A New, Titanium-Mediated Approach to Pyrroles: First Synthesis of Lukianol A and Lamellarin *O* Dimethyl Ether

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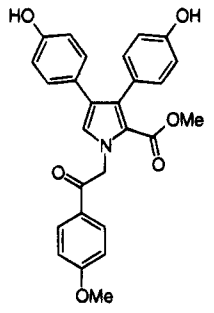
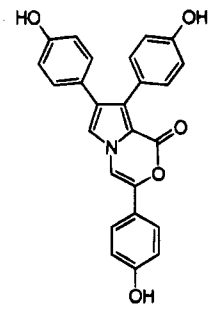
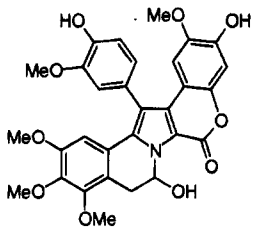
A rapidly increasing number of pyrrole alkaloids (e.g. **1**–**4**) has been isolated in recent years from marine sources.[1-3] Intriguingly, some of these chemically closely related metabolites were found in taxonomically quite distinct organisms such as prosobranch molluscs, ascidians, and sponges collected at remote places in the Indian or Pacific ocean. While for example lukianol A (**2**) has been found in an unidentified encrusting tunicate collected in the lagoon of the Palmyra atoll,[2] lamellarin O (**1**), which may be considered as the ring-opened analogue of **2**, was extracted from the marine sponge *Dendrilla cactos* living in the south Australian Bass strait.[3] Lukianol A exhibits some activity against a cell line derived from human epidermatoid carcinoma,[2] while no biological data could be obtained for lamellarin O due to its reported instability and to the small amounts of this alkaloid available from natural sources.



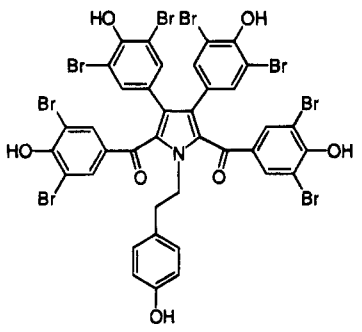
Lamellarin O (**1**)



Lukianol A (**2**)



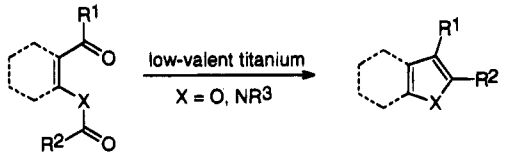
Lamellarin A (**3**)



Polycitone A (**4**)

In order to provide material for an evaluation of the pharmacological profile of these compounds we wanted to gain ready and flexible access to these alkaloids.

Scheme 1



Rather than taking recourse to one of the established methods for the formation of pyrroles,[4,5] we intended to pursue their synthesis by an entirely new approach. Herein we report a titanium-induced cyclization of readily accessible amido-enones to substituted pyrrole derivatives and apply this method to the first total synthesis of lukianol A and of lamellarin O dimethyl ether.

Titanium-Mediated Synthesis of Pyrroles: Model Compounds. Quite recently we have been able to show that acyloxy (X = O) or acylamido carbonyl compounds (X = NR^3) readily cyclize to furans, benzo[*b*]furans or indoles, respectively, on treatment with a variety of low-valent titanium reagents (Scheme 1).[6,7] This approach may also lead to pyrroles when appropriately substituted amido-enones are used as the starting materials.

A set of suitable substrates (**7a**–**f**, **11a,b**) was prepared according to literature procedures (Scheme 2).[8] Treatment of these oxo-amides with low-valent titanium led to the smooth formation of the corresponding pyrroles **8a**–**f** and **12a,b** in fair to good yields (Table 1). Different substitution patterns are accessible; in particular the substituent at C-2 on the newly formed heteroarene ring can be easily varied by acylating a parent keto-enamine (e.g. **6** or **10**) with different acyl halides or anhydrides. In this context it is worth mentioning that the titanium-induced oxo-amide coupling reaction can be performed under quite different experimental conditions, which may be adapted to a given synthesis problem. Thus, either activated titanium–graphite formed in a separate step from $TiCl_3$ and C_8K prior to the addition of the substrate may be used as the reagent (method A),[9] or the reductive coupling reaction can be done in a short-cut fashion, in which the active species is prepared from $TiCl_3$ and Zn in the presence of the oxo-amide ("instant" method,

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(6) (a) Fürstner, A.; Jumbam, D. N.; Weidmann, H. *Tetrahedron Lett.* **1991**, 6695–6696. (b) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991–6010. (c) Fürstner, A.; Jumbam, D. N. *J. Chem. Soc. Chem. Commun.* **1993**, 211–212. (d) Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, 1125–1130. (e) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773–786. (f) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475.

(7) (a) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215–5229. (b) Fürstner, A.; Ptock, A.; Weintritt, H.; Goodard, R.; Krüger, C. *Angew. Chem.* **1995**, *107*, 725–728; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 678–681.

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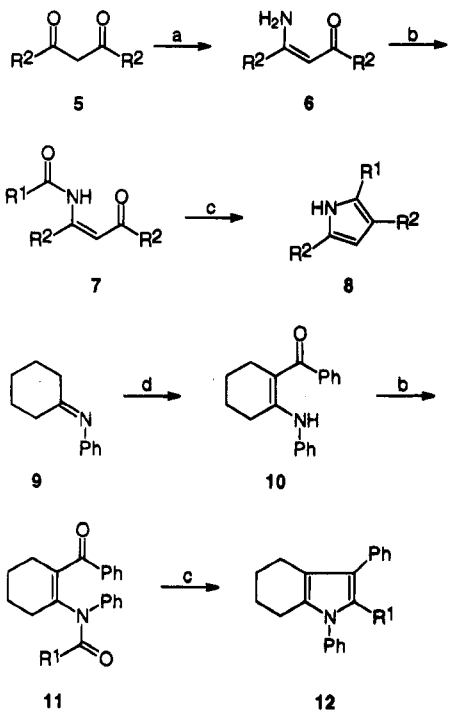
Scheme 2



[a] Key: (a) NH_4^+ AcO^-, toluene, reflux, 72% (R_2 = Ph), 90% (R_2 = Me), *c.f.* ref 8a; (b) R_1COCl, pyridine, CH_2Cl_2; (c) low-valent titanium, *c.f.* Table 1; (d) (i) LDA, THF, 0 °C, 30 min; (ii) PhCOOMe, 1 h, 0 °C → rt; (iii) H^+/H_2O, 74%, *c.f.* ref 8b.

Table 1. Titanium-Induced Reductive Pyrrole Synthesis

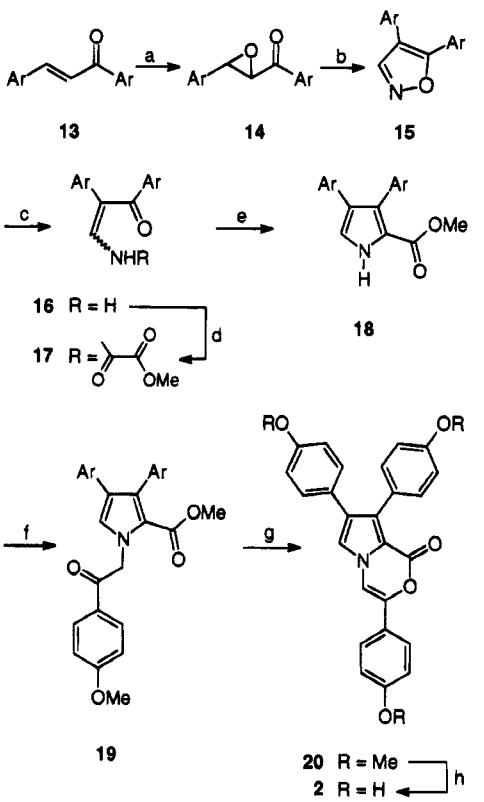
entry	substrate	R_1	R_2	method[a]	product (% yield)[b]
1	**7a**	Ph	Ph	B	**8a** (78)
2	**7b**	t-Bu	Ph	B	**8b** (60)
3	**7c**	$CF_2CF_2CF_3$	Ph	B	**8c** (54)
4	**7d**	2-naphthyl	Ph	B	**8d** (77)
5	**7e**	COOEt	Ph	A	**8e** (60)
6	**7f**	Ph	Me	B	**8f** (38)[c]
7	**11a**	Ph	–	B	**12a** (85)
8	**11b**	t-Bu	–	B	**12b** (58)

[a] Method A: the substrate is added to a preformed suspension of Ti–graphite ($TiCl_3$:C_8K = 1:2) as the reagent. Method B ("instant" method): preparation of the active species from $TiCl_3$ and Zn in the presence of the substrate, *c.f.* experimental. [b] Isolated Yield. [c] The lower yield is partly due to some loss of the product during workup.

method B).[7] This latter procedure is particularly simple and avoids the handling of hazardous compounds such as C_8K; however, it can only be applied to substrates which are reasonably stable toward the Lewis-acidic $TiCl_3$.

Synthesis of Lamellarin O Dimethyl Ether and of Lukianol A. In order to adapt this new entry into the pyrrole series to the synthesis of these alkaloids, good access to the labile 3-unsubstituted keto-enamine **16** was mandatory (Scheme 3). We used isoxazole **15** as its surrogate, which is readily prepared from commercially available 4,4′-dimethoxychalcone **13** on a multigram scale. Specifically, treatment of **13** with H_2O_2/NaOH under standard conditions afforded epoxy ketone **14** in 98% yield, which was easily amenable to the isoxazole

Scheme 3



[a] Key: Ar = *p*-$MeOC_6H_4$ (a) H_2O_2, NaOH, EtOH/H_2O, 0 °C → rt, 98%; (b) (i) BF_3·Et_2O, Et_2O, reflux; (ii) NH_2OH·HCl, pyridine, EtOH, reflux, 67% (over both steps); (c) H_2 (1 atm), Pd (5%) on charcoal, THF, 94%, (*Z*):(*E*) = 1:1; (d) ClOCCOOMe, pyridine, THF, 73%, (*Z*):(*E*) = 2.5:1; (e) Ti–graphite ($TiCl_3$:C_8K = 1:2), DME, reflux, 52%; (f) *p*-MeO-$C_6H_4COCH_2Br$, K_2CO_3, acetone, reflux, 91%; (g) (i) KO-tBu, H_2O, Et_2O, 0 °C → rt; (ii) Ac_2O, NaOAc, reflux, 59% (over both steps); (h) BBr_3, CH_2Cl_2, −78 °C → rt, 99%.

15 in one pot. On reaction with an excess of BF_3·Et_2O, compound **14** undergoes a clean pinacol/pinacone-type rearrangement; the crude 1,3-keto-aldehyde thus formed was trapped by hydroxylamine leading to isoxazole **15** in 67% isolated yield.[10] Reductive cleavage of its N–O bond (H_2, Pd on charcoal, 5% w/w) gave the desired keto-enamine **16** in almost quantitative yield, quite unexpectedly, however, as a ≈1:1 mixture of the (*E*)- and (*Z*)-isomers. Acylation of this mixture with methyl oxalyl chloride under standard conditions afforded the coupling precursor **17**. The fact that the isomeric ratio of the resulting oxo-amides (*Z*)-**17**:(*E*)-**17** was 2.5:1 rather than 1:1 indicates the low configurational stability of such 3-unsubstituted keto-enamine derivatives. These isomers could be separated by flash chromatography, and pure (*Z*)-**17**[11] was used for the subsequent titanium-induced ring closure.

Upon treatment with preformed Ti–graphite ($TiCl_3$:C_8K = 1:2)[9] in DME, compound **17** bearing three different carbonyl groups underwent a chemo- and regioselective oxo-amide coupling reaction with formation of pyrrole **18** in 52% yield without the ester group interfering. Due to the instability of **17** toward Lewis acids, attempted cyclization under "instant" conditions gave only poor

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(10) Subba Raju, G. V.; Rao, K. S. *Curr. Sci.* **1987**, *56*, 1280–1281.

(11) NOESY-spectra of the resolved isomers allowed an unambiguous assignment of their double bond configuration, *c.f.* experimental. Interestingly, the isomers are configurationally unstable in the presence of $TiCl_3$ and under reactions conditions. Thus, pyrrole **18** can also be formed from (*E*)-**17** although in lower yield (30–40%).

results. *N*-Alkylation of **18** with 4-methoxyphenacyl bromide proceeded smoothly affording the moderately stable lamellarin O dimethyl ether **19** in 91% isolated yield. Deprotonation of **19** with LDA led directly to enol lactone **20**, but this transformation turned out to be capricious and rather low-yielding. A much more reliable method for the formation of the 1*H*-pyrrolo[2,1-*c*][1,4]-oxazin-1-one core of lukianol consisted in the saponification of the methyl ester of **19** according to the procedure of Gassman *et al.*[12] followed by enol-lactonization of the crude oxo-acid formed with Ac_2O/NaOAc as described by Woodward *et al.* in his classical steroid syntheses.[13] Cleavage of the OMe groups of **20** with BBr_3 in CH_2Cl_2 gave lukianol A (**2**) in quantitative yield, the spectral properties of which perfectly matched those reported in the literature.

In summary, a concise approach to lukianol A (**2**) based on a new pyrrole synthesis is reported which affords this alkaloid in eight steps with 12% overall yield starting from commercially available 4,4′-dimethoxychalcone. As this synthesis passes through lamellarin O dimethyl ether (**19**), it highlights the close chemical relationship between these natural products isolated from distinctly different organisms.

Further work on the application of titanium-induced heterocycle formation is in progress.

Experimental Section

General. For the instrumentation used see ref 6e. All reactions were carried out under Ar using Schlenk techniques unless stated otherwise. C_8K was prepared using graphite powder (KS 5-44) provided by Lonza AG, Switzerland according to ref 9b. The following chemicals were purchased and used as received: $TiCl_3$ (Aldrich, 99% purity), 4,4′-dimethoxychalcone **13** (Lancaster), methyl oxalyl chloride, 4-methoxyphenacyl bromide (Merck-Schuchardt), BBr_3 (Aldrich). Flash chromatography: Merck silica gel 60 (230–400 mesh) with hexane/ethyl acetate in various proportions as eluent. The solvents were dried by distillation over the following drying agents prior to use and were transferred under Ar: THF (Mg–anthracene), DME (Na/K alloy), DMF, CH_2Cl_2 (CaH_2), pyridine (KOH). Substrates: Ketoenamines **7a–f**[8a] and **11a,b**[8b] were prepared as depicted in Scheme 2 according to the literature procedures cited.

Titanium–Graphite-Induced Pyrrole Formation (Method A): Synthesis of Ethyl 3,5-diphenylpyrrole-2-carboxylate (8e). $TiCl_3$ (377 mg, 2.44 mmol) was added to a suspension of C_8K (662 mg, 4.88 mmol) in DME (20 mL), and the resulting mixture was refluxed for 1.5 h under Ar. Substrate **7e** (195 mg, 0.60 mmol) was added to the suspension of Ti–graphite thus formed, and reflux was continued for another 15 min. After being cooled to ambient temperature, the reaction mixture was filtered through a pad of silica, the inorganic residues were thoroughly washed with EtOAc (50 mL in several portions), the combined filtrates were evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 10/1) affording pyrrole **8e** as colorless crystals (105 mg, 60%): mp 133–135 °C (ref[14c] 135–136 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.12 (t, 3H, J = 7.1 Hz), 4.15 (q, 2H, J = 7.1 Hz), 6.52 (d, 1H, J = 3.1 Hz), 7.16–7.34 (m, 6H), 7.46–7.55 (m, 4H), 9.64 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 60.4, 109.9, 118.6, 124.8, 127.0, 127.6, 127.8, 128.9, 129.5, 131.1, 133.4, 135.2, 135.6, 161.4; MS *m/z* (rel intensity) 291 (100, [M$^+$]), 246 (23), 245 (83), 218 (16), 217 (67), 216 (26), 191 (12), 189 (19), 29 (14).

Representative Procedure for the Reductive Cyclization of Oxo-amides to Pyrroles under "Instant" Conditions (Method B). Synthesis of 2,3,5-Triphenylpyrrole (8a). Oxo-amide **7a** (280 mg, 0.86 mmol), $TiCl_3$ (657 mg, 4.26 mmol), and Zn dust (557 mg, 8.52 mmol) were suspended in THF (25 mL), and the resulting mixture was refluxed under Ar for 3 h. The inorganic residues were then filtered off and thoroughly washed with ethyl acetate (50 mL in several portions), the combined filtrates were evaporated, and the crude product was purified by flash chromatography with hexane/ethyl acetate (10/1) as eluent affording the product as colorless crystals (198 mg, 78%): mp 135–137 °C (ref[14a] 139–140 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.68 (d, 1H, J = 2.9 Hz), 7.15–7.41 (m, 13H), 7.52 (d, 2H, J = 7.2 Hz), 8.36 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 108.6, 123.7, 125.9, 126.5, 126.9, 127.5, 128.3, 128.4, 128.7, 128.9, 129.3, 132.2, 133.0, 136.3; MS *m/z* (rel intensity) 295 (100, [M$^+$]), 294 (9), 191 (8), 189 (7).

2-*tert*-Butyl-3,5-diphenylpyrrole (8b). Prepared according to the procedure described above using substrate **7b** (440 mg, 1.43 mmol), $TiCl_3$ (822 mg, 5.33 mmol), and Zn (697 mg, 10.7 mmol) in DME (20 mL) as solvent. After 30 min reaction time and a standard workup, the product was obtained as colorless syrup (234 mg, 60%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 9H), 6.29 (dd, 1H, J = 1.2, 3.0 Hz), 6.83–7.38 (m, 10H), 8.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.1, 32.8, 109.9, 120.3, 123.3, 125.7, 126.2, 126.9, 127.4, 127.5, 128.8, 130.6, 131.5, 139.2; MS *m/z* (rel intensity) 275 (45, [M$^+$]), 261 (21), 260 (100).

3,5-Diphenyl-2-(heptafluoropropyl)pyrrole (8c). Obtained according to method B on reaction of oxo-amide **7c** (322 mg, 0.768 mmol), $TiCl_3$ (365 mg, 2.37 mmol), and Zn (310 mg, 4.74 mmol) in THF (50 mL) for 2 h. The product was isolated as colorless syrup (161 mg, 54%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.45 (d, 1H, J = 2.9 Hz), 7.25-7.49 (m, 10H), 8.33 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 110.1, 124.5, 126.8, 127.1, 127.5, 128.8, 129.0, 129.3, 129.7, 131.2, 134.9; MS *m/z* (rel intensity) 387 (50, [M$^+$]), 367 (23), 311 (11), 280 (13), 269 (19), 268 (100), 249 (16), 248 (82), 124 (14), 77 (10), 28 (14).

3,5-Diphenyl-2-(2′-naphthyl)pyrrole (8d). Obtained by method B, when oxoamide **7d** (313 mg, 0.83 mmol) was reacted with $TiCl_3$ (633 mg, 4.10 mmol) and Zn (536 mg, 8.20 mmol) in DME (10 mL) for 1 h. The product was isolated in the form of colorless crystals (222 mg, 77%): mp 55–60 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.71 (br s, 1H), 7.14–7.95 (m, 13H), 7.66–7.78 (m, 4H), 8.44 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 108.8, 124.3, 126.0, 127.7, 128.3; MS *m/z* (rel intensity) 345 (100, [M$^+$]).

3,5-Dimethyl-2-phenylpyrrole (8f). Formed upon reaction of substrate **7f** (509 mg, 2.5 mmol) with $TiCl_3$ (2.31 g, 15.0 mmol) and Zn (1.96 g, 30 mmol) in DME (50 mL) for 3 h. Standard workup gave **8f** as a colorless syrup (161 mg, 38%):[14e] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H), 2.24 (s, 3H), 5.82 (d, 1H, J = 3.0 Hz), 7.12–7.26 (m, 1H), 7.33–7.36 (m, 4H), 7.74 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.4, 12.8, 110.2, 116.3, 125.3, 125.8, 126.6, 127.4, 128.5, 133.8; MS *m/z* (rel intensity) 171 (100, [M$^+$]), 170 (95), 156 (10), 128 (7), 77 (8).

1,2,3-Triphenyl-4,5,6,7-tetrahydroindole (12a). Prepared from substrate **11a** (320 mg, 0.84 mmol), $TiCl_3$ (606 mg, 3.93 mmol), and Zn (514 mg, 7.85 mmol) in DME (10 mL) as outlined above in 15 min reaction time. Standard workup afforded the title compound as colorless crystals (248 mg, 85%): mp 172–173 °C (ref[14b] 174 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.82 (m, 4H), 2.49 (t, 2H, J = 5.0 Hz), 2.64 (t, 2H, J = 5.0 Hz), 6.90–7.32 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.0, 23.5, 23.6, 23.8, 117.4, 121.9, 125.3, 126.0, 126.8, 127.5, 127.6, 127.7, 127.9, 128.2, 128.6, 130.1, 131.1, 131.2, 132.6, 136.1; MS *m/z* (rel intensity) 349 (100, [M$^+$]), 348 (12), 321 (17), 320 (22).

2-*tert*-Butyl-1,3-diphenyl-4,5,6,7-tetrahydroindole (12b). Obtained from oxo-amide **11b** (256 mg, 0.71 mmol), $TiCl_3$ (505

(12) More conventional methods for the saponification of methyl esters were unsuccessful or led to the destruction of the starting material; the *Gassman* procedure, however, worked nicely and gave well reproducible results, c.f. Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918–920.

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(14) (a) Sawa, Y.; Hashimoto, I.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* **1968**, *33*, 2159–2161. (b) Roth, H. J.; George, H.; Assadi, F.; Rimek, H. J. *Angew. Chem., Int. Ed. Engl.* **1968**, *12*, 946. (c) Alberola, A.; Andres, J. M.; Gonzalez, A.; Pedrosa, R.; Vicente, M. *Heterocycles* **1990**, *31*, 1049–1058. (d) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, 227–232. (e) Izumi, T.; Alper, H. *Organometallics* **1982**, *1*, 322–325.

mg, 3.27 mmol), and Zn (428 mg, 6.54 mmol) in THF (50 mL) after 30 min reaction time. Standard workup afforded the title compound as colorless crystals (135 mg, 58%): mp 185–187 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01 (s, 9H), 1.66 (m, 4H), 2.08 (t, 2H, J = 5.3 Hz), 2.16 (t, 2H, J = 5.1 Hz), 7.19–7.48 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 22.7, 23.4, 23.5, 33.2, 34.4, 117.0, 121.4, 125.7, 127.4, 127.7, 128.4, 128.5, 130.1, 131.1, 136.3, 140.0, 141.7; MS *m/z* (rel intensity) 329 (31, [M$^+$]), 315 (25), 314 (100).

(*E*)-2,3-Epoxy-1,3-bis(4-methoxyphenyl)propanone (14). H_2O_2 (30%, 4.0 mL) was added dropwise to a stirred suspension of 4,4′-dimethoxychalcone **13** (7.0 g, 26.1 mmol) in EtOH (110 mL) and aqueous NaOH (2 N, 6.6 mL) at 0 °C. After complete addition the ice-bath was removed and the mixture was stirred for 6.5 h at ambient temperature. The precipitated colorless crystals of **14** were filtered off, washed with cold EtOH, and dried in vacuo (7.30 g, 98%): mp 117–119 °C (ref[14d] 114–116 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.82 (s, 3H), 3.87 (s, 3H), 4.01 (d, 1H, J = 1.9 Hz), 4.24 (d, 1H, J = 1.9 Hz), 6.89 (d, 2H, J = 8.7 Hz), 6.94 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 8.7 Hz), 8.00 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.3, 55.5, 59.1, 60.8, 114.0, 114.1, 127.1, 127.5, 128.6, 130.6, 160.2, 164.1, 191.4; MS *m/z* (rel intensity) 284 (19, [M$^+$]), 135 (100), 121 (23), 77 (18).

4,5-Bis(4-methoxyphenyl)isoxazole (15). A solution of epoxy ketone **14** (3.372 g, 11.9 mmol) in Et_2O (120 mL) and BF_3·Et_2O (15 mL) was refluxed under Ar for 45 min. The mixture was diluted with Et_2O (90 mL) and washed with water. The layers were separated, the organic phase was evaporated, and the residue was dissolved in EtOH (technical grade, 60 mL) and pyridine (1.5 mL). NH_2OH·HCl (1.668 g, 24.0 mmol) was added, and the resulting mixture was refluxed for 20 h. Evaporation of the solvent followed by flash chromatography with hexane/ethyl acetate (6/1) as eluent afforded the title compound as colorless crystals (2.227 g, 67%): mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3H), 3.83 (s, 3H), 6.87 (d, 2H, J = 8.9 Hz), 6.91 (d, 2H, J = 8.9 Hz), 7.28 (d, 2H, J = 9.1 Hz), 7.56 (d, 2H, J = 9.1 Hz), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.2, 114.1, 114.3, 114.6, 120.3, 122.4, 128.6, 129.8, 151.9, 159.3, 160.7, 163.6; MS *m/z* (rel intensity) 281 (95, [M$^+$]), 238 (20), 211 (22), 135 (100), 92 (14), 77 (18).

Keto-enamide 17. Palladium on charcoal (5% w/w, 390 mg) was added to a solution of isoxazole **15** (1.95 g, 6.94 mmol) in THF (130 mL), and the resulting suspension was stirred under hydrogen (1 atm) for 19 h at ambient temperature. Filtration of the catalyst under Ar and evaporation of the solvent afforded keto-enamine **16** (1.855 g, 94%) as a mixture of the double bond isomers (*E*:*Z* ≈ 1:1), which was directly used in the next step. Characteristic analytical data of **16**: mp 191–193 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.66 (s, 1.5H), 3.68 (s, 1.5H), 3.74 (s, 1.5H), 3.76 (s, 1.5H), 6.40 (br s, 1H), 6.69–7.43 (m, 9H), 8.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.4, 191.9; MS *m/z* (rel intensity) 283 (94, [M$^+$]), 282 (100), 148 (15), 135 (53), 132 (12), 92 (12), 77 (19). A solution of methyl oxalyl chloride (1.44 mL, 15.6 mmol) and pyridine (1.26 mL, 15.55 mmol) in THF (50 mL) was slowly dropped into a solution of the crude keto-enamine **16** (3.666 g, 12.94 mmol) under Ar. Precipitated pyridinium salts were filtered off, the solvent was evaporated, and the residue was purified by column chromatography with hexane/ethyl acetate (2/1 → 1/1) as eluent. This allowed separation of the isomers (*E*)-**17** and (*Z*)-**17** (combined yield: 3.474 g, 73%, (*E*):(*Z*) = 2.5:1). Analytical data of (*Z*)-**17**: mp 136–137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H), 3.77 (s, 3H), 3.94 (s, 3H), 6.72 (d, 2H, J = 9.0 Hz), 6.78 (d, 2H, J = 8.8 Hz), 7.09 (d, 2H, J = 8.8 Hz), 7.50 (d, 2H, J = 9.0 Hz), 7.51 (d, 1H, J = 11.3 Hz), 11.56 (br d, 1H, J = 11.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.0 (q), 55.2 (q), 55.3 (q), 113.3 (d), 114.1 (d), 123.7 (s), 129.5 (d), 130.3 (s), 130.8 (s), 131.1 (d), 132.0 (d), 154.6 (s), 159.1 (s), 159.7 (s), 163.0 (s), 195.2 (s); MS *m/z* (rel intensity) 369 (77, [M$^+$]), 310 (27), 266 (13), 234 (20), 202 (12), 146 (13), 135 (100), 77 (15). Analytical data of (*E*)-**17**: mp 111–112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 6.87 (d, 2H, J = 9.0 Hz), 6.97 (d, 2H, J = 8.9 Hz), 7.22 (d, 2H, J = 8.9 Hz), 7.65 (d, 1H, J = 12.1 Hz), 7.69 (d, 2H, J = 8.9 Hz), 9.00 (br d, 1H, J = 12.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.1 (q), 55.3 (q), 55.4 (q), 113.6 (d), 114.9 (d), 125.5 (s), 126.6 (s), 130.1 (d), 130.4 (d), 130.7 (s), 131.8 (d), 153.6 (s), 159.7 (s), 160.1 (s), 162.9 (s), 193.5 (s); MS *m/z* (rel. intensity) 369 (63, [M$^+$]), 310 (24), 266 (12), 234 (19), 202 (12), 146 (10), 135 (100), 77 (14).

Methyl 3,4-Bis(4-methoxyphenyl)pyrrole-2-carboxylate (18). $TiCl_3$ (1.57 g, 10.2 mmol) was added to a stirred suspension of C_8K (2.75 g, 20.4 mmol) in DME (300 mL), and the resulting mixture was refluxed for 1.5 h under Ar. A solution of oxo-amide (*Z*)-**17** (373 mg, 1.01 mmol) in DME (30 mL) was added dropwise over a period of 2.5 h to the refluxing suspension of Ti–graphite thus obtained. After complete addition reflux was continued for 15 min and the hot mixture was filtered through a short pad of silica. The insoluble residues were carefully washed with EtOAc (120 mL) and CH_2Cl_2 (120 mL) since the product tends to remain adsorbed on the graphite. Even after repeated washings an additional crop of the pyrrole could be obtained when the graphite residue was stirred in fresh CH_2Cl_2 for several hours. Evaporation of the combined organic phases and flash chromatography of the residue with hexane/ethyl acetate (2/1) afforded the title compound as pale-yellow crystals (176 mg, 52%): mp 169–171 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.72 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 6.74 (d, 2H, J = 9.0 Hz), 6.84 (d, 2H, J = 8.8 Hz), 7.00–7.04 (m, 3H), 7.19 (d, 2H J = 9.0 Hz), 9.29 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 51.2, 55.08, 55.12, 113.0, 113.6, 119.3, 120.1, 126.4, 127.1, 129.4, 131.8, 158.0, 158.5, 161.6; MS *m/z* (rel intensity) 337 (53, [M$^+$]), 306 (24), 305 (100), 290 (16).

Lamellarin O Dimethyl Ether (19). A suspension of pyrrole **18** (326 mg, 0.97 mmol), 4-methoxyphenacyl bromide (425 mg, 1.85 mmol), and K_2CO_3 (1.15 g, 8.3 mmol) in acetone (70 mL) was refluxed overnight (21 h) under Ar. Filtration of the salts and evaporation of the solvent, followed by flash chromatography with hexane/ethyl acetate (4/1 → 2/1) as eluent, gave compound **19** as pale yellow crystals (425 mg, 91%): mp 55–58 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.45 (s, 3H), 3.72 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 5.71 (s, 2H), 6.70 (d, 2H, J = 8.9 Hz), 6.81 (d, 2H, J = 8.8 Hz), 6.90 (s, 1H), 6.97 (d, 2H, J = 9.0 Hz), 6.98 (d, 2H, J = 8.9 Hz), 7.14 (d, 2H, J = 8.8 Hz), 8.00 (d, 2H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.7, 55.1, 55.48, 55.53, 112.9, 113.5, 114.1, 119.8, 124.7, 127.0, 127.1, 127.9, 128.0, 129.4, 130.3, 131.2, 131.8, 157.9, 158.3, 162.3, 164.0, 191.8; MS *m/z* (rel intensity) 485 (97, [M$^+$]), 351 (10), 350 (42), 135 (100), 77 (10), 45 (16); HR-MS ($C_{29}H_{27}NO_6$) calcd 485.18384, found 485.18429.

1*H*-3,7,8-Tris(4-methoxyphenyl)pyrrolo[2,1-*c*][1,4]-oxazin-1-one (20). Water (12 μL, 0.66 mmol) was syringed into a suspension of *t*-BuOK (238 mg, 2.124 mmol) in Et_2O (10 mL) at 0 °C under Ar. After being stirred for 5 min at that temperature, this mixture was added to a solution of compound **19** (115 mg, 0.237 mmol) in Et_2O (10 mL) at 0 °C. The ice bath was removed and the mixture was stirred for 45 min at ambient temperature. The reaction was quenched with water, and the aqueous phase was extracted with Et_2O and then acidified (HCl 1 N, pH ≈ 1). The precipitated oxo-acid was extracted with Et_2O (175 mL) and CH_2Cl_2 (50 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The remaining residue was suspended in Ac_2O (20 mL), NaOAc (350 mg, 4.3 mmol) was added, and the mixture was heated at 100 °C (bath temperature) for 2.5 h. Excess Ac_2O was removed by coevaporation with toluene in vacuo. The crude product was taken up in Et_2O (100 mL) and washed with aqueous $NaHCO_3$ (200 mL in three portions), the organic layer was dried, and the solvent was removed in vacuo. Flash chromatography with hexane/ethyl acetate (4/1 → 2/1) then afforded lukianol A trimethyl ether **20** (63 mg, 59%)[2] as colorless crystals: mp 206–207 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.71 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 6.84 (d, 2H, J = 9.0 Hz), 6.89 (d, 2H, J = 8.9 Hz), 7.06 (d, 2H, J = 9.2 Hz), 7.07 (d, 2H, J = 8.9 Hz), 7.18 (d, 2H, J = 8.9 Hz), 7.65 (s, 1H), 7.67 (d, 2H, J = 9.0 Hz), 8.16 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 55.2, 55.5, 103.8, 112.4, 113.4, 114.1, 114.6, 120.4, 123.0, 124.9, 125.6, 127.3, 128.6, 129.6, 131.9, 140.7, 153.3, 158.4, 158.7, 160.2; MS *m/z* (rel intensity) 453 (100, [M$^+$]), 135 (16).

Lukianol A (2). BBr_3 (106 μL, 1.134 mmol) dissolved in CH_2Cl_2 (1 mL) was added to a solution of trimethyl ether **20** (57 mg, 0.126 mmol) in CH_2Cl_2 (15 mL) at −78 °C under Ar via syringe. The mixture was stirred for 1 h at that temperature and then allowed to warm to room temperature overnight. Dilution with Et_2O (100 mL) and EtOAc (20 mL), and quenching of the reaction with water (50 mL), followed by a standard

extractive workup and flash chromatography (hexane/ethyl acetate 1/2 followed by ethyl acetate/EtOH 1/1), gave lukianol A (**2**) as colorless crystals (51 mg, 99%):[2] mp 264–266 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.65 (d, 2H, J = 8.7 Hz), 6.69 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.9 Hz), 6.94 (d, 2H, J = 8.7 Hz), 7.05 (d, 2H, J = 8.7 Hz), 7.55 (d, 2H, J = 8.8 Hz), 7.58 (s, 1H), 8.05 (s, 1H), 9.37 (br s, 1H), 9.41 (br s, 1H), 9.83 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 103.2, 112.1, 114.8, 115.4, 116.0, 120.1, 121.5, 123.3, 124.1, 125.7, 127.5, 129.0, 129.6, 131.9, 141.0, 153.7, 156.5, 156.8, 158.6; MS *m/z* (rel intensity) 411 (100, [M$^+$]), 354 (13), 262 (15), 121 (23); HR-MS ($C_{25}H_{17}NO_5$) calcd 411.11067, found 411.10857.

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Supporting Information Available: List of the IR-absorptions of all products; elemental analyses or copies of the ^{1}H and ^{13}C NMR spectra of all new compounds (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; ordering information is given on any current masthead page.

JO951088F

Additions and Corrections

Vol. 59, 1994

Clayton H. Heathcock* and Stephen C. Smith. Synthesis and Biological Activity of Unsymmetrical Bis-Steroidal Pyrazines Related to the Cytotoxic Marine Natural Product Cephalostatin 1.

Pages 6831 and 6832. All references to compound **31** should be changed to compound **25**. There is no compound **31** in this Article.

JO9540155

Vol. 60, 1995

John L. Wood,* Susan Jeong, Annalee Salcedo, and Jonathan Jenkins. Total Syntheses of (+)- and (−)-Syringolides 1 and 2.

Page 287. The first structure in Scheme 2 should be labeled (−)-**6** and the following changes should be made to the text: page 286, column 2, line 11 should read (−)-2,3-*O*-isopropylidine-D-threitol; page 287, column 2, line 2 should read stereochemistry of (−)-**6**; page 287, ref 12 should read (+)-2,3-*O*-isopropylidine-L-threitol.

JO954012S

Jean Suffert* and Dominique Toussaint. An Easy and Useful Preparation of Propynyllithium from (*Z*/*E*)-1-Bromopropene.

Page 3550, column 1. In our statement "there are no reports on an easy preparation of propynyllithium from commercially available compounds" and in spite of a careful search of the CAS databases, we omitted to cite an earlier report by Gordon Gribble (*Synth. Commun.* **1992**, *22*, 2997) in which this reagent was prepared from 1,2-dibromopropane. We acknowledge this oversight of the Gribble reference.

JO954019+

Hirokazu Urabe, Koki Yamashita, Ken Suzuki, Katsushige Kobayashi, and Fumie Sato*. Lewis Acid–Enhanced Reactivity of α,β-Unsaturated Ester and Amide toward Radical Addition.

Page 3577, column 2, line 22 should read controlled by a chiral LA.[17] and the following note should be added: (17) Most recently a related report appeared. Murakata M.; Tsutsui H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481. We are grateful to professor O. Hoshino for sending us a copy of the reprint.

JO954018H

William R. Roush* and Paul T. Grover. *N*,*N*′-Bis(2,2,2-trifluoroethyl)-*N*,*N*′-ethylenetartramide: An Improved Chiral Auxiliary for the Asymmetric Allylboration Reaction.

Page 3810. The ratio **38**:**39** reported in entry 6 of Table 4 for the mismatched double asymmetric reaction of D-glyceraldehyde acetonide (**33**) and (*S*,*S*)-**11** and the comparative ratio for the reaction of **33** with (*S*,*S*)-**3** should be reversed. The correct data are as follows: **38**:**39** = 61:39 for the reaction of **33** and (*S*,*S*)-**11** and **38**:**39** = 84:16 for the reaction of **33** and (*S*,*S*)-**3**.

JO954014C