JOC Article

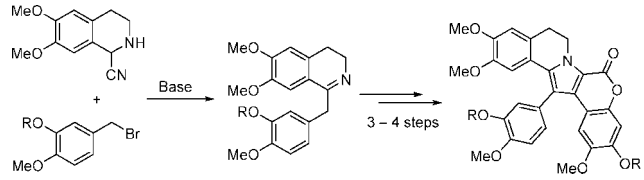
Synthesis of Lamellarin U and Lamellarin G Trimethyl Ether by Alkylation of a Deprotonated α-Aminonitrile

Johannes C. Liermann[†,‡] and Till Opatz*[,†,‡]

Institut für Organische Chemie, Universität Mainz, Duesbergweg 10-14, D-55128 Mainz, Germany, and Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

opatz@chemie.uni-hamburg.de

Received February 28, 2008



1,2,3,4-Tetrahydroisoquinoline-1-carbonitriles can serve as starting materials for the one-pot synthesis of 5,6-dihydropyrrolo[2,1*a*]isoquinolines and 1-benzyl-3,4-dihydroisoquinolines. The latter compounds were transformed to lamellarin G trimethyl ether and lamellarin U in short reaction sequences. This method allows the introduction of acid-sensitive protecting groups for the phenolic hydroxy functions which would be cleaved under the harsh conditions of the classical Bischler−Napieralski reaction.

Introduction

Starting with the pioneering synthetic work of Steglich et al. in 1997,[1] the development of procedures for the preparation of the lamellarins, a large group of polycyclic marine pyrrole alkaloids isolated from molluscs and ascidians,[2,3] has attracted considerable attention (Figure 1).[4,5] The interest in these compounds largely originates from their antiproliferative activity.[4,5] Moreover, lamellarin D turned out to be a potent inhibitor of human topoisomerase I, and the ability of lamellarin α-20-sulfate to inhibit HIV-1 integrase has been reported.[6,7] Consequently, various methods for the construction of the lamellarin skeleton have been developed, among them the formation of the central pyrrole ring at a late stage by combining suitable fragments[8–13] or the successive substitution of a preformed pyrrole derivate in a series of C−C-couplings.[14,15] Here, we report on the use of a readily available deprotonated α-aminonitrile[16–19] as an AB ring building block in a convergent synthesis of lamellarin U and lamellarin G trimethyl ether.

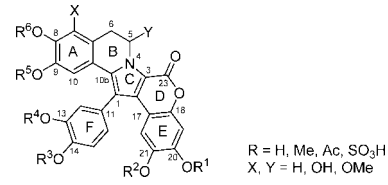


FIGURE 1. The pentacyclic ring system of the 5,6-saturated lamellarins.

Results and Discussion

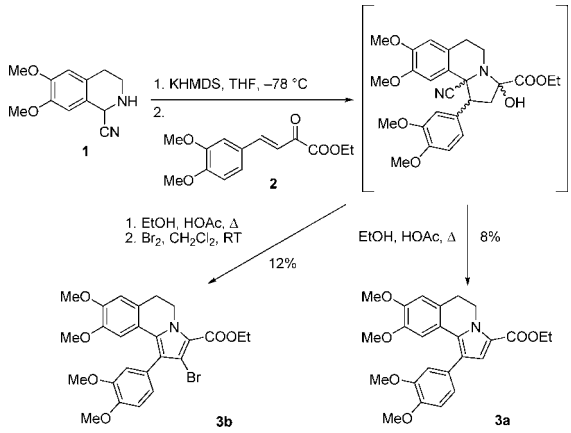
The crystalline 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **1** can be readily prepared in multigram quantities from homoveratrylamine in 59% yield over three synthetic

[†] Universität Mainz.
[‡] Universität Hamburg.

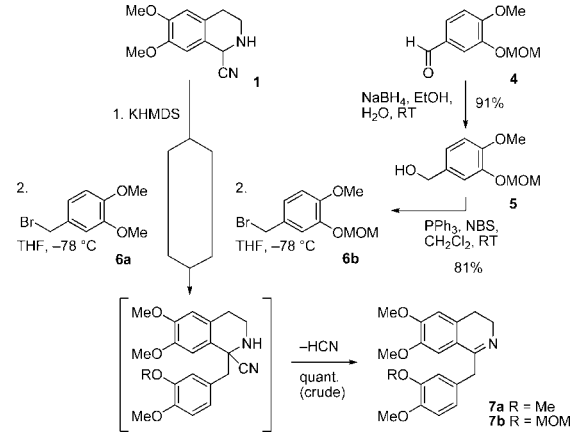
(1) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155–156.
(2) Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492–5495.
(3) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113–158.
(4) Bailly, C. *Curr. Med. Chem.* **2004**, *4*, 363–378.
(5) Fan, H.; Peng, J.-N.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264–287.
(6) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392–7399.
(7) Reddy, M. V.; Rao, M. R.; Rhodes, D.; Hansen, M. S.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907.
(8) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951–5962.
(9) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259–2260.
(10) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363–1366.
(11) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866–868.
(12) Ploypradith, P.; Kagan, R. K.; Ruchirawat, S. *J. Org. Chem.* **2005**, *70*, 5119–5125.
(13) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440–9448.
(14) Handy, S. T.; Zhang, Y. N.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362–2366.
(15) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Álvarez, M. *J. Org. Chem.* **2005**, *70*, 8231–8234.

10.1021/jo800467e CCC: $40.75
Published on Web 05/24/2008

SCHEME 1. Synthesis of Pyrroles 3a and 3b in a Modified von Miller–Plöchl Reaction



SCHEME 2. Synthesis of the Dihydroisoquinolines 7a and 7b



steps.[20,21] As this compound is a suitable starting material for the one-pot synthesis of mono- and disubstituted 5,6-dihydropyrrolo[2,1*a*]isoquinolines in a modified von Miller–Plöchl reaction (Scheme 1),[16,22] we anticipated the vinylogous addition of its anion to a suitably functionalized benzylidenepyruvate to furnish an advanced intermediate in which only the coumarin part of the lamellarin skeleton is missing. The synthesis could then be completed by halogenation and attachment of the E ring in a cross-coupling reaction followed by closure of the lactone ring. However, in contrast to the appreciable yields observed in the reaction of **1** with other α,β-unsaturated ketones, the reaction of ethyl benzylidenepyruvate **2**[23] with the deprotonated aminonitrile **1** followed by elimination of HCN and water from the unstable intermediate furnished pyrrole **3a** in an unsatisfactory yield of only 8%. Along with this compound, colored side products were formed which may result from oxidation of **3a** during workup and purification. If crude pyrrole **3a** was brominated with molecular bromine before column chromatography to prevent side reactions at the unsubstituted position of the pyrrole ring, bromopyrrole **3b** was obtained in an overall yield of 12%. Although compounds **3a** and **3b** were already used by Handy et al.[14] in their total synthesis of lamellarin G trimethyl ether, this synthetic approach was abandoned due to the poor yields.

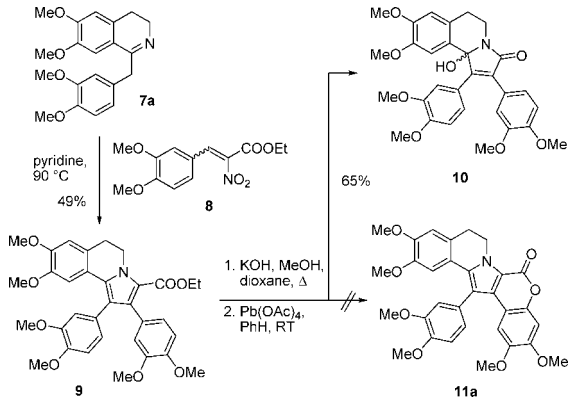
An alternative route to the lamellarin skeleton involves the α-alkylation of **1** with a suitably functionalized benzylic bromide which directly yields the 1-benzyl-3,4-dihydroisoquinoline after spontaneous elimination of HCN from the primary alkylation product.[21] Compounds of this type have been successfully converted to lamellarins, for example, by direct formation of the pentasubstituted pyrrole ring in a Grob cyclization[24] as demonstrated by Ruchirawat et al.[10–13] Moreover, this novel approach permits the introduction of acid-sensitive protecting groups to the tricyclic ABF fragment. In combination with, for example, benzylic protection of the eastern half of the target structure, the preparation of orthogonally protected lamellarin precursors whose phenolic hydroxy groups can be differentiated at a late stage becomes feasible. Deprotonation of **1** with 2.5 equiv of KHMDS in THF at −78 °C and subsequent reaction with 3,4-dimethoxybenzyl bromide **6a** and the MOM-protected benzylic bromide **6b** furnished the dihydroisoquinolines **7a** and **7b**, respectively (Scheme 2). Due to their sensitivity toward aerial oxidation,[25] these compounds were not purified but directly subjected to the Grob cyclization. Nevertheless, NMR analysis of the crude products indicated a surprisingly high purity.

Nitrocinnamate **8**, obtained by Knoevenagel condensation of veratraldehyde and ethyl nitroacetate,[26] was used to construct the eastern half of the lamellarin ring system. While the Grob cyclization of **7a** and **8** with $NaHCO_3$ in boiling acetonitrile[11–13] gave an unsatisfactory yield of only 21%, we found the reaction in pyridine at 90 °C to furnish pyrrole **9** in 49% yield. An intriguing method of synthesizing a lactone from a 3,4-diarylpyrrole-2,5-dicarboxylic acid by C–H activation with $Pb(OAc)_4$ was employed by Steglich et al. in their syntheses of various lamellarins.[1,27] Unfortunately, ester hydrolysis and subsequent oxidation of **9** with either $Pb(OAc)_4$ or bis(trifluoroacetoxy)iodobenzene furnished the same unstable product which did not exhibit the expected spectral properties. Elucidation of its structure by NMR spectroscopy revealed the product to be lactam **10**, resulting from an oxidative decarboxylation (Scheme 3). Presumably, the larger electron density in the pyrrole ring accounts for this deviant behavior.

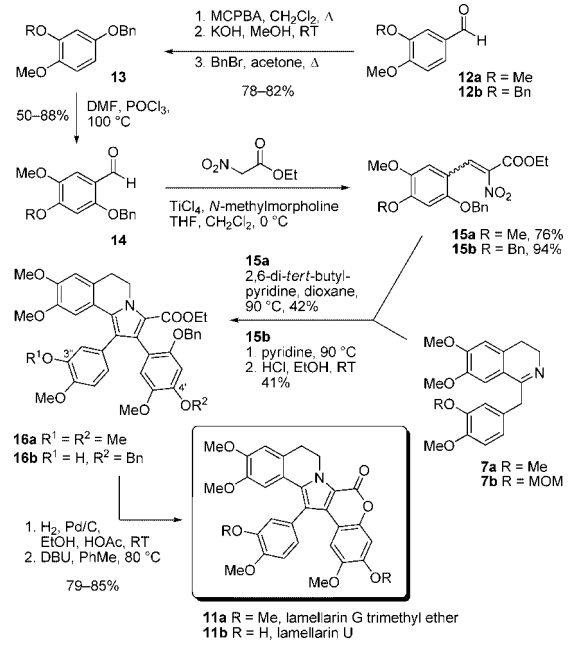
Therefore, nitrocinnamates with an additional hydroxy function in the ortho-position were synthesized (Scheme 4). Aldehydes **12a** and **12b** were converted to phenols by Baeyer–Villiger oxidation and subsequent hydrolysis of the resulting formates. The phenols **13** were protected by benzylation and formylated in a Vilsmeier reaction. Knoevenagel condensation with ethyl nitroacetate using $TiCl_4$/*N*-methylmorpholine furnished nitrocinnamates **15a** and **15b** as *E*/*Z*-mixtures in yields of 76 and 94%, respectively. The Grob reaction of dihydroisoquinoline **7a** with **15a** leads to pyrrole **16a** in a yield of 38% in pyridine at 90 °C. Optimization resulted in a 42% yield if the reaction

(16) Meyer, N.; Opatz, T. *Eur. J. Org. Chem.* **2006**, 3997–4002.
(17) Meyer, N.; Opatz, T. *Synlett* **2003**, 1427–1430.
(18) Meyer, N.; Werner, F.; Opatz, T. *Synthesis* **2005**, 945–956.
(19) Kison, C.; Meyer, N.; Opatz, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5662–5664.
(20) Kobor, J.; Koczka, K. *Szegedi Tanarkepzo Foiskola Tudomanyos Kozlemenyei* **1969**, 179–183.
(21) Werner, F.; Blank, N.; Opatz, T. *Eur. J. Org. Chem.* **2007**, 3911–3915.
(22) von Miller, W.; Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2718–2720.
(23) Reimer, M.; Tobin, E.; Schaffner, M. *J. Am. Chem. Soc.* **1935**, *57*, 211–215.
(24) Grob, C. A.; Camenisch, K. *Helv. Chim. Acta* **1953**, *36*, 49–58.
(25) Kapadia, G. J.; Shah, N. J.; Highet, R. J. *J. Pharm. Sci.* **1964**, *53*, 1431–1432.
(26) Dauzonne, D.; Royer, R. *Synthesis* **1987**, 399–401.
(27) Peschko, C.; Winklhofer, C.; Terpin, A.; Steglich, W. *Synthesis* **2006**, 3048–3057.

SCHEME 3. Grob Cyclization and Attempted Oxidative Ring Closure



SCHEME 4. Preparation of the Lamellarins



was run in dioxane with 2,6-di-*tert*-butylpyridine as the base for 20 h and a 38% yield under the identical conditions using microwave heating to 90 °C for 5 min. Pyrrole **16b** is formed by reaction of **7b** and **15b** in pyridine at 90 °C. Since cleavage of the MOM ether occurred to a minor extent during the cyclization, the protecting group was removed completely to furnish **16b** in 41% yield from **15b** after chromatographic purification. Lamellarin G trimethyl ether **11a** and lamellarin U **11b** were obtained from **16a** and **16b** by hydrogenolytic removal of the benzyl groups and heating with DBU in toluene in 79 and 85% yield, respectively.

As demonstrated for pyrrole **16b**, the phenolic functions at positions 4′ and 3″ can be differentiated by using a combination of the MOM protecting group and the benzyl ether. In contrast to employing the Bischler−Napieralski cyclization[28] to prepare the western half of the lamellarin ring system, the C-alkylation of aminonitrile **1** allows the direct introduction of the MOM-protected aryl residue.

(28) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903–1908.

Experimental Section

Ethyl 8,9-Dimethoxy-1-(3,4-dimethoxyphenyl)-5,6-dihydropyrrolo[2,1*a*]isoquinoline-3-carboxylate (3a). The title compound was synthesized in analogy to the procedure of Meyer et al.[16] Aminonitrile **1** (300 mg, 1.37 mmol) was dissolved in dry THF (5 mL) under argon atmosphere and careful exclusion of moisture. The solution was cooled to −78 °C, and a solution of KHMDS (411 mg, 2.06 mmol) in dry THF (0.8 mL) was added dropwise over 1 min. After 15 min, a solution of ester **2** (400 mg, 1.51 mmol) in dry THF (0.8 mL) was added. The reaction mixture was stirred for 1 h at −78 °C. After the addition of ethanol (5 mL) and acetic acid (0.5 mL), the reaction mixture was heated to reflux for 45 min. Saturated aq $NaHCO_3$ (10 mL) was added, and the solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to yield a brown oil (532 mg). Purification by silica gel flash chromatography (4:4:1 petroleum ether/CH_2Cl_2/EtOAc, $R_f = 0.30$) furnished the product as a slightly yellow solid (47 mg, 8%): mp 144−145 °C (lit.[14] 147.2−149.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.99 (dd, ^3J = 8.1 Hz, ^4J = 1.9 Hz, 1H, H-6′), 6.97 (s, 1H, H-2), 6.95 (d, ^4J = 1.9 Hz, 1H, H-2′), 6.87 (d, J = 8.1 Hz, 1H, H-5′), 6.87 (s, 1H, H-7), 6.71 (s, 1H, H-10), 4.59 (t, J = 6.6 Hz, 2H, H_2-5), 4.29 (q, J = 7.1 Hz, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.00 (t, J = 6.6 Hz, 2H, H_2-6), 1.35 (t, J = 7.1 Hz, 3H, CH_3) ppm. The recorded data are in accordance with those reported in the literature.[14]

Ethyl 2-Bromo-8,9-dimethoxy-1-(3,4-dimethoxyphenyl)-5,6-dihydropyrrolo[2,1*a*]isoquinoline-3-carboxylate (3b). Bromination of **3a** was performed in analogy to a procedure by Clezy et al.[29] Crude **3a** (100 mg) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. A solution of bromine (46.9 mg, 294 μmol) in CH_2Cl_2 (1.1 mL) was added. The solution was stirred at room temperature for 1 h. CH_2Cl_2 (10 mL) and 10% aq $Na_2S_2O_3$ (10 mL) were added. The organic phase was washed with saturated aq $NaHCO_3$ (10 mL), dried over Na_2SO_4, and evaporated in vacuo to furnish a brown oil (116 mg). A portion of this material (113 mg) was purified by silica gel flash chromatography (4:4:1 petroleum ether/CH_2Cl_2/EtOAc, $R_f = 0.38$) to yield the title compound as a yellow foam (14 mg, 12% from **1**): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.96 (d, J = 8.1 Hz, 1H, H-5′), 6.92 (dd, ^3J = 8.1 Hz, ^4J = 1.7 Hz, 1H, H-6′), 6.88 (d, ^4J = 1.7 Hz, 1H, H-2′), 6.69 (s, 1H, H-10), 6.56 (s, 1H, H-7), 4.60 (t, J = 6.6 Hz, 2H, H_2-5), 4.39 (q, J = 7.1 Hz, 2H, OCH_2), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.01 (t, J = 6.6 Hz, 2H, H_2-6), 1.43 (t, J = 7.1 Hz, 3H, CH_3) ppm. The spectroscopic data are in accordance with those reported in the literature.[14]

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3,4-dihydroisoquinoline (7a). [30] Aminonitrile **1** (300 mg, 1.37 mmol) was dissolved in dry THF (10.5 mL) under argon atmosphere. The solution was cooled to −78 °C, and a solution of KHMDS (684 mg, 3.43 mmol) in dry THF (2.3 mL) was added slowly. After 5 min, a solution of 3,4-dimethoxybenzyl bromide[31,32] (**6a**, 349 mg, 1.51 mmol) in dry THF (2.3 mL) was added. The reaction mixture was stirred overnight while it gradually reached room temperature. 1 M aq NaOH (45 mL) was added, followed by extraction of the reaction mixture with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo to furnish the crude 3,4-dihydroisoquinoline as an orange oil (471 mg). This compound is prone to benzylic oxidation[25] and was subjected to the Grob reaction without further purification: ^{1}H NMR (300 MHz,

(29) Clezy, P. S.; Salek, A. *Aust. J. Chem.* **1996**, *49*, 265–272.

(30) Pictet, A.; Finkelstein, M. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1979–1989.

(31) Pinza, M.; Dorigotti, L.; Pifferi, G. *Eur. J. Med. Chem.* **1976**, *11*, 395–398.

(32) Perales, J. B.; Makino Narubumi, F.; Van Vranken, D. L. *J. Org. Chem.* **2002**, *67*, 6711–6717.

$CDCl_3$) δ = 7.00 (s, 1H, H-8), 6.85−6.81 (m, 2H, H-2′, H-6′), 6.76 (d, J = 8.7 Hz, 1H, H-5′), 6.65 (s, 1H, H-5), 3.99 (s, 2H, Ar-CH_2), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.73 (t, J = 7.7 Hz, 2H, H_2-3), 2.65 (t, J = 7.7 Hz, 2H, H_2-4) ppm. The spectroscopic data are in accordance with those reported in the literature.[33]

6,7-Dimethoxy-1-(3-methoxymethoxy-4-methoxybenzyl)-3,4-dihydroisoquinoline (7b). The benzylic bromide was prepared in analogy to a procedure by Yamaguchi et al.[34] Benzyl alcohol **5** (416 mg, 2.10 mmol) was dissolved in CH_2Cl_2 (20 mL) under argon atmosphere and cooled to 0 °C. PPh_3 (826 mg, 3.15 mmol) and NBS (560 mg, 3.15 mmol) were added. The mixture was stirred at room temperature for 30 min. Water (15 mL) was added, and the solution was extracted with ether (2 × 15 mL). The combined extracts were washed with 2 M aq NaOH (15 mL) and brine. The organic phase was dried over Na_2SO_4 and evaporated in vacuo to furnish the crude product as a brownish solid (1.2 g). The solid was dissolved in a mixture of ethyl acetate (5 mL), CH_2Cl_2 (2 mL), and petroleum ether (5 mL) and was quickly filtered through a short pad of silica (eluent 1:1 petroleum ether/ethyl acetate, R_f = 0.73). 4-Methoxy-3-methoxymethoxybenzyl bromide (**6b**) was obtained as a moisture-sensitive brown oil (441 mg, 81%), which was stored in THF solution over $CaCO_3$ until use: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20 (d, ^4J = 2.1 Hz, 1H, H-2), 7.03 (dd, ^3J = 8.3 Hz, ^4J = 2.1 Hz, 1H, H-6), 6.84 (d, J = 8.3 Hz, 1H, H-5), 5.24 (s, 2H, OCH_2O), 4.48 (s, 2H, CH_2Br), 3.88 (s, 3H, $ArOCH_3$), 3.53 (s, 3H, OCH_3) ppm. The compound decomposes in $CDCl_3$ solution. Aminonitrile **1** (299 mg, 1.37 mmol) was dissolved in dry THF (10.5 mL) under argon atmosphere. The solution was cooled to −78 °C, and a solution of KHMDS (684 mg, 3.43 mmol) in dry THF (2.3 mL) was added slowly. After 5 min, a solution of bromide **6b** (395 mg, 1.51 mmol) in dry THF (4 mL) was added. The reaction mixture was stirred overnight while it gradually reached room temperature. 1 M aq NaOH (45 mL) was added, followed by extraction of the reaction mixture with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo to furnish the crude 3,4-dihydroisoquinoline as an orange oil (580 mg). This compound is prone to benzylic oxidation[25] and was subjected to the Grob reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.12 (d, ^4J = 1.8 Hz, 1H, H-2′), 6.98 (s, 1H, H-5), 6.92 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H, H-6′), 6.79 (d, J = 8.4 Hz, 1H, H-5′), 6.65 (s, 1H, H-8), 5.17 (s, 2H, OCH_2), 3.98 (s, 2H, $ArCH_2$), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.72 (t, J = 7.8 Hz, 2H, H_2-3), 3.46 (s, 3H, OCH_3), 2.65 (t, J = 7.8 Hz, 2H, H_2-4) ppm.

General Procedure for the Synthesis of the Nitrocinnamates. These compounds were prepared as previously described by Lehnert.[35] Dry THF (10 mL) under argon atmosphere was cooled to 0 °C, and a solution of $TiCl_4$ (2 equiv) in 1 mL dry CH_2Cl_2 was added, leading to the precipitation of a yellow solid. A solution of the aldehyde **14** in dry CH_2Cl_2 (3 mL) and ethyl nitroacetate (1 equiv) were added to the stirred mixture. After 15 min, *N*-methyl morpholine (4 equiv) in dry THF was added dropwise. The reaction mixture was stirred at 0 °C for 22 h. Water (25 mL) was added, and the resulting mixture was extracted with ether (2 × 25 mL). The combined extracts were washed with brine (25 mL), dried over Na_2SO_4, and evaporated in vacuo to furnish the nitrocinnamates as *E/Z*-isomeric mixtures.

(*E/Z*)-Ethyl 2-Benzyloxy-4,5-dimethoxy-α-nitrocinnamate (15a). This compound was prepared from **14a** (918 mg, 3.37 mmol) according to the general procedure: orange solid (994 mg, 76%); *E/Z* = 38:62. Recrystallization of an analytical sample (50 mg) from MeOH furnished the pure *Z*-isomer (21 mg), orange crystals, mp 127−128 °C. The mixture of isomers was employed in the subsequent Grob cyclization. Analytical data of the *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (s, 1H, β-H), 7.41−7.33 (m, 5H, Bn-H), 6.81 (s, 1H, H-6), 6.52 (s, 1H, H-3), 5.14 (s, 2H, $PhCH_2$), 4.34 (q, J = 7.2 Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 1.34 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 159.9 (C═O), 154.1, 153.9 (2 × C-OCH_3), 143.8 (C-OBn), 138.0 (C-1), 136.1 (Bn-C-1), 128.8 (2C, Bn-C-2,6), 128.3 (Bn-C-4), 127.5 (β-C), 127.3 (2C, Bn-C-3,5), 110.1 (α-C), 110.0 (C-6), 98.4 (C-3), 71.9 ($PhCH_2$), 62.5 (OCH_2), 56.2, 56.0 (2 × OCH_3), 14.1 (CH_3) ppm; the spectroscopic data are in accordance with those reported in the literature;[12] IR (NaCl) ν = 2938, 1728, 1608, 1510, 1261, 1220, 1016 cm^{-1}; FD-MS (*m/z*) 387.2 (100, M^+). Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.99; H, 5.51; N, 3.59.

Characteristic data of the *E*-isomer (from isomeric mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.55 (s, 1H, β-H), 7.41−7.33 (m, Bn), 6.98 (s, 1H, H-6), 6.53 (s, 1H, H-3), 5.16 (s, 2H, $PhCH_2$), 4.40 (q, J = 7.2 Hz, 2H, OCH_2), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 1.36 (t, J = 7.2 Hz, 3H, CH_3) ppm.

(*E/Z*)-Ethyl 2,4-Bis(benzyloxy)-5-methoxy-α-nitrocinnamate (15b). This compound was prepared from **14b** (400 mg, 1.15 mmol) according to the general procedure: orange solid (592 mg, 94%); *E/Z* = 44:56. Recrystallization of an analytical sample (50 mg) from petroleum ether furnished the pure *Z*-isomer (18 mg), orange crystals, mp 136−137 °C. The mixture of isomers was employed in the subsequent Grob cyclization. Analytical data of the *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (s, 1H, β-H), 7.39−7.27 (m, 10H, Bn), 6.83 (s, 1H, H-6), 6.50 (s, 1H, H-3), 5.12 (s, 2H, $PhCH_2$), 5.00 (s, 2H, $PhCH_2$), 4.34 (q, J = 7.1 Hz, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 1.34 (t, J = 7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 159.9 (C═O), 153.8, 152.9, 144.3 (C-OMe, 2 × C-OBn), 138.1 (C-1), 136.0, 135.9 (2 × Bn-C-1), 128.8 (2C, 2 × Bn), 128.7 (2C, 2 × Bn), 128.3 (2C, 2 × Bn), 127.5 (β-C), 127.1 (2C, 2 × Bn), 127.1 (2C, 2 × Bn), 110.6 (C-6), 110.5 (α-C), 100.6 (C-3), 71.7, 71.0 (2 × $PhCH_2$), 62.5 (OCH_2), 56.3 (OCH_3), 14.1 (CH_3) ppm; the spectroscopic data are in accordance with those reported in the literature;[12] IR (NaCl) ν = 2932, 1718, 1607, 1521, 1261, 1219, 1023 cm^{-1}; FD-MS (*m/z*) 463.2 (100, M^+). Anal. Calcd for $C_{26}H_{35}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.37; H, 5.33; N, 2.90.

Characteristic data of the *E*-isomer (from isomeric mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.51 (s, 1H, β-H), 7.39−7.27 (m, Bn), 6.99 (s, 1H, H-6), 6.52 (s, 1H, H-3), 5.13 (s, 2H, $PhCH_2$), 5.03 (s, 2H, $PhCH_2$), 4.39 (q, J = 7.1 Hz, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 1.39 (t, J = 7.1 Hz, 3H, CH_3) ppm.

General Procedure for the Grob Cyclization. The dihydroisoquinoline (1.2−1.5 equiv) was dissolved in dry pyridine (2 mL/mmol) under argon atmosphere. A solution of the corresponding nitrocinnamate (1 equiv) in dry pyridine (5 mL/mmol) was added while stirring. The solution was stirred for 20 h at 90 °C. Saturated aq citric acid (10 mL) was added, followed by extraction with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to furnish the crude products. Further purification was achieved by silica gel flash chromatography.

Ethyl 1,2-Bis(3,4-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1*a*]isoquinoline-3-carboxylate (9). The title compound was prepared from **7a** (182 mg, 0.53 mmol) and **8** (100 mg, 0.36 mmol) according to the general procedure: yellow oil (94 mg, 49%), R_f (3:2 petroleum ether/ethyl acetate) = 0.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.75−6.65 (m, 8H, Aryl-H), 4.62 (t, J = 6.6 Hz, 2H, H_2-5), 4.09 (q, J = 7.1 Hz, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.34 (s, 3H,9-OCH_3), 3.05 (t, J = 6.6 Hz, 2H, H_2-6), 1.01 (t, J = 7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 162.0 (C═O), 148.6, 148.0, 147.6, 147.6, 147.4, 147.2 (C-OCH_3), 132.6 (C-2), 130.9 (C-10b), 128.1 (C-1′), 128.0 (C-1″), 126.0 (C-6a), 123.4, 123.1 (C-6′, 6″), 121.4 (C-1), 120.8 (C-10a), 118.3 (C-3), 114.3, 114.2 (C-2′, 2″), 111.0 (C-5′/5″) 110.6 (C-7), 110.0 (C-5′/5″), 108.7 (C-10), 59.7 (OCH_2), 55.8,

(33) Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689–2693.
(34) Yamaguchi, S.; Tsuchida, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505–7511.
(35) Lehnert, W. *Tetrahedron* **1972**, *28*, 663–666.

55.8, 55.8, 55.8, 55.6, 55.2 (6 × OCH_3), 42.8 (C-5), 29.1 (C-6), 13.9 (CH_3) ppm; the spectroscopic data are in accordance with those reported in the literature;[13] IR (NaCl) ν = 3430, 2096, 1680, 1254, 1232, 1135, 1066, 1027 cm^{-1}; FD-MS (*m/z*) 573.2 (100, M^+). Anal. Calcd for $C_{33}H_{35}NO_8$: C, 69.10; H, 6.15; N, 2.44. Found: C, 68.89; H, 6.14; N, 2.29.

Ethyl 2-(2-Benzyloxy-4,5-dimethoxyphenyl)-8,9-dimethoxy-1-(3,4-dimethoxyphenyl)-5,6-dihydropyrrolo[2,1*a*]isoquinoline-3-carboxylate (16a). Dihydroisoquinoline **7a** (198 mg, 0.58 mmol) was dissolved in dry dioxane (1 mL) under argon atmosphere. Solutions of **15a** (187 mg, 0.48 mmol) and 2,6-di-*tert*-butylpyridine (185 mg, 0.97 mmol, 217 μL) in dry dioxane (1 mL each) were added, and the resulting mixture was heated to 90 °C for 20 h. Following workup and purification were performed according to the general procedure: yellow oil (138 mg, 42%), R_f (3:2 petroleum ether/ethyl acetate) = 0.16; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.26−7.14 (m, 5H, Bn), 6.76−6.71 (m, 5H, H-2″, H-5″, H-6″, H-7, H-10), 6.61 (s, 1H, H-3′), 6.44 (s, 1H, H-6′), 4.83 (br s, 2H, $PhCH_2$), 4.64 (t, J = 6.2 Hz, 2H, H_2-5), 4.05 (q, J = 7.1 Hz, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.07 (t, J = 6.2 Hz, 2H, H_2-6), 0.93 (t, J = 7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 162.0 (C═O), 150.6 (C-2′) 148.4, 148.1, 147.9, 147.5, 147.1, 142.9 (C-OCH_3), 137.9 (Bn-C-1), 130.8 (C-10b), 128.6 (C-1′), 128.2 (3C, C-1″, 2 × Bn) 127.4 (Bn) 126.9 (2C, 2 × Bn), 125.8 (C-6a), 123.1 (C-6″), 121.8 (C-1), 121.0 (C-10a), 119.1 (C-3), 118.1 (C-2), 115.5 (C-3′), 114.0 (C-2″), 110.8 (C-5″), 110.6 (C-7), 108.7 (C-10), 100.5 (C-6′), 72.1 ($PhCH_2$), 59.6 (OCH_2), 56.2, 55.9, 55.8, 55.8, 55.6, 55.2 (6 × OCH_3), 42.8 (C-5), 29.1 (C-6), 13.8 (CH_3) ppm; the spectroscopic data are in accordance with those reported in the literature;[12] IR (NaCl) ν = 3529, 2936, 1685, 1610, 1517, 1465, 1336, 1260, 1154, 1064, 1027 cm^{-1}; FD-MS (*m/z*) 679.4 (100, M^+); ESI-HRMS calcd for [$C_{40}H_{41}NO_9$ + H^+] 680.2860, found 680.2866.

Ethyl 2-[2,4-Bis(benzyloxy)-5-methoxyphenyl]-8,9-dimethoxy-1-(3-hydroxy-4-methoxyphenyl)-2-(5,6-dihydropyrrolo[2,1*a*]isoquinoline-3-carboxylate (16b). The title compound was prepared from **7b** (167 mg, 0.45 mmol) and **15b** (174 mg, 0.38 mmol) according the general procedure. The MOM group was cleaved by dissolving the crude product in ethyl acetate (5 mL) and adding 2 M hydrogen chloride in ethanol (1 mL). The solution was stirred at room temperature for 40 min, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. Purification by column chromatography (3:2 petroleum ether/ethyl acetate, R_f = 0.29) furnishes the product as a yellow oil (96 mg, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.21 (m, 8H, Bn), 7.13−7.10 (m, 2H, Bn), 6.82−6.79 (m, 1H, H-2″), 6.73−6.67 (m, 3H, H-5″, H-6″, H-6′), 6.65 (s, 1H, H-7), 6.59 (s, 1H, H-10), 6.44 (s, 1H, H-3′), 5.47 (s, 1H, OH), 5.02 (br s, 2H, $PhCH_2$), 4.78 (s, 2H, $PhCH_2$), 4.63 (br s, 2H, H_2-5), 3.99 (q, J = 7.2, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.05 (t, J = 6.6 Hz, 2H, H_2-6), 0.83 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 162.0 (C═O), 150.6 (C-2′), 147.9, 147.2, 146.9, 145.3, 145.3, 143.5 (6 × C-OR), 137.9, 137.2 (2 × Bn-C-1), 130.9 (C-10b), 129.1 (C-1′), 128.4 (2C, 2 × Bn), 128.3 (C-1″), 128.2 (2C, 2 × Bn), 127.7, 127.4 (2 × Bn), 127.3 (2C, 2 × Bn), 126.9 (2C, 2 × Bn), 125.7 (C-6a), 122.7 (C-6″), 121.6 (C-1), 121.1 (C-10a), 119.1 (C-3), 118.8 (C-2), 117.3 (C-3′), 116.0 (C-2″), 110.6 (C-5″), 110.4 (C-7), 108.8 (C-10), 103.2 (C-6′), 71.9 ($PhCH_2$), 71.2 ($PhCH_2$), 59.6 (OCH_2), 56.4, 56.0, 55.9, 55.1 (4 × OCH_3), 42.8 (C-5), 29.1 (C-6), 13.7 (CH_3) ppm; although the presence of an impurity could be detected in the NMR spectra, debenzylation and lactonization of **16b** furnished analytically pure lamellarin U without further purification; IR (NaCl) ν = 3424, 2936, 1684, 1610, 1499, 1464, 1336, 1255, 1213, 1176, 1025 cm^{-1}; FD-MS (*m/z*) 741.4 (100, M^+); ESI-HRMS calcd for [$C_{45}H_{43}NO_9$ + H^+] 742.3016, found 742.3019.

1,2-Bis(3,4-dimethoxyphenyl)-8,9-dimethoxy-10b-hydroxy-6,10b-dihydro-5*H*-pyrrolo[2,1*a*]isoquinolin-3-one (10). Pyrrole **9** (18 mg, 31.4 μmol) was dissolved in a mixture of 4 M aq NaOH (110 μL), dioxane (1.54 mL), and MeOH (0.55 mL) and heated to reflux for 3.5 h. The solution was acidified to pH 2 with 1 N aq HCl, and brine (10 mL) was added, followed by extraction with ethyl acetate (10 mL). The organic extract was dried over Na_2SO_4 and evaporated in vacuo to furnish the pyrrole carboxylic acid as a brown solid. The acid was dissolved in dry benzene (2 mL), $Pb(OAc)_4$ (41.4 mg, 93.4 μmol) was added, and the mixture was stirred at room temperature for 2 h. CH_2Cl_2 (10 mL) and 1 M aq HCl (10 mL) were added, and the organic layer was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by filtration over silica gel (EtOAc, R_f = 0.38) to furnish a green oil (10.0 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 1H, H-6″), 7.03 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H, H-6′), 6.99 (d, ^4J = 2.0 Hz, 1H, H-2′), 6.94 (d, ^4J = 1.5 Hz, 1H, H-2″), 6.90 (d, J = 8.3 Hz, 1H, H-5″), 6.68 (d, J = 8.5 Hz, 1H, H-5′), 6.59 (s, 1H, H-10), 6.46 (s, 1H, H-7), 4.43−4.37 (m, 1H, H_a-5), 3.90 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 3.71 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.36 (dt, ^2J = 12.7 Hz, ^3J = 3.9 Hz, 1H, H_b-5), 3.30 (s, 3H, OCH_3), 3.06−2.97 (m, 1H, H_a-6), 2.65 (dd, ^2J = 16.3 Hz, ^3J = 2.8 Hz, 1H, H_b-6) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 169.7 (C═O), 152.9 (C-1), 149.3, 149.0, 148.8, 148.8, 148.0, 146.9 (C-OCH_3), 130.1 (C-2), 127.4 (C-10a), 126.5 (C-6a), 126.3 (C-1″), 123.0 (C-1′), 122.6 (C-6″), 122.6 (C-6′), 113.0 (C-2′), 112.5 (C-2″), 111.1 (C-5″), 111.0 (C-10), 110.8 (C-7), 110.5 (C-5′), 86.8 (C-10b), 56.0, 56.0, 55.8, 55.7, 55.5, 55.1 (6 × OCH_3), 35.7 (C-5), 29.2 (C-6) ppm; the compound is unstable in $CDCl_3$ solution, and both ^{1}H and ^{13}C NMR spectra show the presence of decomposition products; IR (NaCl) ν = 3360, 2926, 2852, 1678, 1516, 1464, 1260, 1142, 1026 cm^{-1}; ESI-HRMS calcd for [$C_{30}H_{31}NO_8$ + H^+] 534.2128, found 534.2133.

General Procedure for the Lactonization. Pyrroles were dissolved in EtOH (1 mL/μmol). Acetic acid (0.1 mL/μmol) and palladium (3 mg/μmol, 10% on charcoal) were added, and the resulting mixture was stirred for 2 h under hydrogen atmosphere at room temperature. The mixture was filtered through a plug of Celite with ethyl acetate, and the combined filtrates were washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. The oily residue was dissolved in toluene (5 mL), and few drops of DBU (approximately 50 μL) were added and the solution was heated to 80 °C for 40 min. The solution was washed with 2 M aq HCl, dried over Na_2SO_4, and evaporated in vacuo to furnish the lamellarins.

Lamellarin G Trimethyl Ether (11a): Colorless solid (24 mg, 79%); mp 235−239 °C (lit.[1] 235 °C); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.11 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 1H, H-12), 7.07 (d, J = 8.1 Hz, 1H, H-15), 7.05 (d, J = 1.8 Hz, 1H, H-16), 6.90 (s, 1H, H-22), 6.76 (s, 1H, H-7), 6.71 (s, 1H, H-10), 6.66 (s, 1H, H-19), 4.85−4.73 (m, 2H, H_2-5), 3.95 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.12 (t, J = 6.8 Hz, 2H, H_2-6) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 155.5 (C═O), 149.7, 149.0, 148.8, 148.8, 147.5 (5 x C-OCH_3), 146.1 (C-18), 145.5 (C-OCH_3), 135.9 (C-10b), 128.2 (C-17), 128.0 (C-11), 126.6 (C-6a), 123.6 (C-16), 120.0 (C-10a), 114.7 (C-1), 114.0 (C-12), 113.7 (C-3), 111.9 (C-15), 111.0 (C-7), 110.3 (C-2), 108.7 (C-10), 104.5 (C-19), 100.5 (C-22), 56.2, 56.1, 56.0, 55.9, 55.5, 55.2 (6 × OCH_3), 42.4 (C-6), 28.7 (C-5) ppm; the spectroscopic data are in accordance with those reported in the literature;[1,14] IR (NaCl) ν = 3424, 2925, 1703, 1515, 1463, 1416, 1264, 1166, 1041 cm^{-1}; FD-MS (*m/z*) 543.2 (100, M^+); ESI-HRMS calcd for [$C_{31}H_{29}NO_8$ + H^+] 544.1971, found 544.1980.

Lamellarin U (11b): Colorless solid (20 mg, 85%); mp 198−200 °C (lit.[36] 200−204 °C); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.13 (d, ^4J = 1.6 Hz, 1H, H-12), 7.04 (d, J = 8.2 Hz, 1H, H-15), 6.99 (dd, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1H, H-16), 6.94 (s, 1H, H-22),

(36) Reddy, M. V. R.; Faulkner, D. J.; Venkateswarlu, Y.; Rao, M. R. *Tetrahedron* **1997**, *53*, 3457–3466.

6.75 (s, 1H, H-7), 6.72 (s, 1H, H-10), 6.70 (s, 1H, H-19), 5.82 (br s, 1H, OH), 5.77 (br s, 1H, OH), 4.86−4.68 (m, 2H, H_2-5), 3.97 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.10 (t, $J = 6.7$ Hz, 2H, H_2-6) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 155.6 (C=O), 148.9, 147.4, 146.4, 146.4, 146.4, 145.4, 143.2 (7 × C-OR), 135.9 (C-10b), 128.7 (C-17), 128.2 (C-11), 126.7 (C-6a), 123.0 (C-16), 120.0 (C-10a), 117.4 (C-12), 114.5 (C-1), 113.6 (C-3), 111.3 (C-15), 110.9 (C-7), 110.3 (C-2), 108.9 (C-10), 104.2 (C-19), 103.3 (C-22), 56.3, 55.9, 55.5, 55.1 (4 × OCH_3), 42.4 (C-5), 28.7 (C-6) ppm; the spectroscopic data are in accordance with those reported in the literature;[37,38] IR (NaCl) ν = 3386, 2934, 1684, 1515, 1487, 1415, 1274, 1164, 1045 cm^{-1}; FD-MS (*m*/*z*) 515.2 (100, M^+); ESI-HRMS calcd for [$C_{29}H_{25}NO_8 + H^+$] 516.1658, found 516.1671.

(37) Cironi, P.; Cuevas, C.; Albericio, F.; Álvarez, M. *Tetrahedron* **2004**, *60*, 8669–8676.

(38) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959–2962.

Acknowledgment. Dedicated to Professor Wolfgang Steglich on the occasion of his 75th birthday. This work was supported by the Deutsche Forschungsgemeinschaft and the University of Mainz. We thank H. Kolshorn for the NMR spectroscopic analyses.

Supporting Information Available: General methods, additional experimental procedures, detailed characterization, and copies of ^1H, ^{13}C, and 2D NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800467E