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A Total Synthesis of the Marine Alkaloid Ningalin B from (*S*)-Proline

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The title alkaloid **1** has been synthesized from (*S*)-proline (**2**) using a sequence of reactions involving oxidative bromination (of **2**), *N*-alkylation, Suzuki–Miyaura cross-coupling, and bromination steps.

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Introduction

The marine alkaloid ningalin B (**1**, Fig. 1) was isolated, together with three related natural products, by Fenical et al. from an ascidian belonging to the genus *Didemnum* and collected at the Ningaloo Reef in Western Australia.[1] Its structure was first established by detailed NMR analyses and then proved through a total synthesis carried out by Boger and coworkers (see below).[2] Biogenetically speaking, the compound is probably derived via a series of oxidative coupling and condensation reactions involving the amino acid 3,4-dihydroxyphenylalanine (DOPA). These same sorts of processes are thought to lead to structurally related alkaloids such as the lamellarins, the lukianols, the polycitrins, and the storniamides, all of which have attracted considerable attention because of their interesting biological properties.[3] Although ningalin B may be implicated in the pronounced metal-sesquestering properties of the producing organism,[1] it does not appear to display many other notable biological effects. It is certainly not particularly cytotoxic, at least as determined by its evaluation in a cancer cell-line panel.[2] The permethyl ether of ningalin B is similarly non-cytotoxic but it and several amide derivatives do show a significant capacity to reverse multidrug resistance by, for example, resensitizing a resistant human colon cancer cell line HCT116/VM46 to vinblastine and doxorubicin.[2,4,5] As such, this ningalin B derivative behaves in a similar fashion to certain of the lamellarins and their congeners.[3]

Ningalin B has been the subject of several synthetic studies, the first of which was reported by Boger et al.[2] in 2000. This group employed a heterocyclic azadiene Diels–Alder cycloaddition/zinc-metal induced ring-contraction protocol to construct a tetrasubstituted pyrrole from a tolan precursor. Various manipulations of this pyrrole, including those involving *N*-alkylation, lactonization and decarboxylation steps, provided the permethyl ether of ningalin B. Exhaustive demethylation of this last compound using boron tribromide then gave, in 98% yield, ningalin B itself.

Iwao's synthesis of target **1**, reported in 2003,[6] has some similarities to Boger's approach[2] in that a symmetrical 2,5-dicarboalkoxy-substituted pyrrole intermediate is involved and thus requiring that a decarboxylation reaction is carried out at a relatively late stage in the synthesis. As with all but one of the other syntheses, Iwao's reaction sequence provides ningalin B permethyl ether as the immediate precursor to the natural product **1**.

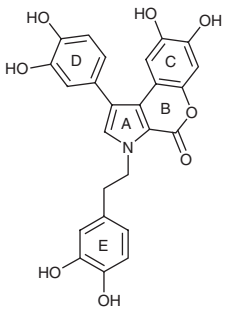

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Fig. 1.

The Bullington synthesis of ningalin B[7] is quite distinct in that a symmetrical intermediate is not involved and no decarboxylation step is required. It is also particularly concise and starts with a base-promoted [2 + 3] 'cycloaddition' reaction between the relevant α-cyanostilbene and methyl isocyanoacetate to give a trisubstituted pyrrole that is readily *N*-alkylated, demethylated, and lactonized to give the target compound.

Gupton's synthesis of ningalin B permethyl ether involves the application of his versatile vinylogous iminium salt derivative methodology for forming substituted pyrroles.[8] As with the Bullington approach, symmetrical intermediates are not involved and the starting material is the readily prepared 1,2-diarylethanone derivative desoxyveratroin. The final step in the reaction sequence is a 'Steglich-type' lead tetraacetate-mediated lactonization[9] of a 3-arylpyrrole-2-carboxylic acid derivative.

The Steglich synthesis of ningalin B, which was reported in 2006,[9] is modelled on the proposed biogenesis of the natural product and also delivers a symmetrical tetrasubstituted pyrrole

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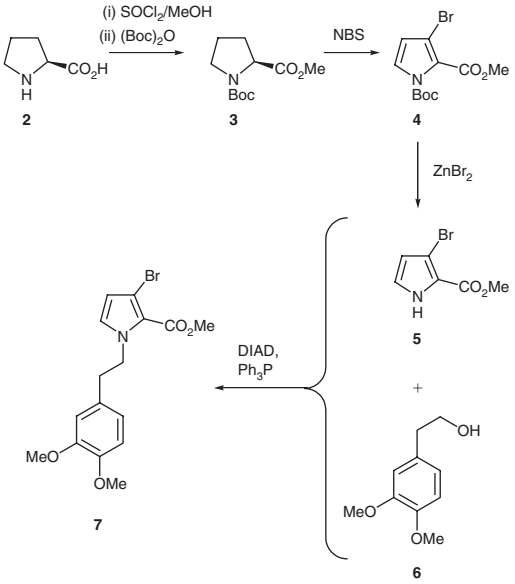
that requires a late-stage decarboxylation. An especially attractive feature of this work is the use of a lead tetraacetate-mediated process to establish the lactone moiety within target **1**.

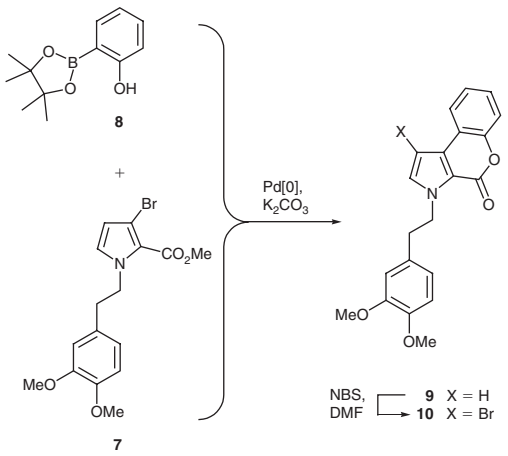
Our continuing interest in the chemistry of pyrroles and in the synthesis of marine alkaloids containing this ring system[10,11] has prompted us to establish a synthesis of ningalin B which we now report. Our approach uses (*S*)-proline as the precursor to the pyrrole ring of target **1** and avoids the need to employ a decarboxylation step in the synthetic sequence. Details are reported in the following sections.

Results and Discussion

The early stages of our synthesis of ningalin B are shown in Scheme 1 and involve the conversion of (*S*)-proline **2** into the 3-bromo-2-carbomethoxypyrrole **4** using a novel oxidative bromination protocol first described by Easton et al.[12] and recently refined by us.[11] The substrate **3** required for this key step was prepared by converting acid **2** into the corresponding and well-known[11] methyl ester using thionyl chloride/methanol. Boc-protection of the secondary amine residue within this last compound was achieved under standard conditions and the ensuing carbamate **3** treated with *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride. By such means, compound **4** was obtained in 72% yield[11] and the Boc-group associated with it was readily cleaved with zinc bromide to give the pivotal pyrrole **5** (89%), the structure of which had been confirmed by a single-crystal X-ray analysis carried out during our earlier studies.[11] The *N*-alkylation of compound **5** with the β-phenethyl alcohol **6** was readily achieved under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and so gave the previously reported[11] compound **7** in 75% yield. All the spectral data acquired on pyrrole **7** were in accord with the assigned structure. In particular, the electrospray ionization (ESI) mass spectrum of this material displayed molecular associated ions at *m/z* 390 and 392 (corresponding to $[M + Na]^+$) while the ^{13}C NMR spectrum displayed the expected 16 signals, 10 of which appeared in the aromatic region.



Scheme 1.



Scheme 2.

The planned elaboration of pyrrole **7** to ningalin B was explored through the model study outlined in Scheme 2. Thus, the former compound was subjected to a Suzuki–Miyaura cross-coupling, under standard conditions, with the commercially available aryl boronic acid **8**[13] incorporating an *o*-hydroxy group that it was expected would participate, after the C–C bond-forming process, in a spontaneous lactonization reaction with the ester residue originally present in substrate **7**. In accord with such expectations, the product of the cross-coupling process was lactone **9** and this was obtained in 79% yield.

The reaction of compound **9** with *ca.* two molar equivalents of NBS in DMF at 0°C provided a single mono-brominated derivative in 74% yield and while it was expected, on electronic grounds, to be the required one, namely compound **10**, this could be readily proved by single-crystal X-ray analysis. The derived *ORTEP* is shown in Fig. 2 and this clearly reveals that the desired bromopyrrole **10** had been obtained. The acquisition of compound **10**, incorporating a bromine in the correct position for a second Suzuki–Miyaura cross-coupling that would allow installation of the isolated aryl unit of ningalin B, was a pleasing outcome and the adaptation of this chemistry to the synthesis of the natural product was thus pursued as described in the following sections.

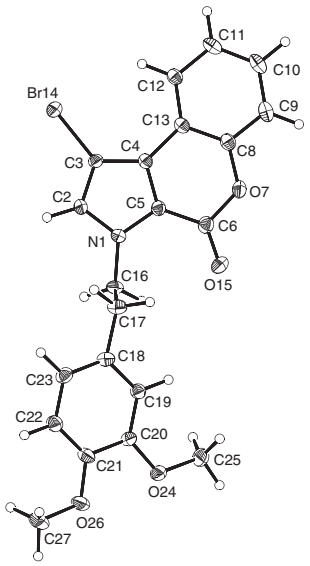
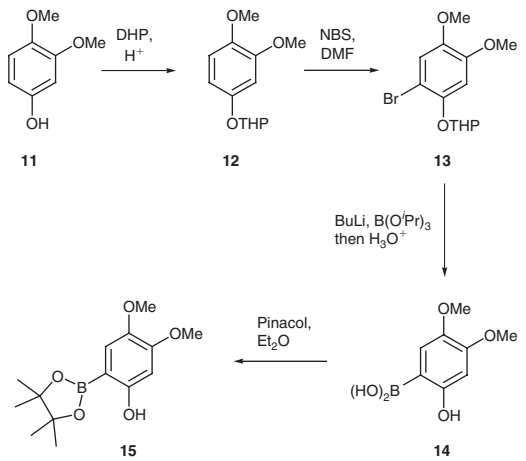


Fig. 2. Molecular structure of compound **10** ($C_{21}H_{14}BrNO_4$) with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

The completion of the synthesis of ningalin B from compound **7** required securing quantities of the 4,5-dimethoxysubstituted derivative of aryl boronate **8** or an equivalent thereof. Handy et al. have described[14] the preparation of such a species, namely 2-hydroxy-4,5-dimethoxyphenyl boronic acid, so we sought to obtain this compound by the reported means, then use it in a Suzuki–Miyaura cross-coupling reaction with compound **7**. In our hands, however, this boronic acid proved unstable and was, therefore, difficult to purify. Accordingly, we pursued the synthesis of the corresponding pinacolato derivative using a modification of Handy's protocols.[14] The reaction sequence used is shown in Scheme 3 and starts with the conversion, under standard conditions, of commercially available 3,4-dimethoxyphenol **11** into the corresponding THP ether **12** by reacting the former compound with 3,4-dihydro-2*H*-pyran (DHP) in the presence of an acid catalyst.[14] Bromination of compound **12** using NBS in DMF proceeded smoothly to give the required bromide **13**[14] in 83% yield over the two steps. Reaction of a mixture of halide **13** and tri-isopropylborate with *n*-BuLi followed by acidic workup then afforded Handy's boronic acid **14**, which was immediately esterified using pinacol. By such means, the ester **15** was obtained as a light-yellow oil and in 69% overall yield from precursor **13**. The electron-impact (EI) mass spectrum of compound **15** showed a molecular ion at *m/z* 280 while the ^{1}H NMR spectrum showed two one-proton singlets in the aromatic region (δ 6.99 and 6.44), two three-proton singlets at δ 3.86 and 3.84 and a 12-proton singlet at δ 1.21, as would be expected for the assigned structure.

With compounds **7** and **15** in hand, these were subjected to a Suzuki–Miyaura cross-coupling process (Scheme 4) and this provided the anticipated lactone **16**, albeit in only 43% yield. The NMR spectral data obtained on this product were completely consistent with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis. The derived *ORTEP* is shown in Fig. 3.

Various modifications to the procedure used for the conversion **7** + **15** → **16** failed to provide a better yield of the coupling



Scheme 3.

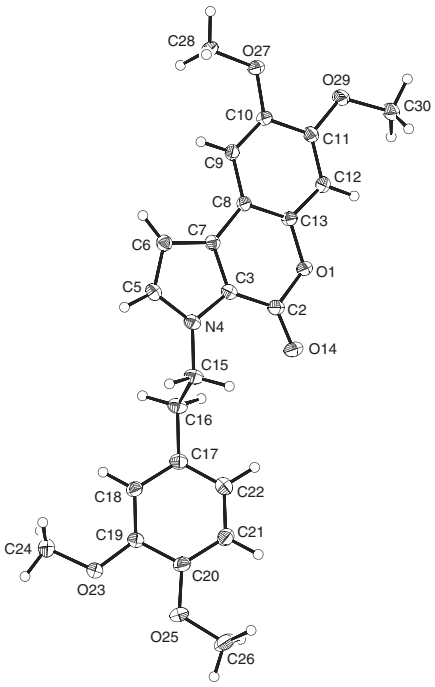
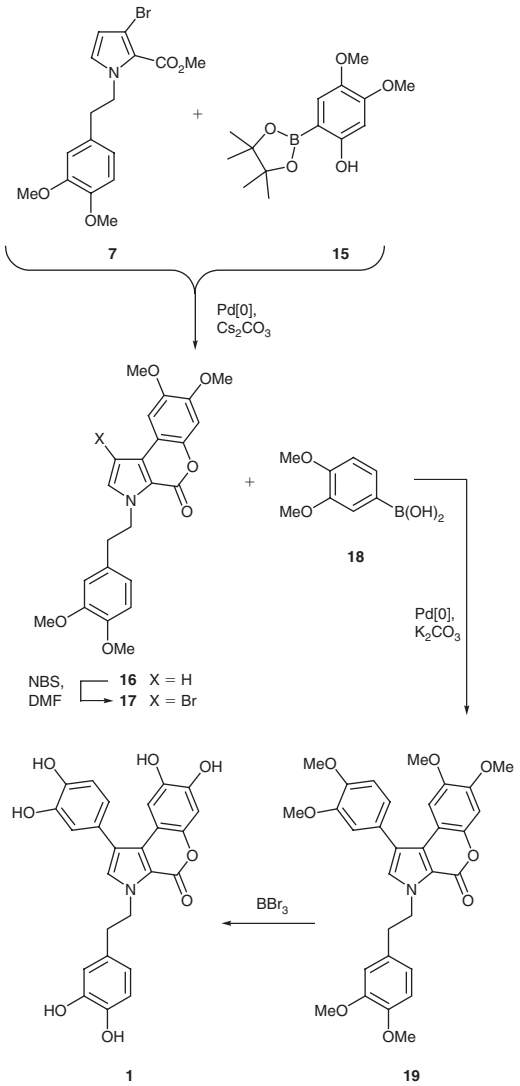


Fig. 3. Molecular structure of compound **16** ($C_{23}H_{23}NO_6$) with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

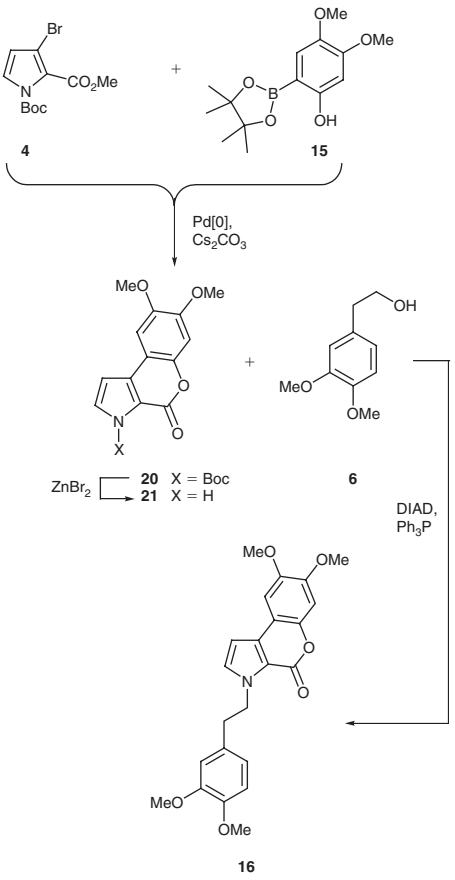


Scheme 4.

product. Nevertheless, sufficient quantities of compound **16** could be accumulated by this means to allow completion of the synthesis of ningalin B. Towards such ends, this material was brominated with NBS in DMF and the ensuing bromide **17** (97%) was then cross-coupled with the commercially available arylboronic acid **18**[13] in the presence of potassium carbonate and tetra-*n*-butylammonium bromide (TBAB) to give the previously reported[2] ningalin B permethyl ether **19** in 69% yield. Following a protocol established by Boger et al.,[2] treatment of this last compound with boron tribromide in dichloromethane at −78° to 18°C gave ningalin B **1** in 96% yield.

The ^{13}C and ^{1}H NMR spectral data derived from compounds **19** and **1** (Tables 1 and 2, respectively) compare very favourably with those reported previously. The slight variations between the carbon chemical shifts recorded for naturally derived ningalin B and those arising from the synthetic material can be attributed to the differing sample concentrations and solvent systems used to record the cited data.

In an effort to establish an improved synthesis of ningalin B, we investigated alternate points in the abovementioned reaction sequence at which the pivotal Suzuki–Miyaura cross-coupling reaction involving compound **15** could be carried out. In particular, the linking of substrates **4** and **15** by such means was studied (Scheme 5) and this allowed the preparation of lactone **20** in 55% yield. This was accompanied by ∼14% of the free pyrrole **21**. Removal of the Boc group within compound **20** was readily achieved in 84% yield using zinc bromide and the resulting pyrrole **21** was *N*-alkylated with alcohol **6**, under the same conditions used earlier to produce compound **7**, thus affording lactone **16** in 54% yield. Despite these efforts, the yield of compound **16** obtained using the route shown in Scheme 5 is only marginally better than that observed earlier (33% versus 27%).



Scheme 5.

Summary and Conclusions

A comparison of the key features of all the reported syntheses of ningalin B, including the one detailed herein, is provided in Table 3. The Steglich[9] and Bullington[7] syntheses are the shortest (each involves just four steps) and particularly notable for their efficiency. The Steglich synthesis[9] is remarkable for the rapidity with which the basic framework of the target compound is assembled but the Bullington approach is likely to be the more effective for preparing analogues of ningalin B in which the substituents on the C and D rings are different. It is also worth noting that the Bullington,[7] Boger,[2] and Gupton[8] syntheses share a common sequence of ring-forming events (Table 3) and that this is related to the one used by Steglich and coworkers. These involve a mid-stage pyrrole-forming step while the construction of the B-ring lactone is left to the end of the synthetic sequence. In contrast, the synthesis of target **1** reported herein starts with an intact pyrrole and uses this ring system as a template for introducing the remaining structural components of ningalin B. Although the present approach is not as efficient as some of the others described to date, it should be particularly useful for the preparation of ningalin B analogues in which the substitution patterns associated with the C, D, and E rings are quite different from one another.

Work directed towards exploitation of the present protocols for the preparation of biologically active analogues of ningalin B, especially permethyl ethers related to compound **19**,[2] is now under way in these laboratories. Results will be reported in due course.

Experimental

General Procedures

Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In certain cases, a Varian Inova 500 spectrometer, operating at 500 MHz for proton and 125 MHz for carbon nuclei, was used. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ_H) (multiplicity, coupling constant(s) J (Hz), relative integral) where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The residual $CHCl_3$ peak (δ 7.26), residual DMSO peak (δ 2.50) and the residual MeOH peak (δ 3.30) were used as references for ^{1}H NMR spectra. The central peak (δ 77.0) of the $CDCl_3$ 'triplet' and the central peak (δ 39.5) of the [D_6]DMSO 'heptet' were used as references for proton-decoupled ^{13}C NMR spectra. The data for ^{13}C NMR spectra are given as: chemical shift (δ_C), (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl. Assignments of signals observed in various NMR spectra were often assisted by conducting Attached Proton Test (APT) experiments. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series Fourier-transform (FT)-IR Spectrometer. Samples were analysed as thin films on NaCl plates. A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution EI mass spectra. Low- and high-resolution ESI mass spectra were obtained on a VG Quattro II triple-quadrupole

Table 1. Comparison of the ^{13}C NMR data recorded for naturally occurring ningalin B (1), synthetically derived 1, and permethyl ether 19

δ_C					
Natural **1**[A]	Synthetic **1** (present work)[B]	Synthetic **1** (Boger work)[C]	Synthetic **19** (present work)[D]	Synthetic **19** (Boger work)[E]	Synthetic **19** (Gupton work)[F]
156.0	155.2	155.0	155.7	155.7	155.5
146.8	146.4	146.2	149.2	149.2	149.1
146.0	145.6	145.4	149.1	149.1	148.9
145.9	145.5	145.3	149.0	149.0	148.8
145.8	145.4	145.2	148.7	148.7	148.6
145.5	145.1	144.9	148.0	148.0	147.8
144.4	144.2	144.0	146.4	146.4	146.2
142.9	142.5	142.3	145.8	145.8	145.6
133.5	133.1	133.0	132.2	132.1	131.9
130.2	129.6	129.4	130.8	130.7	130.6
127.6	126.8	126.6	127.4	127.4	127.2
126.4	125.8	125.6	126.9	126.9	126.7
120.6	121.2	121.0	122.3	122.3	122.1
120.0	120.1	119.9	121.1	121.1	120.0
117.7	119.6	119.4	119.3	119.3	119.1
116.9	117.4	117.2	115.1	115.1	114.9
116.4	116.7	116.4	113.2	113.2	113.1
116.1	116.2	116.0	112.2	112.3	112.1
114.8	116.0	115.8	111.4	111.4	111.3
112.7	114.4	114.2	111.2	111.2	111.1
110.6	110.1	109.9	110.7	110.6	110.4
109.3	109.0	108.8	104.9	104.9	104.8
104.0	103.9	103.7	100.8	100.8	100.6
50.9	50.4	50.2	56.4	56.3	56.1
37.9	37.6	37.4	56.3	56.2	56.0
			56.1(1) (1C)	56.1 (3C)	55.9
			56.1(0) (2C)		
			56.0	56.0	55.8
			51.3	51.3	51.0
			38.0	38.0	37.8

[A]Data from ref. [1] and recorded in 5:1 v/v [D_6]DMSO/CD_3OD at 125 MHz.
[B]Data arising from work reported in the present paper and recorded in 79% [D_6]DMSO/21% CD_3OD at 75 MHz.
[C]Data from ref. [2] and recorded in 83% [D_6]DMSO/17% CD_3OD at 100 MHz.
[D]Data arising from work reported in the present paper and recorded in $CDCl_3$ at 75 MHz.
[E]Data from ref. [2] and recorded in $CDCl_3$ at 100 MHz.
[F]Data from ref. [8] and recorded in $CDCl_3$ at 125 MHz.

MS instrument operating in positive ionization mode. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical TLC was performed on aluminium-backed 0.2-mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254-nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). The retardation factor (R_F) values cited here have been rounded at the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[15] using silica gel 60 (0.040–0.0063 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem, or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab chemical companies. Tetrahydrofuran (THF), dichloromethane, and diethyl ether were dried using a Glass Contour solvent purification system that is based on a technology originally described by Grubbs et al.[16] Methanol was distilled from its magnesium alkoxide salt. Where necessary, reactions were performed under a nitrogen atmosphere.

Synthetic Studies

Compound 7

DIAD (428 mg, 2.12 mmol) was added, dropwise, to a magnetically stirred solution of compound **5** (215 mg, 1.06 mmol), triphenylphosphine (556 mg, 2.12 mmol), and alcohol **6** (386 mg, 2.12 mol) in THF (10 mL) maintained at 18°C. The resulting solution was left stirring at this temperature for 15 h then concentrated, under reduced pressure, onto TLC-grade silica (1.5 g). The solid thus obtained was added to the top of a flash chromatography column that was then subjected to gradient elution (silica, CH_2Cl_2 → 9:1 v/v CH_2Cl_2/ethyl acetate gradient elution). Concentration of the appropriate fractions (R_F 0.5) then afforded carboxylate **7**[11] (291 mg, 75%) as a clear, colourless oil. The spectral data derived from this material were identical, in all respects, with those reported[11] for an authentic sample.

Table 2. Comparison of the ^{1}H NMR data recorded for naturally occurring ningalin B (1), synthetically derived 1, and permethyl ether 19

	δ_H				
Natural **1**[A]	Synthetic **1** (present work)[B]	Synthetic **1** (Boger work)[C]	Synthetic **19** (present work)[D]	Synthetic **19** (Boger work)[E]	Synthetic **19** (Gupton work)[F]
7.13 (s, 1H)	7.15 (s, 1H)	7.17 (s, 1H)	7.09 (s, 1H)	7.09 (s, 1H)	7.09 (s, 1H)
7.06 (s, 1H)	7.05 (s, 1H)	7.07 (s, 1H)	6.95–6.92 (m, 3H)	6.95–6.92 (m, 3H)	6.96–6.92 (m, 3H)
6.86 (d, *J* 8, 1H)	6.79 (d, *J* 8.1, 1H)	6.80 (d, *J* 8.2, 1H)	6.88 (br s, 1H)	6.88 (d, *J* 1.2, 1H)	6.88 (d, *J* 1.4, 1H)
6.84 (d, *J* 1.5, 1H)	6.76 (d, *J* 2.1, 1H)	6.77 (d, *J* 2.0, 1H)	6.79 (d, *J* 8.2, 1H)	6.79 (d, *J* 8.2, 1H)	6.79 (d, *J* 8, 1H)
6.80 (s, 1H)	6.74 (s, 1H)	6.75 (s, 1H)	6.74 (s, 1H)	6.74 (s, 1H)	6.74 (s, 1H)
6.70 (dd, *J* 8 and 1.5, 1H)	6.63 (dd, *J* 8.1 and 2.1, 1H)	6.63 (m, 2H)	6.71 (dd, *J* 8.2 and 1.8, 1H)	6.71 (dd, *J* 7.9 and 1.8, 1H)	6.70 (dd, *J* 8 and 2, 1H)
6.67 (d, *J* 8, 1H)	6.60 (d, *J* 8.1, 1H)		6.58 (d, *J* 1.8, 1H)	6.58 (d, *J* 1.5, 1H)	6.58 (d, *J* 1.5, 1H)
6.60 (d, *J* 1.5, 1H)	6.57 (d, *J* 2.1, 1H)	6.59 (d, *J* 1.8, 1H)	4.65 (t, *J* 7.0, 2H)	4.65 (t, *J* 7.0, 2H)	4.65 (t, *J* 7, 2H)
6.47 (dd, *J* 8 and 1.5, 1H)	6.41 (dd, *J* 8.1 and 1.5, 1H)	6.43 (dd, *J* 7.9 and 2.1, 1H)	3.93 (s, 3H)	3.93 (s, 3H)	3.92 (s, 3H)
4.55 (t, *J* 7.3, 2H)	4.47 (t, *J* 7.2, 2H)	4.54 (t, *J* 7.0, 2H)	3.91 (s, 3H)	3.91 (s, 3H)	3.90 (s, 3H)
2.94 (t, *J* 7.3, 2H)	2.85 (t, *J* 7.2, 2H)	2.92 (t, *J* 7.4, 2H)	3.87 (s, 3H)	3.87 (s, 3H)	3.87 (s, 3H)
–	–	–	3.85 (s, 3H)	3.85 (s, 3H)	3.84 (s, 3H)
–	–	–	3.77 (s, 3H)	3.77 (s, 3H)	3.76 (s, 3H)
–	–	–	3.57 (s, 3H)	3.57 (s, 3H)	3.56 (s, 3H)
–	–	–	3.11 (t, *J* 7.0, 2H)	3.11 (t, *J* 7.0, 2H)	3.07 (t, *J* 7, 2H)

[A]Data from ref. [1] and recorded in 5:1 v/v [D_6]DMSO/CD_3OD at 500 MHz.
[B]Data arising from work reported in the present paper and recorded in 79% [D_6]DMSO/21% CD_3OD at 300 MHz.
[C]Data from ref. [2] and recorded in 83% [D_6]DMSO/17% CD_3OD at 400 MHz.
[D]Data arising from work reported in the present paper and recorded in $CDCl_3$ at 75 MHz.
[E]Data from ref. [2] and recorded in $CDCl_3$ at 400 MHz.
[F]Data from ref. [8] and recorded in $CDCl_3$ at 500 MHz.

Table 3. Comparison of key features associated with the six reported syntheses of ningalin B

Lead author	Publication date	Ring-forming sequence[A]	Longest linear sequence	Overall yield [%]	Permethyl ether **19** as precursor to **1**
Boger[2]	2000	C+D→CD→ →CDA→CDAE→CDAEB	Nine steps	16	Yes
Bullington[7]	2002	CD+A→CDA→CDAE→CDAEB	Four steps	41[B]	No
Iwao[6]	2003	E→EA→EACD→EACDB	Nine steps	11	Yes
Gupton[8]	2003	CD→CDA→CDAE→CDAEB	Seven steps	13	Yes
Steglich[9]	2006	C+D+E→CDAE→CDAEB	Four steps	52	Yes
Present work	2009	A+E→AE+C→AECB→AECBD	Seven steps[C]	17	Yes

[A]See Fig. 1 for labelling of the ring system associated with ningalin B.
[B]For the purposes of this calculation it has been assumed that the first step of the sequence leading to the required α,β-unsaturated nitrile proceeds in 80% yield.
[C]Step count starts from compound **5**.

Compound ***9***

A mixture of pyrrole **7** (45 mg, 0.12 mmol) in THF/water (2.0 mL of a 3:1 v/v mixture), boronic ester **8**[13] (81 mg, 0.37 mmol), K_2CO_3 (85 mg, 0.62 mmol), TBAB (8 mg, 20 mol-%), and $Pd(PPh_3)_4$ (7 mg, 5 mol-%) was irradiated in a microwave reactor at 70°C for 1 h. The cooled reaction mixture was diluted with water (40 mL) and ethyl acetate (50 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 40 mL) and the combined organic phases were washed with brine (1 × 20 mL), then dried (Na_2SO_4), before being filtered and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions (R_F 0.2) gave compound **9** (34 mg, 79%) as white crystalline solid. The spectral data derived from this material were identical, in all respects, with those reported[11] for an authentic sample.

Compound ***10***

A magnetically stirred solution of pyrrole **9** (68 mg, 0.095 mmol) in DMF (2 mL) was cooled to 0°C then treated, in one portion, with NBS (36 mg, 0.2 mmol) and the ensuing mixture was allowed to warm to 18°C. After stirring at this temperature for 18 h, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (4 × 40 mL). The combined organic phases were washed with water (1 × 40 mL) and brine (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 3:1 → 1:2 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_F 0.3 in 1:2 v/v pentane/diethyl ether) gave a crystalline solid. Recrystallization (pentane/diethyl ether) of this material afforded compound **10** (62 mg, 74%) as a white, crystalline solid, mp 142–153°C (Found: $M^{+\bullet}$, 427.0417. $C_{21}H_{18}{}^{79}BrNO_4$ requires $M^{+\bullet}$, 427.0419). δ_H (300 MHz, $CDCl_3$) 8.55 (d, *J* 8.3, 1H), 7.40 (m, 2H), 7.30 (m, 1H), 6.89 (s, 1H), 6.77 (d, *J* 8.1, 1H), 6.66 (dd, *J* 8.1 and 1.8, 1H), 6.58 (d, *J* 1.8, 1H), 4.61 (t, *J* 6.9, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.05 (t, *J* 6.9, 2H). δ_C (75 MHz, $CDCl_3$) 154.4, 151.4, 149.2, 148.1, 132.9, 130.1, 128.6, 126.7, 124.3, 122.9, 121.1, 117.6, 117.4, 116.2, 112.1, 111.5, 90.5, 56.1, 56.0, 51.5, 37.9. ν_{max}(NaCl)/cm^{-1} 3119, 2999, 2955, 2834, 1717, 1612, 1591, 1516, 1447, 1377, 1262, 1236, 1157, 1050, 1028, 964, 805, 766, 751, 733. *m/z* (EI, 70 eV) 429 and 427 ($M^{+\bullet}$, 26%), 164 (100), 151 (48).

Compound ***12***

Acetal **12** was prepared in near-quantitative yield from phenol **11** according to the method of Handy et al.[14] The spectral data recorded on product **12** matched those reported previously.[14]

Compound ***13***

Bromide **13** was prepared in ~83% yield from acetal **12** according to the method of Handy et al.[14] The spectral data recorded on product **13** matched those reported previously.[14]

Compound ***15***

n-Butyllithium (1.6 M solution in hexane, 7.1 mL, 11.4 mmol) was added dropwise over 0.25 h to a magnetically stirred solution of compound **13** (2.79 g, 8.80 mmol) and tri-isopropyl borate (2.21 mL, 9.62 mmol) in THF (70 mL) maintained at −78°C, and stirring was continued at this temperature for 0.66 h. The reaction mixture was then allowed to warm to 18°C over 12 h. After the addition of HCl (20 mL of a 1 M aqueous solution) and stirring for another 0.5 h, the phases were separated and the aqueous one was diluted with brine (20 mL) and extracted with THF (3 × 50 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow, mud-like solid (2.12 g). This solid was dissolved in diethyl ether (80 mL). Then pinacol (1.78 g, 15.1 mmol) was added and the ensuing slurry was stirred magnetically for 24 h. Concentration of the resulting mixture under reduced pressure, subjection of the residue thus obtained to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane → ethyl acetate gradient elution) and concentration of the appropriate fractions (R_F 0.6 in ethyl acetate) afforded compound **15** (1.70 g, 69% over three steps) as a clear, colourless oil (Found: $M^{+\bullet}$, 280.1483. $C_{14}H_{21}BO_5$ requires $M^{+\bullet}$, 280.1482). δ_H (300 MHz, $CDCl_3$) 7.65 (s, 1H), 6.99 (s, 1H), 6.44 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 1.35 (s, 12H). δ_C (75 MHz, $CDCl_3$) 159.8 (C), 154.1 (C), 142.7 (C), 116.4 (CH), 99.7 (CH), 84.5 (C), 56.6 (CH_3), 56.0 (CH_3), 25.0 (CH_3) (one signal obscured or overlapping). ν_{max}(NaCl)/cm^{-1} 3447, 2978, 2936, 1622, 1511, 1459, 1414, 1387, 1300, 1250, 1237, 1211, 1158, 1140, 992, 859. *m/z* (EI, 70 eV) 280 ($M^{+\bullet}$, 80%), 223 (42), 180 (100), 165 (55), 129 (78), 85 (55).

Compound ***16***

A solution of pyrrole **7** (23 mg, 0.06 mmol), caesium carbonate (102 mg, 0.31 mmol), TBAB (4 mg, 0.01 mmol, 20 mol-%), and compound **15** (61 mg, 0.22 mmol) in THF/H_2O (0.5 mL of 4:1 v/v mixture) was placed in a glass reaction tube that was flushed with nitrogen. $(PPh_3)_4Pd$ (7 mg, 0.01 mmol, 10 mol-%) was then added to the tube which was flushed with nitrogen once more then sealed and the resulting mixture subjected to microwave irradiation (150 W, 80°C, 1 min ramp time) for 2 h. To effect full conversion, the cooled reaction mixture was treated with further aliquots of boronic ester **15**, caesium carbonate, and $(PPh_3)_4Pd$ (same amounts as above). The resulting mixture was irradiated under the abovementioned conditions for another 2 h then cooled, diluted with H_2O (30 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → diethyl ether gradient elution) and concentration of the appropriate fractions (R_F 0.2 in 1:3 v/v pentane/diethyl ether) afforded a white solid. Recrystallization of this material (pentane/diethyl ether) afforded the title compound **16** (11 mg, 43%) as white prisms, mp 159–160°C (Found: $M^{+\bullet}$, 409.1527. $C_{23}H_{23}NO_6$ requires $M^{+\bullet}$, 409.1525). δ_H (300 MHz, $CDCl_3$) 7.08 (s, 1H), 6.92 (s, 1H), 6.82 (d, *J* 2.7, 1H), 6.75 (d, *J* 8.1, 1H), 6.63 (dd, *J* 8.1 and 2.1, 1H), 6.56 (d, *J* 2.1, 1H), 6.42 (d, *J* 2.7, 1H), 4.60 (t, *J* 6.9, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.07 (t, *J* 6.9, 2H). δ_C (75 MHz, $CDCl_3$) 155.6 (C), 149.6 (C), 149.1 (C), 147.9 (C), 146.5 (C), 146.4 (C), 133.1 (CH), 131.4 (C), 130.7 (C), 121.1 (CH), 115.1 (C), 112.2 (CH), 111.4 (CH), 110.4 (C), 104.3 (CH), 100.9 (CH), 100.7 (CH), 56.6 (CH_3), 56.4 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 51.2 (CH_2), 38.0 (CH_2). ν_{max}(NaCl)/cm^{-1} 2936, 1705, 1516, 1426, 1261, 1236, 1205, 1192, 1155, 1066, 1029,

1004. *m/z* (EI, 70 eV) 409 ($M^{+\bullet}$, 100%), 258 (28), 245 (76), 164 (40), 151 (53).

*Compound **17***

N-Bromosuccinimide (12 mg, 0.07 mmol) was added, in one portion, to a magnetically stirred solution of compound **16** (13 mg, 0.03 mmol) in anhydrous DMF (0.3 mL) maintained at 0°C. The ensuing mixture was allowed to warm to 18°C, stirred at this temperature for 4 h, then diluted with H_2O (10 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with H_2O (1 × 30 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:3 → 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_F 0.3 in 1:1 v/v ethyl acetate/hexane) afforded bromide **17** (15 mg, 97%) as a white solid, mp 142–144°C (Found: $M^{+\bullet}$, 487.0639. $C_{23}H_{22}BrNO_6$ requires $M^{+\bullet}$, 487.0630). δ_H (300 MHz, $CDCl_3$) 8.02 (s, 1H), 6.93 (s, 1H), 6.89 (s, 1H), 6.78 (d, *J* 8.1, 1H), 6.65 (dd, *J* 8.1 and 1.5, 1H), 6.59 (d, *J* 1.5, 1H), 4.61 (t, *J* 6.9, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.06 (t, *J* 6.9, 2H). δ_C (75 MHz, $CDCl_3$) 154.7 (CO), 149.8 (C), 149.2 (C), 148.1 (C), 146.4 (C), 146.1 (C), 132.8 (CH), 130.2 (CH), 127.3 (C), 121.1 (CH), 115.3 (C), 112.1 (CH), 111.4 (CH), 109.7 (C), 104.0 (C), 100.7 (CH), 89.5 (C), 56.5 (CH_3), 56.4 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 51.5 (CH_2), 38.0 (CH_2). ν_{max}(NaCl)/cm^{-1} 2925, 1711, 1516, 1463, 1414, 1263, 1221, 1157, 1115, 1029, 1012, 966. *m/z* (EI, 70 eV) 489 and 487 ($M^{+\bullet}$, 70 and 69%), 323 and 321 (73 and 74), 164 (100), 151 (95).

*Ningalin B Permethyl Ether **19***

A mixture of pyrrole **17** (26 mg, 0.05 mmol), boronic acid **18**[13] (29 mg, 0.11 mmol), K_2CO_3 (37 mg, 0.19 mmol), TBAB (3 mg, 20 mol-%), and $Pd(PPh_3)_4$ (6 mg, 10 mol-%) in THF/water (0.65 mL of a 4:1 v/v mixture) was irradiated at 80°C for 1 h in a microwave reactor. The cooled reaction mixture was diluted with water (20 mL) and ethyl acetate (20 mL) then the separated aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, dichloromethane → 9:1 v/v dichloromethane/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_F 0.3 in 1:9 v/v dichloromethane/ethyl acetate) gave a white, crystalline solid. Recrystallization (ethyl acetate/hexane) of this material afforded compound **19** (20 mg, 69%) as a white crystalline solid, mp 190–191°C (lit.[2] mp 186–187°C) (Found: $M^{+\bullet}$, 545.2050. $C_{31}H_{31}NO_8$ requires $M^{+\bullet}$, 545.2050). δ_H (300 MHz, $CDCl_3$) see Table 2. δ_C (75 MHz, $CDCl_3$) see Table 1. ν_{max}(NaCl)/cm^{-1} 2927, 1709, 1515, 1464, 1415, 1259, 1244, 1174, 1139, 1027, 731. *m/z* (EI, 70 eV) 545 ($M^{+\bullet}$, 100%), 394 (50), 381 (73).

*Ningalin B (**1**)*

Following the procedure detailed by Boger et al.,[2] a magnetically stirred solution of compound **19** (17 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) maintained under nitrogen was cooled to −78°C, then treated with BBr_3 (0.23 mL of a 2 M solution in hexane, 0.47 mmol) and the ensuing mixture then allowed to warm to 18°C over 16 h. The reaction mixture was then diluted with methanol (1.5 mL) and concentrated under reduced pressure to give ningalin B (14 mg, 96%) as an amorphous and dark-yellow solid (Found: $[M + H]^+$, 462.1182. $C_{25}H_{19}NO_8$ requires $[M + H]^+$, 462.1189). δ_H (300 MHz, $CDCl_3$) see Table 2. δ_C (75 MHz, $CDCl_3$) see Table 1. ν_{max}(NaCl)/cm^{-1} 2920, 1601. *m/z* (ESI) 484 ($[M + Na]^+$, 16%), 484 ($[M + H]^+$, 85), 279 (100), 149 (20).

*Compound **20***

A solution of pyrrole **4** (27 mg, 0.09 mmol) in THF/H_2O (0.6 mL of 5:1 v/v mixture) was treated with caesium carbonate (145 mg, 0.45 mmol), TBAB (6 mg, 0.02 mmol, 20 mol-%), and boronate ester **15** (94 mg, 0.37 mmol). The resulting mixture was flushed with nitrogen then $(PPh_3)_4Pd$ (11 mg, 0.01 mmol, 11 mol-%) was added and the reaction vessel again flushed with nitrogen then sealed. The reaction mixture was subjected to microwave irradiation (150 W, 70°C, 1 min ramp time) for 1 h then cooled and further portions of boronate **15** (80 mg, 0.29 mmol), caesium carbonate (128 mg, 0.39 mmol) and $(PPh_3)_4Pd$ (10 mg, 0.01 mmol, 10 mol-%) were added. The resulting mixture was, once again, irradiated under the abovementioned conditions for 1 h. The cooled reaction mixture was then diluted with H_2O (50 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, CH_2Cl_2 → 9:1 v/v CH_2Cl_2/ethyl acetate gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_F 0.5 in 9:1 v/v CH_2Cl_2/ethyl acetate) afforded carboxylate **20** (17 mg, 55%) as a white solid, no melting point, decomposition above 250°C (Found: $M^{+\bullet}$, 345.1212. $C_{18}H_{19}NO_6$ requires $M^{+\bullet}$, 345.1212). δ_H (300 MHz, $CDCl_3$) 7.75 (d, *J* 3.3, 1H), 7.09 (s, 1H), 6.90 (s, 1H), 6.66 (d, *J* 3.3, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 1.67 (s, 9H). δ_C (75 MHz, $CDCl_3$) 152.9 (C), 150.9 (C), 148.0 (C), 147.6 (C), 146.5 (C), 136.5 (C), 132.6 (CH), 115.8 (C), 108.8 (C), 104.5 (CH), 104.3 (CH), 100.5 (CH), 86.1 (C), 56.6 (CH_3), 56.5 (CH_3), 28.0 (CH_3). ν_{max}(NaCl)/cm^{-1} 1735, 152, 1453, 1406, 1339, 1270, 1224, 1158, 995, 847. *m/z* (EI, 70 eV) 345 ($M^{+\bullet}$, 10%), 245 (90), 205 (88), 154 (100), 139 (75), 129 (57), 57 (62).

Concentration of fraction B (R_F 0.3 in 9:1 v/v CH_2Cl_2/ethyl acetate) afforded compound **21** (3 mg, 14%) as a white solid, no melting point, decomposition above 250°C (Found: $M^{+\bullet}$, 245.0688. $C_{13}H_{11}NO_4$ requires $M^{+\bullet}$, 245.0688). δ_H (300 MHz, $CDCl_3$) 9.98 (br s, NH, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 6.68 (2, 1H), 3.99 (s, 3H), 3.94 (s, 3H). δ_C (75 MHz, $CDCl_3$) 156.3 (C), 149.7 (C), 146.7 (C), 146.3 (C), 130.7 (C), 129.0 (CH), 116.5 (C), 110.4 (CH), 104.6 (CH), 103.0 (CH), 101.1 (CH), 56.6 (CH_3), 56.4 (CH_3). ν_{max}(NaCl)/cm^{-1} 3242, 2919, 1722, 1625, 1535, 1498, 1446, 1421, 1296, 1261, 1222, 1187, 1155, 1109, 1065, 1006, 772. *m/z* (EI, 70 eV) 245 ($M^{+\bullet}$, 100%), 230 (25), 129 (35), 85 (40), 69 (34).

*Compound **21***

Zinc bromide (20 mg, 0.087 mmol) was added to a magnetically stirred solution of pyrrole **20** (10 mg, 0.029 mmol) in CH_2Cl_2 (2 mL) maintained under nitrogen at 18°C. After 2.5 h the reaction mixture was treated with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) before being dried (Na_2SO_4),

filtered, and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 3:1 v/v pentane/diethyl ether → diethyl ether → 1:1 v/v diethyl ether/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_F 0.3 in diethyl ether) afforded compound **21** (6 mg, 84%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample of compound **21** obtained via the procedure described immediately above.

*Compound **16***

DIAD (22 mg, 0.11 mmol) was added dropwise to a magnetically stirred solution of compound **21** (18 mg, 0.073 mmol), triphenylphosphine (29 mg, 0.11 mmol), and alcohol **6** (20 mg, 0.11 mmol) in THF (1 mL) maintained at 18°C. The resulting solution was left stirring at this temperature for 15 h then, so as to ensure complete conversion, the same quantities of DIAD and triphenylphosphine specified above were again added to the reaction mixture. This was allowed to stir at 18°C for a further 15 h then concentrated under reduced pressure onto TLC-grade silica gel (0.4 g). The free-flowing solid thus obtained was added to the top of a flash chromatography column. Elution of the column (with 3:1 v/v pentane/diethyl ether → diethyl ether gradient elution) and concentration of the appropriate fractions (R_F 0.3 in diethyl ether) afforded lactone **16** (16 mg, 54%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample of compound **16** obtained via the procedure described above.

*X-Ray Crystallographic Studies on Compounds **10** and **16***

Crystal Data

Compound **10**: $C_{21}H_{18}BrNO_4$, $M = 428.28$, $T = 200(1)$ K, triclinic, space group $P\bar{1}$, $Z = 2$, $a = 7.3505(3)$, $b = 8.9299(4)$, $c = 14.1446(7)$ Å, $\alpha = 97.197(2)°$, $\beta = 96.320(3)°$, $\gamma = 93.102(3)°$, $V = 913.36(7)$ Å^3, $D_x = 1.557$ g cm^{-3}, 4201 unique data ($2\theta_{max} = 55.2°$); $R = 0.037$ (for 3120 reflections with $I > 2.0\sigma(I)$), $Rw = 0.082$ (all data), $S = 0.93$.

Compound **16**: $C_{23}H_{23}NO_6$, $M = 409.44$, $T = 200$ K, monoclinic, space group $C2/c$, $Z = 8$, $a = 33.6193(7)$, $b = 7.24830(10)$, $c = 16.4673(3)$ Å, $\beta = 95.6376(12)°$, $V = 3993.39(12)$ Å^3, $D_x = 1.362$ g cm^{-3}, 4609 unique data ($2\theta_{max} = 55.2°$); $R = 0.035$ (for 2895 reflections with $I > 2.0\sigma(I)$), $Rw = 0.083$ (all data), $S = 0.79$.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ 0.71073 Å) and the data extracted using the *DENZO* package.[17] The structure solutions were by direct methods (SIR92).[18] The structures of compounds **10** and **16** were refined using the *CRYSTALS* program package.[19] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC numbers 723557 and 723558 for compounds **10** and **16**, respectively). These data can be obtained free-of-charge from www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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