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The total synthesis of the marine-derived cyclic depsipeptide alternaramide

Alexandra E. Horton, Oliver S. May, Mark R. J. Elsegood and Marc C. Kimber*

The Department of Chemistry, Loughborough University, Loughborough, Leicester, LE11 3TU, UK

Fax: +44(0)-150-922-3925

E-mail: M.C.Kimber@lboro.ac.uk

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Abstract: The first synthesis of the marine fungus derived natural product alternaramide is described using solution phase coupling protocols and *via* a macrolactonization and macrolactamization route. The structure of alternaramide was confirmed and was supported by single crystal X-ray analysis which exhibited three similar molecules in the asymmetric unit, each with trans-annular hydrogen bonds.

Key words: Natural product, depsipeptide, peptide coupling, macrolactonization, macrolactamization.

Alternaramide **1** (Figure 1) is a cyclic depsipeptide¹ isolated from the marine-derived fungus *Alternaria sp.* SF-5016 by Oh and co-workers in 2009.²

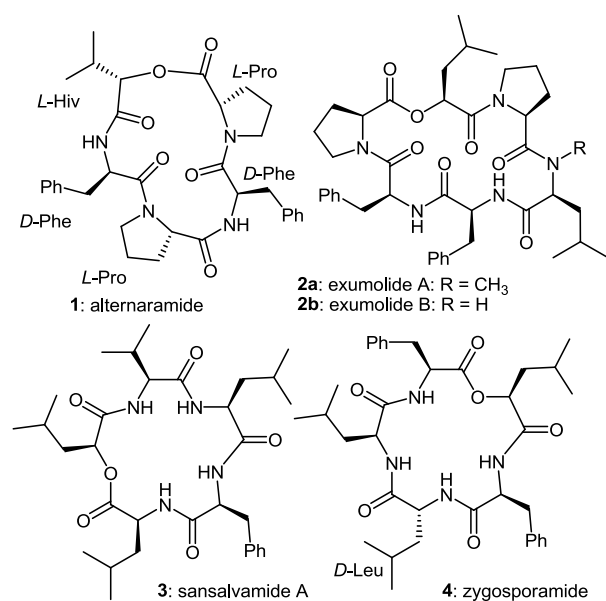
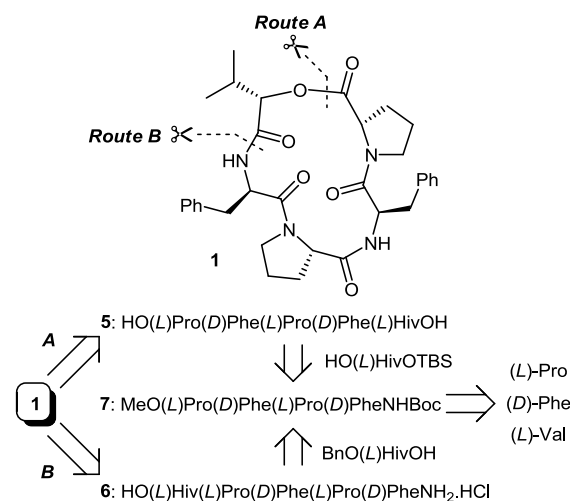


Figure 1. The reported² structure of alternaramide **1** and related marine-derived depsipeptide natural products.

The structure of **1** is related to several depsipeptides isolated from marine-derived fungi, such as the exumolides **2** from *Scytalidium sp.*,³ sansalvamide **3** from *Fusarium sp.*,⁴ and zygosporamide **4** from *Zygosporium masonii*,⁵ and was confirmed using a mixture of ¹H / ¹³C NMR, degradation and Mosher's ester derivitization studies. This showed that the depsipeptide contained 4 amino acid residues (two L-Pro and two D-Phe) and one hydroxy acid residue (L-Hiv) linked by 4 amide and 1 ester linkage. While all these peptides possess hydrophobic amino acid residues, the presence of the D-Phe residue in **1** is unusual since the only other depsipeptide in this group to have D-amino acid residues is zygosporamide **4** (Figure 1). Additionally, the importance of a D-amino acid in analogues of sansalvamide **A**, in relation to anticancer activity, has been determined by

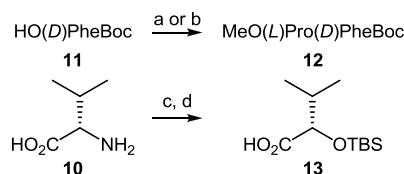
McGuire and McAlpine *via* SAR studies.⁶⁻¹⁰ Total syntheses of **3**¹¹ and **4**¹² have been described previously, however the total synthesis of **1** has yet to be reported. Therefore, in this letter, we would like to report a short, efficient, solution phase total synthesis of **1**, confirmation of its reported structure and a single crystal X-ray analysis.

The retrosynthesis of **1** is shown in Scheme 1. Alternaramide **1** can be obtained *via* either a macrolactonization or a macrolactamization event on the precursor linear peptides **5** and **6**, respectively. While there are examples of the use macrolactonization in the synthesis of depsipeptides,¹³⁻¹⁶ such a cyclisation performed on **5** may be problematic. However, due to the short synthetic sequence to give the precursor **5** we thought this would be a viable route to explore, alongside the macrolactamization approach. The synthesis of both precursor linear peptides **5** and **6** would be from the key tetrapeptide **7** using standard peptide coupling protocols. The tetrapeptide **7** would be obtained from L-Pro, D-Phe, and L-Hiv, which can be obtained from L-Val *via* hydrolytic diazotization.



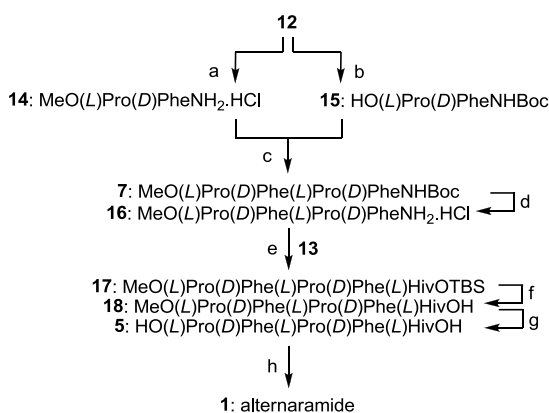
Scheme 1. Retrosynthetic analysis of alternaramide **1**.

Coupling of proline methyl ester **8** with HO(D)PheHNBoc **9** was initially performed using two coupling methods, either EDC or formation of the mixed anhydride which gave the diamino acid **12** in a good yield of 87% and 86%, respectively (Scheme 2). PyBOP[®] was also employed but yields using this coupling reagent were moderate to poor. The TBS protected α -hydroxy acid **13** was obtained in 3-steps in 65% yield *via* the hydrolytic diazotization of L-Val **10** followed by TBS protection.¹⁷



Scheme 2. (a) EDC, MeO(L)ProNH₂·HCl, CH₂Cl₂, ^tPr₂NEt, [87%]; (b) EtO₂CCl, NMM, CH₂Cl₂, 0°C then, MeO(L)ProNH₂·HCl, [86%]; (c) NaNO₂, H₂SO₄ (d) (i) TBSCl, DMF, imidazole (ii) K₂CO₃, MeOH, H₂O [65% over 2-steps].

The key tetrapeptide **7** was obtained in 2-steps from **12**, by Boc deprotection of **12** with 4M HCl in 1,4-dioxane to give **14**, and the hydrolysis of **12** to the free acid using LiOH to give **15**, both of which were used without further purification. The salt **14** and free acid **15** were then coupled under EDC conditions to give the key tetra-aminoacid **7** in 52% yield over the 2-steps (Scheme 3).

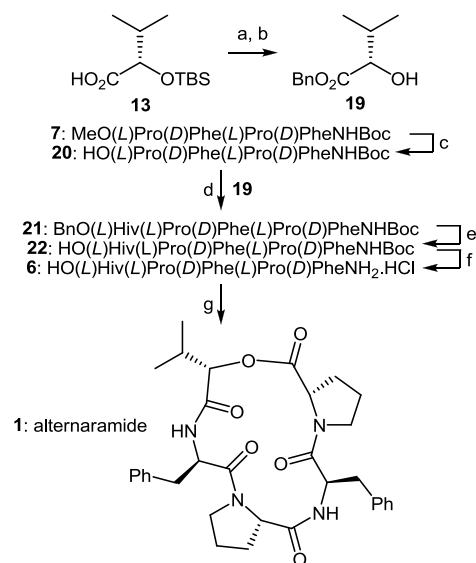


Scheme 3. (a) 4M HCl in 1,4-dioxane; (b) LiOH, THF, MeOH, H₂O; (c) EDC, CH₂Cl₂, ^tPr₂NEt₂ [52% over 2-steps]; (d) 4M HCl in 1,4-dioxane; (e) PyBOP[®], CH₂Cl₂, ^tPr₂NEt [71% over 2-steps]; (f) TBAF, THF; (g) LiOH, THF, MeOH, H₂O; (h) PyBOP[®], CH₂Cl₂, ^tPr₂NEt [5% over 3-steps].

Subsequently, **7** was Boc deprotected and the resultant salt **16** then coupled with the **13** using PyBOP[®] giving **17** in a good yield of 71% over 2-steps. The free alcohol and acid on **17** were then sequentially revealed by deprotection using TBAF and followed by treatment with excess aqueous LiOH. Attempted final ring closure of **5** was then trialed with a number of coupling reagents including PyBOP[®], DCC, EDC and 1,3,5-trichlorobenzoyl chloride.¹⁸ The only successful conditions were using excess PyBOP[®] and diisopropylethylamine which provided alternaramide **1** in a poor isolated yield of only 5% over the 3-steps, presumably due to the low nucleophilicity of the hydroxyl group. Consequently, route B (Scheme 1) with the final ring closure *via* a macrolactamization was pursued.

The requisite substrate for the macrolactamization was synthesized in 4-steps from the key tetrapeptide **7** (Scheme 4). A protecting group switch on the *L*-Hiv fragment was achieved in 2-steps to give the benzyl ester protected *L*-Hiv fragment **19** in 52% yield. This was then successfully coupled to the saponified tetrapeptide **20** in 73% yield over the 2-steps. Finally, the free acid and amine on **20** were revealed by sequential hydrogenolysis followed by acid mediated Boc deprotection. The macrolactamization of **6** was then achieved using excess PyBOP[®] with diisopropyl

amine and catalytic DMAP, giving alternaramide **1** in 48% yield over the 3-steps.¹⁹



Scheme 4. (a) BnC(O)Cl, CH₂Cl₂, Et₃N, DMAP; (b) TBAF, THF [52% over 2-steps]; (c) LiOH, MeOH, THF, H₂O; (d) PyBOP[®], CH₂Cl₂, ^tPr₂NEt [73% over 2-steps]; (e) Pd-C (10%), H₂, MeOH; (f) 4M HCl in 1,4-dioxane; (g) PyBOP[®], CH₂Cl₂, ^tPr₂NEt, DMAP (cat.) [48% over 3-steps].

The spectroscopic data for our synthetic alternaramide sample agreed well with that reported by Oh and co-workers and copies of the relevant ¹H and ¹³C NMR spectra are contained within the supplementary information.^{20,21} Crystals suitable for single crystal X-ray analysis were obtained and Figure 2 shows the molecular depiction of one of three similar molecules of (-)-**1** in the asymmetric unit.²² Despite the use of Mo-K α radiation for this light atom structure, determination of the absolute structure parameter²³ via Parson's Q-value method²⁴ led to a value that supported the proposed absolute structure for the molecule. The molecular conformation is stabilised by trans-annular hydrogen bonds.

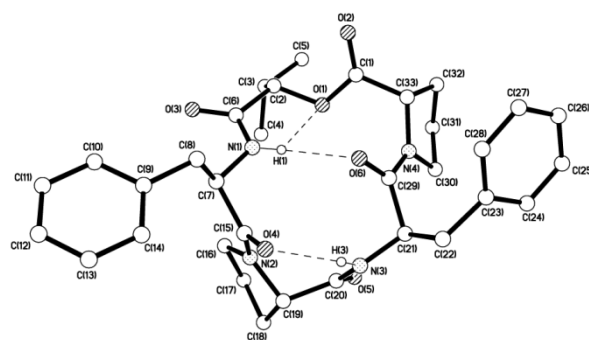


Figure 2. Crystal structure representation of alternaramide (-)-**1**.²²

In conclusion, we have reported the first total synthesis of alternaramide (-)-**1** using standard solution phase peptide coupling protocols. Two synthetic pathways have been investigated using a macrolactonization and a macrolactamization approach giving alternaramide in a best overall yield of 11% in 8-steps. Finally, the structure of synthetic alternaramide (-)-**1** was confirmed by single crystal X-ray analysis.

Supporting Information for this article includes the ^1H and ^{13}C NMR spectra of synthetic alternaramide (-)-**1** and crystallographic data for (-)-**1**.

Acknowledgments

The authors thank the Department of Chemistry at Loughborough University for financial support.

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- (19) Selected physical data for new compounds:
MeO(L)Pro(D)PheNHBoc, (-)-**12**. Colourless oil (3.05 g, 87%); R_f (3:1 ethyl acetate:petroleum ether) 0.65; $[\alpha]_D^{19}$ -5.5 (c 1, CHCl_3); ν_{max} (solution, CHCl_3) 3584, 3430, 2978, 1746, 1707, 1645, 1437, 1171 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 7.33–7.24 (m, 5H), 5.55 (d, $J = 8.8$ Hz, 1H), 4.71–4.69 (m, 1H), 4.36 (dd, $J = 3.6, 7.6$ Hz, 1H), 3.75 (s, 3H), 3.62–3.60 (m, 1H), 3.09–3.07 (m, 1H), 3.02–2.98 (m, 1H), 2.76–2.74 (m, 1H), 1.98–1.90 (m, 4H), 1.49 (s, 9H); δ_{C} (100 MHz; CDCl_3) 172.21 (C), 170.22 (C), 154.91 (C), 136.42 (C), 129.40 (CH), 128.28 (CH), 126.81 (CH), 79.44 (C), 58.65 (CH), 53.53 (CH), 52.05 (CH₃), 46.66 (CH₂), 40.07 (CH₂), 28.85 (CH₂), 28.25 (CH₃), 24.33 (CH₂); HRMS MNa^+ , $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5$, found 399.1885, requires 399.1896.
MeO(L)Pro(D)Phe(L)Pro(D)PheNHBoc (-)-**7**. White foam (0.97 g, 52% over 2-steps); R_f (3:1 ethyl acetate:petroleum ether) 0.38; $[\alpha]_D^{21}$ -8.1 (c 1, CHCl_3); ν_{max} (solution, CHCl_3) 3584, 3295, 2980, 1742, 1642, 1497, 1449, 1171 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 7.25–7.17 (m, 10H), 5.51 (d, $J = 7.6$ Hz, 1H), 4.86 (dt, $J = 6.4, 8.4$ Hz, 1H), 4.57–4.54 (m, 1H), 4.36 (dd, $J = 2.4, 8.0$ Hz, 1H), 4.27 (dd, $J = 4.0, 8.4$ Hz, 1H), 3.68 (s, 3H), 3.53–3.49 (m, 2H), 3.02–2.93 (m, 4H), 2.77–2.75 (m, 1H), 2.63–2.60 (m, 1H), 2.46 (s, 1H), 2.03–1.98 (m, 1H), 1.93–1.78 (m, 4H), 1.61–1.50 (m, 3H), 1.41 (s, 9H); δ_{C} (100 MHz; CDCl_3) 172.31 (C), 171.08 (C), 170.43 (C), 169.53 (C), 155.21 (C), 136.62 (C), 129.54 (CH), 129.50 (CH), 129.33 (C), 128.46 (CH), 128.34 (CH), 126.94 (CH), 126.84 (CH), 79.75 (C), 60.16 (CH), 58.80 (CH), 53.92 (CH₃), 52.42 (CH), 52.22 (CH), 46.84 (CH₂), 46.69 (CH₂), 39.63 (CH₂), 39.00 (CH₂), 28.91 (CH₂), 28.37 (CH₃) (NB masked CH₂), 24.51 (CH₂), 24.18 (CH₂); HRMS MNa^+ , $\text{C}_{34}\text{H}_{44}\text{N}_4\text{O}_7$, found 643.3098, requires 643.3108.
MeO(L)Pro(D)Phe(L)Pro(D)Phe(L)HivOTBS (-)-**17**. Colourless foam (0.52 g, 71% over 2-steps); R_f (ethyl acetate) 0.78; $[\alpha]_D^{16}$ -12.4 (c 1, CHCl_3); ν_{max} (solution, CHCl_3) 3416, 3290, 2957, 1743, 1658, 1515, 1451, 1254, 1052 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 7.27–7.13 (m, 10H), 7.07 (d, $J = 7.6$ Hz, 2H), 4.87–4.82 (m, 1H), 4.77–4.73 (m, 1H), 4.41 (dd, $J = 2.4, 8.4$ Hz, 1H), 4.23 (dd, $J = 4.0, 7.6$ Hz, 1H), 3.96 (s, 3H), 3.01–2.88 (m, 4H), 2.68–2.64 (m, 1H), 2.57–2.52 (m, 1H), 2.48–2.44 (m, 1H), 2.09–2.02 (m, 1H), 1.99–1.95 (m, 1H), 1.88–1.75 (m, 5H), 1.66–1.60 (m, 1H), 1.51–1.46 (m, 2H), 0.92–0.90 (m, 15H), 0.40 (s, 3H), -0.05 (s, 3H); δ_{C} (100 MHz; CDCl_3) 173.83 (C), 172.28 (C), 170.63 (C), 170.51 (C), 169.91 (C), 136.72 (C), 135.69 (C), 129.44 (CH), 129.31 (CH), 128.68 (CH), 128.34 (CH), 127.33 (CH), 126.82 (CH), 77.38 (CH), 60.53 (CH), 58.72 (CH), 52.45 (CH), 52.28 (CH), 52.09 (CH₃), 46.77 (CH₂), 46.68 (CH₂), 38.79 (CH₂), 38.76 (CH₂), 32.62 (C), 29.39 (CH₂), 28.91 (CH₂), 25.76 (CH₂), 24.40 (CH₂), 23.69 (CH₂), 19.60 (CH₃), 18.07 (CH₃), 16.00 (C), -5.00 (CH₃), -5.09 (CH₃); HRMS MNa^+ , $\text{C}_{40}\text{H}_{58}\text{N}_4\text{O}_7\text{Si}_1$, found 757.3955, requires 757.3972.
BnO(L)Hiv(L)Pro(D)Phe(L)Pro(D)PheNHBoc (-)-**21**. Colourless foam (0.19 g, 73% over 2-steps); R_f (3:1 ethyl acetate:petroleum ether) 0.65; $[\alpha]_D^{18}$ -6.4 (c 1, CHCl_3); ν_{max} (film) 3584, 3413, 2965, 2248, 1747, 1685, 1645, 1454, 1172 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 7.27–7.14 (m, 15H), 7.07–7.05 (m, 1H), 5.41 (d, $J = 7.6$ Hz, 1H), 5.08 (dd, $J = 12.0, 12.4$ Hz, 2H), 4.94 (t, $J = 4.4$ Hz, 1H), 4.87 (q, $J = 7.2$ Hz, 1H), 4.59–4.56 (m, 1H), 4.40 (dd, $J = 3.6, 8.4$ Hz, 1H), 4.32 (dd, $J = 2.8, 8.4$ Hz, 1H), 3.56–3.53 (m, 2H), 2.99–2.94 (m, 4H), 2.74–2.68 (m, 1H), 2.61–2.49 (m, 2H), 2.30–2.29 (m, 1H), 2.27–2.24 (m, 1H), 1.96–1.50 (m, 6H), 1.39 (s, 9H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H); δ_{C} (100 MHz; CDCl_3) (one carbon masked) 172.10 (C), 171.12 (C), 170.60 (C), 169.68 (C), 169.46 (C), 168.93 (C), 136.59 (C), 135.21 (C), 135.02 (C), 129.53 (CH), 129.49 (CH), 128.63 (CH), 128.57 (CH), 128.45 (CH), 128.39 (CH), 128.32 (CH), 126.93 (CH), 126.84 (CH), 79.72 (CH), 77.58 (CH), 67.18 (CH₂), 66.93 (CH₂), 60.36 (CH), 58.42 (CH), 53.86 (CH), 52.44 (CH), 46.88 (CH₂), 46.73 (CH₂), 38.97 (CH₂), 31.92 (CH₂), 30.18 (CH₃), 29.69 (CH₂), 28.38 (CH₂), 24.23 (CH₂), 18.62 (CH₃), 17.15 (CH₃); HRMS MNa^+ , $\text{C}_{45}\text{H}_{56}\text{N}_4\text{O}_9$, 819.3899, requires 819.3945.
- (20) Alternaramide (-)-**1**. Colourless crystalline solid (77 mg, 48% over 3-steps) m.p. 217–218.5 °C (recrystallised from CH_2Cl_2 / petroleum ether); R_f (3:1 ethyl

acetate:petroleum ether) 0.48; $[\alpha]_D^{19}$ -2.8 (c 0.5, MeOH); ν_{\max} (film) 3584, 3480, 3300, 3029, 2961, 2929, 2875, 2248, 1744, 1683, 1643, 1634, 1529, 1452, 1275, 1094 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 8.12 (d, $J = 9.6$ Hz, 1H), 7.32 – 7.17 (m, 11H), 5.34 (d, $J = 2.4$ Hz, 1H), 5.02 – 4.91 (m, 2H), 4.85 (d, $J = 7.2$ Hz, 1H), 4.30 (dd, $J = 5.2, 8.8$ Hz, 1H), 3.46 – 3.41 (m, 1H), 3.35 (dd, $J = 9.2, 13.2$ Hz, 1H), 3.26 (m, 2H), 3.03 – 2.99 (m, 2H), 2.90 (dd, $J = 5.2, 13.2$ Hz, 1H), 2.54 – 2.49 (m, 2H), 2.44 – 2.42 (m, 1H), 1.99 – 1.93 (m, 2H), 1.93 – 1.84 (m, 2H), 1.78 – 1.72 (m, 1H), 1.69 – 1.63 (m, 1H), 1.46 (sept, $J = 6.8$ Hz, 1H), 0.82 (d, $J = 6.8$ Hz, 3H), 0.71 (d, $J = 6.8$ Hz, 3H); δ_{C} (100 MHz; CDCl_3) 171.16 (C), 169.66 (C), 169.19 (C), 168.86 (C), 167.26 (C), 136.49 (C), 135.00 (C), 128.66 (CH), 128.30 (CH), 127.58 (CH), 127.36 (CH), 126.29 (C), 125.48 (C), 75.95 (CH), 58.92 (CH), 57.28 (CH), 51.85 (CH), 51.13 (CH), 45.89 (CH_2), 44.94 (CH_2), 39.43 (CH_2), 35.95 (CH_2), 28.65 (CH), 28.50 (CH_2), 23.75 (CH_2), 23.48 (CH_2), 18.09 (CH_3), 14.83 (CH_3); HRMS MNa^+ , $\text{C}_{33}\text{H}_{40}\text{N}_4\text{O}_6$, found 611.2833, requires 611.2846.

- (21) See supporting information for copies of the ^1H , ^{13}C NMR spectra for synthetically prepared alternaramide (-)-**1**.
- (22) Crystal data for (-)-**1**: $\text{C}_{33}\text{H}_{40}\text{N}_4\text{O}_6$, $M = 588.69$, orthorhombic, $P2_12_12_1$; $a = 12.0808(4)$ $b = 22.0624(7)$, $c = 34.9650(11)$ \AA , $V = 9319.3(5)$ \AA^3 ; $D_{\text{calc}} = 1.259$ g/cm^3 ; $\mu(\text{Mo-K}\alpha) = 0.087$ mm^{-1} ; $\lambda = 0.71073$ \AA , $T = 150(2)$ K; 104556 total reflections, 26198 unique data ($R_{\text{int}} = 0.0456$); Solved by direct methods and refined on F^2 values to give $R1 = 0.0473$ [$F^2 > 2\sigma(F^2)$] (19948 observed reflections), $wR2 = 0.1107$ (all data). Absolute structure parameter = $-0.09(22)^{23,24}$. CCDC: 801185 contains the supplementary crystallographic data for compound (-)-**1**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: (+44) 1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk.
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