HETEROCYCLES, Vol. 84, No. 2, 2012, pp. 1141 - 1170. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 5th August, 2011, Accepted, 1st September, 2011, Published online, 8th September, 2011
DOI: 10.3987/COM-11-S(P)95

CONVERGENT TOTAL SYNTHESES OF THE PENTACYCLIC LAMELLARINS K, T, U AND W *VIA* THE ADDITION OF AZOMETHINE YLIDES TO TETHERED TOLANS†

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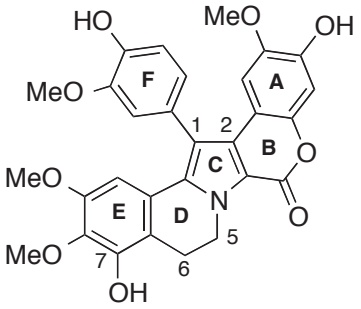
†***Dedicated to Professor Al Padwa on the occasion of his 75th birthday and in recognition of his seminal contributions to heterocyclic chemistry***

Abstract – The title compounds, **1**–**4** respectively, have been prepared in a concise and fully regiocontrolled manner *via* the addition of an azomethine ylide to an ester-linked tolan. The resulting annulated dihydropyrrole was oxidized to the corresponding fully aromatic system and the associated isopropyl ethers then selectively cleaved with aluminium trichloride to reveal the free phenolic hydroxyl groups associated with the target compounds.

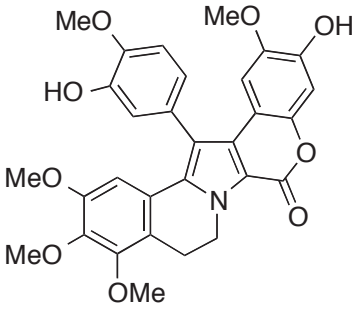
INTRODUCTION

The large family of pentacyclic lamellarins, of which the title compounds **1**–**4** are representative members, only vary in the degree, position and nature (hydroxy *vs*. methoxy and 5,6-single bond *vs*. 5,6-double bond) of the oxygenation pattern around their aromatic perimeters.[1] They have been isolated from diverse sources of marine organisms including molluscs, ascidians and sponges but are most likely the products of bacterial symbionts associated with such species.[2] The lamellarins have been subjected to a wide range of biological assays and these have revealed that they possess a remarkable array of useful properties, many of which have been highlighted in recent reviews.[1] Lamellarin D, for example, the C8-hydroxy analogue of compound **3**, is a potent inhibitor of topoisomerase I but exerts its impressive cytotoxicity primarily by inducing mitochondrial apoptosis independently of nuclear signaling.[1a] This compound is currently in preclinical development as an anti-cancer drug. Given all of this, it is unsurprising that

considerable effort has been devoted to the synthesis of the lamellarins and a wide-range of approaches have been described.[1] One of the earliest of these was reported by us in communication form[3] in 1997 and involved, as a pivotal step, the addition of an azomethine ylide to a tolan that are tethered to one another through an ester linkage. This very efficient process allowed for the rapid assembly of the pentatcyclic framework, **5**, of the target compounds and enabled us to prepare multigram quantities of lamellarin K (**1**).[4] Others have since exploited this approach to prepare a wide range of lamellarin analogues for biological evaluation.[5] Herein we now provide full details of our original work as well as extensions of it to the total synthesis of lamellarins T (**2**),[6] U (**3**)[6] and W (**4**).[6] The preparation of the (thus far) non-natural system **6** (7-deoxylamellarin K) is also described.



1
(lamellarin K)



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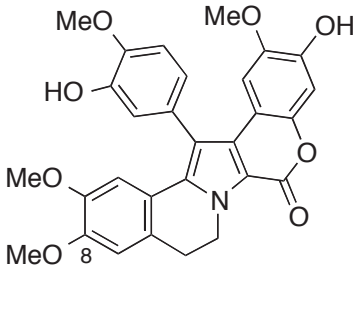
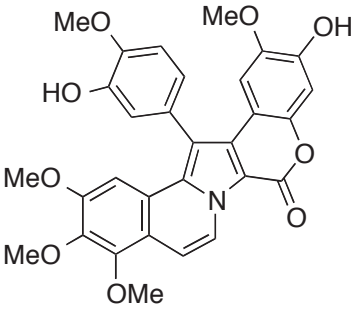
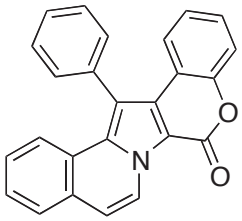
(lamellarin T)



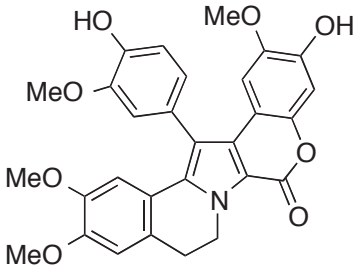
3
(lamellarin U)



4
(lamellarin W)



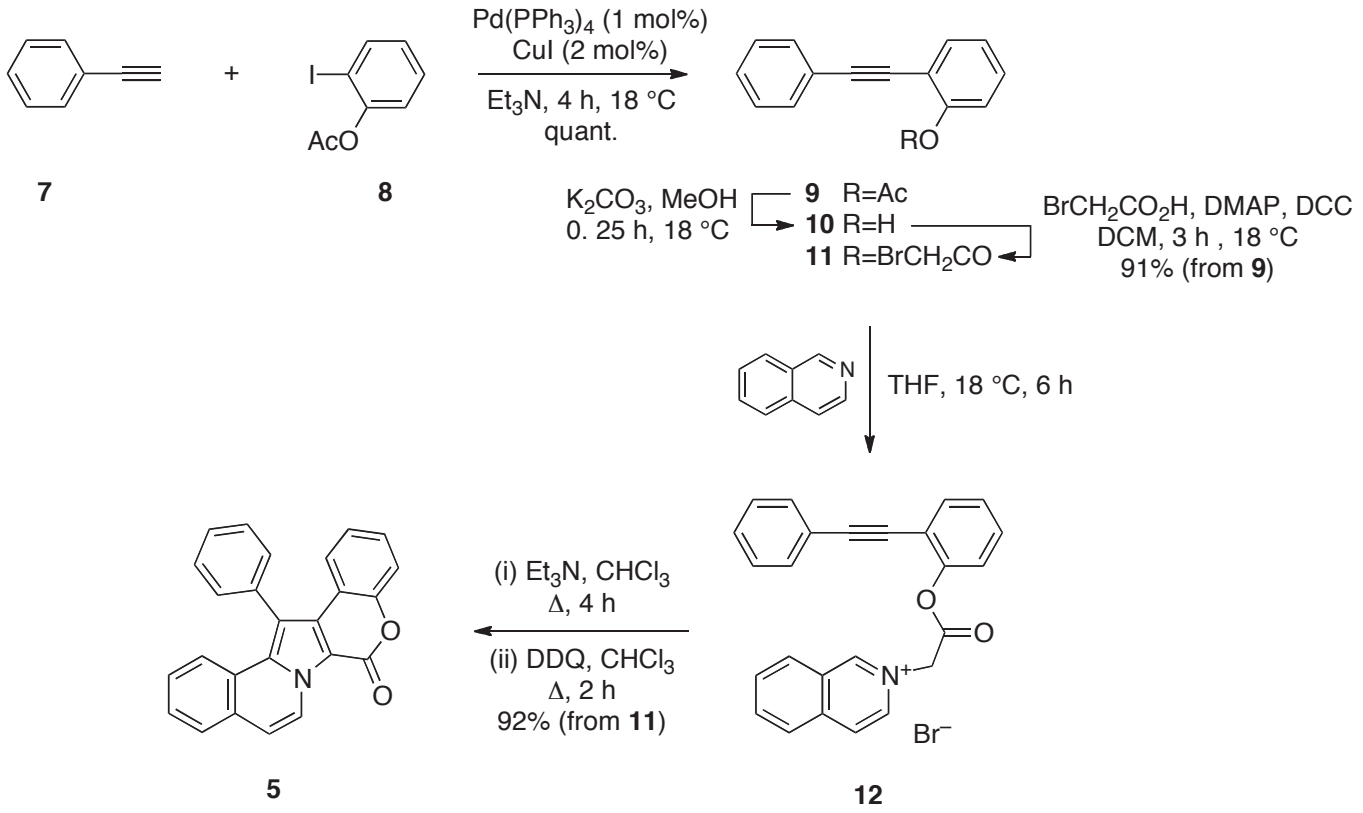
5



6
(7-deoxylamellarin K)

RESULTS AND DISCUSSION

Our initial investigations[3] were focused on establishing the basic framework, **5**, of the title natural products and the ultimately successful route is shown in Scheme 1.

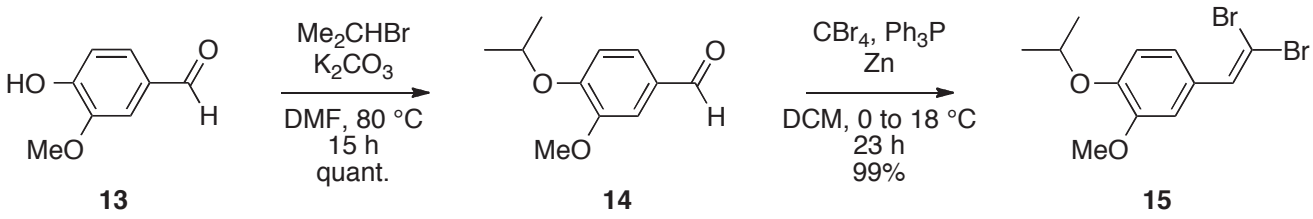


Scheme 1

Thus, phenylacetylene (**7**) was subjected Sonogashira cross-coupling[7] with the acetate derivative, **8**, of *o*-iodophenol. The resulting tolan derivative **9** (quant.)[8] was hydrolyzed using potassium carbonate in methanol and the *o*-hydroxytolan (**10**)[8] so-formed was re-esterified using α-bromoacetic acid in dichloromethane (DCM) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and dicyclohexylcarbodiimide (DCC). The ensuing ester **11** (91% from **9**) was treated with isoquinoline and the quinolinium salt **12** thus generated was immediately treated with triethylamine so as to form the corresponding azomethine ylide. This could not be isolated because it engaged in a seemingly spontaneous [3 + 2] cycloaddition reaction[9] to give a mixture of dihydropyrroles. Accordingly, the crude reaction mixture was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) so as to effect oxidation of these dihydro-species to the fully aromatic system **5** and, after silica gel chromatography, this was obtained in 92% yield (from precursor **11**). All the spectral data acquired on this compound were in complete accord with the assigned structure but final confirmation of this came from a single-crystal X-ray analysis, details of which have been reported previously.[2]

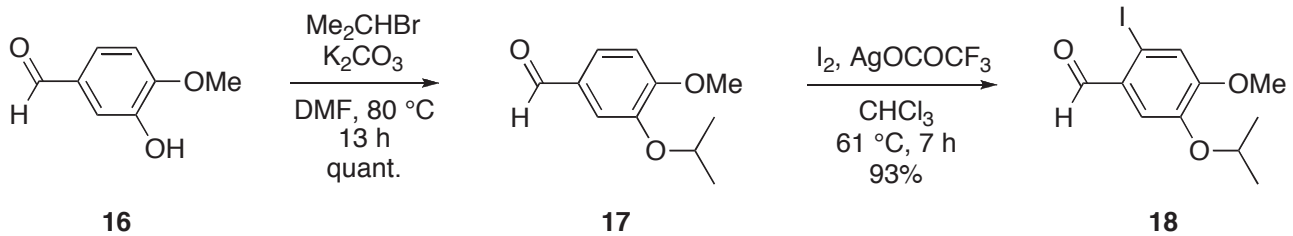
As a necessary prelude to extending the chemistry described immediately above to the synthesis of lamellarin K (**1**) several "building blocks" had to be prepared. In the construction of each of these the free hydroxyl groups associated with the target compound were carried through the reactions sequences as isopropyl ethers on the basis that these could be cleaved selectively in the presence of the corresponding

methyl ethers using aluminium trichloride or boron trichloride.[10] The first of the building blocks to be prepared was that corresponding to the isolated F-ring of target **1** as well as C-1 and C-2 of the central pyrrole ring. Thus, vanillin (**13**) (Scheme 2) was protected as the corresponding isopropyl ether **14**[1c] by treating the former compound with a mixture of isopropyl bromide and potassium carbonate in DMF at 80 °C for 15 h. Ether **14** (quant.) so obtained was subjected to a Corey–Fuchs olefination reaction[11] using carbon tetrabromide in the presence of triphenylphosphine and zinc metal and thereby forming the β,β-dibromostyrene **15** (99%) which would serve (see below) as a precursor to a metal acetylide that engaged in a Sonogashira-type cross-coupling reaction with an aryl iodide so as to generate the relevant tolan derivative.



Scheme 2

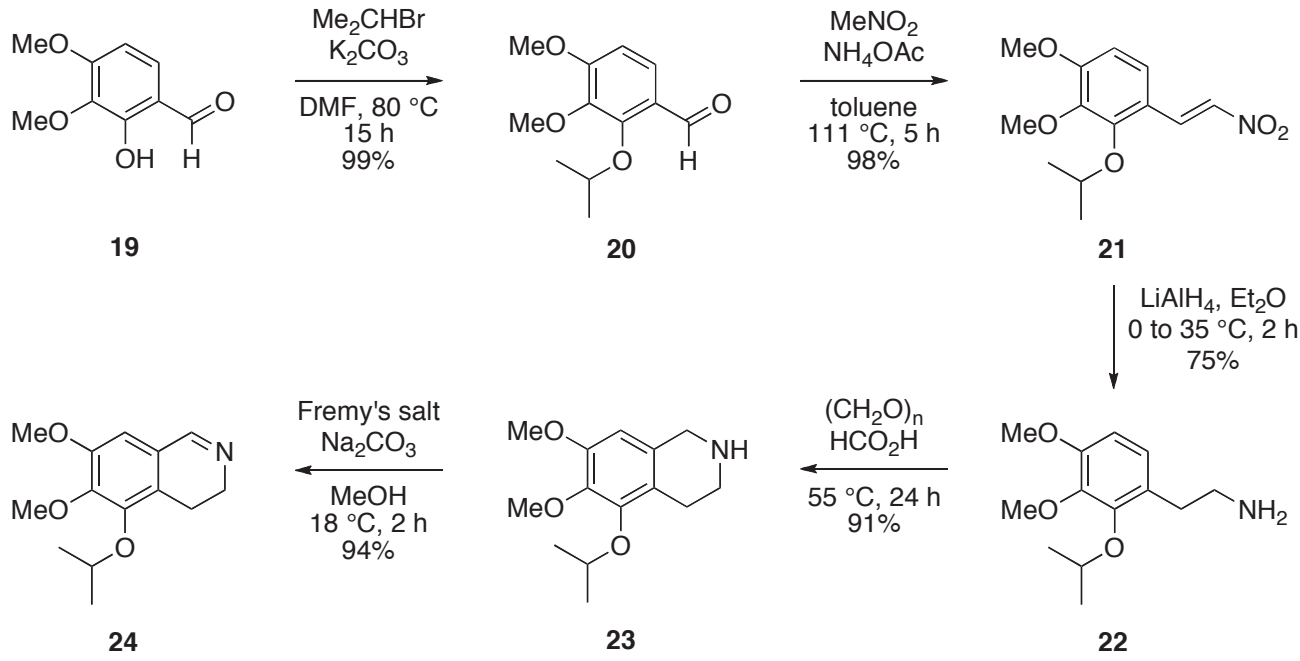
The aryl iodide required for the abovementioned cross-coupling reaction, and which would become the A-ring of target **1**, was prepared by first converting isovanillin (**16**) (Scheme 3) into the corresponding isopropyl ether using essentially the same conditions as employed for the conversion **13** → **14**. Compound **17**[12] so formed (in quantitative yield) was then subject to electrophilic aromatic iodination using molecular iodine in the presence of silver trifluoroacetate and thus producing the target iodide **18**[5b,13] in 93% yield. The 1,2,4,5-substitution pattern about the aromatic ring of this product was evident from the ^{1}H NMR spectrum that displayed two one-proton singlets at δ 7.34 and 7.24 and which arise from the 3,6-related aromatic protons.



Scheme 3

The third and final building block required for the assembly of lamellarin K was that corresponding to the D- and E-rings of the target. This was prepared by the route shown in Scheme 4 and involved initial conversion of readily available 2-hydroxy-3,4-dimethoxybenzaldehyde (**19**)[14] into the corresponding isopropyl ether **20** (96%) under the same conditions as used earlier. Compound **20** was subjected to a

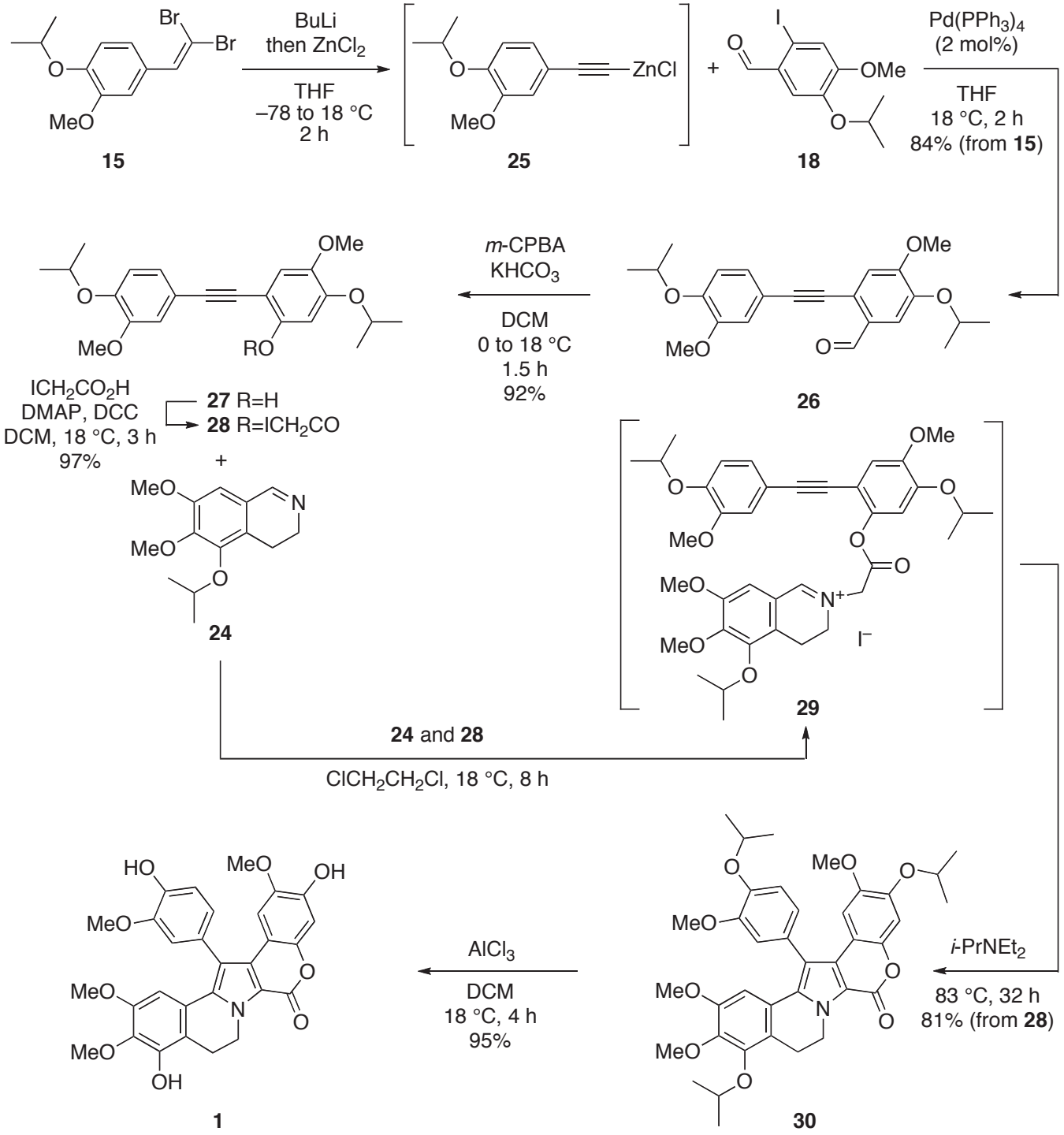
Henry reaction[15] with nitromethane using ammonium acetate as base. The β-nitrostyrene **21** so formed (in 98% yield) was treated with lithium aluminium hydride in diethyl ether and thereby producing the β-phenethylamine **22** (75%) that was subjected to a Pictet–Spengler[16] reaction using paraformaldehyde and formic acid. By such means the tetrahydroisoquinoline **23** was obtained in 91% yield. Selective oxidation of compound **23** to its 1,2-dehydro-congener **24** was readily effected (in 94% yield) by exposing the former compound to Fremy's salt in the presence of sodium carbonate.[17]



Scheme 4

With compounds **15**, **18** and **24** to hand the assembly of lamellarin K from these *via* the approach shown in Scheme 1 could be pursued. To such ends the first of these compounds, *viz*. β,β-dibromostyrene **15**, was treated with butyllithium (to effect a Fritsch–Buttenberg–Wiechell rearrangement)[18] and the ensuing lithium acetylide was *trans*-metallated using anhydrous zinc chloride to generate the corresponding zincated species **25** (Scheme 5). Compound **25** was not isolated but subjected to *in situ* cross-coupling with aryl iodide **18** and using $Pd(PPh_3)_4$ as catalyst. In this way the *o*-formylated tolan **26** was obtained in 84% yield. Upon exposure to *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of potassium bicarbonate compound **26** underwent a Dakin oxidation[19] to give phenol **27** (92%) that was immediately esterified with α-iodoacetic acid in the presence of DMAP and DCC. Ester **28** (97%) so-formed was treated with the 3,4-dihydroisoquinoline **24** and the isoquinolinium salt **29** thus obtained was treated, in refluxing 1,2-dichloroethane, with Hünig's base. Interestingly, under these conditions the fully aromatic triisopropyl ether, **30**, of lamellarin K was obtained in 81% yield. Presumably the aromatization process involved in this conversion is effected *via* the combination of iodide ion and molecular oxygen present in the reaction mixture. The completion of the synthesis of lamellarin K (**1**)[20] was readily achieved by

reacting compound **30** with *ca*. three molar equivalents of aluminium trichloride in DCM at ambient temperatures. In this way compound **1** was obtained in 95% yield as a white, crystalline solid. The spectroscopic data derived from this material were in complete accord with the assigned structure and compared favorably those reported[4] for the natural product (Table 1).



Scheme 5

Table 1. Comparison of the ^{13}C and ^{1}H NMR data recorded on synthetically- and naturally-derived samples of lamellarin K (**1**).

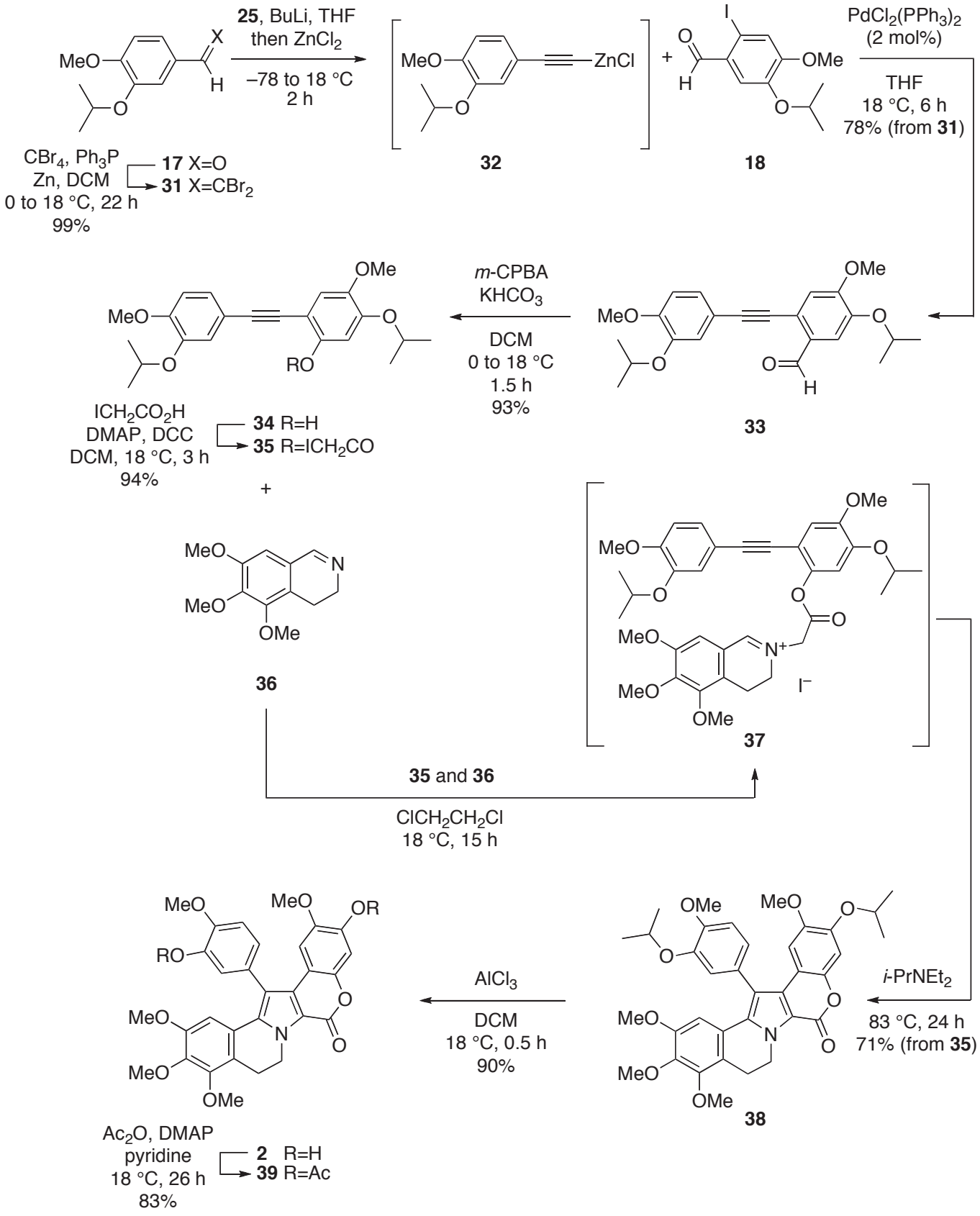
^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
Synthetic **1**[a]	Natural **1**[b]	Synthetic **1**[c]	Natural **1**[d]
154.6 (C)	154.6 (C)	7.13, d, *J* = 8.1 Hz, 1H	7.13, d, *J* = 8.1 Hz, 1H
151.0 (C)	151.1 (C)	7.07, dd, *J* = 8.1 and 1.5 Hz, 1H	7.08, dd, *J* = 8.1 and 1.9 Hz, 1H
148.7 (C)	148.8 (C)	6.97, d, *J* = 1.5 Hz, 1H	6.97, d, *J* = 1.9 Hz, 1H
147.5 (C)	146.7 (C)	6.96, s, 1H	6.93, s, 1H
147.0 (C)	147.0 (C)	6.59, s, 1H	6.57, s, 1H
146.7 (C)	146.8 (C)	6.38, s, 1H	6.36, s, 1H
145.9 (C)	145.9 (C)	5.95, s, 1H	5.98, s, 1H
144.6 (C)	144.7 (C)	5.75, s, 1H	5.78, s, 1H
136.6 (C)	136.7 (C)	5.71, s, 1H	5.76, s, 1H
135.5 (C)	135.5 (C)	4.90, m, 1H	4.92, m, 1H
127.8 (C)	127.8 (C)	4.60, m, 1H	4.61, m, 1H
125.8 (C)	125.9 (C)	3.89, s, 3H	3.89, s, 3H
123.6 (CH)	123.8 (CH)	3.87, s, 3H	3.88, s, 3H
122.7 (C)	122.8 (C)	3.49, s, 3H	3.49, s, 3H
116.5 (CH)	116.5 (CH)	3.36, s, 3H	3.38, s, 3H
115.7 (C)	115.7 (C)	3.12, m, 2H	3.12, m, 2H
114.9 (CH)	115.1 (CH)	3.12, m, 2H	3.12, m, 2H
114.5 (C)	114.5 (C)		
112.8 (C)	112.9 (C)		
108.9 (C)	109.0 (C)		
105.2 (CH)	105.3 (CH)		
103.8 (CH)	103.8 (CH)		
101.1 (CH)	101.3 (CH)		
60.5 (CH_3)	60.5 (CH_3)		
56.2 (CH_3)	56.3 (CH_3)		
55.2 (CH_3)	55.3 (CH_3)		
54.9 (CH_3)	54.9 (CH_3)		
41.9 (CH_2)	41.9 (CH_2)		
21.5 (CH_2)	21.5 (CH_2)		

[a] Recorded at 75.5 MHz in $(CD_3)_2SO$, this work. [b] Recorded at 75.5 MHz in $(CD_3)_2SO$, see Ref. 4. [c] Recorded at 300 MHz in $CDCl_3$, this work. [d] Recorded at 300 MHz in $CDCl_3$, see Ref. 4.

A synthesis of lamellarin T (**2**)[21] using the same chemistry and related building blocks is shown in Scheme 6. Thus, the previously prepared isopropyl ether **17** was engaged in a Corey–Fuchs olefination reaction and the ensuing β,β-dibromostyrene **31**[13] (99%) subjected to sequential reaction with butyllithium then zinc chloride. Acetylide **32** so-formed was cross-coupled with iodide **18** and thereby generating tolan **33**[5b,13] in 92% yield. Dakin oxidation of compound **33** and *in situ* hydrolysis of the ensuing formate ester[5b] then afforded phenol **34**[5b,13] (93%) that was esterified with α-iodoacetic acid in the presence of DMAP and DCC to give compound **35**[5b] (94%). Reaction of ester **35** with the readily available 3,4-dihydroisoquinoline **36**[22] followed by treatment of the ensuing salt **37** with Hünig's base in refluxing 1,2-dichloroethane afforded the diisopropyl ether, **38**, of lamellarin T in 71% yield. Cleavage of these ether residues within compound **38** using $AlCl_3$ in DCM then gave lamellarin T (**2**) itself in 90% yield.

Once again, the derived spectroscopic data were in complete accord with the assigned structure and matched those reported for earlier by Ruchirawat[20b] for synthetically-derived material (Table 2). Since the ^{13}C NMR spectrum of naturally-derived lamellarin T has not been reported appropriate comparisons could not be made. However, the comparison of the corresponding ^{1}H NMR spectral data was possible[6] and the levels of agreement were very good.

For the purposes of obtaining material for biological screening, the diacetate derivative, **39**, of lamellarin T was prepared in 83% yield by reacting the latter compound with acetic anhydride in the presence of DMAP and pyridine (Scheme 6).


25, BuLi, THF
then ZnCl2
–78 to 18 °C
2 h
CBr4, Ph3P
Zn, DCM
0 to 18 °C, 22 h
99%
17 X=O
31 X=CBr2
32
18
PdCl2(PPh3)2
(2 mol%)
THF
18 °C, 6 h
78% (from 31)
m-CPBA
KHCO3
DCM
0 to 18 °C
1.5 h
93%
33
ICH2CO2H
DMAP, DCC
DCM, 18 °C, 3 h
94%
34 R=H
35 R=ICH2CO
36
37
35 and 36
ClCH2CH2Cl
18 °C, 15 h
AlCl3
DCM
18 °C, 0.5 h
90%
i-PrNEt2
83 °C, 24 h
71% (from 35)
38
Ac2O, DMAP
pyridine
18 °C, 26 h
83%
2 R=H
39 R=Ac

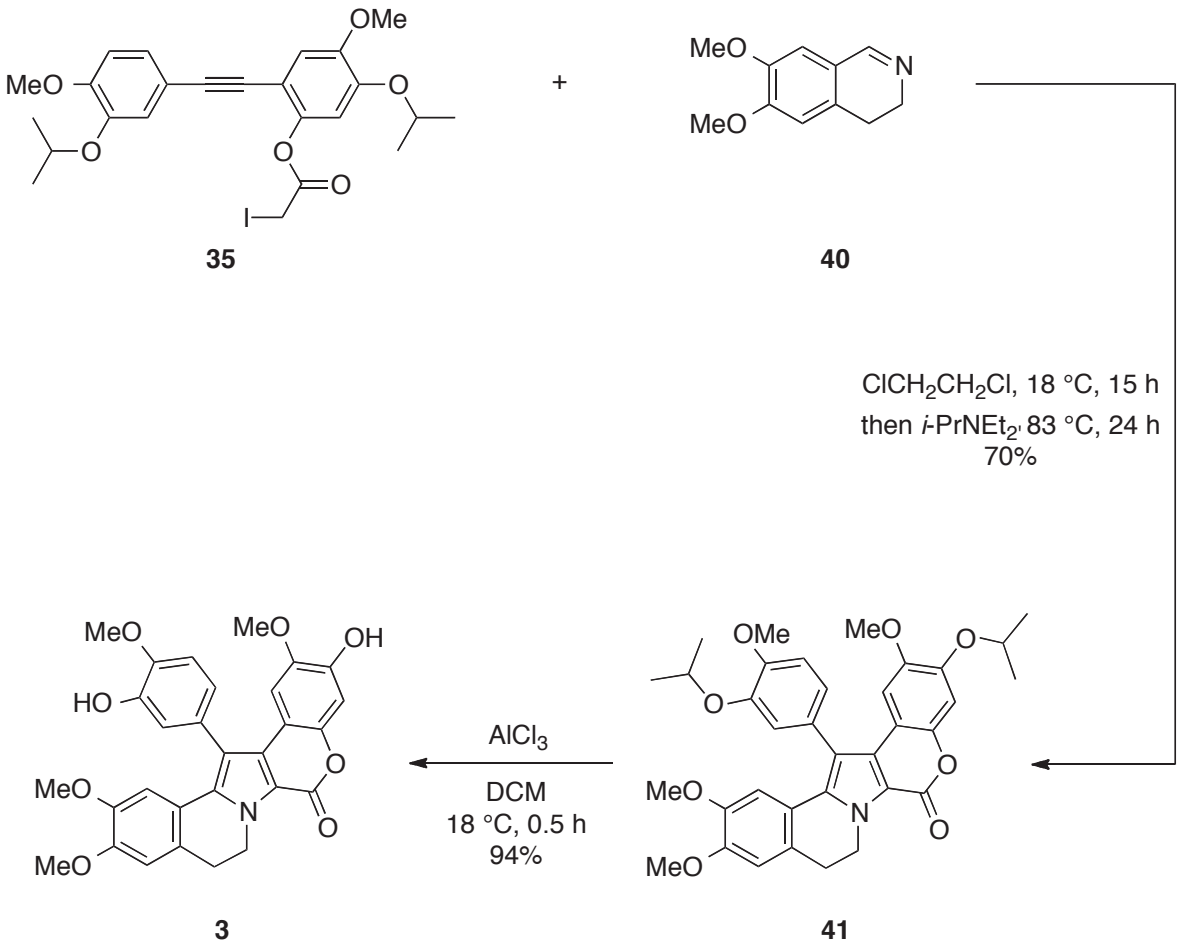
Scheme 6

Table 2. Comparison of the ^{13}C and ^{1}H NMR data recorded on synthetically-derived samples of lamellarin T (**2**).

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
Synthetic **2**[a]	Synthetic **2**[b]	Synthetic **2**[c]	Synthetic **2**[d]
154.3 (C)	154.7	9.65, s, 1H	9.72, s, 1H
151.3 (C)	151.8	9.29, s, 1H	9.34, s, 1H
150.2 (C)	150.7	7.13, d, *J* = 8.7 Hz, 1H	7.15, d, *J* = 8.8 Hz, 1H
147.7 (C)	148.2	6.90, m, 1H	6.88, d, *J* = 6.6 Hz, 1H
147.5 (C)	148.1	6.90, m, 1H	6.87, s, 1H
146.8 (C)	147.4	6.80, s, 1H	6.79, s, 1H
145.6 (C)	146.1	6.65, s, 1H	6.63, s, 1H
144.4 (C)	145.0	6.58, s, 1H	6.58, s, 1H
141.8 (C)	142.4	4.65, m, 1H and 4.56, m, 1H	4.50–4.72, m, 2H
134.6 (C)	135.1	3.83, s, 3H	3.81, s, 3H
127.3 (C)	127.7	3.79, s, 3H	3.78, s, 3H
127.1 (C)	signal not observed	3.75, s, 3H	3.73, s, 3H
122.4 (C)	122.9	3.38, s, 3H	3.37, s, 3H
121.5 (CH)	122.0	3.30, s, 3H	3.27, s, 3H
120.0 (C)	120.5	3.06, broad t, *J* = 7.0 Hz, 2H	3.05, apparent t, *J* = 6.6 Hz, 2H
117.7 (CH)	118.3		
115.2 (C)	115.7		
113.3 (CH)	114.1		
112.8 (C)	113.3		
108.5 (C)	109.0		
105.1 (CH)	105.6		
104.9 (CH)	signal not observed		
103.6 (CH)	104.1		
60.8 (CH_3)	61.2		
60.5 (CH_3)	60.9		
56.0 (CH_3)	56.6		
55.0 (CH_3)	55.6		
54.7 (CH_3)	55.3		
41.6 (CH_2)	42.1		
21.4 (CH_2)	21.9		

[a] Recorded at 75.5 MHz in $(CD_3)_2SO$, this work. [b] Recorded at 50 MHz in $(CD_3)_2SO$, see Ref. 20b. [c] Recorded at 300 MHz in $(CD_3)_2SO$, this work. [d] Recorded at 200 MHz in $(CD_3)_2SO$, see Ref. 20b.

The tolan-based ester **35** proved to be an effective precursor to lamellarin U (**3**).[23] Thus, as shown in Scheme 7, reaction of compound **35** with 6,7-dimethoxy-3,4-dihydroisoquinoline (**40**)[24] in 1,2-dichloroethane at room temperature and then Hünig's base at reflux afforded the diisopropyl ether, **41**,[5b] of compound **3** in 70% yield. Once again, treatment of this last compound with $AlCl_3$ in DCM resulted in selective cleavage of the more substituted ether residues and thereby generating lamellarin U (**3**) in 94% yield. The derived spectroscopic data were in complete accord with the assigned structure and matched those reported earlier by Ruchirawat[20b] for synthetically-derived material (Table 3). As was the case with congener **2** (lamellarin T), the ^{13}C NMR spectrum of naturally-derived lamellarin U (**3**) hasn't been reported so appropriate comparisons with our synthetic material could not be made. However, a comparison of the corresponding ^{1}H NMR data sets was possible[6] and the levels of agreement were very good.



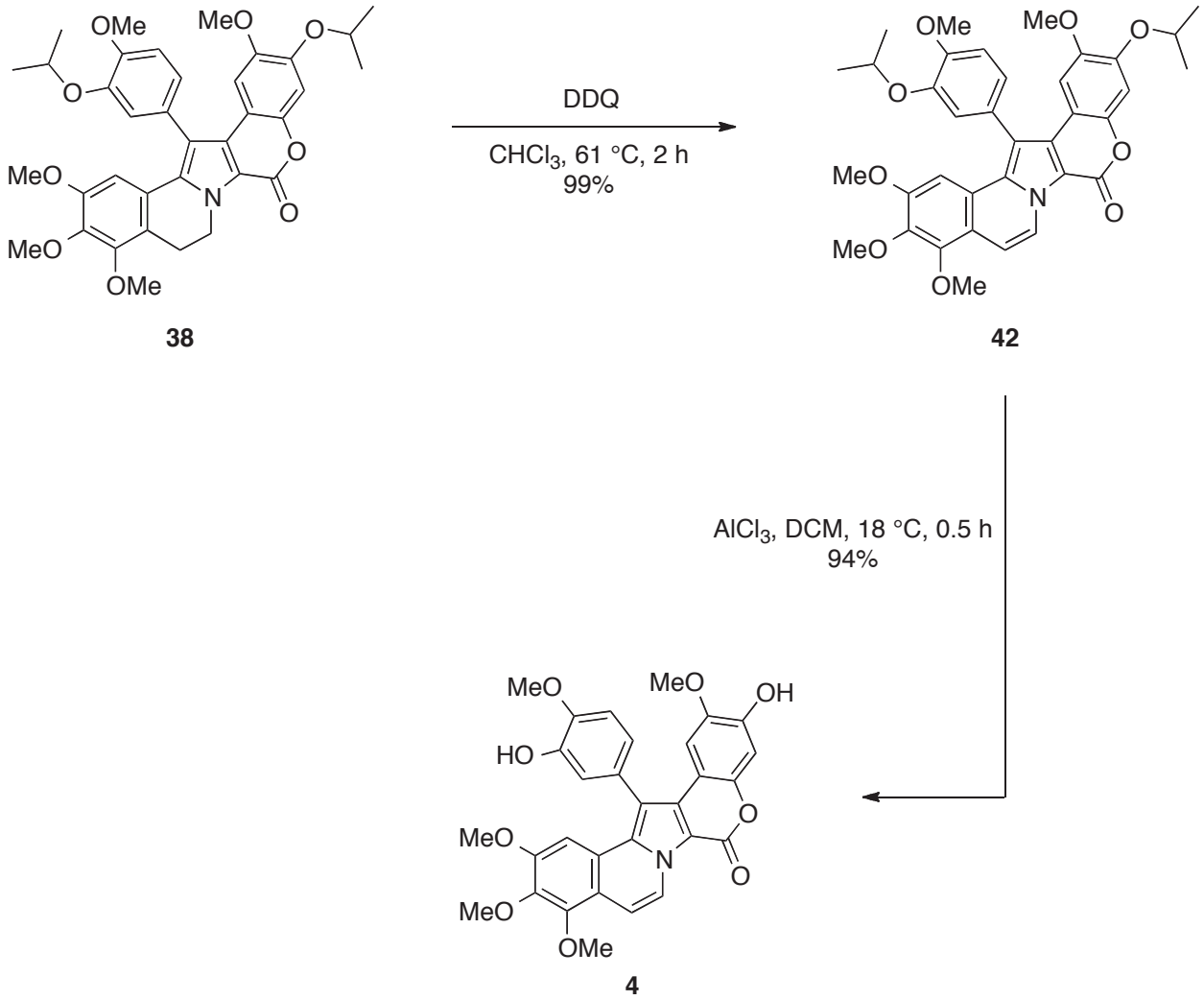
Scheme 7

Table 3. Comparison of the ^{13}C and ^{1}H NMR data recorded on synthetically-derived samples of lamellarin U (**3**).

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
Synthetic **3**[a]	Synthetic **3**[b]	Synthetic **3**[c]	Synthetic **3**[d]
154.6 (C)	154.7	9.67, s, 1H	9.71, s, 1H
149.2 (C)	149.4	9.30, s, 1H	9.33, s, 1H
148.0 (C)	148.2	7.15, d, *J* = 8.1 Hz, 1H	7.14, d, *J* = 8.8 Hz, 1H
147.9 (C)	148.0	6.98, s, 1H	6.97, s, 1H
147.3 (C)	147.5	6.90, m, 1H	6.89, d, *J* = 6.6 Hz, 1H
147.2 (C)	147.3	6.90, m, 1H	6.87, s, 1H
146.0 (C)	146.1	6.80, s, 1H	6.79, s, 1H
144.8 (C)	144.9	6.69, s, 2H	6.67, s, 2H
135.7 (C)	135.8	4.62, m, 2H	4.70–4.52, m, 2H
127.7 (C)	127.8	3.84, s, 3H	3.81, s, 3H
127.6 (C)	signal not observed	3.78, s, 3H	3.76, s, 3H
127.3 (C)	127.4	3.39, s, 3H	3.38, s, 3H
122.0 (CH)	122.1	3.26, s, 3H	3.24, s, 3H
119.6 (C)	119.8	3.10, broad t, *J* = 7.0 Hz, 2H	3.08, apparent t, *J* = 6.0 Hz, 2H
118.2 (C)	118.3		
114.7 (C)	114.8		
113.8 (CH)	114.1		
112.9 (C)	113.0		
112.1 (CH)	112.4		
109.0 (C)	109.3		
108.9 (CH)	109.1		
105.4 (CH)	105.7		
104.0 (CH)	104.1		
56.4 (CH_3)	56.6		
55.9 (CH_3)	56.1		
55.4 (CH_3)	55.6		
54.8 (CH_3)	55.0		
42.3 (CH_2)	42.4		
28.1 (CH_2)	28.1		

[a] Recorded at 75.5 MHz in $(CD_3)_2SO$, this work. [b] Recorded at 50 MHz in $(CD_3)_2SO$, see Ref. 20b. [c] Recorded at 300 MHz in $(CD_3)_2SO$, this work. [d] Recorded at 200 MHz in $(CD_3)_2SO$, see Ref. 20b.

Since lamellarin W (**4**)[25] is the 5,6-dehydro-analogue of lamallerin T (**2**) we sought to effect the necessary oxidation of the diisopropyl ether, **38**, of the latter compound (Scheme 8). In the event, treatment of compound **38** with DDQ in refluxing $CHCl_3$ afforded the corresponding fully aromatic system **42** in essentially quantitative yield.[26] Deprotection of compound **42** in the usual manner then gave the natural product **4** in 94% yield and, once again, all the derived spectral data were in accord with the assigned structure and in relatively good agreement with those reported[6] for the natural product. It seems reasonable to attribute the minor discrepancies between the two data sets shown in Table 4 to the different solvent systems used in acquiring them [$CDCl_3$/$(CD_3)_2SO$ mixtures *vs*. $(CD_3)_2SO$ alone].



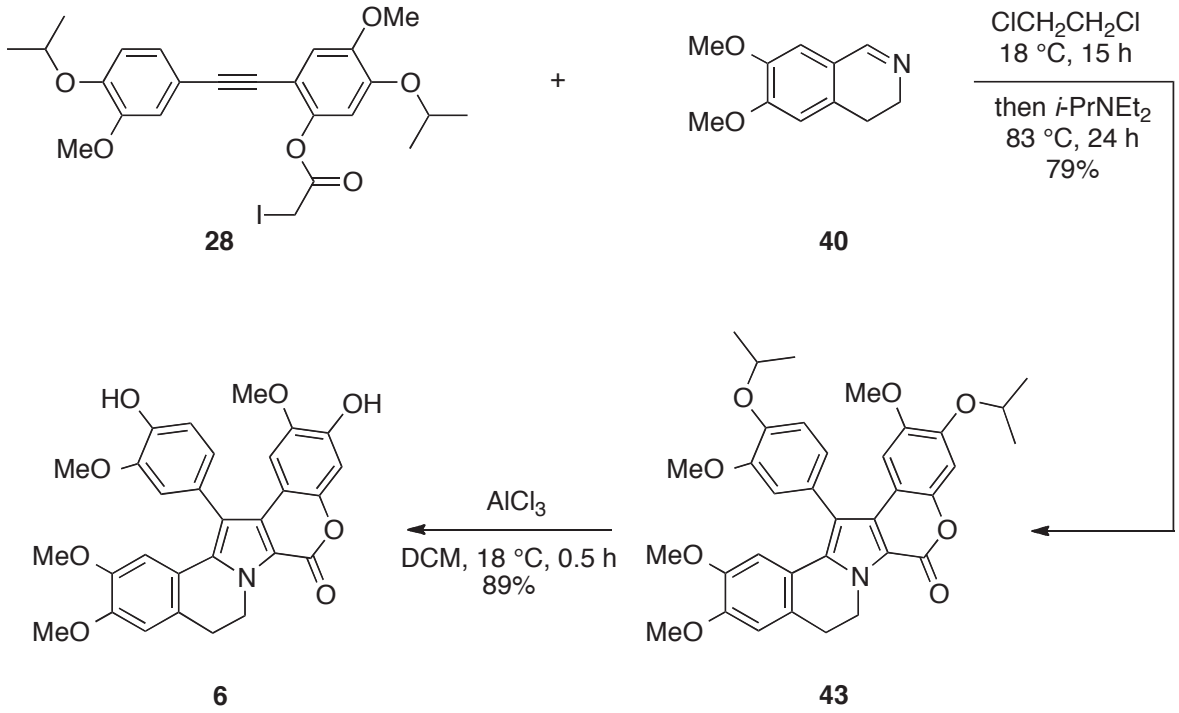
Scheme 8

Table 4. Comparison of the ^{13}C and ^{1}H NMR data recorded on synthetically- and naturally-derived samples of lamellarin W (**4**).

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
Synthetic **4**[a]	Natural **4**[b]	Synthetic **4**[c]	Natural **4**[d]
154.8 (C)	154.3 (C)	9.50, broad s, 2H	9.84, s, 1H and 9.37, s, 1H
152.4 (C)	153.0 (C)	8.89, d, *J* = 7.8 Hz, 1H	9.03, d, *J* = 7.5 Hz, 1H
147.5 (C)	148.0 (C)	7.28, d, *J* = 7.8 Hz, 1H	7.38, d, *J* = 7.5 Hz, 1H
147.1 (C)	148.0 (C)	7.09, d, *J* = 8.1 Hz, 1H	7.22, d, *J* = 8.0 Hz, 1H
146.9 (C)	147.9 (C)	6.96, s, 1H	7.04, s, 1H
146.8 (C)	147.7 (C)	6.96, s, 1H	6.99, dd, *J* = 8.0 and 2.0 Hz, 1H
146.0 (C)	146.2 (C)	6.87, d, *J* = 8.1 Hz, 1H	6.98, d, *J* = 2.0 Hz, 1H
143.9 (C)	144.6 (C)	6.82, s, 1H	6.86, s, 1H
141.3 (C)	141.8 (C)	6.70, s, 1H	6.72, s, 1H
133.0 (C)	132.8 (C)	3.92, s, 3H	3.93, s, 3H
128.8 (C)	128.7 (C)	3.84, s, 3H	3.85, s, 3H
127.4 (C)	127.0 (C)	3.81, s, 3H	3.81, s, 3H
121.9 (CH)	122.1 (CH)	3.37, s, 3H	3.37, s, 3H
121.8 (CH)	121.9 (CH)	3.37, s, 3H	3.36, s, 3H
120.6 (C)	120.6 (C)		
118.4 (C)	118.5 (C)		
117.7 (CH)	118.1 (CH)		
111.7 (CH)	113.7 (CH)		
111.3 (C)	111.9 (C)		
108.3 (C)	108.0 (C)		
107.1 (C)	107.1 (C)		
106.0 (CH)	106.8 (CH)		
104.8 (CH)	105.6 (CH)		
103.2 (CH)	103.7 (CH)		
101.2 (CH)	101.4 (CH)		
60.9 (CH_3)	61.6 (CH_3)		
60.3 (CH_3)	60.7 (CH_3)		
55.6 (CH_3)	56.1 (CH_3)		
54.7 (CH_3)	55.0 (CH_3)		
54.4 (CH_3)	54.8 (CH_3)		

[a] Recorded at 75.5 MHz in $CDCl_3$/$(CD_3)_2SO$, this work. [b] Recorded at 75.5 MHz in $(CD_3)_2SO$, see Ref. 6. [c] Recorded at 300 MHz in $CDCl_3$/$(CD_3)_2SO$, this work. [d] Recorded at 400 MHz in $(CD_3)_2SO$, see Ref. 6.

Unsurprisingly, the tolan ester **28** that had served as a precursor to lamellarin K also proved to be a useful synthon in the preparation of related systems. As part of a proposed development of a structure-activity relationship (SAR) profile for the pentacyclic lamellarins, we sought to make 7-deoxylamellarin K (**6**) and were able to do so using compound **28** as shown in Scheme 9. Thus, reaction of this α-iodoacetate with the 1,2-dihydroisoquinoline **40** used earlier in the synthesis of lamellarin U and treatment of the ensuing salt with Hünig's base in refluxing 1,2-dichloroethane afforded the diisopropyl ether, **43**, of the final target in 79% yield. Exposure of this last compound to aluminium trichloride in DCM at 18 °C for 0.5 h then gave compound **6** as a white, crystalline solid in 89% yield. The spectral data derived from this material, which are presented in the Experimental section, were in complete accord with the assigned structure.



Scheme 9

CONCLUSIONS

The ready assembly of the pentacyclic lamellarins K, T, U and W by the methods detailed above serves to highlight the utility of this highly modular approach to such natural products. Indeed, its exploitation by others[5] during the course of developing SAR profiles for the lamellarins suggests the title process will continue serve as a useful tool for the development of analogues with therapeutic potential. It may also prove useful for the assembly of lamellarins that incorporate unusual isotopic labeling patterns.

EXPERIMENTAL

General Protocols

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 NMR spectrometer operating at 300 MHz (for proton) and 75 MHz (for carbon). Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as thin films on KBr plates. Low resolution mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-MS or VG Quattro II triple quadrupole MS instrument using electron impact techniques. High resolution mass spectra were recorded on an AUTOSPEC spectrometer. Dichloromethane (DCM) was distilled from calcium hydride and THF was distilled, under nitrogen, from sodium benzophenone ketyl. Where necessary, reactions were performed under a nitrogen atmosphere. Flash chromatographic separations were carried out using protocols defined by Still *et al*.[27]

Specific Transformations

Compound 9. $Pd(PPh_3)_4$ (132 mg 0.11 mmol), phenylacetylene (**7**) (1.30 mL, 1.20 g, 12.6 mmol) and CuI (44 mg, 0.23 mmol) were added, sequentially, to a magnetically stirred solution of 2-acetoxyiodobenzene (**8**) (3.00 g, 11.45 mmol) in Et_3N (20.0 mL) and the ensuing mixture stirred at 18 °C for 4 h. After this time the reaction mixture was concentrated under reduced pressure and the residue thus obtained dissolved in DCM (50 mL) and the resulting solution washed with HCl (1 × 50 mL of a 0.5 M aqueous solution) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated onto TLC-grade silica gel (8.0 g). The free-flowing solid thus obtained was subjected to flash chromatography (silica gel; 3:1, 2:1, 1:1 then 1:2 v/v hexane/DCM gradient elution) and concentration of the appropriate fractions gave the tolan **9**[8] (2.70 g, 100%). The physical and spectroscopic data acquired on this material were in complete accord with those recorded[8] previously.

Compound 11. Compound **9** (2.24 g, 9.50 mmol) was added to a magnetically stirred slurry of anhydrous K_2CO_3 (2.0 g, mmol) in MeOH (20 mL). After 0.25 h the reaction mixture was diluted with HCl (50 mL of a 0.5 M aqueous solution) and extracted with DCM (2 × 40 mL). The combined extracts were dried ($MgSO_4$) filtered and then concentrated under reduced pressure. The crude sample of *o*-hydroxytolan (**10**)[8] thus obtained was dissolved in DCM (20 mL) and the resulting solution treated with α-bromoacetic acid (1.32 g, 9.5 mmol) and DMAP (58 mg, 0.48 mmol). DCC (2.07 g, 10 mmol) was then added in portions and the ensuing mixture stirred at 18 °C for 3 h before being filtered through Celite™ and the filtrate concentrated onto TLC-grade silica gel (8 g). The free-flowing solid thus obtained was subjected to flash chromatography (silica gel; 2:1, 1:1 then 1:2 v/v hexane/DCM gradient elution) and concentration

of the appropriate fractions (R_f = 0.5 in 2:1 hexane/DCM) gave *compound **11*** (2.73 g, 91%) as an amber-coloured oil (Anal. Calcd for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52; Br, 25.35. Found: C, 61.26; H, 3.45; Br, 25.06%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.54–7.52 (complex m, 2H), 7.41–7.35 (complex m, 4H), 7.29 (m, 1H), 7.17 (dd, *J* = 8.1 and 1.4 Hz, 1H), 4.13 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0 (C), 150.6 (C), 133.0 (CH), 131.4 (CH), 129.3 (CH), 128.5 (CH), 128.2 (CH), 126.3 (CH), 122.4 (C), 121.7 (CH), 116.9 (C), 94.6 (C), 83.5 (C), 25.1 (CH_2); ν_{max} (KBr) 3060, 2221, 1761, 1596, 1571, 1496, 1444, 1258, 1195, 1116, 1099 756, 691 cm^{-1}; MS (70 eV) *m/z* 316 and 314 (30) ($M^{+\bullet}$, 31 and 30%, respectively), 277 (15), 221 (24), 193 (100), 165 (42).

Compound 5. Isoquinoline (98 μL, 0.83 mmol) was added to a magnetically stirred solution of compound **11** (262 mg, 0.83 mmol) in THF (5 mL) and the ensuing mixture allowed to stir at 18 °C for 6 h before being treated with Et_3N (215 μL, 0.83 mmol) and $CHCl_3$ (10 mL). The bright-orange solution thus formed, and presumed to contain the isoquinolinium salt **12** and/or the derived azomethine ylide, was heated at reflux for 4 h then the by now light-yellow solution was cooled and concentrated under reduced pressure. The resulting light-yellow oil was dissolved in DCM (7 mL) and DDQ (189 mg, 0.83 mmol) then added. The ensuing mixture was immediately concentrated onto TLC-grade silica gel (2 g) and the resulting free-flowing solid subjected to flash chromatography (silica gel; 2:1, 1:1 then 1:2 v/v hexane/DCM gradient elution). Concentration of the appropriate fractions (R_f = 0.5 in 1:2 hexane/DCM) gave *compound **5*** (277 mg, 92%) as white, crystalline masses, mp 313–315 °C (Found $M^{+\bullet}$, 361.1101. $C_{25}H_{15}NO_2$ requires $M^{+\bullet}$, 361.1103). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (d, *J* = 7.2 Hz, 1H), 7.67–7.60 (complex m, 4H), 7.56–7.39 (complex m, 5H), 7.32 (dt, *J* = 7.5 and 1.8 Hz, 1H), 7.25 (dt, *J* = 7.5 and 1.5 Hz, 1H), 7.12–7.05 (complex m, 2H), 6.99 (dt, *J* = 7.5 and 1.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.2 (C), 151.7 (C), 135.6 (C), 134.1 (C), 131.0 (CH), 129.9 (CH), 129.6 (C), 128.7 (CH), 128.6 (C), 128.4 (CH), 128.1 (CH), 127.5 (CH), 127.3 (CH), 125.0 (C), 124.4 (CH), 124.1 (CH), 123.9 (CH), 117.9 (C), 117.3 (CH), 114.3 (C), 113.4 (CH), 109.3 (CH) (one signal obscured or overlapping); ν_{max} (KBr) 3047, 1705, 1470, 1445, 1411, 1369, 1312, 1179, 1110, 1049, 790, 741 cm^{-1}; MS (70 eV) *m/z* 361 ($M^{+\bullet}$, 100%).

Compound 14. Isopropyl bromide (40.0 mL, 421 mmol) was added to a magnetically stirred suspension of anhydrous K_2CO_3 (48.0 g, 348 mmol) and vanillin (**13**) (40.0 g, 263 mmol) in DMF (150 mL) and the resulting slurry heated to 80 °C for 15 h. The reaction mixture was then cooled to 18 °C, diluted with Et_2O (200 mL) and washed with water (4 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give compound **14**[1c] (51.0 g, 100%) as a tan-coloured oil. The spectroscopic data acquired on this material were in complete accord with those recorded[1c] previously. This material was used without purification in the next step of the reaction sequence.

Compound 15. Carbon tetrabromide (51.3 g, 154.7 mmol) was added, in portions, to a magnetically

stirred mixture of zinc dust (10.1 g, 154.5 g.atom) and PPh_3 (40.5 g, 159.4 mmol) in DCM (350 mL) maintained at 0 °C on an ice-salt bath. The resulting suspension was allowed to warm to 18 °C and then stirred at this temperature for a further 22 h before being re-cooled to 0 °C then treated, over 0.03 h, with compound **14** (15.0 g, 77.3 mmol). The resulting mixture was allowed to stir at 18 °C for 1 h then diluted with hexane (200 mL) and filtered through a sintered glass funnel and the filtrate concentrated onto TLC-grade silica gel (30.0 g). The resulting free-flowing solid was subjected to flash chromatography (silica gel; 2:1, 1:1 then 1:2 v/v hexane/DCM gradient elution). Concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v hexane/DCM) then afforded *compound **15*** (27.2 g, 99%) as white, crystalline masses, mp 36–38 °C (Anal. Calcd for $C_{12}H_{14}Br_2O_2$: C, 41.17; H, 4.03; Br, 45.65. Found: C, 41.21; H, 3.92; Br, 45.47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.07 (dd, *J* = 8.4 and 2.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.58 (septet, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 1.39 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.7 (C), 147.7 (C), 136.5 (CH), 127.9 (C), 121.9 (CH), 114.4 (CH), 111.8 (CH), 87.1 (C), 71.1 (CH), 56.0 (CH_3), 22.1 (CH_3); ν_{max} (KBr) 2976, 2933, 1599, 1510, 1464, 1418, 1383, 1373, 1267, 1235, 1141, 1110, 1036, 953, 872, 839, 816, 632 cm^{-1}; MS (70 eV) *m/z* 352, 350 and 348 ($M^{+\bullet}$, 28, 49 and 31%, respectively), 310, 308 and 306 (51, 100 and 54, respectively), 295 (34), 293 (38), 291 (36).

Compound 17. Isopropyl bromide (19.0 mL, 200 mmol) was added to a magnetically suspension of anhydrous K_2CO_3 (42.0 g, 302 mmol) and isovanillin (**16**) (23.0 g, 151.3 mmol) in DMF (100 mL). The ensuing slurry was heated at 80 °C for 13 h then cooled to 18 °C before being diluted with Et_2O (200 mL) then washed with water (4 × 200 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the diether **17**[12] (29.3 g, 100%). The spectroscopic data acquired on this material were in complete accord with those recorded[12] previously.

This material was used without purification in the next step of the reaction sequence.

Compound 18. Compound **18** was prepared by electrophilic iodination of aldehyde **17** using a procedure defined earlier.[13] The physical and spectroscopic data acquired on this material were in complete accord with those recorded[5b,13] previously.

Compound 19. $AlCl_3$ (14.0 g, 10.5 mmol) was added, in portions over 0.5 h, to a rapidly stirred solution of 2,3,5-trimethoxybenzaldehyde (20.0 g, 10.2 mmol) in anhydrous benzene (150 mL) and the resulting mixture heated at reflux for 5 h then the cooled reaction mixture concentrated under reduced pressure. The ensuing residue was dissolved in DCM (200 mL) and the resulting solution washed with HC1 (2 × 80 mL of a 5 M aqueous solution) then the organic layer was extracted with NaOH (2 × 80 mL of 10% w/v aqueous solution). The combined aqueous extracts were cooled to 0 °C and acidified to pH = 2 by the dropwise addition of HCl (32% by weight in water). The resulting slurry was extracted with DCM (2 × 100 mL) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under

reduced pressure. The solid residue thus obtained was suspended in hexane (120 mL) and the ensuing mixture stirred vigorously at 18 °C for 24 h then stored at 0 °C for 6 h before being filtered to give 2-hydroxy-3,4-dimethoxybenzaldehyde (**19**)[14] (18.3 g, 99%). The physical and spectroscopic data acquired on this material were in complete accord with those recorded[14] previously.

This material was used without purification in the next step of the reaction sequence.

Compound 20. Isopropyl bromide (11.5 mL, 121.9 mmol) was added to a magnetically stirred suspension of anhydrous K_2CO_3 (16.9 g, 122.5 mmol) and 2-hydroxy-3,4-dimethoxybenzaldehyde (**19**) (17.0 g, 93.8 mmol) in DMF (100 mL). The resulting mixture was heated at 80 °C for 15 h then cooled to 18 °C, diluted with Et_2O (200 mL) and washed with water (4 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give *compound **20*** (20.0 g, 96%) as a clear, colourless oil (Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.05; H, 7.18%). ^{1}H NMR (300 MHz, $CDC1_3$) δ 10.26 (s, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 1H), 4.71 (septet, *J* = 6.3 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 1.32 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDC1_3$) δ 189.0 (CH), 159.0 (C), 154.6 (C), 141.7 (C), 124.4 (C) 123.5 (CH), 107.1 (CH), 76.5 (CH), 60.3 (CH_3), 55.9 (CH_3), 22.1 (CH_3); ν_{max} (KBr) 2976, 2937, 2843, 1680, 1587, 1493, 1455, 1427, 1382, 1289, 1261, 1229, 1198, 1092 cm^{-1}; MS (70 eV) *m/z* 224 ($M^{+\bullet}$, 67%), 182 (100), 167 (60), 139 (72).

Compound 21. Nitromethane (8.0 mL, 146.5 mmol) and NH_4OAc (4.0 g, 51.4 mmol) were added to a solution of aldehyde **20** (14.5 g, 64.7 mmol) in toluene (150 mL) contained in an apparatus fitted with a condenser and Dean–Stark trap. The reaction mixture was heated at reflux for 5 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica gel; 2:1, 1:1 then 1:2 v/v hexane/DCM gradient elution) and concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v hexane/DCM) then gave *β-nitrostyrene **21*** (17.0 g, 98%) as a white, crystalline solid, mp 63–65 °C (Anal. Calcd for $C_{11}H_{17}IO_3$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.39; H, 6.43; N, 5.16%). ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.12 (d, *J* = 13.5 Hz, 1H), 7.72 (d, *J* = 13.5 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 1H) 4.71 (septet, *J* = 6.3 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDC1_3$) δ 157.1 (C), 152.0 (C), 142.4 (C), 135.9 (CH), 135.5 (CH), 125.5 (CH), 118.0 (C), 107.4 (CH), 76.5 (CH), 60.3 (CH_3), 55.9 (CH_3), 22.4 (CH_3); ν_{max} (KBr) 3108, 2976, 2935, 1626, 1598, 1495, 1465, 1451, 1440, 1384, 1337, 1274, 1245, 1222, 1172, 1096, 1034, 986, 965, 796 cm^{-1}; MS (70 eV) *m/z* 267 ($M^{+\bullet}$, 54%), 225 (32), 178 (100), 163 (66).

Compound 22. A solution of β-nitrostyrene **21** (4.00 g, 14.96 mmol) in Et_2O/THF (4.0 mL of a 3:1 v/v mixture) was added dropwise, over a period of 0.66 h, to a magnetically stirred suspension of $LiAlH_4$ (2.27g, 59.81 mmol) in dry Et_2O (200 mL) (**CAUTION**: the reaction is strongly exothermic and causes reflux). After the addition was complete and the reaction mixture had been cooled to 18 °C it was allowed to stir at this temperature for 1 h before being further cooled to 0 °C and treated, dropwise over 1.5 h,

with H_2SO_4 (60 mL of a 1.5 M aqueous solution). The two phases were separated and the aqueous one extracted with Et_2O (2 × 100 mL). The aqueous layer was cooled to 0 °C and treated with KOH (1 M aqueous solution) until pH = 9 was attained. The resulting mixture was extracted with Et_2O (2 × 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give *amine* ***22*** (2.70 g, 75%) as an amber-coloured oil (Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.13; H, 8.76; N, 5.59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H) 4.46 (septet, *J* = 6.3 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.11 (d, *J* = 6.3 Hz, 6H) (signals due to NH_2 group protons not observed); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.7 (C), 149.4 (C), 141.9 (C), 126.1 (C), 123.7 (CH), 106.3 (CH), 74.4 (CH), 59.9 (CH_3), 55.5 (CH_3), 42.4 (CH_2), 33.9 (CH_2), 22.3 (CH_3); ν_{max} (KBr) 2974, 2935, 2837, 1682, 1600, 1494, 1456, 1424, 1382, 1371, 1285, 1257, 1229, 1098, 1044 cm^{-1}; MS (70 eV) *m/z* 239 ($M^{+\bullet}$, 34%), 210 (52), 168 (98), 167 (100), 153 (33).

Compound 23. Paraformaldehyde (330 mg, 11.0 mmol) was added to a magnetically stirred solution of amine **22** (2.60 g, 10.88 mmol) in formic acid (15 mL) and the ensuing mixture stirred at 55 °C for 24 h before being cooled and concentrated under reduced pressure to give a light-yellow oil. This was dissolved in EtOH (35 mL), the resulting solution treated with oxalic acid (1.96 g, 21.8 mmol) and the slurry thus obtained concentrated under reduced pressure. The solid so-formed was washed with EtOH (2 × 15 mL) then dried under reduced pressure to give a white solid. This material, which is presumed to be the oxalate salt of the target tetrahydroisoquinoline, was not characterized but converted into the free base by suspending it in cold water (20 mL) and then adding KOH (673 mg, 12.0 mmol) in portions. The emulsion thus formed was extracted with Et_2O (2 × 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give *compound* ***23*** (2.49 g, 91%) as an amber-coloured oil (Anal. Calcd for $C_{14}H_{21}NO_3$ $M^{+\bullet}$, 251.1521. Found 251.1516). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 1H), 4.58 (septet, *J* = 6.0 Hz, 1H), 3.91 (s, 2H), 3.78 (s, 6H), 3.05 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 1.95 (broad s, 1H), 1.25 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.5 (C), 149.4 (C), 140.3 (C), 131.2 (C), 121.8 (C), 104.4 (CH), 74.7 (CH), 60.4 (CH_3), 55.8 (CH_3), 48.3 (CH_2), 43.7 (CH_2), 24.0 (CH_2), 22.8 (CH_3); ν_{max} (KBr) 3311, 2972, 2933, 1601, 1492, 1465, 1452, 1424, 1381, 1323, 1298, 1276, 1238, 1222, 1176, 1116, 1027 cm^{-1}; MS (70 eV) *m/z* 251 ($M^{+\bullet}$, 49%), 208 (52), 192 (56), 180 (100).

This material was used without purification in the next step of the reaction sequence.

Compound 24. Na_2CO_3 (100 mL of a 4% w/v aqueous solution) was added to a magnetically stirred solution of compound **23** (4.73 g, 18.8 mmol) in MeOH (15 mL) maintained at 18 °C and the ensuing mixture was treated with Fremy's salt (10.1 g, 37.7 mmol). The resulting dark-purple solution was stirred at 18 °C for 2 h then concentrated under reduced pressure and extracted with DCM (3 × 70 mL). The

combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing residue to column chromatography (alumina; Et_2O then 98:2, 95:5 and 9:1 v/v Et_2O/MeOH gradient elution) and concentration of the relevant fractions (R_f = 0.2 in 9:1 v/v Et_2O/MeOH on silica gel) gave *compound* ***24*** (4.41 g, 94%) as a clear, colourless oil (Anal. Calcd for $C_{14}H_{19}NO_3$: $M^{+\bullet}$, 249.1365. Found: $M^{+\bullet}$, 249.1365). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.1 Hz, 1H), 6.29 (s, 1H), 4.43 (septet, *J* = 6.3 Hz, 1H), 3.80 (s, 6H), 3.61 (dt, *J* = 7.8 and 2.1 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.20 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.5 (CH), 152.0 (C), 148.0 (C), 144.8 (C), 123.8 (C), 123.4 (C), 106.5 (CH), 75.3 (CH), 60.4 (CH_3), 55.9 (CH_3), 47.1 (CH_2), 22.5 (CH_3), 19.0 (CH_2); ν_{max} (KBr) 2973, 2937, 2841, 1629, 1596, 1571, 1489, 1454, 1421, 1367, 1352, 1318, 1124, 1110, 1100 cm^{-1}; MS (70 eV) *m/z* 249 ($M^{+\bullet}$, 49%), 207 (50), 192 (100).

Compound 26. Butyllithium (5.25 mL of a 2.5 M solution in hexane, 13.15 mmol) was added, dropwise over 0.05 h, to a magnetically stirred solution of styrene **15** (2.30 g, 6.58 mmol) in THF (30 mL) maintained at –78 °C on a dry-ice acetone bath. The light-tan coloured solution thus obtained was allowed to stir for a further 0.83 h at –78 °C then anhydrous $ZnCl_2$ (dried under high vacuum at 120 °C for 20 h) was added to the reaction mixture which slowly became colourless as it was warmed to 18 °C over 1 h. $Pd(PPh_3)_4$ (145 mg, 0.125 mmol) and aldehyde **18**[5b,13] (2.00 g, 6.26 mmol) were then added to the reaction mixture which was stirred at 18 °C for 4 h before being diluted with EtOAc (150 mL) and washed with brine (2 × 100 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated on to TLC-grade silica (10 g). The resulting free-flowing solid was subjected to flash chromatography (silica gel; 1:1, 1:2 v/v hexane/DCM then 9:1 v/v DCM/EtOAc gradient elution). Concentration of the appropriate fractions (R_f = 0.4 in DCM) then afforded *compound* ***26*** (2.01 g, 84%) as white, crystalline masses, mp 121–122 °C (Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.08; H, 6.92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.41 (s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.04 (s, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.68 (septet, *J* = 6.0 Hz, 1H), 4.58 (septet, *J* = 6.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.2 (CH), 154.4 (C), 149.7 (C), 148.1 (C), 147.6 (C), 129.6 (C), 124.7 (CH), 121.3 (C), 114.6 (CH), 114.5 (CH), 114.3 (CH), 110.6 (CH), 94.9 (C), 83.4 (C), 71.0(3) (CH), 70.9(7) (CH), 56.0 (CH_3), 55.7 (CH_3), 21.8 (CH_3), 21.6 (CH_3) (one signal obscured or overlapping); ν_{max} (KBr) 2978, 2933, 2837, 2204, 1687, 1589, 1515, 1509, 1397, 1357, 1275, 1241, 1217, 1133, 953 cm^{-1}; MS (70 eV) *m/z* 382 ($M^{+\bullet}$, 47%), 298 (100), 283 (54), 255 (18).

Compound 27. *m*-Chloroperoxybenzoic acid [1.20 g, ALDRICH, 50% (remainder 3-chlorobenzoic acid and water), *ca*. 7.0 mmol] was added, in portions over 0.25 h, to a magnetically stirred mixture of compound **26** (2.20 g, 5.75 mmol) and anhydrous $KHCO_3$ (1.73 g, 17.3 mmol) in DCM (50 mL) maintained at 0 °C (ice-bath). The resulting slurry was stirred for a further 1 h between 0 and 18 °C then filtered through Celite™ and the retained solids were rinsed with DCM (1 × 50 mL). The combined

filtrates were concentrated under reduced pressure and the residue thus obtained treated with NH_3 (30 mL of a saturated methanolic solution). After 1 h at 18 °C the reaction mixture was concentrated under reduced pressure and the ensuing residue dissolved in DCM (200 mL) then concentrated onto TLC-grade silica gel (5.0 g). The resulting free-flowing solid was subjected to flash chromatography (silica gel; 2:1, 1:1 then 1:2 v/v hexane/DCM then DCM gradient elution). Concentration of the appropriate fractions (R_f = 0.3 in 1:2 v/v hexane/DCM) gave *compound* ***27*** (1.97 g, 92%) as white, crystalline masses, mp 130–131 °C (Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 70.91; H, 7.24.%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 8.4 and 1.8 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.87 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H), 5.81 (s, 1H), 4.52 (septet, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.8 (C), 149.7 (C), 149.3 (C), 147.8 (C), 143.6 (C), 124.6 (CH), 115.0 (C), 114.7 (CH), 114.6 (CH), 114.3 (CH), 102.0 (CH), 100.1 (C), 94.7 (C), 82.2 (C), 71.1 (CH), 71.0 (CH), 56.4 (CH_3), 55.7 (CH_3), 21.9 (CH_3), 21.8 (CH_3); ν_{max} (KBr) 3404, 2981, 2935, 1620, 1599, 1573, 1513, 1467, 1450, 1418, 1383, 1373, 1330, 1269, 1240, 1214, 1166, 1135, 1113, 1027, 951, 863 cm^{-1}; MS (70 eV) *m/z* 370 ($M^{+\bullet}$, 89%), 328 (18), 327 (20), 286 (100), 271 (42).

Compound 28. DCC (1.60 g, 7.75 mmol) was added to a magnetically stirred solution of α-iodoacetic acid (1.44 g, 7.74 mmol), compound **27** (2.60 g, 7.03 mmol) and DMAP (43 mg, 0.35 mmol) in DCM (30 mL) and the ensuing mixture stirred at 18 °C for 3 h then filtered through a sintered glass funnel. The retained solid was washed with DCM and the combined filtrates concentrated under reduced pressure. The residue thus obtained was suspended, *via* magnetic stirring, in Et_2O (30 mL) at 0 °C then filtered [rinsing with Et_2O (20 mL) pre-cooled to 0 °C] to give *compound* ***28*** (3.67 g, 97%) as a cream-coloured solid, mp 127–128 °C (Anal. Calcd for $C_{24}H_{27}IO_6$: $M^{+\bullet}$, 538.0852. Found: $M^{+\bullet}$, 538.0854). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.4 and 1.8 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 7.01 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.65 (s, 1H), 4.53 (septet, *J* = 6.0 Hz, 2Hz), 3.95 (s, 2H), 3.85 (s, 6H), 1.38 (d, *J* = 6.0 Hz, 6H), 1.37 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.3 (C), 150.0 (C), 148.4 (C), 148.3 (C), 148.2 (C), 145.1 (C), 125.2 (CH), 115.6 (C), 115.3 (CH), 115.2 (CH), 115.1 (CH), 108.8 (CH), 93.6 (C), 82.8 (C), 72.0 (CH), 71.6 (CH), 56.6 (CH_3), 56.3 (CH_3), 22.3 (CH_3), 22.0 (CH_3), –6.2 (CH_2) (one signal obscured or overlapping); ν_{max} (KBr) 2969, 2930, 2833, 1755, 1611, 1575, 1516, 1467, 1416, 1402, 1385, 1365, 1320, 1252, 1236, 1212, 1187, 1175, 1157, 1135, 1108 954, 851 cm^{-1}; MS (70 eV) *m/z* 538 ($M^{+\bullet}$, 80%), 496 (10), 328 (34), 286 (100), 196 (54), 153 (38), 86 (76), 84 (96).

Compound 30. 3,4-Dihydroisoquinoline **24** (1.20 g, 4.81 mmol) was added to a magnetically stirred solution of ester **28** (2.30 g, 4.27 mmol) in dry 1,2-dichloroethane (40 mL) and the resulting mixture maintained at 18 °C for 8 h then treated with diisopropylethylamine (750 μL, 4.30 mmol) and heated at reflux for 32 h. The cooled reaction mixture was treated with TLC-grade silica gel (6.0 g) then concentrated under reduced pressure and subjected to flash chromatography (silica gel; 2:1:0 then 2:3:1

v/v/v hexane/DCM/Et_2O gradient elution). Concentration of the appropriate fractions (R_f = 0.4 in 5:5:2 v/v/v hexane/DCM/Et_2O) gave *compound **30*** (2.28 g, 81%) as a white, crystalline solid, mp 244–245 °C (Anal. Calcd for $C_{38}H_{43}NO_9$: $M^{+\bullet}$, 657.2938. Found $M^{+\bullet}$, 657.2938). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (m, 2H), 7.05 (s, 1H), 6.92 (s, 1H), 6.64 (s, 1H), 6.60 (s, 1H), 4.74 (broad t, *J* = 6.6 Hz, 2H), 4.56 (m, 3H), 3.83 (s, 6H), 3.42 (s, 3H), 3.34 (s, 3H), 3.15 (broad t, *J* = 6.6 Hz, 2H), 1.41 (d, *J* = 6.0 Hz, 6H), 1.39 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6, 151.7, 151.2, 148.5, 147.0, 146.9, 146.5, 145.9, 142.5, 135.5, 128.5, 128.1, 123.3, 123.0, 121.1, 116.8, 115.5, 114.5, 113.8, 110.3, 104.9, 104.8, 104.7, 103.4, 75.7, 71.7, 71.4, 60.6, 56.1, 55.4, 55.1, 42.3, 22.7, 21.8, 21.7; ν_{max} (KBr) 2974, 2935, 2832, 1702, 1620, 1539, 1506, 1476, 1465, 1444, 1420, 1259, 1237, 1203, 1175, 1161, 1110, 1083, 1040 cm^{-1}; MS (70 eV) *m/z* 657 ($M^{+\bullet}$, 100%), 615 (44), 572 (9), 516 (11), 265 (13).

Lamellarin K (1). Aluminium chloride (1.33 g, 9.94 mmol) was added to a magnetically stirred solution of compound **30** (1.80 g, 2.76 mmol) in dry DCM (20 mL) and the ensuing mixture maintained at 18 °C for 4 h then treated with NH_4Cl (20 mL of a saturated aqueous solution) and EtOAc (50 mL). The resulting mixture was washed with water (40 mL) and the separated aqueous layer extracted with EtOAc (2 × 40 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated onto TLC-grade silica gel (8.0 g). The resulting free-flowing solid was subjected to flash chromatography (silica gel; 20:1, 10:1 then 5:1 v/v DCM/MeOH gradient elution). Concentration of the relevant fractions (R_f = 0.6 in 10:1 v/v DCM/MeOH) gave lamellarin K (**1**)[4,20] (1.40 g, 95%) as a white, crystalline solid, mp 230–232 °C (lit.[6] mp 196–198 °C) (Anal. Calcd for $C_{29}H_{25}NO_9$: $M^{+\bullet}$, 531.1529. Found $M^{+\bullet}$, 531.1524). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.1 Hz, 1H), 7.07 (dd, *J* = 8.1 and 1.5 Hz, 1H), 6.97 (s, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.59 (s, 1H), 6.38 (s, 1H), 5.95 (s, 1H), 5.75 (s, 1H), 5.71 (s, 1H), 4.90 (m, 1H), 4.64 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.49 (s, 3H), 3.36 (s, 3H), 3.12 (m, 2H). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ see Table 1; ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$] δ see Table 1; ν_{max} (KBr) 3472, 2940, 2839, 1709, 1667, 1600, 1549, 1511, 1479, 1458, 1428, 1407, 1265, 1207, 1142, 1122, 1031 cm^{-1}; MS (70 eV) *m/z* 531 ($M^{+\bullet}$, 100%), 516 (18).

Compound 31. Compound **31** was prepared by Corey–Fuchs olefination of aldehyde **17** using a procedure defined earlier.[13] The physical and spectroscopic data acquired on this material were in complete accord with those recorded[13] previously.

Compound 33. Compound **33** was prepared from precursors **18** and **31** using a procedure defined earlier.[13] The physical and spectroscopic data acquired on this material were in complete accord with those recorded[13] previously.

Compound 34. Compound **34** was prepared by Dakin oxidation of aldehyde **33** using a procedure defined earlier.[13] The physical and spectroscopic data acquired on this material were in complete accord with those recorded[13] previously.

Compound 35. DCC (6.43 g, 31.1 mmol) was added to a magnetically stirred solution of α-iodoacetic acid (5.80 g, 31.2 mmol), phenol **34** (11.0 g, 29.7 mmol) and DMAP (36 mg, 0.30 mmol) in DCM (200 mL) and the resulting mixture maintained at 18 °C for 3 h then filtered and the solids thus retained rinsed with DCM (100 mL). The combined filtrates were concentrated under reduced pressure and the ensuing residue was suspended, *via* magnetic stirring, in Et_2O (150 mL) at 0 °C. After 2 h the reaction mixture was filtered and the retained solids rinsed with Et_2O (70 mL cooled to 0 °C) and thus giving ester **35**[5b] (15.0 g, 94%) as a cream solid, mp 136–137 °C (Anal. Calcd for $C_{24}H_{27}IO_6$: $M^{+\bullet}$, 538.0852. Found $M^{+\bullet}$, 538.0843). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.4 and 1.8 Hz, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 7.02 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.66 (s, 1H), 4.55 (septet, *J* = 6.0 Hz, 2H), 3.96 (s, 2H), 3.87 (s, 6H), 1.40 (d, *J* = 6.0 Hz, 6H), 1.38 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.9 (C), 150.8 (C), 147.9 (C), 147.8 (C), 146.7 (C), 144.6 (C), 125.1 (CH), 118.3 (CH), 115.0 (C), 114.7 (CH), 111.5 (CH), 108.3 (CH), 93.2 (C), 82.3 (C), 71.5 (CH), 71.3 (CH), 56.1 (CH_3), 55.8 (CH_3), 22.0 (CH_3), 21.8 (CH_3), –6.6 (CH_2) (one signal obscured or overlapping); ν_{max} (KBr) 3021, 2978, 2930, 1771, 1607, 1512, 1460, 1444, 1420, 1330, 1241, 1211, 1133, 1110, 1096 cm^{-1}; MS (70 eV) *m/z* 538 ($M^{+\bullet}$, 100%), 496 (12), 412 (18), 411 (17), 370 (26), 328 (62), 286 (81), 271 (57).

Compound 38. 3,4-Dihydroisoquinoline **36**[22] (986 mg, 4.46 mmol) was added to a magnetically stirred solution of ester **35** (2.0 g, 3.71 mmol) in dry 1,2-dichloroethane (50 mL) and the resulting mixture maintained at 18 °C for 15 h at which point diisopropylethylamine (677 μL, 3.90 mmol) was added and the reaction mixture then heated at reflux for 24 h. After this time the reaction mixture was cooled to 18 °C, treated with TLC-grade silica gel (5.0 g) and then concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash chromatography (silica gel; 9:1 then 6:1 v/v DCM/Et_2O gradient elution) and concentration of the appropriate fractions (R_f = 0.5 in 7:1 v/v DCM/Et_2O) gave *compound **38*** (1.67 g, 71%) as a white, crystalline solid, mp 192–195 °C (Anal. Calcd for $C_{36}H_{39}NO_9$: $M^{+\bullet}$, 629.2625. Found: $M^{+\bullet}$, 629.2642). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (broad s, 2H), 7.03 (s, 1H), 6.89 (s, 1H), 6.63 (s, 1H), 6.56 (s, 1H), 4.74 (broad t, *J* = 6.6 Hz, 2H), 4.52 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.42 (s, 3H), 3.33 (s, 3H), 3.12 (broad t, *J* = 6.6 Hz, 2H), 1.36 (d, *J* = 6.0 Hz, 6H), 1.32 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 151.8 (C), 150.6 (C), 150.0 (C), 148.0 (C), 147.0 (C), 146.5 (C), 145.9 (C), 142.1 (C), 135.3 (C), 128.1 (C), 127.9 (C), 123.6 (CH), 123.0 (C), 120.0 (C), 117.7 (CH), 115.5 (C), 113.8 (C), 112.6 (CH), 110.3 (C), 105.1 (CH), 104.8 (CH), 103.3 (CH), 71.3 (CH), 71.2 (CH), 61.0 (CH_3), 60.9 (CH_3), 56.3 (CH_3), 55.4 (CH_3), 55.1 (CH_3), 42.1 (CH_2), 22.0 (CH_3), 21.9 (CH_2), 21.8 (CH_3); ν_{max} (KBr) 2975, 2935, 2834, 1700, 1620, 1540, 1506, 1476, 1455, 1442, 1416, 1259, 1239, 1208, 1175, 1156, 1137, 1116, 1084, 1037, 1013 cm^{-1}; MS (70 eV) *m/z* 629 ($M^{+\bullet}$, 100%), 587 (70).

Lamellarin T (2). Aluminium chloride (480 mg, 3.60 mmol) was added to a magnetically stirred solution

of compound **38** (945 mg, 1.50 mmol) in dry DCM (10 mL) and the ensuing mixture maintained at 18 °C for 0.5 h then treated with NH_4Cl (5 mL of a saturated aqueous solution) and water (100 mL). The separated aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered and then treated with TLC-grade silica gel (4.0 g). The resulting mixture was concentrated under reduced pressure and the free-flowing solid thus obtained subjected to flash chromatography (silica: 99:1 then 20:1 v/v DCM/MeOH gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 20:1 v/v DCM/MeOH) gave lamellarin T (**2**)[6,20b] (737 mg, 90%) as a white, crystalline solid, mp 283–284 °C (lit.[6] mp 214–218 °C; lit.[20b] mp >250 °C) (Anal. Calcd for $C_{30}H_{27}NO_9$: $M^{+\bullet}$, 545.1686. Found: $M^{+\bullet}$, 545.1690). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ see Table 2; ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$] δ see Table 2; ν_{max} (KBr) 3492, 3303, 2998, 2928, 2835, 1677, 1624, 1604, 1582, 1551, 1532, 1507, 1476, 1462, 1450, 1413, 1273, 1249, 1207, 1160, 1122, 1041, 1023, 859 cm^{-1}; MS (70 eV) *m/z* 545 ($M^{+\bullet}$, 100%), 530 (31), 272 (24).

Compound 39. Lamellarin T (**2**) (48 mg, 0.09 mmol) was added to a magnetically stirred mixture of acetic anhydride (1.0 mL) and pyridine (1.0 mL) containing DMAP (*ca*. 2 mg) and the ensuing mixture maintained at 18 °C for 26 h then diluted with EtOAc (15 mL) and washed, sequentially, with $NaHCO_3$ (20 mL of a saturated aqueous) then citric acid (20 mL of a 10% w/v aqueous solution) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was thus obtained was subjected to flash chromatography (silica gel; 2:1 then 1:1 v/v hexane/EtOAc gradient elution). Concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v hexane/EtOAc) then gave *diacetate* ***39*** (47 mg, 83%) as a white, crystalline solid, mp 251–252 °C (Anal. Calcd for $C_{34}H_{31}NO_{11}$: $M^{+\bullet}$, 629.1897. Found: $M^{+\bullet}$, 629.1907). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 6.70 (s, 1H), 6.48 (s, 1H), 4.90 (m, 1H), 4.60 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.13 (m, 2H), 2.30 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.7 (C), 168.4 (C), 155.0 (C), 151.9 (C), 151.2 (C), 150.5 (C), 147.5 (C), 144.8 (C), 142.2 (C), 140.6 (C), 138.7 (C), 135.6 (C), 129.5 (CH), 127.6 (C), 127.2 (C), 125.4 (CH), 122.6 (C), 119.8 (C), 116.1 (C), 114.8 (C), 114.4 (C), 112.9 (CH), 111.7 (CH), 105.4 (CH), 105.0 (CH), 60.9 (CH_3), 60.8 (CH_3), 56.2 (CH_3), 55.5 (CH_3), 55.2 (CH_3), 42.1 (CH_2), 21.7 (CH_2), 20.5 (CH_3), 20.4 (CH_3); ν_{max} (KBr) 2937, 2840, 1769, 1718, 1603, 1545, 1507, 1475, 1456, 1442, 1414, 1385, 1370, 1295, 1266, 1201, 1141, 1131, 1117, 1084, 1036, 1013 cm^{-1}; MS (70 eV) *m/z* 629 ($M^{+\bullet}$, 1%), 587 (8), 412 (10), 370 (32), 328 (100).

Compound 41. 3,4-Dihydro-6,7-dimethoxyisoquinoline (**40**)[24] (425 mg, 2.23 mmol) was added to a magnetically stirred solution of compound **35** (1.00 g, 1.86 mmol) in dry 1,2-dichloroethane (30 mL). The resulting mixture was maintained at 18 °C for 17 h then treated with diisopropylethylamine (340 μL, 1.95 mmol) before being heated at 83 °C for 20 h then cooled, treated with TLC-grade silica gel (5.0 g) and concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash

chromatography (silica gel; 9:1 v/v DCM/Et_2O elution) and concentration of the appropriate fractions (R_f = 0.5 in 7:1 v/v DCM/Et_2O) gave *compound* ***41*** (780 mg, 70%) as a white, crystalline solid, mp 213–214 °C (Anal. Calcd for $C_{35}H_{37}NO_8$: $M^{+\bullet}$, 599.2519. Found: $M^{+\bullet}$, 599.2526). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (broad s, 2H), 7.03 (s, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 6.69 (s, 1H), 6.65 (s, 1H), 4.75 (m, 2H), 4.50 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.41 (s, 3H), 3.35 (s, 3H), 3.10 (broad t, *J* = 6.9 Hz, 2H), 1.34 (d, *J* = 6.0 Hz, 6H), 1.32 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 150.0 (C), 148.8 (C), 147.9 (C), 147.4 (C), 146.9 (C), 146.4 (C), 145.9 (C), 135.8 (C), 128.2 (C), 127.8 (C), 126.5 (C), 123.6 (CH), 120.0 (C), 117.7 (CH), 114.8 (C), 113.6 (C), 112.5 (CH), 110.9 (CH), 110.3 (C), 108.5 (CH), 104.8 (CH), 103.3 (CH), 71.3 (CH), 71.2 (CH), 56.3 (CH_3), 55.9 (CH_3), 55.5 (CH_3), 55.1 (CH_3), 42.3 (CH_2), 28.6 (CH_2), 21.9 (CH_3), 21.8 (CH_3); ν_{max} (KBr) 2975, 2936, 2836, 1694, 1620, 1608, 1580, 1542, 1511, 1484, 1463, 1440, 1415, 1271, 1259, 1241, 1213, 1167, 1043, 1026 cm^{-1}; MS (70 eV) *m/z* 599 ($M^{+\bullet}$, 100%), 557 (81), 515 (41), 412 (45), 328 (82), 258 (37).

Lamellarin U (3). Aluminium chloride (315.8 mg, 2.36 mmol) was added to a magnetically stirred solution of compound **41** (430 mg, 0.72 mmol) in dry DCM (20 mL) and the ensuing mixture maintained at 18 °C for 14 h then treated with NH_4Cl (10 mL of a saturated aqueous solution) and EtOAc (40 mL). The resulting mixture was washed with water (1 × 20 mL) and the separated aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic phases were then dried ($MgSO_4$), filtered and treated with TLC-grade silica gel (2.0 g). The ensuing mixture was concentrated under reduced pressure and the resulting free-flowing solid subjected to flash chromatography (silica gel; 20:1 then 10:1 v/v DCM/MeOH gradient elution). Concentration of the relevant fractions (R_f = 0.7 in 10:1 v/v DCM/MeOH) afforded lamellarin U (**3**)[6,23] (347 mg, 94%) as white, crystalline solid, mp 242–243 °C (lit.[6] mp 200–204 °C; lit.[20b] mp 247–250 °C; lit.[23a] mp 198–200 °C) (Anal. Calcd for $C_{29}H_{25}NO_8$: $M^{+\bullet}$, 515.1580. Found: $M^{+\bullet}$, 515.1586). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ see Table 3; ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$] δ see Table 3; ν_{max} (KBr) 3526, 3449, 3296, 3001, 2954, 2933, 2838, 1683, 1674, 1609, 1584, 1548, 1515, 1485, 1464, 1440, 1413, 1273, 1247, 1215, 1171, 1130, 1048, 1022, 865 cm^{-1}; MS (70 eV) *m/z* 515 ($M^{+\bullet}$, 100%).

Compound 42. DDQ (219 mg 0.96 mmol) was added to a magnetically solution of compound **38** (485 mg, 0.77 mmol) in dry $CHCl_3$ (10 mL) and the resulting mixture heated at reflux for 2 h then cooled, treated with TLC-grade silica gel (3.0 g) and concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica gel; 9:1 then 4:1 v/v DCM/Et_2O gradient elution) and concentration of the appropriate fractions (R_f = 0.6 in 6:1 v/v DCM/Et_2O) gave *compound* ***42*** (479 mg, 99%) as a white, crystalline solid, mp 200–201 °C (Anal. Calcd for $C_{36}H_{37}NO_9$: $M^{+\bullet}$, 627.2468. Found: $M^{+\bullet}$, 627.2475). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (broad s, 2H), 7.14 (s, 1H), 7.01 (s, 1H), 6.97 (s, 1H), 6.72 (s, 1H), 4.58 (m, 2H), 4.03 (s, 3H), 3.97

(s, 3H), 3.94 (s, 3H), 3.46 (s, 6H), 1.41 (d, *J* = 6.3 Hz, 6H), 1.36 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 153.2 (C), 150.2 (C), 148.4 (C), 148.2 (C), 147.9 (C), 146.6 (C), 146.5 (C), 142.6 (C), 133.8 (C), 129.3 (C), 128.1 (C), 124.0 (CH), 122.8 (CH), 121.3 (C), 119.3 (C), 114.1 (CH), 112.7 (CH), 111.9 (C), 109.8 (C), 108.1 (C), 106.8 (CH), 105.4 (CH), 103.3 (CH), 101.5 (CH), 71.3 (CH), 61.6 (CH_3), 61.1 (CH_3), 56.4 (CH_3), 55.4 (CH_3), 55.1 (CH_3), 21.9 (CH_3), 21.8 (CH_3) (one signal obscured or overlapping); ν_{max} (KBr) 2975, 2935, 2834, 1698, 1621, 1606, 1536, 1498, 1480, 1453, 1429, 1418, 1395, 1375, 1329, 1260, 1233, 1206, 1177, 1158, 1137, 1117, 1073, 1045, 975 cm^{-1}; MS (70 eV) *m/z* 627 ($M^{+\bullet}$, 100%), 585 (85).

Lamellarin W (4). Aluminium chloride (112 mg, 0.836 mmol) was added to a magnetically stirred solution of compound **42** (175 mg, 0.279 mmol) in dry DCM (10.0 mL). The ensuing mixture was allowed to stir at 18 °C for 14 h then treated with NH_4Cl (5 mL of a saturated aqueous) and water (40 mL) before being extracted with EtOAc (3 × 40 mL). The combined organic phases were then dried ($MgSO_4$), filtered, treated with TLC-grade silica gel (2.0 g) and concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica gel; 99:1 then 20:1 v/v DCM/MeOH gradient elution) and concentration of the relevant fractions (R_f = 0.2 in 20:1 v/v DCM/MeOH) gave lamellarin W (**4**)[6,20b] (143 mg, 94%) as a white, crystalline solid, mp 284–286 °C (lit.[6] mp 224–228 °C; lit.[20b] mp >250 °C) (Anal. Calcd for $C_{30}H_{25}NO_9$: $M^{+\bullet}$, 543.1529. Found: $M^{+\bullet}$, 543.1533). ^{1}H NMR [300 MHz, $CDCl_3$/$(CD_3)_2SO$] δ see Table 4; ^{13}C NMR [75.5 MHz, $CDCl_3$/$(CD_3)_2SO$] δ see Table 4; ν_{max} (KBr) 3413, 3135, 2937, 2841, 1667, 1606, 1481, 1424, 1382, 1275, 1240, 1207, 1176, 1156, 1116, 1075, 1045, 1021, 965 cm^{-1}; MS (70 eV) *m/z* 543 ($M^{+\bullet}$, 100%).

Compound 43. The 3,4-dihydroisoquinoline **28** (170 mg, 0.82 mmol) was added to a magnetically solution of α-iodoacetate **40** (400 mg, 0.74 mmol) in dry 1,2-dichloroethane (4 mL) and the ensuing mixture maintained at 18 °C for 5 h. After this time diisopropylethylamine (136 μL, 0.78 mmol) was added to the reaction mixture which was heated at reflux for 28 h then cooled, treated with TLC-grade silica gel (3.0 g) and concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash chromatography (silica gel; 1:2:0, 3:6:1 then 0:5:1 v/v/v hexane/DCM/Et_2O gradient elution) and concentration of the appropriate fractions (R_f = 0.7 in 9:1 v/v DCM/Et_2O) gave *compound **43*** (352 mg, 79%) as a white, crystalline solid, mp 222–223 °C (Anal. Calcd for $C_{35}H_{37}NO_8$: $M^{+\bullet}$, 599.2519. Found: $M^{+\bullet}$, 599.2519). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–6.98 (complex m, 3H), 6.92 (s, 1H), 6.77 (s, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 4.80 (m, 2H), 4.57 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.43 (s, 3H), 3.37 (s, 3H), 3.12 (broad t, *J* = 7.0 Hz, 2H), 1.41 (d, *J* = 6.0 Hz, 6H), 1.39 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.2 (C), 148.9 (C), 147.4 (C), 147.0 (C), 146.9 (C), 146.5 (C), 146.0 (C), 135.9 (C), 128.5 (C), 128.3 (C), 126.6 (C), 123.4 (CH), 120.1 (C), 116.8 (CH), 114.9 (C), 114.5 (CH), 113.7 (C), 110.9 (CH), 110.3 (C), 108.6 (CH), 104.8 (CH), 103.4 (CH), 71.7 (CH), 71.4 (CH), 56.2 (CH_3), 55.9

(CH_3), 55.5 (CH_3), 55.1 (CH_3), 42.4 (CH_2), 28.7 (CH_2), 21.9 (CH_3), 21.8 (CH_3) (one signal obscured or overlapping); ν_{max} (KBr) 2975, 2933, 2831, 1709, 1611, 1578, 1543, 1514, 1485, 1464, 1438, 1415, 1383, 1339, 1271, 1240, 1212, 1165, 1138, 1042, 1008, 959, 858 cm^{-1}; MS (70 eV) *m/z* 599 ($M^{+\bullet}$, 100%), 557 (61), 515 (49).

Compound 6. Aluminium chloride (80.3 mg, 0.60 mmol) was added to a magnetically stirred solution of compound **43** (120 mg, 0.20 mmol) in dry DCM (10 mL) and the ensuing mixture maintained at 18 °C for 1 h then treated with NH_4Cl (10 mL of a saturated aqueous solution), EtOAc (40 mL) and water (40 mL). The separated aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and treated with TLC-grade silica gel (2.0 g) before being concentrated under reduced pressure. Subjection of the resulting free-flowing solid to flash chromatography (silica gel; 20:1 then 10:1 v/v DCM/MeOH gradient elution) and concentration of the relevant fractions (R_f = 0.7 in 10:1 v/v DCM/MeOH) gave *7-deoxylamellarin K (**6**)* (92 mg, 89%) as a white, crystalline solid, mp 292–294 °C (Anal. Calcd for $C_{29}H_{25}NO_8$: $M^{+\bullet}$, 515.1580. Found: $M^{+\bullet}$, 515.1576). ^1H NMR [300 MHz, $CDCl_3$/$(CD_3)_2SO$] δ 9.40 (s, 1H), 9.09 (s, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.85 (dd, *J* = 8.1 and 1.5 Hz, 1H), 6.82 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 6.59 (s, 1H), 4.62 (m, 2H), 3.78 (s, 6H), 3.39 (s, 3H), 3.27 (s, 3H), 3.05 (broad t, *J* = 7.0 Hz, 2H); ^{13}C NMR [75.5 MHz, $CDCl_3$/$(CD_3)_2SO$] δ 152.9 (C), 147.0 (C), 146.7 (C), 145.3 (C), 145.0 (C), 144.9 (C), 144.1 (C), 142.7 (C), 133.8 (C), 126.2 (C), 124.8 (C), 123.9 (C), 121.8 (CH), 117.9 (C), 114.5 (CH), 113.0 (C), 112.8 (CH), 111.0 (C), 109.7 (CH), 107.3 (C), 107.0 (CH), 103.4 (CH), 101.9 (CH), 54.3 (CH_3), 53.9 (CH_3), 53.4 (CH_3), 52.9 (CH_3), 40.3 (CH_2), 26.3 (CH_2); ν_{max} (KBr) 3529, 3105, 3003, 2937, 2833, 1667, 1609, 1546, 1520, 1486, 1464, 1439, 1416, 1274, 1256, 1234, 1217, 1184, 1163, 1047 cm^{-1}; MS (70 eV) *m/z* 515 ($M^{+\bullet}$, 100%).

ACKNOWLEDGEMENTS

We thank the Institute of Advanced Studies for financial support and Professor Bruce Bowden (James Cook University) for providing copies of the ^1H and ^{13}C NMR spectra recorded on naturally-derived lamellarin K.

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