and 172.0 (8×4°C).

MS(FAB): m/z = 358 (MH^+, 100%).

We gratefully acknowledge the support of EPSRC and Zeneca Pharmaceuticals for a CASE award to MDA, ICI for a Strategic Research Award to MGM, and we wish to acknowledge the use of the EPSRC Chemical Database Service at Daresbury[16] and the EPSRC Mass Spectrometric Service Centre at Swansea.

(1) Horikawa, M.; Shirahama, H. *Synlett.* **1996**, 95.
(2) Horikawa, M.; Shima, Y.; Hashimoto, K.; Shirahama, H. *Heterocycles* **1995**, *40*, 1009.
(3) Baldwin, J.E.; Rudolph, M. *Tetrahedron Lett.* **1994**, 35, 6163.
(4) Baldwin, J.E.; Bamford, S.J.; Fryer, A.M.; Wood, M.E. *Tetrahedron Lett.* **1995**, *36*, 4869.
(5) Baldwin, J.E.; Fryer, A.M.; Spyvee, M.R.; Whitehead, R.C.; Wood, M.E. *Tetrahedron Lett.* **1996**, 6923.
(6) Andrews, M.D.; Brewster, A.; Moloney, M.G. *Tetrahedron: Asymmetry* **1994**, *5*, 1477.
(7) Seebach, D.; Aebi, J.D. *Tetrahedron Lett.* **1984**, *25*, 2545.
(8) Seebach, D.; Aebi, J.D.; Gander-Copouz, M.; Naef, R. *Helv. Chim. Acta.* **1987**, *70*, 1194.
(9) Bentrude, W.G.; Day, R.O.; Holmes, J.M.; Quin, G.S.; Setzer, W.N.; Sopchik, A.E.; Holmes, R.R. *J. Am. Chem. Soc.* **1984**, *106*, 106.
(10) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A.K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon, B.; Hidber, P.C.; Irwin, J.J.; Locher, R.; Maestro, M.; Maetzke, T.; Mourino, A.; Pfammatter, E.; Plattner, D.A.; Schlickli, C.; Schweizer, W.B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, 75, 913.
(11) Crystallographic data were collected on an Enraf-Nonius CAD-4 diffractometer, and the structures were solved and refined with full matrix least squares analysis using SHELX-86 (G.M. Sheldrick, "Crystallographic Computing 3", OUP, 1985). Full data for compounds **7** and **9** has been lodged at the Cambridge Crystallographic Database.
Crystallographic summary for **7**: $C_{20}H_{27}NO_6$, $M_r = 377.44$, monoclinic, $P2_1$, $a = 9.965$, $b = 10.096$, $c = 10.234$ Å, $\alpha = 90$, $\beta = 94.626$, $\gamma = 90$, V = 1026 Å^3, Z = 2, $D_c = 1.22$ gcm^{-3}, CuK_α radiation, $\lambda = 1.54184$ Å, $\mu = 0.706$ mm^{-1}, F(000) = 404, T = 293 K, R = 0.0441 for 1962 unique reflections $I > 3\sigma(I)$.
Crystallographic summary for **9**: $C_{24}H_{27}NO_6$, $M_r = 425.480$, orthorhombic, $P\ 2_12_12_1$, $a = 10.978(2)$, $b = 12.475(2)$, $c = 16.456(5)$ Å, V = 2254 Å^3, Z = 4, $D_c = 1.25$ gcm^{-3}, CuK_α radiation, $\lambda = 1.5418$ Å, $\mu = 7.03$ cm^{-1}, F(000) = 840, T = 295(2) K, R = 0.0402 for 3944 unique reflections $I > 3\sigma(I)$.
(12) Cooke, M.P.; Burman, D.L. *J. Org. Chem.* **1982**, *47*, 4955.
(13) Brewster, J.H.; Fusco, A.M. *J. Org. Chem.* **1963**, *28*, 501.
(14) Wuonola, M.A.; Smallheer, J.M.; Read, J.M.; Calabrese, J.C. *Tetrahedron Lett.* **1991**, *32*, 5481.
(15) Ciganek, E.; Wuonola, M.A.; Harlow, R.L.; *J. Heterocycl. Chem.* **1994**, *31*, 1251.
(16) Fletcher, D.A.; McMeeking, R.F.; Parkin, R.F. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.