First syntheses of the pyrroloketopiperazine marine natural products (±)-longamide, (±)-longamide B, (±)-longamide B methyl ester and (±)-hanishin

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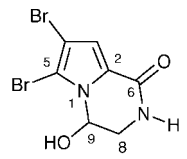
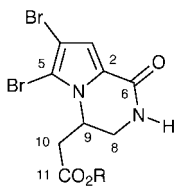
The marine natural products (±)-longamide (1), (±)-longamide B methyl ester (2), (±)-longamide B (3) and (±)-hanishin (4), each of which embodies a pyrroloketopiperazine core, have been synthesised in a concise fashion from pyrrole.

More than fifty bromopyrrole alkaloids have been isolated from various marine organisms, especially *Agelasidae* sponges and the taxonomically related order *Axinellida*.[1–3] A number of these secondary metabolites display interesting biological properties. For example, agelongine[4] acts as a specific inhibitor of serotonergic receptors and dispacamide A [5] is a potent non-competitive antihistamine while clathramides A–D [2,6] are all active antifungal agents. The bromopyrrole longamide (**1**)[7,8] was originally obtained from the Caribbean sponge *Agelas longissima* and more recently from a *Homaxinella* species of Japanese marine sponge.[1] Some antibacterial activity (MIC 60 μg ml^{-1}) has been ascribed to the optically active material obtained from the Caribbean sponge while the racemic modification isolated from the Japanese source is inactive against P388 lymphocytic leukemia cells. Longamide B methyl ester (**2**),[1] which has been isolated, for the first time and in racemic form, from the Japanese sponge mentioned above, exhibits weak (ED_{50} 30 μg ml^{-1}) cytotoxic activity, *in vitro*, against the same leukemia cell line. The corresponding acid (**3**, longamide B) [2] has been isolated, again in racemic form, from the Caribbean marine sponge *Agelas dispar* and shows modest (MIC 50 μg ml^{-1}) antibiotic activity against several strains of Gram-positive bacteria. "Semi-racemic" hanishin (**4**), the ethyl ester of longamide B, was obtained from extracts of the highly polymorphic sponge *Acanthella carteri* and is cytotoxic towards NSCLC-N6 human non-small-cell-lung carcinoma (IC_{50} of 9.7 μg ml^{-1}).[9]

Despite their rather interesting structures and biological properties, compounds **1**–**4**, each of which embodies the pyrroloketopiperazine core,[10] have not been the subject of previous synthetic studies.[11] Consequently, we now report the first total syntheses of the title compounds by routes capable of providing useful quantities of these materials as well as many derivatives.



(±)-**1**

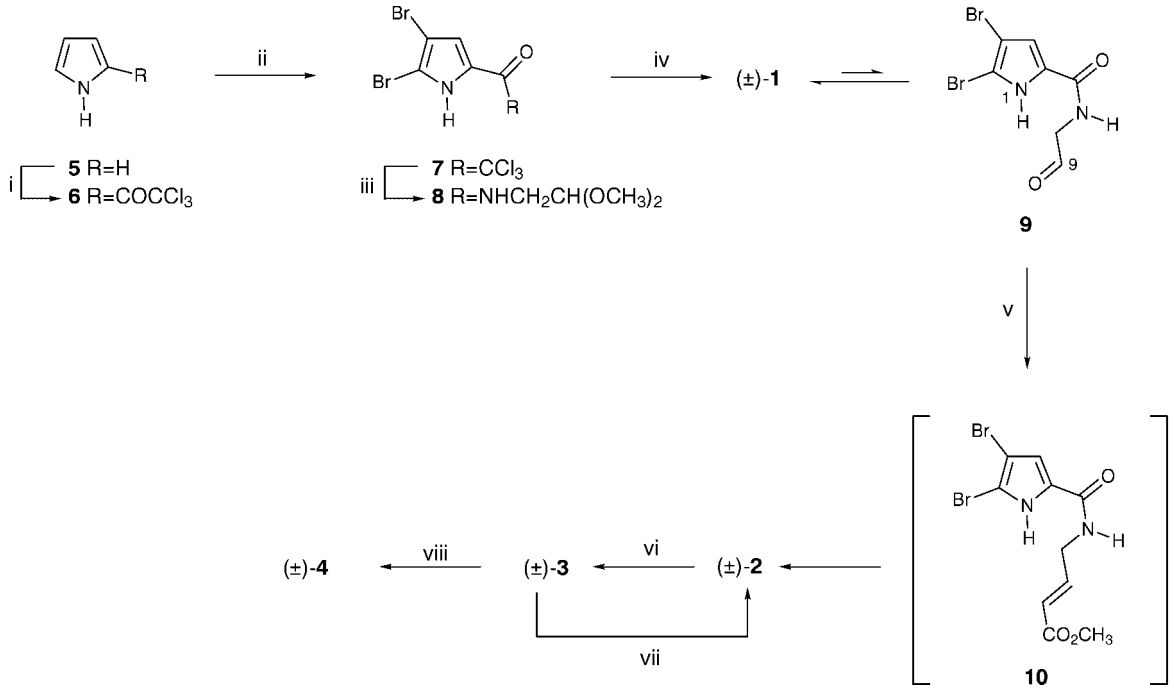


(±)-**2** R=CH_3
(±)-**3** R=H
(±)-**4** R=CH_2CH_3

The reaction sequences leading to the above-mentioned natural products are shown in Scheme 1 and start with the well-known[12] and completely regioselective electrophilic aromatic substitution of pyrrole (**5**) involving trichloroacetyl chloride as electrophile. The ketone (**6**, 95%)[12] so-formed reacts readily with a two-fold excess of molecular bromine in acetic acid at 18–60 °C to give the previously reported[13] 4,5-dibromo derivative (**7**, 99%) as the only detectable product of reaction. Treatment of this last compound with commercially available aminoacetaldehyde dimethyl acetal, under conditions defined by Bailey[14] and Horne and colleagues[11a] for the reaction of trichloromethyl ketone (**6**) with various amines, resulted in the smooth formation of amide (**8**, 97%). Acid-catalysed hydrolysis of the latter compound then gave longamide (**1**, 99%), the spectral data for which matched those reported for the natural product. Presumably the conversion **8** → **1** involves initial production of aldehyde (**9**), which cyclises to produce longamide. While there is chemical evidence (*vide infra*) to suggest that compounds **9** and **1** are in equilibrium with one another,[15] the steady state concentration of the former species must be rather low because ^1H NMR and IR spectroscopic analysis of longamide did not reveal any signals due to an aldehydic species.

Reaction of longamide (**1**) with three molar equivalents of the sodium salt of methyl diethylphosphonoacetate afforded longamide B methyl ester (**2**, 45%) directly. It is presumed that the initially formed product of this reaction is acrylate (**10**), which derives from a Wadsworth–Horner–Emmons olefination involving aldehyde (**9**) and the above-mentioned salt. In keeping with the behaviour of related systems,[16] compound **10** must undergo a facile intramolecular Michael addition reaction involving the pyrrolic nitrogen as nucleophile so as to generate the observed compound **2**. Once again, the spectral properties of the latter were completely consistent with the assigned structure and matched those data reported[1] for the natural product. However, final confirmation of structure followed from a single crystal X-ray analysis (Fig. 1, Table 1). Despite various attempts, the rather poor yields associated with the conversion **1** → **2** could not be improved upon and this situation is attributed, at least in part, to the formation of the various unidentified by-products.

The synthesis of longamide B (**3**, 97%) was readily achieved by saponification of ester **2** followed by protonation of the resulting acid salt with mineral acid.[16] Our sample of longamide B was obtained as a fine microcrystalline solid that could not be dissolved in any of the common organic solvents save for methanol. In contrast, the natural product is described as an amorphous solid that readily dissolves in chloroform. A further difference between the natural and synthetic samples of compound (±)-(**3**) is that the former material



Scheme 1 Reagents and conditions: (*i*) $ClCOCCl_3$ (1.07 mole equiv.), $(CH_3CH_2)_2O$, 18 °C, 4 h; (*ii*) Br_2 (2.0 mole equiv.), CH_3CO_2H, 18–60 °C, 2 h; (*iii*) $H_2NCH_2CH(OMe)_2$ (1.1 mole equiv.), CH_3Cl, 18 °C, 20 h; (*iv*) 3 M aq. HCl (10 mole equiv.), $(CH_3)_2CO$, 18 °C, 16 h; (*v*) $H_3CO_2CCH_2PO(OCH_2CH_3)_2$ (3.0 mole equiv.), $NaOCH_3$ (3.0 mole equiv.), CH_3OH, 18 °C, 18 h; (*vi*) 10% aq. NaOH, CH_3OH, reflux, 0.5 h; (*vii*) CH_2N_2 (excess), $(CH_3CH_2)_2O$, 0–18 °C, 20 h; (*viii*) CH_3CH_2OH, conc. HCl, reflux, 3 h.

is reported to display an infrared absorption band at 1780 cm^{-1} while the synthetic material does not.[2] As a consequence of these discrepancies, it was deemed prudent to confirm the structure of the synthetic material by reacting it with diazomethane in ether. As expected, this reaction afforded the corresponding methyl ester (**2**), which was obtained in essentially quantitative yield.

The ^1H NMR spectrum of the naturally derived sample of longamide B, a copy of which was kindly provided to us by Professor Fattorusso,[2] proved a good match with the equivalent spectrum derived from the synthetic material, especially when allowances were made for the different NMR solvents employed (deuterochloroform *vs.* perdeuteromethanol). The differing physical properties of natural and synthetic longamide B might result from differing levels of purity of the two samples. A similar explanation may account for the infra-red absorption band observed at 1780 cm^{-1} for the natural material. On balance, then, there seems to be good evidence to suggest that the structure **3** assigned[2] to the natural product longamide B is correct.

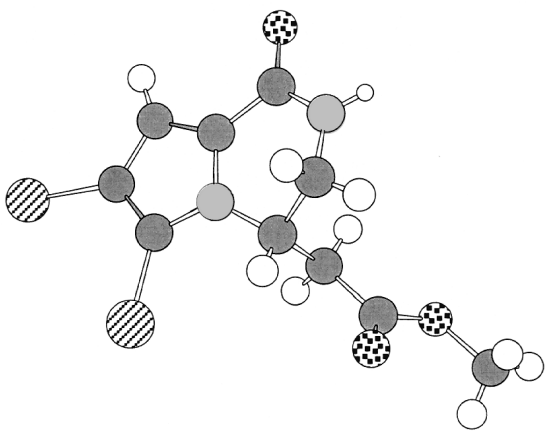


Fig. 1 CS Chem3D Pro™ drawing of longamide B methyl ester [(±)-(**2**)] generated using data derived from an X-ray crystallographic study.

The racemic modification of hanishin [(±)-(**4**)] was readily prepared by treating acid (±)-(**3**) with acidic ethanol and the spectroscopic data obtained on the product of this reaction were in reasonable agreement with those reported[9] for the natural product. While the naturally occurring and semi-racemic compound was obtained as a "semisolid", the synthetically derived (±)-hanishin is a crystalline material with a melting point of 148–150 °C.

Experimental

Unless otherwise specified, ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer using $CDCl_3$ as solvent. Infrared spectra were recorded on either a Perkin–Elmer 683 or 1800 FTIR instrument while mass spectral analyses were conducted on a VG Micromass 7070F double-focussing spectrometer. Melting points were recorded on a

Table 1 Crystallographic data for (±)-longamide B methyl ester [(±)-(**2**)]

Formula	$C_{10}H_{10}Br_2N_2O_3$
M	366.01
Size/mm	0.34 × 0.14 × 0.06
Space group	$P\bar{1}$ (no. 2)
a/Å	8.168(1)
b/Å	9.279(2)
c/Å	9.875(2)
α/°	65.47(2)
β/°	80.99(1)
γ/°	67.69(1)
U/Å^3	629.9(2)
Z	2
ρ_{calcd}/g m^{-3}	1.93
T/K	296 (±1)
Radiation	Cu-Kα, graphite monochromated
λ/Å	1.54178
μ/cm^{-1}	82.6
No. of reflections	2025
Unique reflections	1873 (R_{int} = 0.037)
R	0.040
R_w	0.049
S	2.63

Reichert hot-stage microscope and are uncorrected. Thin layer chromatographic analyses were carried out on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} plates supplied by Merck while flash chromatographic purifications were conducted according to the method of Still *et al.*[17] and using Merck silica gel 60 (230–400 mesh) as adsorbent. All solvents and common reagents were purified by established procedures.[18]

Synthetic Studies

4,5-Dibromo-*N*-(2,2-dimethoxyethyl)pyrrole-2-carboxamide, (8). A solution of 4,5-dibromopyrrol-2-yl trichloromethyl ketone (**7**,[13] 984 mg, 2.65 mmol) in acetonitrile (15 ml) containing aminoacetaldehyde dimethyl acetal (307 mg, 2.92 mmol, ex Aldrich) was stirred at 18 °C for 20 h. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between water (100 ml) and ethyl acetate (100 ml). The separated aqueous phase was extracted with ethyl acetate (2 × 100 ml) and the combined organic phases were then washed with water (3 × 50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce a light-brown solid. Recrystallisation of this material (diethyl ether) then gave the title acetal (**8**, 914 mg, 97%) as white needles, mp 121–123 °C (Found: $M^{+\cdot}$, 353.9223; C, 30.5; H, 3.5; N, 8.1; Br, 44.9. $C_9H_{12}{}^{79}Br_2N_2O_3$ requires $M^{+\cdot}$, 353.9215; C, 30.4; H, 3.4; N, 7.9; Br, 44.9%). ν_{max} (KBr/cm^{-1}) 1636, 1563, 1522; δ_H ($CDCl_3$) 10.44 (br s, 1H, H-1), 6.61 (d, J = 3.0 Hz, 1H, H-3), 6.07 (br t, *J ca.* 5 Hz, 1H, H-7), 4.46 (t, J = 5.2 Hz, 1H, H-9), 3.59 (t, J = 5.4 Hz, 2H, H-8), 3.43 (s, 6H, 2 × OCH_3); δ_C ($CDCl_3$) 159.9 (C, C-6), 126.6 (C, C-2), 112.7 (CH, C-3), 106.1 (C, C-5), 102.7 (CH, C-9), 99.5 (C, C-4), 54.7 (CH_3, 2 × OCH_3), 41.1 (CH_2, C-8); *m/z* 358 (4%), 356 (8), 354 (4, $M^{+\cdot}$), 254 (14), 252 (24), 250 {15, [M − $(H_3CO)_2CHCH_2NH^{\cdot}]^+$}, 75 {100, $[(H_3CO)_2CH]^+$}.

(±)-Longamide, (±)-(1). A solution of compound **8** (880 mg, 2.47 mmol) in acetone (50 ml) containing HCl (2.1 ml of a 3 M aqueous solution) was allowed to stand at 18 °C for 16 h, then concentrated under reduced pressure to afford a light-brown solid. Recrystallisation (diethyl ether) of this material afforded (±)-longamide [(±)-(**1**), 716 mg, 99%] as white needles, mp 204–207 °C (Found: $M^{+\cdot}$, 307.8801; C, 27.2; H, 1.8; N, 9.3; Br, 51.6. $C_7H_6{}^{79}Br_2N_2O_2$ requires $M^{+\cdot}$, 307.8796; C, 27.1; H, 2.0; N, 9.0; Br, 51.6%). ν_{max} (KBr/cm^{-1}) 3173, 1650, 1637 (sh), 1615; δ_H (CD_3OD) 6.97 (s, 1H, H-3), 5.79 (m, 1H, H-9), 3.85 (dd, J = 13.7 and 2.8 Hz, 1H, H-8a), 3.63 (dd, J = 13.7 and 1.6 Hz, 1H, H-8b); δ_C [$(CD_3)_2SO$] 158.3 (C, C-6), 126.9 (C, C-2), 114.8 (CH, C-3), 106.9 (C, C-5), 101.0 (C, C-4), 74.6 (CH, C-9), 47.4 (CH_2, C-8); *m/z* 312 (21%), 310 (40), 308 (24, $M^{+\cdot}$), 254 (61), 252 (100), 250 (64, [M − $HCOCH_2NH^{\cdot}]^+$).

(±)-Longamide B methyl ester, (±)-(2). A solution of (±)-longamide (**1**, 780 mg, 2.52 mmol) and methyl diethylphosphonoacetate (1.59 g, 7.54 mmol) in anhydrous methanol (65 ml) was added to methanolic sodium methoxide (7.54 mmol, prepared by reacting 174 mg of sodium metal with 25 ml of methanol). The resulting mixture was stirred at 18 °C for 18 h then concentrated under reduced pressure. The oily residue thus obtained was diluted with water (100 ml) and the resulting mixture extracted with $CHCl_3$ (6 × 100 ml), then the combined organic phases were washed with water (2 × 100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid. Recrystallisation (diethyl ether) of this material afforded the title compound [(±)-(**2**), 412 mg, 45%] as white needles, mp 173–175 °C (Found: $M^{+\cdot}$, 363.9051; C, 32.6; H, 2.6; N, 7.6; Br, 43.7. $C_{10}H_{10}{}^{79}Br_2N_2O_3$ requires $M^{+\cdot}$, 363.9058; C, 32.8; H, 2.8; N, 7.7; Br, 43.7%). ν_{max} (KBr/cm^{-1}) 3218, 1735, 1669, 1549; δ_H (C_5D_5N) 8.96 (d, J = 4.0 Hz, 1H, H-7), 7.32 (s, 1H, H-3), 4.92 (m, 1H, H-9), 3.95 (dd, J = 13.6 and 3.9 Hz, 1H, H-8a), 3.85 (dd, J = 13.6 and 4.9 Hz, 1H, H-8b), 3.54 (s, 3H, OCH_3), 3.07 (dd, J = 16.0 and 10.2 Hz, 1H, H-10a), 2.68 (dd, J = 16.0 and 3.5 Hz, 1H, H-10b); δ_C (C_5D_5N) 170.5 (C, C-11), 159.0 (C, C-6), 126.7 (C, C-2), 115.3 (CH, C-3), 106.2 (C, C-5), 100.9 (C, C-4), 51.9 (CH_3, OCH_3), 51.1 (CH, C-9), 43.1 (CH_2, C-8), 35.9 (CH_2, C-10); *m/z* 368 (48%), 366 (85), 364 (50, $M^{+\cdot}$), 295 (56), 293 (100), 291 (51, $[M - H_3COCOCH_2^{\cdot}]^+$) 294 (56), 292 (91), 290 (52, $[M - C_3H_6O_2^{\cdot}]^+$).

(±)-Longamide B, (±)-(3). A solution of compound **2** (70 mg, 0.19 mmol) in methanol (5 ml) was treated with sodium hydroxide (5 ml of a 10% w/w aq. solution) and the resulting mixture heated at reflux for 0.5 h. The cooled reaction mixture was washed with diethyl ether (1 × 3 ml) and the separated aqueous phase acidified to pH 1 with HCl (3 M aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 50 ml) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid. Recrystallisation (methanol) of this material afforded (±)-longamide B [(±)-(**3**), 65 mg, 97%] as white needles, mp 273–274 °C (Found: $M^{+\cdot}$, 349.8908; C, 30.6; H, 2.2; N, 8.1; Br, 45.4. $C_9H_8{}^{79}Br_2N_2O_3$ requires $M^{+\cdot}$, 349.8902; C, 30.7; H, 2.3; N, 8.0; Br, 45.4%). ν_{max} (KBr/cm^{-1}) 3196, 1710, 1647, 1563; δ_H (CD_3OD) 6.94 (s, 1H, H-3), 4.81 (m, 1H, H-9), 3.89 (ddd, J = 11.5, 3.3 and 1.5 Hz, 1H, H-8a), 3.67 (dd, J = 11.5 and 1.5 Hz, 1H, H-8b), 2.87 (dd, J = 16.0 and 10.8 Hz, 1H, H-10a), 2.55 (ddd, J = 16.0, 3.3 and 1.5 Hz, 1H, H-10b); *m/z* 354 (63%), 352 (100), 350 (65, $M^{+\cdot}$). A ^{13}C NMR spectrum of this material could not be obtained because of its poor solubility in all of the usual solvents.

Reaction of (±)-longamide B with diazomethane. Regeneration of (±)-longamide B methyl ester. A magnetically stirred suspension of (±)-longamide B [(±)-(**3**), 11 mg, 0.03 mmol] in anhydrous diethyl ether (5 ml) was cooled to 0 °C then treated, in one portion, with diazomethane (4 ml of a 1 M solution in diethyl ether). The resulting mixture was allowed to warm to 18 °C over *ca.* 1.5 h, stirred at this temperature for 20 h, then concentrated under reduced pressure to give (±)-longamide B methyl ester [(±)-(**2**), 11 mg, 99%] as a white solid, mp 171–173 °C. This material was identical, by ^1H NMR spectroscopic and thin layer chromatographic criteria, with authentic material.

(±)-Hanishin, (±)-(4). A solution of (±)-longamide B (90 mg, 0.26 mmol) in ethanol (10 ml) containing conc. HCl (3.0 ml) was heated at reflux for 3 h. The cooled reaction mixture was then diluted with water (20 ml) and extracted with diethyl ether (3 × 30 ml). The combined organic phases were washed with sodium carbonate (1 × 30 ml of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid. Recrystallisation (diethyl ether) of this material afforded (±)-hanishin [(±)-(**4**), 91 mg, 93%] as white needles, mp 148–150 °C (Found: $M^{+\cdot}$, 377.9209; C, 35.0; H, 3.1; N, 7.6; Br, 41.9. $C_{11}H_{12}{}^{79}Br_2N_2O_3$ requires $M^{+\cdot}$, 377.9215; C, 34.8; H, 3.2; N, 7.4; Br, 42.1%). ν_{max} (KBr/cm^{-1}) 3265, 1731, 1667, 1549; δ_H [$(CD_3)_2CO$] 6.97 (br s, 1H, H-7), 6.90 (s, 1H, H-3), 4.86 (m, 1H, H-9), 4.19 (q, J = 7.1 Hz, 2H, OCH_2), 4.04 (dd, J = 13.4 and 4.1 Hz, 1H, H-8a), 3.71 (br dd, J = 13.4 and 4.1 Hz, 1H, H-8b), 3.00 (dd, J = 15.9 and 10.2 Hz, 1H, H-10a), 2.68 (br dd, J = 15.9 and 3.8 Hz, 1H, H-10b), 1.27 (t, J = 7.1 Hz, 3H, CH_3); δ_C [$(CD_3)_2CO$] 170.3 (C, C-11), 158.8 (C, C-6), 126.9 (C, C-2), 115.3 (CH, C-3), 106.3 (C, C-5), 100.6 (C, C-4), 61.5 (CH_2, OCH_2), 51.6 (CH, C-9), 43.6 (CH_2, C-8), 36.5 (CH_2, C-10), 14.3 (CH_3, OCH_2CH_3); *m/z* 382 (25%), 380 (50), 378 (25, $M^{+\cdot}$), 295 (49), 293 (100), 291 (51, [M − $H_3CCH_2OCOCH_2^{\cdot}]^+$).

Crystal data and refinement details for (±)-longamide B methyl ester [(±)-(2)]

Data collection. Crystallographic data for the title compound are given in Table 1. Intensity data were collected on a Rigaku AFC6R diffractometer using the $\omega - 2\theta$ scan technique to a maximum 2θ value of 120°. Scans of $(1.40 + 0.30 \tan \theta)°$ were made at a speed of 32.0° min^{-1} (in omega). The weak reflections $[I < 10.0\sigma(I)]$ were rescanned (maximum of four scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2 : 1.

Data reduction. Three representative reflections were measured after every 150 reflections which revealed that no decay correction was required. An empirical absorption correction based on azimuthal scans was applied, which resulted in transmission factors ranging from 0.31 to 0.61. The data were corrected for Lorentz and polarisation effects.

Structure solution and refinement. The structure was solved by direct methods[19] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at geometrically determined positions, which were periodically recalculated but were not refined. The final cycle of full-matrix least-squares refinement was based on 1661 observed reflections $[I > 2.0\sigma(I)]$ and 154 variable parameters. The maximum and minimum peaks on the final difference Fourier map correspond to 0.70 and −0.52 e $Å^{-3}$, respectively. All calculations were performed using the teXsan[20] crystallographic software package of Molecular Structure Corporation.

CCDC reference number 440/114. See http://www.rsc.org/suppdata/nj/1999/687/ for crystallographic files in .cif format.

Acknowledgements

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