Convergent total synthesis of lamellarin K†

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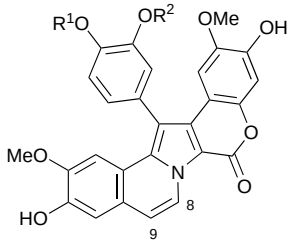
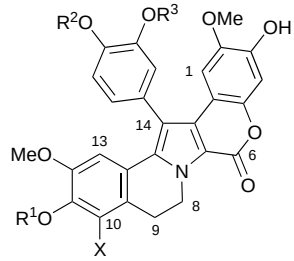
The azomethine ylide derived from dihydroisoquinolinium salt 24 undergoes an intramolecular [3 + 2] cycloaddition reaction to give pyrrole 25 which upon de-isopropylation affords the marine alkaloid lamellarin K 4.

In 1985 Faulkner and his colleagues reported[1] the isolation of four members of a new class of marine natural product which they had obtained from a *Lamellaria* sp. of marine prosobranch mollusc collected in the waters off Palau. These compounds were called lamellarins A–D and through a combination of spectroscopic and X-ray crystallographic studies were shown to be highly oxygenated derivatives of 14-phenyl-6*H*-[1]benzopyrano[4′,3′ : 4,5]pyrrolo[2,1-*a*]isoquinolin-6-one or its 8,9-dihydro analogue. Thus, lamellarin D possesses structure **1** while congener C has structure **2**. Subsequently, Fenical[2] isolated further members of this type of compound (lamellarins E–H) from the Indian Ocean marine ascidian *Didemnum chartaceum*. More recently Bowden[3] reported obtaining lamellarins I–N from a Pacific ascidian *Didemnum* sp. collected off the north east coast of Australia, while Urban and Capon[4] have isolated lamellarin S from the same species.§ In 1997, Faulkner described[5] the isolation of nine new alkaloids of the lamellarin class, including the first examples of lamellarin sulfates, from an unidentified ascidian found in the Arabian Sea.



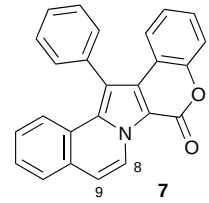
1 R^1 = H, R^2 = Me
6 R^1 = Me, R^2 = H



2 X = OMe, R^1 = R^3 = Me, R^2= H
3 X = OMe, R^1 = R^2 = R^3 = Me
4 X = OH, R^1 = R^3 = Me, R^2 = H
5 X = R^1 = R^3 = H, R^2 = Me

A number of the lamellarins exhibit highly interesting biological properties. For example, at concentrations of 19 μg ml^{-1}, compound **1** caused a 78% inhibition of cell division in a fertilised sea urchin assay while congener **2** caused 15% inhibition.[1] Lamellarins I **3**, K **4** and L **5** all showed comparable and significant cytotoxicity against P388 and A549 cell lines in culture (IC_{50} ≈ 0.25 μg ml^{-1} against each cell line).[3] Lamellarins K and L also exhibited moderate immunomodulatory activity (LcV : MLR 147 and 98, respectively).[3] In the NCl 60 cell-line panel, lamellarin N **6** showed some selectivity toward melanoma cell lines SK-MEL-5 (LC_{50} 1.87 × 10^{-7} M) and UACC-62 (LC_{50} 9.88 × 10^{-6} M).[5] Perhaps most significantly, very recent work at Pharma Mar S. A.[6] has raised the possibility that certain of the lamellarins, especially lamellarin K, may be highly effective in the treatment of multidrug resistant tumours.

Despite the intriguing biological properties and the unprecedented structures of lamellarins A–N and S–X (the parent frameworks are unknown) only two studies directed towards the total synthesis of these marine natural products appear to have been reported to date.§ Thus, very recently Steglich[7] described a biomimetic synthesis of lamellarin G trimethyl ether, while Ishibashi *et al*.[8] have completed total syntheses of lamellarins D and H. These reports prompt us to disclose a quite different and highly convergent method for the synthesis of the title compound **4** and the parent ring-system **7**.



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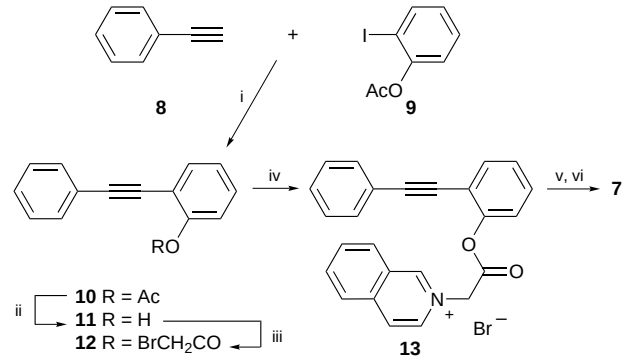
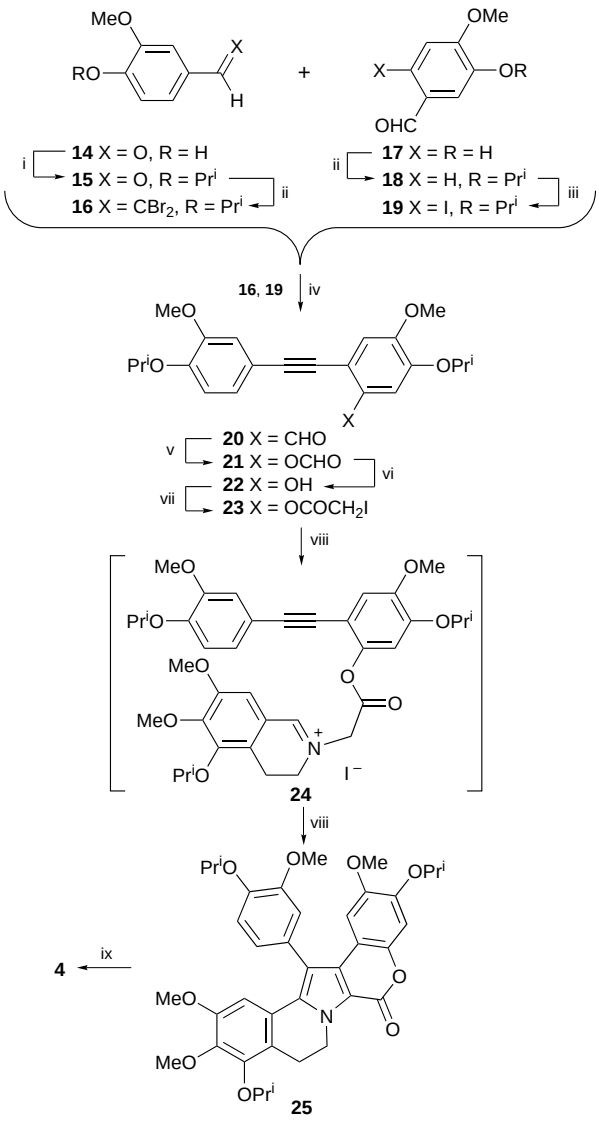
The pivotal step in our approach to the lamellarin ring systems involves construction of the central pyrrole moiety *via* an intramolecular [3 + 2] cycloaddition of an isoquinoline-based azomethine ylide to a suitably tethered tolan,[9] a hitherto unproven process. The reaction sequence leading to the parent framework (Scheme 1) starts with Sonogashira cross-coupling[10] of phenylacetylene **8** and *o*-iodophenyl acetate **9**[11] to give, after hydrolysis of the initial coupling product **10**[11] (99%), *o*-hydroxytolan **11**.[11] This last compound was subjected to dicyclohexylcarbodiimide (DCC)-promoted coupling with α-bromoacetic acid and the resulting ester **12** (91% from **10**) treated with isoquinoline to give the isoquinolinium salt **13**. Compound **13** was immediately reacted with Et_3N so as to generate the associated azomethine ylide which underwent intramolecular cycloaddition to the tethered triple bond upon heating. The resulting mixture of dihydropyrrole-type products thereby obtained was subjected to oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In this manner, the target compound **7** (92% from **12**, mp 313–315 °C) was obtained and its structure established by single-crystal X-ray analysis.‖

The highly convergent nature of the reaction sequence outlined here would suggest that this approach could be readily



Scheme 1 *Reagents and conditions*: i, $Pd(PPh_3)_4$ (1 mol%), CuI (2 mol%), Et_3N, 18 °C, 4 h; ii, K_2CO_3 (1.5 equiv.), MeOH, 18 °C, 0.25 h; iii, $BrCH_2COBr$ (1 equiv.), DMAP (5 mol%), DCC (1.05 equiv.), CH_2Cl_2, 18 °C, 3 h; iv, isoquinoline (1 equiv.), THF, 18 °C, 6 h; v, Et_3N (1 equiv), THF, 66 °C, 4 h; vi, DDQ (1 equiv.), CH_2Cl_2, 18 °C, then silica gel chromatography



Scheme 2 *Reagents and conditions*: i, Pr^{i}Br (1.2 equiv.), K_2CO_3 (3.5 equiv.), DMF, 18 °C, 19 h; ii, CBr_4 (2 equiv.), Zn (2 equiv.), PPh_3 (2 equiv.), 0 to 18 °C, 22 h, then 0 °C, **15**, 18 °C, 1 h; iii, $AgOCOCF_3$ (1.1 equiv.), I_2 (1.1 equiv.), $CHCl_3$, reflux, 7 h; iv, **16**, Bu^{n}Li (2.05 equiv.), THF, −78 °C, 0.83 h then $ZnCl_2$ (1.1 equiv.), −78 to 18 °C, 1 h then **19** (0.95 equiv.), $Pd(PPh_3)_4$ (*ca*. 2 mol%), 18 °C, 4 h; v, MCPBA (1.5 equiv.), $KHCO_3$ (3 equiv.), CH_2Cl_2, 18 °C, 1 h; vi, NH_3 in MeOH (sat.), 18 °C, 1 h; vii, ICH_2CO_2H (1.05 equiv.), DCC (1.05 equiv.), DMAP (5 mol%), CH_2Cl_2, 18 °C, 3 h; viii, 3,4-dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline (1.1 equiv.), $ClCH_2CH_2Cl$, 18 °C, 7 h, then Hünig's base (1.0 equiv.), 83 °C, 32 h; ix, $AlCl_3$ (3.6 equiv.), CH_2Cl_2, 18 °C, 2 h

adapted to the preparation of lamellarins A–N and S–X as well as many analogues thereof. Certainly, compounds in the 8,9-dihydroseries would seem to be readily accessible as evidenced by our synthesis of lamellarin K **4** (Scheme 2). Thus, the isopropyl ether **15**[12] (100%), prepared from vanillin **14** under standard conditions,[13] was subjected to a Corey–Fuchs *gem*-dibromomethylenation reaction[14] thereby affording styrene **16** (100%, mp 36–38 °C). This latter compound was treated with Bu^{n}Li and the lithium acetylide so formed was *trans*-metallated using zinc(II) chloride. Palladium-mediated cross-coupling of the resulting alkynylzinc chloride with aryl iodide **19** (mp 75–76 °C) (obtained in 93% yield by iodination of the isopropyl ether **18**[15] of isovanillin **17** using $AgOCOCF_3$–I_2) then gave tolan **20** (84%, mp 121–122 °C) which was subjected to a Baeyer–Villiger reaction using MCPBA as oxidant. The resulting formate ester **21** was readily hydrolysed to the corresponding phenol **22** (92% from **20**, mp 130–131 °C). DCC-mediated condensation of this last compound with α-iodoacetic acid then provided ester **23** (97%, mp 127–128 °C) which was reacted with 3,4-dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline (readily available by standard methods) to give salt **24**. This last compound was not isolated but immediately treated with Hünig's base. The resulting mixture was heated at reflux in 1,2-dichloroethane and in this manner cycloaddition (followed by *in situ* aromatisation) took place to give lamellarin K triisopropyl ether **25** (81% from **23**, mp 244–245 °C). Treatment of this last compound with 3.6 mol equiv. of $AlCl_3$ in CH_2Cl_2 at 18 °C resulted in three-fold de-isopropylation and formation of the target compound **4** (96%, mp 230–232 °C) which was identical, by ^{1}H and ^{13}C NMR spectroscopy, with an authentic sample.

We thank the Institute of Advanced Studies for financial support including the provision of a post-doctoral Research Fellowship to B. L. F. Associate Professor B. Bowden (James Cook University of North Queensland) is thanked for providing spectral data on lamellarin K.

Footnotes and References

† The work described herein is the subject of a patent application (AIPO Patent Office Provisional Application No. PO6565, May 2nd, 1997).

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§ A series of structurally simpler lamellarins (O–R) have been isolated by Capon from a southern Australian marine sponge *Dendrilla cactos* (see work cited in ref. 4). Certain members of this simpler class of lamellarins have been the subject of synthetic studies (see M. G. Banwell, B. L. Flynn, E. Hamel and D. C. R. Hockless, *Chem. Commun.*, 1997, 207 and references cited therein) but the strategies used are quite different from those reported here.

‖ *Crystal data* for **7**: $C_{25}H_{15}NO_2$, M = 361.40, T = 296(1) K, orthorhombic, space group P*nma*, a = 23.441(2), b = 6.804(4), c = 11.175(4) Å, U = 1782(2) Å^3, D_c (Z = 4) = 1.347 g cm^{-3}, F(000) = 752, μ(MoKα) = 0.80 cm^{-1}, semi-empirical absorption correction; 2381 unique data ($2\theta_{max}$ = 55.0°), 661 with $I > 2\sigma(I)$; R = 0.065, wR = 0.049, GOF = 2.88. CCDC 182/606.

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Received in Cambridge, UK, 12th August 1997; 7/05874H