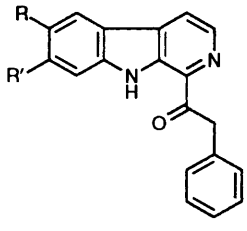
Diastereoselective Pictet–Spengler Reactions of L-(Boc)Phenylalaninal and L-(Boc)Prolinal: Biomimetic Syntheses of Eudistomin T and (−)-Woodinine[1]

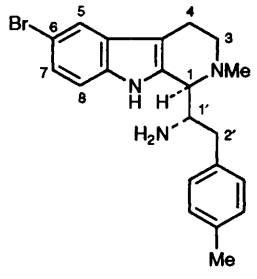
James McNulty and Ian W. J. Still*
J. Tuzo Wilson Research Laboratories, Erindale Campus, University of Toronto in Mississauga, Mississauga, Ontario, Canada L5L 1C6

The diastereoselective Pictet–Spengler reaction of L-(Boc)phenylalaninal with tryptamine and the elaboration of this intermediate to the antibacterial compound eudistomin T and analogues of the antileukaemic compound eudistomidin B are described. We also report an efficient synthesis of the naturally occurring alkaloid (−)-woodinine from L-(Boc)prolinal and 5-bromotryptamine in three steps, using a diastereoselective Pictet–Spengler reaction. This approach affords, in addition, formal syntheses of the marine alkaloids eudistomins H and I.

Marine tunicates have proved to be a rich source of secondary metabolites possessing interesting antiviral, antibacterial and other biological activities. Since the initial reports by Rinehart *et al.*[2] in 1984 of the isolation of 17 indole-containing alkaloids, named eudistomins, from the tunicate *Eudistoma olivaceum*, there has been widespread interest in the isolation and structure determination of further metabolites from this[3] and several closely related species.[4–6] Structural analysis of the eudistomins and related compounds reveals that they may be derived *in vivo* from tryptophan and another amino acid such as cysteine, proline, leucine or phenylalanine, those originating from phenylalanine being exemplified by eudistomins R, S and T **1a–c** and by the C-methylated analogue eudistomidin B **2**.

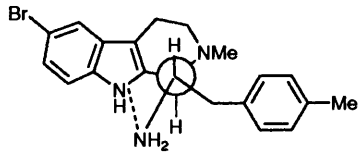


	R	R′
1a;	H	Br
b;	Br	H
c;	H	H



2

We have been interested in developing a reliable general route to the eudistomins following this proposed biomimetic route.[7] We were also intrigued by the structure of the antileukaemic compound eudistomidin B **2**[4a] which, although appearing to be derived from an L-phenylalanine analogue, was shown to have the opposite configuration at C-1 to that expected from previous studies of the Pictet–Spengler reaction[7] and, indeed, the opposite configuration (α-H) at C-1 to that encountered in apparently related marine natural products, such as the antibiotic woodinine.[5a,7a] The configuration of the natural eudistomidin B has been established by the circular dichroic (CD) and ^{1}H NMR spectra[4a] and the molecule probably exists in the hydrogen-bonded conformation shown. We felt it desirable to confirm the stereochemistry of compound **2** by synthetic means. We also report here a new, improved synthesis of the related antibacterial compound eudistomin T **1c** and provide details of our successful synthesis of (−)-woodinine.[7a]



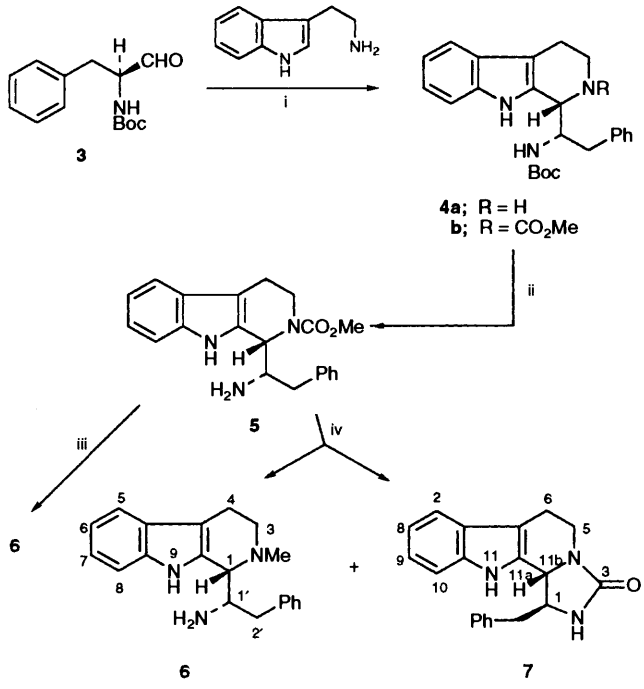
2

Results and Discussion

We initially set out to confirm that the Pictet–Spengler reaction with L-(Boc)phenylalaninal and tryptamine does, as with L-(Boc)prolinal,[7a] lead to the β C-1 hydrogen diastereoisomer and if necessary, to attempt to alter the diastereoselectivity of this reaction to open up a route for the synthesis of eudistomidin B **2**. We believed that the *para*-methyl substituent on the phenylalanine unit in compound **2** and the bromo substituent in the ring A portion would not interfere significantly with the diastereoselectivity observed and so our initial work was performed using the unsubstituted model series.

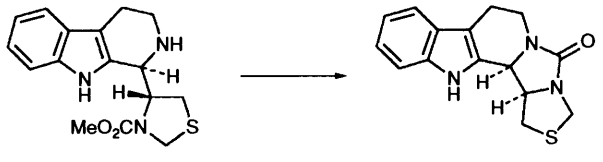
The required L-(Boc)phenylalaninal **3** was prepared by diisobutylaluminium hydride (DIBAL-H) reduction of the corresponding methyl ester.[8] Pictet–Spengler condensation was performed by the addition of two mole equivalents of trifluoroacetic acid (TFA) to a cooled equimolar solution of aldehyde **3** and tryptamine in CH_2Cl_2, followed by neutralization with triethylamine, to give the β-carboline compound **4a** quantitatively as a foam (Scheme 1). ^{1}H NMR analysis showed the product to be highly enriched (>95%) in one diastereoisomer and hence subsequent steps were carried out without extensive purification. Reaction of secondary amine **4a** with methyl chloroformate to give carbamate **4b**, followed by acid-catalysed removal of the Boc group, both steps being conducted at 25 °C, gave amino carbamate **5** in 98% overall yield (Scheme 1).

The reduction of carbamate **5** showed an interesting solvent dependence. Thus, reduction in refluxing tetrahydrofuran (THF) with $LiAlH_4$ gave a mixture of two compounds (94%) in the ratio 2:1. The major product proved to be the expected compound **6** (see below). The minor product was assigned the imidazolidin-2-one structure **7** on the basis of its spectral data: compound **7** was a solid, fully characterized by IR, ^{1}H and ^{13}C NMR, and mass spectral analyses. The C-1 hydrogen in tetracycle **7** appeared as a doublet at δ 4.77 (*J* 6.0 Hz), shifting to δ 4.97 (*J* 7.6 Hz) upon addition of 10% CF_3CO_2D,



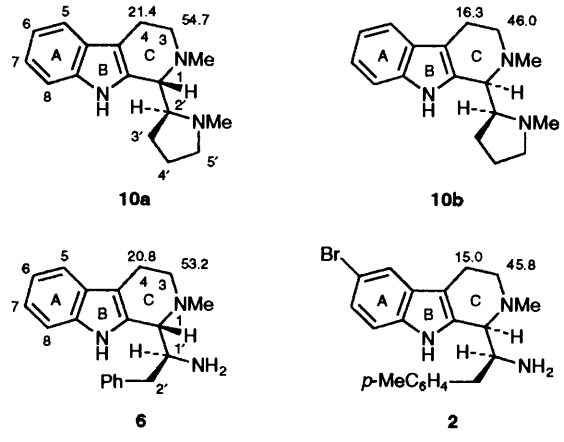
Scheme 1 *Reagents and conditions:* i, CH_2Cl_2, −78 °C, TFA; ii, HCl, MeOH; iii, $LiAlH_4$, Et_2O; iv, $LiAlH_4$, THF. Boc = Bu^{t}OCO; systematic numbering is used for compound **7**, for alternative numbering see Experimental section.

suggesting a *trans* 1-H, 1′-H relationship * and therefore a β C-1 hydrogen.[4a,9] Compound **7** was optically active and the ^{13}C NMR signal at δ 160.3 ppm and the IR carbonyl band at ν 1680 cm^{-1} strongly confirmed the cyclic urea structure. We have shown that formation of tetracycle **7** from carbamate **5** requires the presence of $LiAlH_4$ and is not therefore the result of a purely thermal cyclization. A similar cyclization (without the use of $LiAlH_4$) involving the conversion of the thiazolidine **8** into the cyclic urea **9** in boiling aq. acetic acid has been reported.[10]

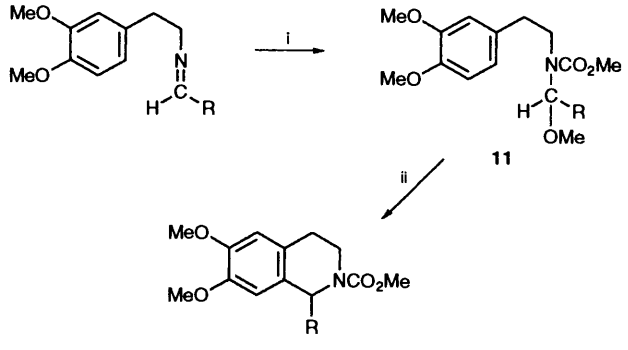


Reagents and conditions: aq. AcOH, reflux

Reduction of carbamate **5** with $LiAlH_4$ in refluxing diethyl ether on the other hand gave only compound **6**. ^1H NMR analysis of the crude product (92% yield) indicated the presence of only trace (< 2%) impurities. No signals attributable to the C-1 α-epimer were observed after purification of compound **6** by flash chromatography. The crystalline compound (70% yield) was optically active and showed a doublet at δ 3.44 (*J* 4.0 Hz) in the ^1H NMR spectrum, which we attribute to the C-1 proton. By analogy with our findings in the L-(Boc)prolinal study,[7a] which were confirmed recently by Mahboobi *et al.*,[11] and in contrast to the much larger coupling reported[4a] for the C-1 hydrogen in eudistomidin B, we conclude that the dominant stereoisomer, not only in compound **6** but, by extrapolation, in compounds **4** and **5** (Scheme 1) also, has a β C-1 hydrogen. In fact, the diastereoselectivity (estimated by ^1H NMR analysis to be at least 95%) which we observe in the L-phenylalanine series is significantly greater than that observed in our L-prolinal work.[7a] Interesting corroboration of these assignments of the C-1 configuration comes from the ^{13}C NMR chemical-shift data for C-3 and C-4 in compound **6** and in debromowoodinine[7a] **10a**. The values for the two β C-1 diastereoisomers (**6**, **10a**) are clearly self-consistent and contrast sharply with the corresponding values shown for *epi*-debromowoodinine **10b**[7c] and eudistomidin B **2**.[4a] It follows that ring C adopts quite different conformations in the α- and the β-series of diastereoisomers. The ^1H and ^{13}C NMR data obtained in these preliminary synthetic studies appear to corroborate the configurational assignment proposed by Kobayashi *et al.*[4a] for eudistomidin B **2**. We are currently exploring a different synthetic pathway to compound **2**.



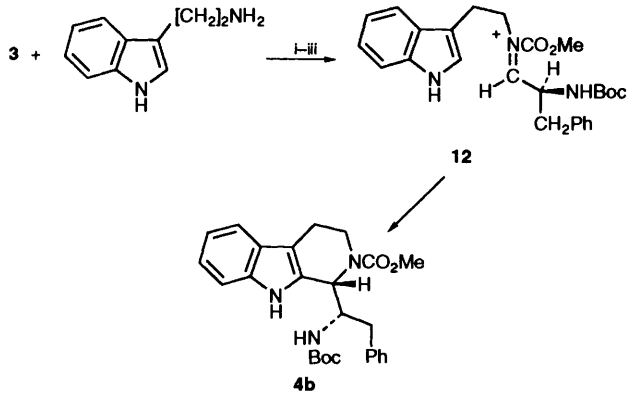
After we had performed these experiments, a publication appeared[12] reporting an interesting Lewis acid-promoted cyclization. These workers used methyl chloroformate in methanol to generate the *N*-(α-methoxyalkyl)-*N*-(alkoxycarbonyl)amine **11** from the preformed imine. Treatment of compound **11** with a Lewis acid such as titanium(IV) chloride or trimethylsilyl triflate (TMSOTf) generated an acyliminium species, which cyclized to form the 1,2,3,4-tetrahydroisoquinoline as shown in Scheme 2.



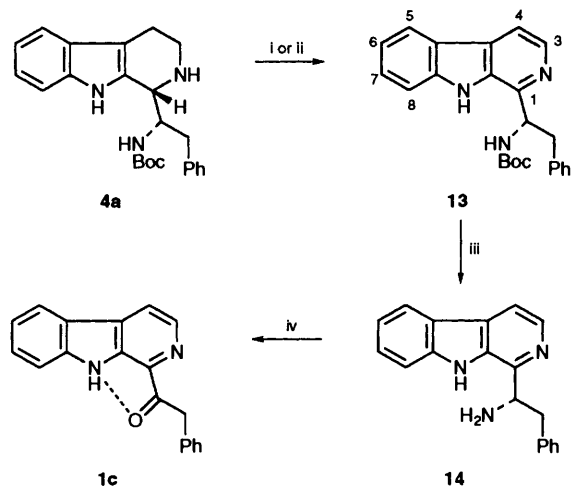
Scheme 2 *Reagents:* i, $ClCO_2Me$, MeOH; ii, Lewis acid

We have extended this reaction to our tetrahydro-β-carboline case. Thus, a mixture of aldehyde **3** and tryptamine was allowed to react with sodium acetate in methanol to form the expected imine:[13] this was subsequently treated with methyl chloroformate in methanol and triethylamine and finally with the Lewis acid *tert*-butyldimethylsilyl triflate (TBDMSOTf) (Scheme 3), to give the cyclized product (100% mass balance), *via* the presumed intermediate **12**. This procedure provided additional synthetic promise since the next step in our Pictet–Spengler approach, that of introducing the (*N*-2)-methoxy-

* Actually 11b-H, 1-H: the alternative numbering more clearly identifies analogous centres in **6** and the precursor molecules (see also Experimental section).



Scheme 3 *Reagents:* i, NaOAc, MeOH; ii, $ClCO_2Me$, Et_3N; iii, TBDMSOTf



Scheme 4 *Reagents and conditions:* i, Pd/C, 200–210 °C; ii, S_8, 200–210 °C; iii, TFA, CH_2Cl_2, 25 °C; iv, NaOCl

carbonyl substituent (see Scheme 1), would already have been effected. Removal of the Boc group from the cyclized product and reduction ($LiAlH_4$, Et_2O), however, led ultimately to the formation of compound **6** as the only cyclized product, with no detectable signals (400 MHz ^1H NMR) for the α C-1 hydrogen isomer, and hence to the conclusion that only compound **4b** was formed in the cyclization step. Despite this disappointment we have successfully achieved the synthesis of a 1,2,3,4-tetrahydro-β-carboline derivative with useful (N-2) functionalization, using this very mild procedure. While clearly not a suitable approach towards eudistomidin B itself, this strategy promises to be useful in providing structural analogues of the natural product. Interestingly, we have also found that neither the carbamate **5** nor compound **6** itself epimerize to the α 1-H isomer when treated with TFA, in contrast to a related epimerization reported for alkaloids of the yohimboid type.[14]

Returning to our second goal of seeking an improved synthetic route to eudistomin T **1c**, we next attempted to carry out the dehydrogenation of the 1,2,3,4-tetrahydro-β-carboline **4a**. This reaction was not as straightforward as had been that in our earlier work on the analogous proline-derived adducts.[7a] Thus, refluxing of compound **4a** with Pd/C in xylenes did not lead to any dehydrogenation (only starting material was isolated), whilst attempted reaction using elemental sulfur led to considerable decomposition. After many attempts it was found that the reaction could be carried out successfully by treatment with either Pd/C or elemental sulfur *without solvent* at ~200 °C for a few minutes. ^1H NMR analysis showed that loss of the Boc group occurred if these conditions were not strictly followed. The reaction with sulfur[15] gave the optically active β-carboline **13** (Scheme 4). Purification of this product, however, was quite troublesome due to the presence of a highly odoriferous side product: the maximum yield of pure compound **13** obtainable was ~35%. The reaction with Pd/C[16] was much superior in this respect but gave *racemic* compound **13**, in yields of 65–70%. Compound **13** had spectral data in complete accord with those expected. The ^1H NMR spectrum, for example, showed the characteristic pair of doublets at δ 8.36 and 7.84 (*J* 5.2 Hz) for the aromatic ring C (3-H and 4-H) hydrogens and the FTIR spectrum showed the urethane C=O stretch at 1669 cm^{-1}.

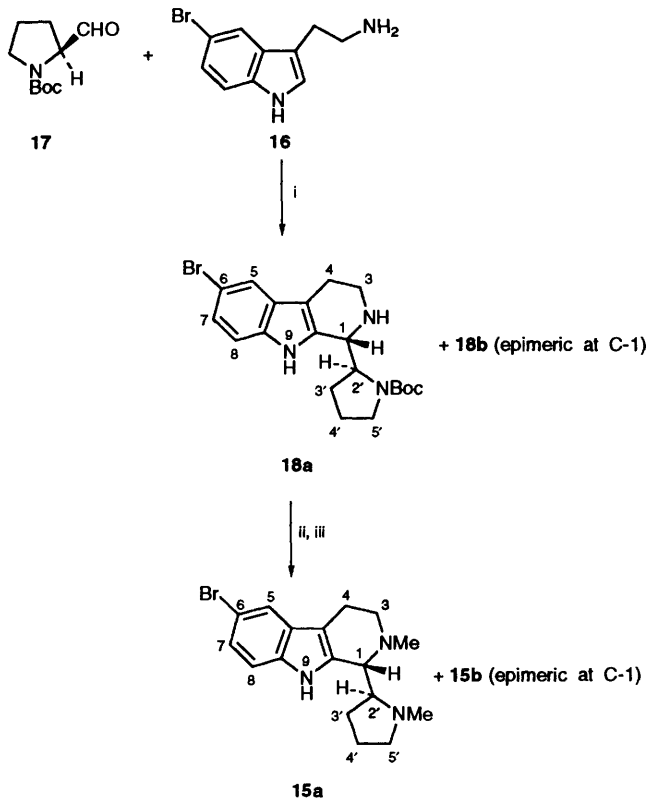
Removal of the Boc protecting group from compound **13** proceeded as expected, using TFA as catalyst, to give compound **14** in 96% yield. Several methods are available for the oxidation of a primary or secondary amine to the carbonyl compound.[17] The reaction usually proceeds by dehydrogenation to the imine, followed by hydrolysis to the carbonyl compound. Following a closely related literature precedent,[2c] compound **14** was successfully oxidized with sodium hypochlorite. The product required chromatographic purification but the first fraction off the column contained eudistomin T **1c** in 59% yield. Subsequent fractions contained unidentifiable side products. The spectra of the major product were identical in all respects with those of the natural product[3] and with those observed for the material previously synthesized by us[18] and by others.[19] The overall yield of eudistomin T obtained by this four-step route is close to 40% but, perhaps more importantly, the intermediacy of compound **4a** makes this route a potentially versatile, biomimetic strategy for the synthesis of phenylalanine-derived eudistomins and their analogues with either saturated or unsaturated ring-C units. Although we ourselves have not carried out these extensions of our method, there appears to be no reason why syntheses of the analogous eudistomins R and S (**1a** and **1b**) could not be readily achieved using the appropriate bromotryptamine as the precursor.

The next synthetic target for our investigation was the alkaloid (−)-woodinine **15a**, first isolated by Païs and co-workers in 1988 from the ascidian *Eudistoma fragum* and shown to possess potent antibiotic activity against *E. coli* and *S. aureus*.[5a] At the time our preliminary communication appeared[7a] no synthesis of woodinine had been reported but since that time Mahboobi[20] has also published a synthesis of compound **15a**, by a rather similar approach. We now describe our synthetic strategy which has yielded not only a total synthesis of (−)-woodinine but also provides a versatile approach to a number of related β-carboline-containing natural products with potential biological activity.

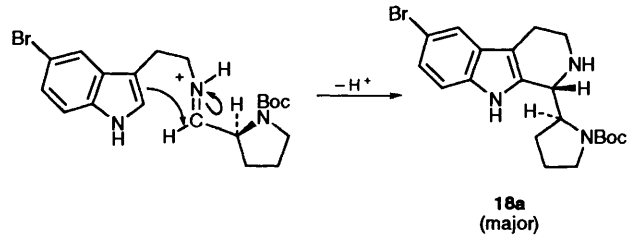
Our planned synthetic route (Scheme 5) called for the availability of 5-bromotryptamine **16** as well as L-(Boc)prolinal **17**.[8] The former is available from 5-bromoindole in 71% overall yield, by a three-step procedure which we have published previously.[7b] No significant debromination in ring A occurred during the final reduction with lithium aluminium hydride.

Natural woodinine **15a** has been shown by its CD spectra[5a] to possess a (β) C-1 hydrogen. The stereochemistry at the C-2′ position on the other hand had not been conclusively determined. We reasoned that if we were to obtain a similar diastereoselectivity to that which we, and others, had observed earlier[7b,c] during the Pictet–Spengler reaction with L-(Boc)-prolinal and 5-bromotryptamine, then the natural (β) C-1 hydrogen diastereoisomer should be the major product. If the iminium ion is drawn in the, presumably more stable, *trans* configuration shown, attack by the nucleophilic indole ring would be expected to occur preferentially from the underside to give compound **18a** as the major adduct.

The classical Pictet–Spengler reaction is normally performed by heating a 1:1 mixture of the tryptamine and aldehyde with a mineral acid such as conc. hydrochloric acid.[21] It was observed



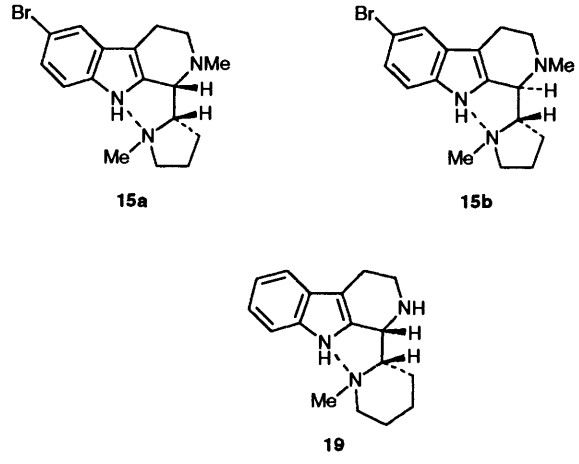
Scheme 5 *Reagents and conditions:* i, TFA, CH_2Cl_2; ii, $ClCO_2Me$, CH_2Cl_2, 25 °C; iii, $LiAlH_4$, THF, 65 °C



previously[7b] that reaction of an *N*-(protected) α-amino aldehyde under these conditions gave racemic Pictet–Spengler adducts, due to the ready enolization and racemization of certain amino aldehydes under acidic conditions. Under modified conditions of low temperature (−78 °C) and using TFA as catalyst,[7c] however, it was found that the products (**18a, b**) retained their optical activity. Thus, treatment of an equimolar mixture of L-(Boc)prolinal and 5-bromotryptamine with two mole equivalents of TFA in dichloromethane at −78 °C led to the isolation of a mixture of diastereoisomers **18a** and **18b** in 93% yield.

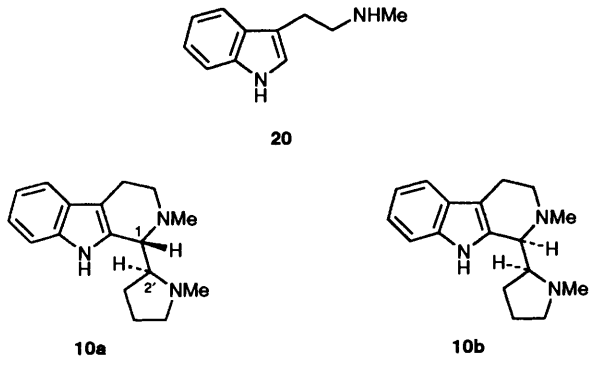
Owing to some difficulty which we experienced in unambiguously assigning the ^1H NMR spectrum of the diastereoisomeric mixture, the Pictet–Spengler adducts **18a, b** were treated directly with methyl chloroformate to give the corresponding mixture (88%) of diastereoisomeric carbamates. Subsequent reduction with excess of lithium aluminium hydride in refluxing THF gave a diastereoisomeric mixture of woodinine **15a** and its C-1 epimer **15b** in >90% yield. The diastereoisomeric ratio **15a**:**15b** was estimated to be 84:16 by ^1H NMR spectroscopy and was verified by subsequent separation by flash column chromatography.[22] The ^1H and ^{13}C NMR spectra of (−)-woodinine **15a** and the mass spectral fragmentation pattern were essentially identical in all respects with those reported[5a] for the natural woodinine. The optical rotation which we observed for compound **15a** $\{[\alpha]_D^{23}$ −34 (MeOH, *c* 0.6)\}* was very close to that reported for the natural product.[5a] From our discussion of the expected Pictet–Spengler diastereoselectivity (above) and the use of L-prolinal (from L-proline) as one of our starting compounds the configuration at C-1 (*R*) and at C-2′ (*S*) in (−)-woodinine can be confidently assigned. Mahboobi *et al.*,[11] in an extensive recent NMR investigation of all four possible stereoisomers of woodinine, have independently confirmed this result.

One of the most important distinctions between (−)-woodinine **15a** and its epimer **15b** (*epi*-woodinine) was noted in the ^1H NMR spectra. In (−)-woodinine the C-1 proton appears as a broad singlet at δ 3.52 while in epimer **15b** the corresponding proton shows up as a doublet (*J* 10.0 Hz) at δ 3.17. This rather striking finding can be rationalized by the not unreasonable assumption that both molecules may exist in the hydrogen-bonded conformations shown below. Models reveal that the dihedral angle between 1-H and 2′-H in isomer **15a** is close to 90°, whereas in isomer **15b** it is approximately 160°. Similar interpretations have been used recently[9] to assign configuration in the interesting analogue **19** of woodinine. The two NMe proton signals were also distinctive, appearing at δ 2.50 and 2.52 in (−)-woodinine **15a** but widely separated at δ 1.96 and 2.44 in epiwoodinine **15b**.



The synthesis of (−)-woodinine herein reported leads to the natural product in 63% overall yield from substrates **16** and **17**. We made several unsuccessful attempts to shorten the synthesis still further by treating *N*′-methyltryptamine (dipterine) **20**, readily prepared from tryptamine by lithium aluminium hydride reduction of the *N*′-formyl analogue,[23] with L-(Boc)prolinal. The synthetic route shown in Scheme 5 should nevertheless prove capable of extension to a variety of tryptamine and α-amino aldehyde precursors. With tryptamine itself, for example, Pictet–Spengler reaction with L-(Boc)prolinal, followed by methoxycarbonylation and reduction, as in Scheme 5, produced a diastereoisomeric mixture of tetrahydro-β-carbolines **10a** and **10b** (85:15) in very similar overall yield. Interestingly, we obtained virtually identical results when we replaced dichloromethane as solvent by toluene and have thus shown that the Pictet–Spengler diastereoselectivity observed in this series does not appear to be sensitive to solvent effects. The C-1 epimers of debromowoodinine **10a, b** so obtained

* Values for specific rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}.



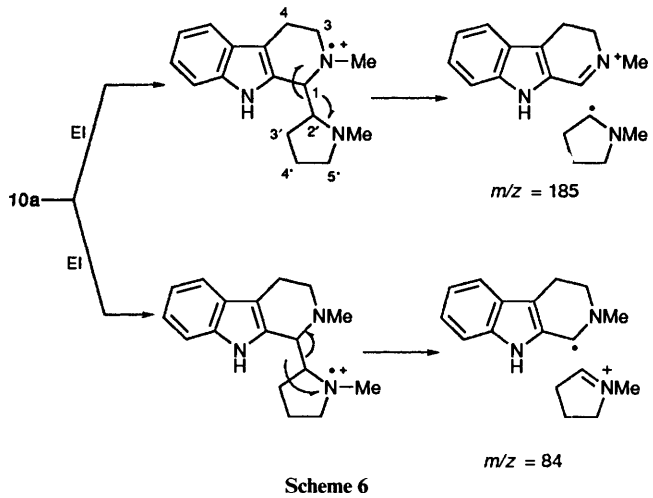
showed, as expected, very similar spectral properties to those discussed above for the woodinines **15a** and **15b**. In spite of promising literature precedents[4a,24] our attempts to brominate compound **10a** using *N*-bromosuccinimide (NBS) gave complex mixtures of products. The use of bromine in acetic acid did lead to (−)-woodinine **15a** but in isolated yields of only 15% and the product required extensive chromatographic purification.

Mass spectral analyses were performed on all our Pictet–Spengler adducts and products derived from them. The most interesting feature of these spectra is the consistent cleavage of the C-1-to-C-2′ bond, as illustrated in Scheme 6 for debromowoodinine **10a**. Thus, upon electron impact, loss of an electron from either of the tertiary nitrogens, followed by homolytic cleavage of the C-1–C-2′ bond, generates the cations with *m/z* 185 and 84. Generally, all of the proline-derived Pictet–Spengler derivatives show both of these peaks arising from C-1/C-2′ cleavage. In addition, ions characteristic of fragmentation of the Boc group [*m/z* 57, (M^+ − 101), (M^+ − 73) and (M^+ − 56)] were observed for all Boc-protected analogues.

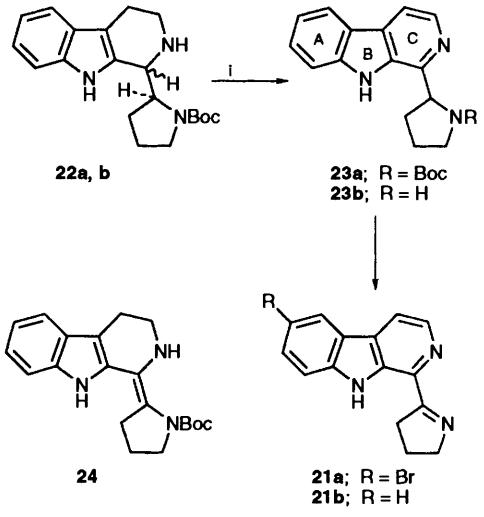
To illustrate further the versatility of these Pictet–Spengler adducts we next turned our attention to the synthesis of the (1-pyrrolin-2-yl)-substituted β-carbolines eudistomin H **21a** and eudistomin I **21b**, which we believed could be obtained from the mixture of diastereoisomers **22a**, **b** (see Experimental section) by the route proposed in Scheme 7. Eudistomins H and I were isolated by Rinehart and co-workers and shown to possess antiviral and antibacterial activity.[2] Syntheses of both natural products have been reported previously. Rinehart *et al.*[2c] employed a rather lengthy synthetic sequence to obtain the β-carboline **23b** and showed that this could be converted into compound **21b** with sodium hypochlorite, in 75% yield. These authors used a parallel sequence to prepare the brominated analogue **21a**. Wasserman and Kelly,[19b] using their novel 1,2,3-tricarbonyl compound strategy, and VanWagenen and Cardellina,[19a] have also synthesized eudistomin I. Hino *et al.* have converted eudistomin I **21b** into eudistomin H **21a** in 80% yield by direct bromination.[24]

As discussed earlier, several methods are available for the dehydrogenation of a 1,2,3,4-tetrahydro-β-carboline to the β-carboline skeleton, the most common being the use of Pd/C,[2] elemental sulfur,[18] or DDQ:[4a] despite this, no method appears to be completely general and each case must be worked on individually. The use of Pd/C, for example, requires fairly high temperatures and we have observed extensive debromination with ring A-brominated 1,2,3,4-tetrahydro-β-carbolines. We decided, however, to attempt this reaction with the mixture of diastereoisomers **22a**, **b**, for which (clearly) debromination is not a concern.

Dehydrogenation of the mixture of tetrahydro-β-carbolines **22a** and **22b** with Pd/C in refluxing xylenes (Scheme 7) required 6 h for the starting material to be consumed. The product **23a** was purified by flash chromatography or by recrystallization



Scheme 6



Scheme 7 *Reagents:* i, Pd/C; ii, TFA

and was found to be racemic, indicating the possible intermediacy of enamine **24** during the dehydrogenation. Compound **23a** (80% yield), after purification, had spectral data in complete agreement with those expected. In particular, the ring C ^{1}H NMR signals at δ 8.28 (3-H) and 7.71 (4-H) are diagnostic for the β-carboline skeleton as noted earlier. Removal of the Boc protecting group from compound **23a** with TFA gave dihydroeudistomin I **23b**, as shown in Scheme 7, in 65% yield after chromatographic purification. In practice, the diastereoisomeric mixture of Pictet–Spengler products **22a**, **b** was usually dehydrogenated and the crude product subsequently deprotected to give compound **23b**, after chromatographic purification, in ~50% overall yield. As discussed above, by preparing compound **23b** formal syntheses of both eudistomins H and I have been completed.

We have therefore shown that, following our biomimetic synthetic pathway outlined in Scheme 5, the natural products (−)-woodinine **15a**, and eudistomins H **21a** and I **21b** may be readily synthesized, starting from L-(Boc)prolinal and either tryptamine or 5-bromotryptamine. The structurally related calmodulin antagonist, eudistomidin A, first reported in 1986 by Kobayashi *et al.*,[25] should also be amenable to synthesis by this route, using the appropriately substituted tryptamine precursor. Our general synthetic procedures (Schemes 1, 3, 5 and 7) will afford access to many other potentially interesting analogues of these biologically active marine natural products.

Experimental

The following chemicals were obtained from the Aldrich Chemical Company, Milwaukee, WI: Boc-ON®, di-*tert*-butyl dicarbonate, DIBAL-H (1.0 mol dm^{-3}, toluene), methyl chloroformate, palladium on charcoal (5%), L-phenylalanine, L-proline, TFA, 5-bromoindole and tryptamine hydrochloride. The following were obtained from BDH, Toronto, Ontario: $LiAlH_4$, (precipitated) sulfur. All of these were used as obtained unless stated otherwise in the procedures. Diethyl ether, THF, toluene and xylenes were distilled from sodium–benzophenone ketyl, dimethylformamide (DMF) and nitromethane were distilled from P_2O_5 under reduced pressure, and methanol and ethanol were distilled from magnesium turnings. The reactions were worked up by extraction of the product from water with several portions of the indicated organic solvent, drying (Na_2SO_4), and evaporation. Flash chromatography was performed with Merck silica gel, grade 60 (230–400 mesh ASTM), using the procedure of Still *et al.*[22] Light petroleum refers to the fraction boiling in the range 40–60 °C.

M.p.s were determined in open-ended capillary tubes on an Electrothermal™ apparatus and are reported without stem correction. IR spectra were obtained on a Nicolet 5-DXB FTIR instrument in the form of KBr discs unless indicated otherwise. Proton NMR spectra were routinely obtained on a Varian EM 360L spectrophotometer (60 MHz) and high-field spectra (^1H and ^{13}C) on a Varian XL 400 spectrophotometer (400 and 100 MHz) at 21 °C). *J* Values are given in Hz. EIMS spectra were obtained from a VG-70-250S mass spectrometer. Elemental analyses were performed by Scandinavian Microanalytical Laboratories, Box 25, 2730 Herlev, Denmark.

Methyl N-(*Boc*)-L-*phenylalaninate*.—The procedure is fully described in ref. 8: $[\alpha]_D^{23}$ −2.25 (*c* 10.0, MeOH) {lit.,[26] $[\alpha]_D$ −2.2 (*c* 10.0, MeOH)}; ν_{max}/cm^{-1} 3363, 3031, 2977, 1749, 1716, 1497, 1364, 1171 and 700; $\delta_H(CDCl_3)$ 7.2 (5 H, s, ArH), 5.1 (1 H, br d, NH), 4.5 (1 H, m, CH), 3.6 (3 H, s, OMe), 3.0 (2 H, m, CH_2) and 1.4 (9 H, s, OBu^t) (HR–EIMS: Found: MH^+, 280.1540. Calc. for $C_{15}H_{22}NO_4$: *m/z*, 280.1540).

L-(*Boc*)*phenylalaninal* **3**.—This procedure is fully described in ref. 8: owing to its relative instability, the crude product was normally treated without recourse to further purification; $\delta_H(CDCl_3)$ 9.6 (1 H, s, CHO), 7.0–7.3 (5 H, m, ArH), 5.0 (1 H, m, NH), 4.3 (1 H, m, CH), 3.0 (2 H, m, CH_2) and 1.4 (9 H, s, OBu^t); δ_C(100 MHz; $CDCl_3$) 199.4 (C-1), 155.3 (urethane C=O), 135.8 (C-1′), 129.3 (C-2′, -6′), 128.7 (C-3′, -5′), 127.0 (C-4′), 80.2 (O*C*Me$_3$), 60.7 (C-2), 35.4 (C-3) and 28.2 (OC*Me*$_3$).

(1R,1′S)-1-[1′-(tert-*Butoxycarbonylamino*)-2′-*phenylethyl*]-1,2,3,4-*tetrahydro*-β-*carboline* (*Mixture of* C-1 *Epimers*) **4a**.—To a solution of tryptamine (1.65 g, 10.3 mmol) and L-(Boc)phenylalaninal **3** (2.56 g, 10.3 mmol) in CH_2Cl_2 (80 cm^3) at −78 °C under nitrogen was added TFA (1.53 cm^3). The mixture was stirred and warmed to 25 °C overnight whereupon triethylamine (4.30 cm^3) was added, followed by water (80 cm^3). Work-up from CH_2Cl_2–water gave compound **4a** as a foam (4.03 g, 100%); ν_{max}/cm^{-1} 3329, 3057, 3031, 2977, 2931, 1690, 1497, 1164 and 739; $\delta_H(CDCl_3)$ 1.2 (9 H, s, OBu^t); EIMS: *m/z* (% rel. int.) 392 (5), 318 (5), 225 (11), 171 (100), 130 (62), 91 (24) and 57 (40) (HR–EIMS: Found M^+, 391.2267. $C_{24}H_{29}N_3O_2$ requires *M*, 391.2260).

Methyl (1R,1′S)-1-[1′-(tert-*Butoxycarbonylamino*)-2′-*phenylethyl*]-1,2,3,4-*tetrahydro*-β-*carboline*-2-*carboxylate* (*Mixture of* C-1 *Epimers*) **4b**.—To a solution of secondary amine **4a** (predominantly β 1-H: see text) (0.80 g, 2.0 mmol) in CH_2Cl_2 (18 cm^3) at 25 °C were added triethylamine (0.43 g) and methyl chloroformate (0.43 cm^3) (*caution:* the reaction is exothermic). The flask was sealed and the contents were stirred under nitrogen overnight, when water (25 cm^3) was added and the mixture worked up from CH_2Cl_2–water to give carbamate **4b** as a foam (0.91 g, 99%); ν_{max}/cm^{-1} 3329, 3064, 3030, 2977, 2931, 1696, 1450, 1164 and 739; $\delta_H(CDCl_3)$ 3.7 (3 H, s, OMe) and 1.3 (9 H, s, OBu^t); EIMS: *m/z* (% rel. int.) 449 (3), 376 (4), 332 (12), 258 (11), 229 (100), 169 (33), 120 (45), 91 (17) and 57 (32) (HR–EIMS: Found: M^+, 449.2314. $C_{26}H_{31}N_3O_4$ requires *M*, 449.2314).

Methyl (1R,1′S)-1-(1′-*Amino*-2′-*phenylethyl*)-1,2,3,4-*tetrahydro*-β-*carboline*-2-*carboxylate* (*Mixture of* C-1 *Epimers*) **5**.—To a solution of the diastereoisomeric mixture **4b** (1.24 g, 2.76 mmol) in MeOH (42 cm^3) was added conc. HCl (4.7 cm^3) and the mixture was stirred at 25 °C overnight. The mixture was poured into saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. Work-up from CH_2Cl_2–water gave the title product (0.95 g, 99%) as an off-white foam; ν_{max}/cm^{-1} 3362, 3057, 3030, 2951, 2924, 1682, 1450, 1231 and 746; $\delta_H(CDCl_3)$ 3.8 (3 H, s, OMe); EIMS: *m/z* (% rel. int.) 350 (2), 349 (1), 285 (11), 258 (7), 229 (88), 169 (29), 143 (40), 130 (71), 120 (100) and 91 (26) (HR–EIMS: Found: M^+, 349.1778. $C_{21}H_{23}N_3O_2$ requires *M*, 349.1790).

(1R,1′S)-1-(1′-*Amino*-2′-*phenylethyl*)-2-*methyl*-1,2,3,4-*tetrahydro*-β-*carboline* **6**.—To a suspension of $LiAlH_4$ (0.52 g) in dry diethyl ether (30 cm^3) stirred at 25 °C under nitrogen was added a solution of the diastereoisomeric ester **5** (0.95 g, 2.7 mmol) in diethyl ether (30 cm^3) *via* addition funnel. The funnel was rinsed with diethyl ether (10 cm^3) and replaced with a condenser. After being refluxed for 20 h, the reaction mixture was quenched by careful addition of ice, and the resulting suspension was filtered through a pad of Celite. The pad was washed successively with several portions of CH_2Cl_2 and water and the filtrate was transferred to a separatory funnel. Work-up from CH_2Cl_2–water gave a crystalline solid (0.76 g, 92%). ^1H NMR analysis (400 MHz) showed the presence of only compound **6**: the minor diastereoisomer (α 1-H) was not detectable. Purification by flash column chromatography[22] (14 × 2.5 cm) with CH_2Cl_2–MeOH (86:14 v/v) as eluent gave pure amine **6** (0.58 g, 70%), m.p. 106–108 °C (from CH_2Cl_2–hexanes); $[\alpha]_D^{23}$ −15.6 (*c* 0.4, MeOH); ν_{max}/cm^{-1} 3369, 3057, 3024, 2931, 2845, 1450 and 746; $\delta_H(CDCl_3$; 400 MHz) 9.91 (1 H, br s, 9-H), 7.51 (1 H, d, *J* 7.6, 5-H), 7.38 (1 H, d, *J* 8.0, 8-H), 7.28–7.13 (6 H, m, ArH), 7.08 (1 H, td, *J* 7.6 and 1.0, 6-H), 3.65 (1 H, ddd, *J* 11.0, 4.0 and 2.6, 1′-H), 3.44 (1 H, d, *J* 4.0, 1-H), 3.15 (1 H, m, 3-H), 3.03 (1 H, dd, *J* 13.8 and 2.6, 2′-H), 2.89 (1 H, m, 4-H), 2.77 (1 H, m, 4-H), 2.71 (1 H, m, 3-H), 2.60 (3 H, s, NMe), 2.00 (1 H, dd, *J* 13.8 and 11.0, 2′-H) and 1.96 (2 H, br s, NH_2); $\delta_C(CDCl_3$; 100 MHz) 139.87 (C-3′), 135.59 (C-8a), 133.52 (C-9a), 129.14 (C-4′ and -8′), 128.55 (C-5′ and -7′), 126.54 (C-4b), 126.22 (C-6′), 120.10 (C-7), 118.82 (C-6), 117.83 (C-5), 111.07 (C-8), 109.28 (C-4a), 65.31 (C-1), 54.77 (C-1′), 53.21 (C-3), 44.02 (NMe), 36.82 (C-2′) and 20.81 (C-4); EIMS: *m/z* (% rel. int.) 305 (1), 186 (31), 185 (100), 171 (13), 169 (12), 144 (15) and 91 (9) (HR–EIMS: Found: M^+, 305.1876. $C_{20}H_{23}N_3$ requires *M*, 305.1892).

(1S,11bR)-1-*Benzyl*-1,2,5,6,11,11b-*hexahydro*-3H-*imidazo*-[1′,5′:1,2]*pyrido*[3,4-b]*indol*-3-*one* **7**.—To a suspension of $LiAlH_4$ (0.33 g) in dry THF (20 cm^3) was added a solution of the diastereoisomeric mixture **5** (1.15 g, 3.29 mmol) in dry THF (20 cm^3) at 25 °C, under nitrogen. The mixture was refluxed for 2 h and quenched by the careful addition of ice. Work-up as described for compound **6** gave a yellow-white foam (0.94 g, 94%). Purification by flash column chromatography[22] with

CH_2Cl_2–MeOH (95:5 v/v) as eluent gave a foam (0.62 g, 72%), which was shown by ^1H NMR analysis to be a 2:1 mixture of compounds **6** and **7**. Compound **7** was isolated by recrystallization from dichloromethane–hexanes as needles (0.18 g, 20%), m.p. 180–185 °C; $[\alpha]_D^{23}$ −35 (*c* 0.43, MeOH); ν_{max}/cm^{-1} 3214, 3082, 2910, 2844, 1680, 1458 and 736; $\delta_H(CDCl_3$; 400 MHz)* 8.41 (1 H, br s, 9-H), 7.50–7.47 (3 H, m, ArH), 7.40 (1 H, d, *J* 7.6, 5-H), 7.36–7.33 (2 H, m, ArH), 7.12–6.98 (3 H, m, ArH), 6.25 (1 H, br s, 1'-NH), 4.77 (1 H, d, *J* 6.0, 1-H), 4.28 (1 H, dd, *J* 13.2 and 6.0, 3-H), 3.87 (1 H, m, 1'-H), 3.25 (1 H, dd, *J* 12.8 and 5.2, 2'-H), 2.95 (1 H, m, 3-H), 2.93 (1 H, dd, *J* 12.8 and 9.6, 2'-H), 2.83 (1 H, tdd, *J* 15.4, 6.0 and 2.0, 4-H), 2.66 (1 H, dd, *J* 15.4 and 4.8, 4-H); $\delta_C(CDCl_3$; 100 MHz) 160.30 (C=O), 136.84 (C-3'), 135.77 (C-8a), 130.82 (C-9a), 129.78 (C-4' and -8'), 129.47 (C-5' and -7'), 127.58 (C-6'), 126.49 (C-4b), 122.12 (C-7), 119.57 (C-6), 118.32 (C-5), 110.75 (C-8), 109.14 (C-4a), 58.95 (C-1'), 57.35 (C-1), 42.46 (C-2'), 38.02 (C-3) and 20.71 (C-4); EIMS: *m/z* (% rel. int.) 317 (65), 226 (89), 225 (100), 185 (29), 169 (59) and 91 (41).

Lewis Acid-promoted Cyclization (*Compound* **6**, via *Intermediates* **12**, **4b**).—A mixture of L-(Boc)phenylalaninal **3** (0.37 g, 1.48 mmol), tryptamine (0.24 g, 1.48 mmol) and sodium acetate (3.36 g) was refluxed in MeOH (12 cm^3) for 30 min. The solution was cooled to 0 °C and methyl chloroformate (0.23 cm^3, 2.96 mmol) was added, followed by triethylamine (0.41 cm^3, 2.96 mmol). After the mixture had been stirred for 2 min at 0 °C, TBDMSOTf (1.02 cm^3, 4.44 mmol) was added to the clear solution, causing a precipitate to form. The ice-bath was removed and the solution was allowed to warm to 25 °C overnight. The mixture was shaken with CH_2Cl_2–water and the organic layers were washed (0.5 mol dm^{-3} NaOH), prior to being dried and concentrated, to give compound **4b** (0.68 g) as a yellow foam. This material was treated with MeOH and conc. HCl as before to give compound **5** (0.52 g, 100%). Reduction with $LiAlH_4$ in diethyl ether was carried out by the procedure already described. Analysis by ^1H NMR (400 MHz) spectroscopy of the product (0.45 g, 100%) showed compound **6** to be the only cyclized product, contaminated with a small amount of *N'*-methyltryptamine. No signals attributable to the α 1-H epimer of compound **6** were observed.

(±)-1-[1'-(tert-*Butoxycarbonylamino*)-2'-*phenylethyl*]-β-*carboline* **13**.—(*Method A*). A mixture of 5% Pd/C (1.00 g) and compound **4a** (2.00 g, 5.10 mmol) was intimately ground in a mortar. The solid was heated slowly over a period of 20 min to 200 °C (oil-bath temp.) and the temperature was maintained at 200–210 °C for a further 8–10 min, when the oil-bath was removed and the mixture allowed to cool. The solid was suspended in dichloromethane and the mixture was filtered by suction through a glass fritted funnel. The filtered solid was washed with several portions of CH_2Cl_2 and MeOH. Concentration of the combined filtrates gave crystals (1.75 g, 88%). Purification by flash column chromatography[22] with CH_2Cl_2–MeOH (94:6 v/v) as eluent gave (±)-**13** (1.39 g, 70%) as needles, m.p. 230–232 °C (from acetone–dichloromethane); ν_{max}/cm^{-1} 3256, 3183, 3064, 2977, 2931, 1669 and 739; $\delta_H(CDCl_3$; 400 MHz) 9.74 (1 H, br s, 9-H), 8.36 (1 H, d, *J* 5.2, 3-H), 8.03 (1 H, d, *J* 7.6, 5-H), 7.84 (1 H, d, *J* 5.2, 4-H), 7.46 (1 H, td, *J* 7.6 and 1.2, 7-H), 7.31 (1 H, d, *J* 8.4, 8-H), 7.22 (1 H, td, *J* 7.6 and 0.8, 6-H), 7.14 (5 H, m, ArH), 5.92 (1 H, d, *J* 9.2, NH), 5.64 (1 H, m, 1'-H), 3.44 (2 H, d, *J* 7.6, 2'-H_2) and 1.38 (9 H, s, OBu^t); $\delta_C(CDCl_3$; 100 MHz) 156.6 (C=O), 143.8 (C-1), 140.5 (C-9a), 138.1 (C-3'), 137.7 (C-3), 134.1 (C-8a), 129.3 (C-4', -8'), 129.0 (C-4b), 128.3 (C-5', -7'), 128.2 (C-7), 126.4 (C-6'), 121.4 (C-5), 121.4 (C-4a), 119.7 (C-6), 114.1 (C-4), 111.7 (C-8), 80.0 ($OCMe_3$), 53.0 (C-1'), 39.7 (C-2') and 28.3 ($OCMe_3$); EIMS: *m/z* (% rel. int.) 387 (10), 314 (14), 296 (50), 286 (27), 240 (52), 196 (100), 168 (27), 91 (18) and 57 (27) [Found: (HR–EIMS) M^+, 387.1935; C, 74.4; H, 6.55; N, 11.0%. $C_{24}H_{25}N_3O_2$ requires *M*, 387.1947; C, 74.39; H, 6.50; N, 10.84%].

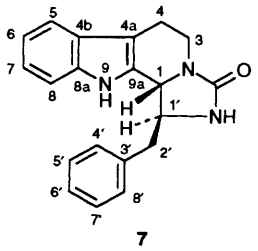
(*Method B*). A mixture of precipitated sulfur (0.10 g) and compound **4a** (0.50 g, 1.3 mmol) was intimately ground and heated in identical fashion to that described in *Method A*. After cooling to 25 °C the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 phases yielded a yellow-white crystalline mass (0.36 g, 73%), which was purified by flash column chromatography,[22] with CH_2Cl_2–MeOH (94:6 v/v) as eluent, to give compound (+)-**13** (0.18 g, 36%), m.p. 208–210 °C (decomp.) (from acetone); $[\alpha]_D^{23}$ +22 (*c* 0.23, MeOH). All other spectral features were identical with those of the racemate obtained by *Method A*.

(±)-1-(1'-*Amino*-2'-*phenylethyl*)-β-*carboline* **14**.—To a solution of compound (±)-**13** (86 mg, 0.22 mmol) in CH_2Cl_2 (10 cm^3) was added TFA (4.25 cm^3). The mixture was stirred at 25 °C for 70 min, when it was slowly poured into 3 mol dm^{-3} NaOH (25 cm^3). The mixture was transferred to a separatory funnel and worked up from CH_2Cl_2–water to give compound **14** (61 mg, 96%) as a yellow-brown foam; ν_{max}/cm^{-1} 3369, 3157, 3064, 2924, 1629, 1430 and 746; $\delta_H(CDCl_3$; 400 MHz) 10.30 (1 H, br s, NH), 8.35 (1 H, d, *J* 5.2, 3-H), 8.09 (1 H, d, *J* 8.0, 5-H), 7.82 (1 H, d, *J* 5.2, 4-H), 7.50 (2 H, m, ArH), 7.20–7.30 (6 H, m, ArH), 4.79 (1 H, dd, *J* 9.8 and 3.4, 1'-H), 3.33 (1 H, dd, *J* 13.1 and 3.4, 2'-H), 2.96 (1 H, dd, *J* 13.1 and 9.8, 2'-H) and 2.22 (2 H, br s, NH_2); $\delta_C(CDCl_3$; 100 MHz) 146.6 (C-1), 140.0 (C-9a), 138.3 (C-3), 137.8 (C-3'), 134.0 (C-8a), 129.38 (C-4b), 129.34 (C-4', -8'), 128.6 (C-5', -7'), 128.2 (C-7), 126.6 (C-6'), 121.5 (C-5), 121.2 (C-4a), 119.5 (C-6), 113.6 (C-4), 111.6 (C-8), 59.1 (C-1') and 42.2 (C-2'); EIMS: *m/z* (% rel. int.) 269 (17), 236 (16), 196 (100), 169 (29) and 91 (17).

Eudistomin T **1c**.—To a solution of amine **14** (0.24 g, 0.84 mmol) in dry MeOH (20 cm^3) was added anhydrous Na_2CO_3 (0.40 g), followed by aq. NaOCl (1.05 cm^3; 5.9% w/w) over a period of 30 s. The solution turned an orange colour. After being stirred at 25 °C for 65 min the mixture was treated with 1 mol dm^{-3} HCl (50 cm^3) and CH_2Cl_2 (50 cm^3) and was then stirred for 10 min before being transferred to a separatory funnel, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed (5% aq. $NaHCO_3$; saturated aq. NaCl), dried, filtered, and concentrated to give yellow-brown needles (0.18 g). Purification by flash column chromatography[22] with CH_2Cl_2–MeOH (98:2 v/v) as eluent gave eudistomin T **1c** (0.14 g, 59%) as a yellow crystalline film, m.p. 155–157 °C (from MeOH) [lit.,[18] 160–161 °C (from MeOH)]; ν_{max}/cm^{-1} 3369, 3057, 3024, 1656, 1629, 1490, 1204, 739, 719 and 693; ^1H NMR data were identical with the literature[3,19b] values; $\delta_C(CDCl_3$; 100 MHz) 202.1 (C=O), 140.9 (C-1), 138.1 (C-3), 135.0, 135.2 and 135.8 (C-3', -8a, -9a), 131.4 (C-4b), 130.0 (C-4', -8'), 129.1 (C-7), 128.4 (C-5', -7'), 126.7 (C-6'), 121.7 (C-5), 120.6 (C-6), 120.4 (C-4a), 119.1 (C-4), 111.8 (C-8) and 43.8 (C-2').

N'-*Methyltryptamine* (*Dipterine*) **20**.—A solution of *N'*-formyltryptamine[23] (8.14 g, 43.2 mmol) in dry THF (80 cm^3)

* Compound **7** is numbered as shown below for ease of spectral assignments and comparison with the other β-carbolines.



7

was added to a suspension of $LiAlH_4$ (4.94 g, 130 mmol) in dry THF (150 cm^3) over a period of 15 min at 0 °C under nitrogen. The solution was refluxed for 3.25 h, cooled to 0 °C, and quenched by careful addition of ice. The product was filtered through Celite and worked up from dichloromethane–water to give dipterine **20** (6.80 g, 90%) as a crystalline solid, m.p. 75–80 °C (lit.,[27] 87–89 °C); ν_{max}/cm^{-1} 3416, 3296, 3057, 2931, 2851, 1450, 1105 and 739; δ_H [28](CDCl$_3$) 9.3 (1 H, br s, NH), 7.5 (1 H, m, 4-H), 7.0–7.3 (3 H, m, ArH), 6.9 (1 H, s, 2-H), 2.8 (4 H, m, CH_2CH_2), 2.3 (3 H, s, NMe) and 1.7 (1 H, br s, NH).

(−)-*Debromowoodinine and* (1S,2′S)-2-*Methyl*-1-(N-*methylpyrrolidin*-2′-*yl*)-1,2,3,4-*tetrahydro*-β-*carboline* **10a**, **b**.—To a solution of tryptamine (1.00 g, 6.24 mmol) and L-(Boc)prolinal **17** (1.25 g, 6.27 mmol) in dichloromethane (37 cm^3) at −78 °C under nitrogen was added TFA (0.93 cm^3) over a period of 30 s and the solution was stirred and allowed to warm to 25 °C. After 2.5 h at room temp. the reaction mixture was quenched by addition of triethylamine (2.61 cm^3). Work-up from dichloromethane–water gave compounds **22a** and **22b** as a foam (2.07 g, 97%); ν_{max}/cm^{-1} 3339, 3057, 2973, 2931, 1680, 1455, 1398, 1166 and 738; δ_H(CDCl$_3$) 1.5 (9 H, s, OBu^t). A small amount of the monotriflate salt was recrystallized from hexanes–dichloromethane and had m.p. 190–192 °C (decomp.); EIMS: *m*/*z* (% rel. int.) 341 (9), 268 (9), 171 (100) and 57 (15) (Found: C, 57.9; H, 6.25; N, 9.2. $C_{22}H_{28}F_3N_3O_4$ requires C, 58.01; H, 6.20; N, 9.23%).

To a solution of compounds **22a**, **b** (2.03 g, 5.95 mmol), obtained as above, in dry dichloromethane (50 cm^3) at 25 °C were added triethylamine (0.72 g) and methyl chloroformate (0.72 g); an exothermic reaction occurred. After the mixture had been stirred for 3 h at 25 °C, water (60 cm^3) was added and the mixture was transferred to a separatory funnel. Work-up from dichloromethane–water gave a diastereoisomeric mixture of the carbamates (2.20 g, 93%) as a foam, m.p. 65–75 °C; ν_{max}/cm^{-1} 3332, 3057, 2973, 2931, 1701, 1406 and 745; δ_H(CDCl$_3$) 3.7 (3 H, s, OMe) and 1.5 (9 H, s, OBu^t); EIMS: *m*/*z* (% rel. int.) 399 (13), 326 (7), 229 (100), 169 (21) and 114 (20) (HR–EIMS: Found: M^+, 399.2157. $C_{22}H_{29}N_3O_4$ requires *M*, 399.2158).

To a stirred suspension of $LiAlH_4$ (0.80 g) in dry THF (24 cm^3) was added a mixture of the above carbamates (1.60 g, 4.00 mmol) in dry THF (24 cm^3), *via* a pressure-equalizing addition funnel, during 2 min under nitrogen. The mixture was then refluxed for 8 h, cooled to 0 °C, and the excess of $LiAlH_4$ was decomposed by careful addition of ice. The white suspension was suction-filtered through a thin pad of Celite and the pad was washed successively several times with dichloromethane and water. Work-up of the filtrate from dichloromethane–water gave the debromowoodinines **10a**/**10b** (1.01 g, 94%). The mixture was a viscous yellow oil which crystallized on the rotary evaporator. The mixture was separated by flash column chromatography[22] (20 × 2.5 cm) with dichloromethane–methanol (94:6) as eluent. Debromowoodinine **10a** (R_f 0.2) eluted first. The solvent polarity was increased slowly to dichloromethane–methanol (80:20) and the epimeric compound **10b** was obtained. Compound **10a** (0.70 g, 65%) was isolated as prisms, m.p. 123–125 °C (from Et_2O); $[\alpha]_D^{23}$ −51.5 (*c* 0.63, MeOH); ν_{max}/cm^{-1} 3328, 3050, 2951, 2787, 1450 and 736; δ_H(400 MHz; CDCl$_3$) 9.91 (1 H, br s, NH), 7.51 (1 H, d, *J* 7.6, 5-H), 7.34 (1 H, d, *J* 8.0, 8-H), 7.07–7.16 (2 H, m, 6- and 7-H), 3.62 (1 H, s, 1-H), 3.16 (1 H, t, *J* 7.6, 5′-H), 3.12 (1 H, ddd, *J* 11.2, 5.2 and 2.0, 3-H), 2.95 (1 H, m, 2′-H), 2.85 (1 H, m, 4-H), 2.76 (1 H, m, 3-H), 2.66 (1 H, td, *J* 11.5 and 4.0, 4-H), 2.57 (3 H, s, NMe), 2.55 (3 H, s, NMe), 2.22 (1 H, m, 5′-H), 1.83 (1 H, m, 3′-H), 1.62 (1 H, m, 4′-H) and 1.38–1.50 (2 H, m, 3′- and 4′-H); δ_C(CDCl$_3$) 135.4 (C-8a), 134.4 (C-9a), 126.7 (C-4b), 120.8 (C-7), 118.6 (C-6), 117.7 (C-5), 110.9 (C-8), 109.5 (C-4a), 66.9 (C-2′), 61.2 (C-1), 57.8 (C-5′), 54.7 (C-3), 41.1 and 43.9 (NMe), 25.4 (C-3′), 22.9 (C-4′) and 21.4 (C-4); EIMS: *m*/*z* (% rel. int.) 269 (2), 197 (12), 185 (42) and 84 (100) [Found: (HR–EIMS): M^+, 269.1890; C, 75.7; H, 8.55; N, 15.6%. $C_{17}H_{23}N_3$ requires *M*, 269.1892; C, 75.80; H, 8.61; N, 15.60%].

Compound **10b** was isolated as an oil (0.10 g, 10%); δ_H(400 MHz; CDCl$_3$) 9.37 (1 H, br s, NH), 7.53 (1 H, d, *J* 7.6, 5-H), 7.39 (1 H, d, *J* 8.0, 8-H), 7.16 (1 H, td, *J* 7.6 and 1.2, 6-H), 7.09 (1 H, td, *J* 8.0 and 1.2, 7-H), 3.38 (1 H, d, *J* 9.6, 1-H), 3.32 (1 H, m, 5′-H), 3.17 (1 H, m, 3-H), 2.9–3.2 (2 H, m, 2′- and 4-H), 2.77 (1 H, m, 3-H), 2.54 (1 H, m, 4-H), 2.48 (3 H, s, NMe), 2.18 (1 H, m, 5′-H), 2.09 (3 H, s, NMe) and 1.85–2.05 (4 H, m, 3′- and 4′-H_2); δ_C(CDCl$_3$) 136.0 (C-8a), 132.9 (C-9a), 126.9 (C-4b), 121.2 (C-7), 118.8 (C-6), 117.9 (C-5), 111.0 (C-8), 107.5 (C-4a), 69.7 (C-2′), 62.5 (C-1), 57.8 (C-5′), 46.0 (C-3), 41.6 and 43.2 (NMe), 30.5 (C-3′), 24.0 (C-4′) and 16.3 (C-4).

(1R,2′S)-6-*Bromo*-1-(N-tert-*butoxycarbonylpyrrolidin*-2′-*yl*)-1,2,3,4-*tetrahydro*-β-*carboline*, **18a** *and its* (1S,2′S) *Isomer* **18b**.—To a stirred dichloromethane (50 cm^3) solution of 5-bromotryptamine **16** (2.04 g, 8.53 mmol) and L-(Boc)prolinal **17** (1.70 g, 8.53 mmol) at −78 °C under nitrogen was added TFA (1.27 cm^3). The mixture was stirred at −78 °C for 2 h and was then allowed to warm to 25 °C during 16 h before being quenched by addition of triethylamine (3.57 cm^3) and worked up from dichloromethane–water to give a yellow foam (3.32 g, 93%); EIMS: *m*/*z* (% rel. int.) 422 (96), 420 (100), 366 (33), 364 (33), 322 (10), 320 (13), 251 (50), 249 (56) and 152 (26) [Found: (HR–EIMS): M^+, 419.1194; C, 56.9; H, 6.2; N, 9.7%. $C_{20}H_{26}{}^{79}BrN_3O_2$ requires *M*, 419.1208; C, 57.15; H, 6.23; N, 10.00%].

(−)-*Woodinine* **15a** *and* (1S,2′S)-6-*Bromo*-2-*methyl*-1-(N-*methylpyrrolidin*-2′-*yl*)-1,2,3,4-*tetrahydro*-β-*carboline* **15b**.—The mixture of compounds **18a**/**18b** obtained above (3.32 g, 7.90 mmol) was dissolved in dichloromethane (66 cm^3), and triethylamine (1.00 g) was added. To this was added methyl chloroformate (0.78 cm^3) and the mixture was stirred under nitrogen at 25 °C for 2.5 h. Water (60 cm^3) was added and the product was worked up from dichloromethane–water to give the diastereoisomeric carbamates as a light yellow foam (3.32 g, 88%); ν_{max}/cm^{-1} 2977, 1676, 1450, 1404, 1164 and 792; δ_H(CDCl$_3$) 3.75 (3 H, s, OMe) and 1.50 (9 H, s, OBu^t).

To a stirred suspension of $LiAlH_4$ (1.36 g) in dry THF (37 cm^3) under nitrogen was added, *via* a pressure-equalizing addition funnel, a solution of the above diastereoisomeric mixture (3.27 g, 6.84 mmol) over a period of 5 min. The mixture was then allowed to reflux for 8 h and worked up to give a mixture of title compounds **15a**/**15b** (2.16 g, 91%) as a yellow foam. Purification by flash column chromatography[22] gave, first, pure compound **15a** (1.32 g, 56%) as a yellow foam, m.p. 55–60 °C; $[\alpha]_D^{23}$ −34 (*c* 0.60, MeOH); ν_{max}/cm^{-1} 3271, 2943, 2845, 2787, 1458, 1384 and 793; δ_H(400 MHz; CDCl$_3$) 10.01 (1 H, br s, NH), 7.57 (1 H, s, 5-H), 7.14 (2 H, s, 7- and 8-H), 3.52 (1 H, s, 1-H), 3.11 (1 H, t, *J* 8.0, 5′-H), 3.02 (1 H, m, 3-H), 2.75–2.90 (2 H, m, 2′- and 4-H), 2.50–2.65 (2 H, m, 3- and 4-H), 2.52 (3 H, s, NMe), 2.50 (3 H, s, NMe), 2.15 (1 H, m, 5′-H), 1.77 (1 H, m, 3′-H), 1.55 (1 H, m, 4′-H) and 1.26–1.42 (2 H, m, 4′- and 3′-H); δ_C(100 MHz; CDCl$_3$) 135.8 (C-9a), 133.9 (C-8a), 128.3 (C-4b), 123.2 (C-7), 120.1 (C-5), 112.2 (C-8), 111.7 (C-6), 109.0 (C-4a), 65.6 (C-2′), 60.8 (C-1), 57.5 (C-5′), 54.2 (C-3), 40.9 and 43.6 (NMe), 25.3 (C-3′), 22.7 (C-4′) and 21.1 (C-4); EIMS: *m*/*z* (% rel. int.) 350 (2), 348 (2), 265 (78), 263 (76), 249 (15), 247 (13), 208 (39), 197 (31) and 185 (100) [Found: (HR–EIMS): MH^+, 348.1094. Calc. for $C_{17}H_{23}{}^{79}BrN_3$; *m*/*z*, 348.1075].

The more polar fraction from the column contained epimer **15b** (0.14 g, 6%) as a dark yellow film, δ_H(400 MHz; CDCl$_3$) 9.10 (1 H, br s, NH), 7.62 (1 H, s, 5-H), 7.20 (2 H, s, 7- and 8-H), 3.17 (1 H, d, *J* 10.0, 1-H), 2.44 (3 H, s, NMe) and 1.96 (3 H, s,

NMe); $\delta_C(CDCl_3)$ 135.5 (C-9a), 134.6 (C-8a), 128.8 (C-4b), 123.7 (C-7), 120.6 (C-5), 112.1 (C-8), 112.0 (C-6), 107.3 (C-4a), 69.1 (C-2'), 63.3 (C-1), 57.6 (C-5'), 46.3 (C-3), 41.6 and 43.6 (NMe), 30.5 (C-3'), 24.4 (C-4') and 16.2 (C-4).

(−)-*Woodinine* **15a** *from Debromowoodinine* **10a**.—To a glacial acetic acid (22 cm^3) solution of debromowoodinine **10a** (0.15 g, 0.56 mmol) was added bromine (0.084 cm^3) and the solution was stirred under nitrogen overnight at 25 °C. The solvent was then removed under reduced pressure and the residue was partitioned between dichloromethane and 5% aq. $NaHCO_3$. The dichloromethane layer was washed (aq. $Na_2S_2O_3$), dried (Na_2SO_4), filtered, and concentrated to give a yellow-orange film (0.22 g). The material was subjected to flash chromatographic purification[22] on silica gel, with dichloromethane–methanol (98:2) as eluent, to give (−)-woodinine **15a** (20 mg) as a yellow solid, $[\alpha]_D^{23}$ −41 (*c* 0.6, MeOH). The ^1H NMR spectrum was identical with that reported above.

1-(N-tert-*Butoxycarbonylpyrrolidin-2'-yl*)-β-*carboline* **23a**.—A suspension of epimers **22a**, **b** (0.50 g, 1.46 mmol) and 5% Pd/C (0.30 g) in xylenes (39 cm^3) was refluxed under nitrogen for 6 h. The catalyst was filtered off and washed with dichloromethane (3 × 10 cm^3). The solvents were removed from the filtrate to give crude compound **23a** (0.47 g, 96%). Purification by flash column chromatography[22] with dichloromethane–methanol (98:2) as eluent gave pure (racemic) title compound **23a** (0.40 g). Crystallization from diethyl ether gave crystals (0.15 g), m.p. 196–198 °C; ν_{max}/cm^{-1} 3442, 3289, 3064, 2977, 2918, 2871, 1669, 1625, 1417, 1237 and 746; δ_H(400 MHz; $CDCl_3$) 10.96 (1 H, s, NH), 8.28 (1 H, br s, 3-H), 7.98 (1 H, br s, 5-H), 7.71 (1 H, br s, 4-H), 7.16–7.50 (3 H, m, 6-, 7- and 8-H), 5.64 (1 H, m, 2'-H) and 1.50 (9 H, s, OBu^t); $\delta_C(CDCl_3)$ 156.2 (C=O), 143.5 (C-1), 140.0 (C-9a), 136.9 (C-3), 134.3 (C-8a), 128.4 (C-4b), 127.4 (C-7), 121.1 (C-4a), 120.8 (C-5), 118.9 (C-6), 113.4 (C-4), 111.5 (C-8), 79.9 (O*C*Me$_3$), 57.9 (C-2'), 46.6 (C-5'), 28.4 (C-3'), 28.1 (OC*Me*$_3$) and 24.4 (C-4'); EIMS: *m*/*z* (% rel. int.) 337 (34), 281 (34), 264 (13), 237 (31), 219 (20), 208 (22), 195 (100), 182 (44), 168 (24) and 57 (29) [Found: (HR–EIMS): M^+, 337.1800; C, 71.0; H, 7.0; N, 12.4%. $C_{20}H_{23}N_3O_2$ requires *M*, 337.1790; C, 71.19; H, 6.87; N, 12.45%].

Dihydroeudistomin I **23b**.—To a solution of the carbamate **23a** (0.25 g, 0.74 mmol) in dichloromethane (7.0 cm^3) was added TFA (3.0 cm^3). The solution turned yellow and was stirred at 25 °C under nitrogen for 30 min. Triethylamine (0.40 g) and water (10 cm^3) were added. Work-up was from dichloromethane–water, the dichloromethane extracts being washed with dil. sodium hydroxide prior to being dried and concentrated. This gave a yellow foam (0.175 g, 100% crude). Purification was effected by flash column chromatography[22] with dichloromethane–methanol (98:2) as eluent, with the polarity slowly being increased during elution. A later fraction contained pure dihydroeudistomin I **23b** (0.11 g, 65%) as crystals, m.p. 155–157 °C. Recrystallization (dichloromethane–light petroleum) gave compound **23b**, m.p. 155–157 °C (lit.,[2c] 153.5–155 °C); δ_H(400 MHz; $CDCl_3$) 10.8 (1 H, br s, NH), 8.25 (1 H, d, *J* 5.2, 3-H), 8.05 (1 H, d, *J* 8.0, 5-H), 7.75 (1 H, d, *J* 5.2, 4-H), 7.46–7.55 (2 H, m, 7- and 8-H), 7.22 (1 H, m, 6-H), 4.90 (1 H, t, *J* 7.6, 2'-H), 4.22 (1 H, br s, NH) and 1.8–3.2 (6 H, m, $CH_2CH_2CH_2$); $\delta_C(CDCl_3)$ 145.4 (C-1), 140.5 (C-9a), 137.7 (C-3), 134.1 (C-8a), 129.4 (C-4b), 128.3 (C-7), 121.7 (C-5), 121.4 (C-4a), 119.6 (C-6), 113.7 (C-4), 112.1 (C-8), 63.1 (C-2'), 47.0 (C-5'), 32.6 (C-3') and 25.7 (C-4').

References

1 Presented in part at the Symposium in Honour of Professor Sir Alan Battersby FRS, Cambridge, UK, September 7–9, 1992.
2 (*a*) K. L. Rinehart, Jr., J. Kobayashi, G. C. Harbour, R. G. Hughes, Jr., S. A. Mizsak and T. A. Scahill, *J. Am. Chem. Soc.*, 1984, **106**, 1524; (*b*) J. Kobayashi, G. C. Harbour, J. Gilmore and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, 1984, **106**, 1526; (*c*) K. L. Rinehart, Jr., J. Kobayashi, G. C. Harbour, J. Gilmore, M. Mascal, T. G. Holt, L. S. Shield and F. Lafargue, *J. Am. Chem. Soc.*, 1987, **109**, 3378.
3 K. F. Kinzer and J. H. Cardellina II, *Tetrahedron Lett.*, 1987, **28**, 925.
4 (*a*) J. Kobayashi, J. Cheng, T. Ohta, S. Nozoe, Y. Ohizumi and T. Sasaki, *J. Org. Chem.*, 1990, **55**, 3666; (*b*) O. Murata, H. Shigemori, M. Ishibashi, K. Sugama, K. Hayashi and J. Kobayashi, *Tetrahedron Lett.*, 1991, **32**, 3539.
5 (*a*) C. Debitus, D. Laurent and M. Païs, *J. Nat. Prod.*, 1988, **51**, 799; (*b*) S. A. Adesanya, M. Chbani, M. Païs and C. Debitus, *J. Nat. Prod.*, 1992, **55**, 525.
6 R. J. Lake, J. W. Blunt and M. H. G. Munro, *Aust. J. Chem.*, 1989, **42**, 1201.
7 (*a*) J. McNulty and I. W. J. Still, *Tetrahedron Lett.*, 1991, **32**, 4875; (*b*) I. W. J. Still and J. R. Strautmanis, *Can. J. Chem.*, 1990, **68**, 1408; (*c*) M. Nakagawa, J. J. Lui and T. Hino, *J. Am. Chem. Soc.*, 1989, **111**, 2721; (*d*) Z. Czarnocki, D. B. MacLean and W. A. Szarek, *Can. J. Chem.*, 1986, **64**, 2205; (*e*) H. Waldmann, G. Schmidt, M. Jansen and J. Geb, *Tetrahedron Lett.*, 1993, **34**, 5867.
8 J. McNulty and I. W. J. Still, *Synth. Commun.*, 1992, **22**, 979.
9 S. Misztal, M. Dukat and J. L. Mokrosz, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2311.
10 M. Nakagawa, J.-J. Lui, K. Ogata and T. Hino, *Tetrahedron Lett.*, 1986, **27**, 6087.
11 S. Mahboobi, T. Burgemeister and W. Wiegrebe, *Arch. Pharm. (Weinheim)*, 1993, **326**, 33.
12 G. K. Cheung, M. J. Earle, R. A. Fairhurst, H. Heaney, K. F. Shuhaibar, S. C. Eyley and F. Ince, *Synlett*, 1991, 721.
13 A. M. Murphy, R. Dagnino, Jr., P. L. Vallar, A. J. Trippe, S. L. Sherman, R. H. Lumpkin, S. Y. Tamura and T. R. Webb, *J. Am. Chem. Soc.*, 1992, **114**, 3156.
14 E. Wenkert, P. D. R. Moeller and Y. J. Shi, *J. Org. Chem.*, 1988, **53**, 2383.
15 D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, 1982, **47**, 4315.
16 N. P. Buu-Hoï, O. Roussel and P. Jacquignon, *J. Chem. Soc.*, 1964, 708.
17 M. Hudlicky, *Oxidations in Organic Chemistry*, A.C.S. Monograph No. 186, Washington, DC, 1990, p. 239.
18 I. W. J. Still and J. McNulty, *Heterocycles*, 1989, **29**, 2057.
19 (*a*) B. C. VanWagenen and J. H. Cardellina II, *Tetrahedron Lett.*, 1989, **30**, 3605; (*b*) H. H. Wasserman and T. A. Kelly, *Tetrahedron Lett.*, 1989, **30**, 7117.
20 S. Mahboobi, *Arch. Pharm. (Weinheim)*, 1992, **325**, 249.
21 W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 151.
22 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
23 C. Schöpf and H. Steuer, *Justus Liebigs Ann. Chem.*, 1947, **558**, 124.
24 T. Hino, Z. Lai, H. Seki, R. Hara, T. Kuramochi and M. Nakagawa, *Chem. Pharm. Bull.*, 1989, **37**, 2596.
25 J. Kobayashi, H. Nakamura, Y. Ohizumi and Y. Hirata, *Tetrahedron Lett.*, 1986, **27**, 1191.
26 J. Boger, L. S. Payne, D. S. Perlow, N. S. Lohr, M. Poe, E. H. Blaine, E. M. Ulm, T. W. Schorn, B. I. LaMont, T. Y. Lin, M. Kawai, D. M. Rich and D. F. Veber, *J. Med. Chem.*, 1985, **28**, 1779.
27 C. J. Pouchert and J. R. Campbell, *The Aldrich Library of NMR Spectra*, Aldrich, Milwaukee, WI, 1974, vol. 8, No. 58b.

Paper 3/07249E
Received 6*th December* 1993
Accepted 10*th February* 1994