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Total Synthesis of Tyrosine-Derived Tetramic Acid Pigments from a Slime Mould

Nassima Riache,[a] Christine Bailly,[a] Alexandre Deville,[a] Lionel Dubost,[a] and Bastien Nay*[a]

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A method for the total synthesis of naturally occurring 3-enoyltetramic acids derived from L-tyrosine is described, allowing for three chemical transformations to occur in one pot by using a multicomponent mixture. The sequence involves (1) a base-promoted Lacey–Dieckmann condensation, (2) a Michaelis–Becker reaction, and (3) a Wittig–Horner–Emmons reaction between the resulting 3-phosphonoacetyltetramic acid and an appropriate aldehyde. This sequence of reactions was applied to the synthesis of polyenic pigments obtained from the slime mould *Leocarpus fragilis* starting from readily available precursors. A series of structurally related compounds was also synthesized and their antibiotic significance was evaluated to elucidate their role in nature.

Introduction

3-Acyltetramic acids are widespread fungal or bacterial metabolites which often feature important biological activities.[1] They are associated with defense or communication processes in the microbial kingdom. Recently for instance, the group of Janda underlined the role of the tetramic acid C_{12}-TA (**1**) as an antibiotic derived from the quorum-sensing molecules of *Pseudomonas aeruginosa* (Figure 1).[2] It was shown to interfere with membranes in Gram-positive bacteria.

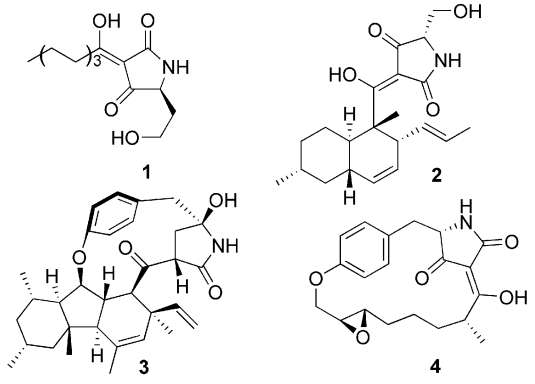


Figure 1. Examples of fungal tetramic acids and derivatives.

Biosynthetically, the structure of the 3-acyltetramic acids is directly derived from an amino acid and a polyketide part in the mixed PKS/NRPS enzymatic route.[1,3] Acylation of the amine thus provides a β-ketoacyl chain which undergoes condensation with the acid functionality of the proximate amino acid moiety to deliver the tetramic acid core. Structural diversity then emerges from the amino acid substrate and from the length and functionalization of the β-ketoacyl chain. Cyclization of the acyl chain to give derivatives, such as in the fungal metabolites trichosetin (**2**)[4] or the compound GKK1032A_2 (**3**), is possible if it is suitably functionalized.[5]

Most frequently, 3-acyltetramic acids have been synthesized using the Lacey–Dieckmann condensation,[1,6] a reaction which is reminiscent of the biosynthetic route described above. This strategy has been applied to the synthesis of naturally occurring tetramic acids, occasionally with some variations to introduce the acyl side chain. In the 1980s, the method was developed by Boeckman[7] and by Schlessinger[8] who focused on the synthesis of unsaturated 3-acyltetramic acids by way of phosphorus-activated intermediates. Recent examples include the synthesis of macrocidin A (**4**) by Suzuki[9] or (+)-cylindramine A by Phillips.[10] Very recently, Schobert described a smart and versatile route to 3-acyltetramic acids, involving the acylation of a 2,4-pyrrolidinedione by a phosphoranylideneketene, followed by Wittig reaction with an aldehyde.[11]

In this article we wish to report an alternative method based on Schlessinger's seminal work.[8] Our results provide a general one-pot process for the synthesis of functionalized tetramic acids. This was applied to the synthesis of pigments **5** and **6** (Figure 2) responsible for the bright yellow to orange color of the myxomycetes slime mould *Leocarpus fragilis* (see the graphical abstract for a picture of the mould).[12] To study their biological properties, a series of structurally related compounds were synthesized along with the shorter 3-acetyltetramic acid **7** isolated from the same

[a] Molécules de Communication et Adaptation des Micro-organismes (FRE 3206 CNRS-MNHN), Muséum National d'Histoire Naturelle, 57 rue Cuvier (CP 54), 75005 Paris, France
Fax: +33-1-40-79-31-35
E-mail: bnay@mnhn.fr

organism. Compound **7** was synthesized by using the classical Lacey–Dieckmann route. All these 3-acyltetramic acids are derived from L-tyrosine. Our method for the synthesis of 3-enoyltetramic acids relies on a multicomponent reaction by allowing the realization of three synthetic steps in one pot: (1) base-promoted Lacey–Dieckmann condensation, (2) Michaelis–Becker reaction, (3) Wittig–Horner–Emmons reaction, giving the desired skeleton from a readily accessible intermediate (i.e., **11a**,**b**).

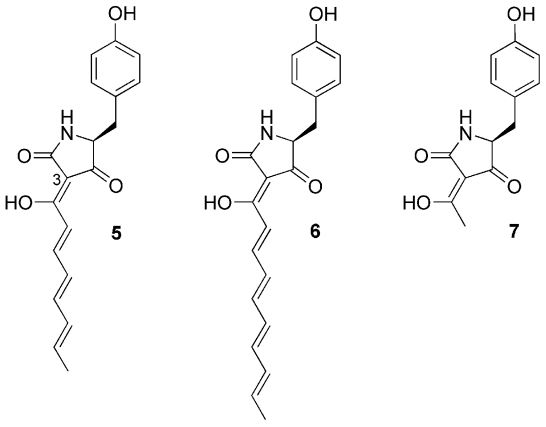


Figure 2. The targeted 3-acyltetramic acids from *Leocarpus fragilis*.

Results and Discussion

It is possible to introduce a phosphonate group on the acyl part in C-3 of the tetramic acid to undertake a Wittig–Horner–Emmons olefination. The acylating agent can then be derived from diketene[8] or from the equivalent 2,2,6-trimethyl-1,3-dioxin-4-one (Figure 3).[7,9]

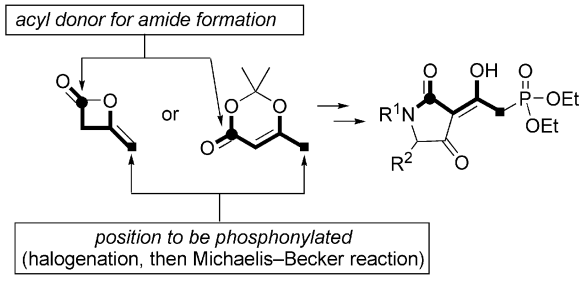
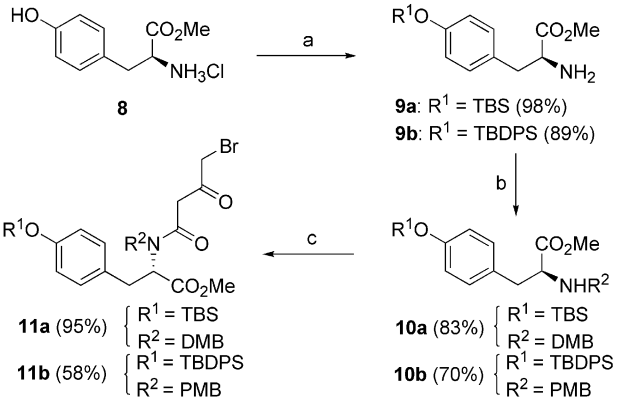


Figure 3. Synthetic strategies to get the 3-phosphonoacetyltetramic acids.

In our work, we chose to use diketene, which reacts easily with bromine to generate the acylating reagent 4-bromo-3-ketobutyryl bromide. This simple reaction allowed the synthesis of bromoacetoacetamides **11a** and **11b** by treatment of *N*,*O*-diprotected tyrosine derivatives **10a** and **10b** with a diketene/Br_2 mixture in the presence of triethylamine (Scheme 1). The choice of appropriate protecting groups was important for this step to proceed in good yields and efficient purification. The phenol was protected as silyl ethers (i.e., **9a**,**b**). The TBS group was preferred to the TBDPS group because the former gave better yields for the deprotection step despite the fact that it was less stable under the basic reaction conditions used for the Lacey–Dieckmann condensation. The 2,4-dimethoxybenzyl (DMB) group was chosen for amide protection on the basis of literature precedent[8,9] and was installed on amine **9a** in 83% yield by reductive amination in the presence of 2,4-dimethoxybenzaldehyde. We will see later that this protecting group proved essential to the Lacey–Dieckmann cyclization.[13] Due to the acid sensitivity of DMB-amides **11a**, it was necessary to avoid purification steps, especially silica gel chromatography (compound **11a** was highly unstable in these conditions). Amide **11a** was thus obtained in 95% yield from **10a** without purification, whereas silica gel chromatography only resulted in poor yields of 20–30%. All contaminants were eliminated by aqueous extraction and evaporation, as confirmed by NMR spectroscopic analysis of the crude extract. Alternatively, amine **9b** was protected with the stable 4-methoxybenzyl (PMB) group while acylation in the presence of diketene/Br_2 furnished amide **11b** in 58% yield from **10b** after purification. However, the PMB group later proved reluctant toward deprotection (see below).



Scheme 1. Synthesis of the bromoacetoacetamide precursors **11a** and **11b**. Reagents and conditions: (a) TBSCl or TBDPSCl (2.5 equiv.), NEt_3 (3 equiv.), DMAP (0.2 equiv.), THF, reflux, 4 h. (b) 2,4-dimethoxybenzaldehyde or 4-methoxybenzaldehyde (1.2 equiv.), $NaBH_3CN$ (1.5 equiv.), MeOH/AcOH (35:1), room temp., 2 h. (c) diketene (1.5 equiv.), Br_2 (1.5 equiv.), CH_2Cl_2, –40 °C, then **10a** or **10b**, Et_3N (1.5 equiv.), –40 °C → –20 °C, 1 h. The yield of **11a** is based on the crude product (no major impurity detected by NMR spectroscopy compared to the product obtained from purification). The yield of **11b** is that after purification by silica gel chromatography.

It is worthy to note that the analysis of compounds **11a** and **11b** was complicated by the occurrence of a ca. 1:1 mixture of the s-*cis* and s-*trans* conformers of the amide (Figure 4). However, 2D NMR experiments allowed us to

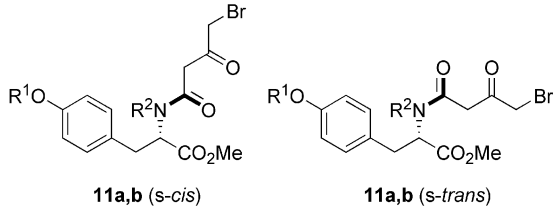
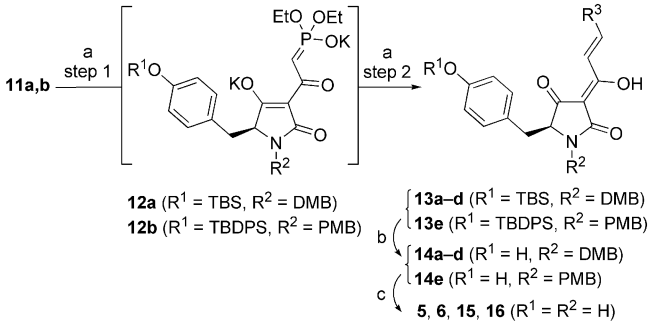


Figure 4. Isomers s-*cis* and s-*trans* observed for amide **11a**,**b**.

distinguish both forms in the mixture. The consequence of the s-*cis* ↔ s-*trans* isomerism for the Lacey–Dieckmann condensation has been discussed by Suzuki in his total synthesis of macrocidin A (**4**), but the step was performed on a strained macrolactam intermediate.[9] We assume that with our linear amides, this isomerism was not detrimental to the condensation.

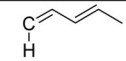
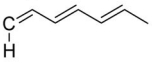
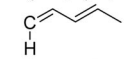
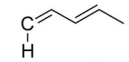
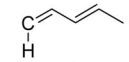
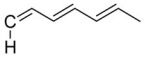
Treatment of substrates **11a** and **11b** with an excess amount of potassium diethylphosphite (formed from an equimolar mixture of diethylphosphite and *t*BuOK) gave transient phosphonates **12a** and **12b**. To achieve the synthesis of 3-enoyltetramic acid skeletons in a tandem fashion, these intermediates were not isolated but directly quenched with the aldehyde R^3CHO (Scheme 2).[14] The expected *N*,*O*-diprotected tetramic acids **13a**–**e** were thus formed in one pot with a multicomponent mixture involving three chemical transformations. The base-promoted Lacey–Dieckmann condensation was undertaken concomitantly with the Michaelis–Becker reaction, releasing activated phosphonates **12a**,**b**. The Wittig–Horner–Emmons reaction could then proceed by addition of the aldehyde. It is worth noting that the early Lacey–Dieckmann condensation did not proceed when the amine was not protected, an observation that had already been reported by others.[8a] Moreover, the reagent ratio used for this step was optimized. An excess of $(EtO)_2POK$ (3 equiv.) was used to perform the Michaelis–Becker step. It was reasoned that to perform the Lacey–Dieckmann condensation simultaneously, 2 equiv. of *t*BuOK were necessary to obtain double potassium adducts **12a**,**b**.



Scheme 2. One-pot synthesis of the *N*,*O*-diprotected tetramic acids **13a**–**e** and subsequent deprotection steps (yields and substituents are given in Table 1). Reagents and conditions: (a) 1. **11a**,**b** added to $(EtO)_2POK$ (3 equiv.), *t*BuOK (2 equiv.), THF, 0 °C, 30 min; 2. R^3CHO (1.5 equiv.), THF, 0 °C, 30 min. (b) KF (10 equiv.), MeOH/H_2O (9:1), room temp., 60 min. (c) CH_2Cl_2/TFA (4:1), room temp., 60 min.

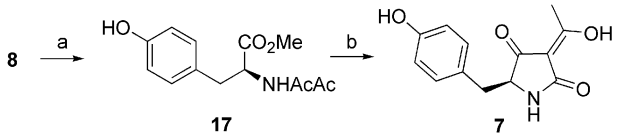
During this one-pot sequence, the TBS group was partially removed, thus making the purification more difficult. Therefore, we chose to complete the removal of the TBS group from **13a**–**d** before purification by using a methanolic solution of potassium fluoride. All products **14a**–**d** from this four-reaction sequence were isolated in ca. 27–35% yield by filtration through Sephadex LH20 (Table 1). Otherwise TBDPS-protected tetramic acid **13e** could be synthesized in 52% yield by the same one-pot process from **11b**. Desilylation of **13e** to give **14e** still proceeded in lower yields (48%). Finally, deprotection of the amine was accomplished in the presence of TFA to afford native tetramic acids **5**, **6**, **15**, and **16** in fair to quantitative yields after purification on Sephadex LH20. Although DMB removal proceeded quickly (1 h), it was not possible to remove the PMB group from **14e** even under more harsh reaction conditions in the presence of pure TFA, CAN, or DDQ.

Table 1. Compound correspondence (see Scheme 2) and yields.

Compound	R^1	R^2	R^3	Yield [%]
14a	H	DMB		35[a]
14b	H	DMB		27[a]
14c	H	DMB	n-C_5H_{11}	31[a]
14d	H	DMB	4-$(CH_3O)C_6H_4$	34[a]
13e	TBDPS	PMB		52[a]
14e	H	PMB		48[b]
5	H	H		90[c]
6	H	H		72[c]
15	H	H	n-C_5H_{11}	99[c]
16	H	H	4-$(CH_3O)C_6H_4$	83[c]

[a] Yields based on bromoacetoacetamides **11a**,**b**. [b] Yield from **13e**. [c] Yield based on the starting DMB-protected compound **14a**–**d**.

To complete this small library of molecules, we synthesized natural tetramic acid **7** in two steps from L-tyrosine methyl ester **8** (Scheme 3). Acylation of **8** in the presence of diketene afforded the corresponding acetoacetamide **17** in 89% yield. The reaction of **17** under Lacey–Dieckmann conditions in the presence of *t*BuOK then afforded natural product **7** in 68% yield. Interestingly, no *N*-protection was required for the cyclization of **17** compared to substrates **11a**,**b**, therefore allowing the reaction to be easily performed on the gram scale.



Scheme 3. Synthesis of compound **7**. Reagents and conditions: (a) diketene (1.2 equiv.), Et_3N (1.3 equiv.), CH_2Cl_2, 0 °C → room temp., 2 h (89%). (b) *t*BuOK (4 equiv.), THF, 0 °C → room temp., 16 h (68%).

Slime moulds (Myxomycetes) are related to the Protist supergroup Amoebozoa.[15] These brightly colored microorganisms feed on fungal spores, bacteria, and other microbes growing in soils or plants. We were interested in the antimicrobial and antifungal activities of the compounds we synthesized, being convinced that such an activity could be important in the life cycle of the slime mould *Leocarpus fragilis*. We evaluated their antibiotic activity against saprophytic microorganisms (*Fusarium oxysporum*, *Aspergillus*

niger), which can be competitors of the mould in nature, and also against microorganisms with medical relevance (*Staphyllococcus aureus*, *Candida albicans*). An inhibition of the growth of *F. oxysporum* in liquid medium was observed for **15** and **16** at 0.08 and 0.37 mM, respectively, with significant inhibition diameters on agar plates (Table 2). Compound **15** was also moderately active against *S. aureus*. It is important to mention that unsaturated natural product **5**, an analogue of **15**, did not show any activity, making the saturation of the side chain particularly important.

Table 2. Antibiotic activities of compounds **15** and **16**.

	Inhibition diameters[a] [mm]		MIC90[b] [mM]	
Micro-organisms[c]	**15**	**16**	**15**	**16**
Fusarium oxysporum	18	15	0.08	0.37
Staphyllococcus aureus	9	0	–	–

[a] Agar plates were inoculated with the microorganism before depositing the 6 mm cellulose discs containing 10 μL of a 10 mg/mL DMSO solution of the tested compound (except for **16**: 13.7 mg/mL). The diameters were determined after a minimum of 48 h of incubation at 25 °C for *F. oxysporum* and at 30 °C for *A. niger*, *S. aureus*, and *C. albicans*. [b] The determination of MIC90 (minimum concentration needed to observe 90% inhibition) was done in 96 well plates containing spores of *F. oxysporum* in PDB medium and various concentrations of the compounds. It was measured after 48 h of incubation at 25 °C. [c] No activity was observed on the other microorganisms tested: *C. albicans* and *A. niger*.

Conclusions

The total synthesis of 3-acyltetramic acids occurring in myxomycetes protists has been described. It involved an original one-pot process during which three different transformations were successfully undertaken. In this work, not only three natural products (i.e., **57**) were synthesized, but also some analogues with different 3-enoyl moieties. Our work is complementary to those already existing and provides some more insight into the reactivity of important chemical intermediates in tetramic acid chemistry. Furthermore, some analogues of the natural products showed significant inhibitory activity against the common saprophytic fungus *Fusarium oxysporum*. Although we did not observe this activity with the natural products, the tetramic acids could be important defensive compounds against microbial competitors in nature.

Experimental Section

General Methods: All reactions were carried out under an atmosphere of argon in anhydrous solvents. THF was distilled from sodium/benzophenone. CH_2Cl_2 and MeOH were distilled from CaH_2. Reagents and starting compounds were purchased from Sigma–Aldrich, Fluka, Acros Organic, or Alfa Aesar and were used without further purification, except diketene, which was distilled before use. Reactions were monitored by TLC on silica gel 60 F254 Merck 1055540001. Visualization was done with a UV lamp and vanillin–H_2SO_4 or ninhydrin stains. Purifications were performed on silica gel 40–60 μm Geduran 9385500 for flash chromatography or on Sephadex LH20 gel. Melting points were measured with a Büchi B-545 apparatus. Optical rotations were recorded at 589 nm with a Perkin–Elmer polarimeter 341. UV/Vis spectra were recorded with a Seconam Uvikon 930 spectrometer. IR spectra were recorded with a Shimadzu 8400S FT spectrometer. NMR spectra were recorded with a Bruker AC 300 spectrometer (Dual probe 5 mm) or with a Bruker Avance I DPX 400 (BBI 1H-BB prode 5 mm). Chemical shifts are given in parts per million and calibrated by using residual solvent traces as internal standards ($CHCl_3$: 7.27 ppm; CHD_2OD: 3.31 ppm. C_5H_5N: 8.74/7.58/7.22 ppm). Mass spectra were recorded with a API QSTAR Pulsar I spectrometer (ESI+).

***N*-(2,4-Dimethoxybenzyl)-*N*-(bromoaceto)acetyl-*O*-*tert*-butyldimethylsilyl-L-tyrosine Methyl Ester (11a):** Bromine (67 μL, 1.3 mmol) was added dropwise at –40 °C to a solution of diketene (100 μL, 1.3 mmol) in CH_2Cl_2 (3 mL). To this mixture was immediately added a solution of *N*,*O*-diprotected aminoester **10a** (400 mg, 0.87 mmol) in CH_2Cl_2 (1 mL) followed by NEt_3 (242 μL, 1.74 mmol). The temperature was slowly warmed up to –20 °C, during this time, TLC analysis showed complete disappearance of the starting material. A saturated solution of $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were washed with brine and concentrated to give 515 mg of crude product **11a** as a clear brown resin (95% yield). No major impurity was detected by NMR spectroscopy. R_f = 0.7 (CH_2Cl_2/MeOH, 99:1). $[\alpha]_D^{20}$ = +1 (*c* = 0.2, MeOH). IR (film on NaCl): $\tilde{\nu}$ = 3005, 2951, 2839, 1739, 1612, 1558, 1516, 1438, 1346, 1269, 1211, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.19 [2 s, 6 H, $(CH_3)_2Si$], 0.99 [s, 9 H, $(CH_3)_3CSi$], 3.10 (dd, *J* = 14.1, 9.3 Hz, 1 H, ArCH_2CH), 3.28 (m, 1 H, ArCH$_2$C*H*), 3.61/3.62 (2 s, 3 H, CO_2CH_3, s-*cis*/s-*trans*), 3.72 (d, *J* = 15.8 Hz, 1 H)/3.90 (d, *J* = 17.0 Hz, 1/2 H)/4.26 (d, *J* = 15.8 Hz, 1/2 H)/ 4.33 (d, *J* = 17.0 Hz, 1/2 H, ArCH_2N, s-*cis*/s-*trans*), 3.76/3.78/3.80/3.81 (4 s, 6 H, ArOCH_3, s-*cis*/s-*trans*), 3.88 (m, 2 H, COCH_2CO), 4.09 (d, *J* = 12.6 Hz, 1 H, COCH_2Br), 4.15 (d, *J* = 12.6 Hz, 1 H, COCH_2Br), 4.12 (dd, *J* = 5.5, *J* = 9.3 Hz, 1/2 H)/4.38 (dd, *J* = 6.0, *J* = 9.0 Hz, 1/2 H, C*H*N, s-*cis*/s-*trans*), 6.40 (m, 2 H, MeO-Ar*H*), 6.74 (m, 2 H, TBSO-Ar*H*), 6.96 (m, 3 H, TBSO-Ar*H* and MeO-Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.4 [(CH_3)$_2$Si], 18.2 [$(CH_3)_3C$Si], 25.7 [(CH_3)$_3$CSi], 34.1 (ArCH_2CH), 34.5 (COCH_2Br), 45.4 (COCH_2CO), 47.1/48.9 (ArCH_2N, s-*cis*/s-*trans*), 52.1/52.2 (CO_2CH_3, s-*cis*/s-*trans*), 60.6/60.7 (*C*HN, s-*cis*/s-*trans*), 98.3/98.5 (MeO-*Ar*H, s-*cis*/s-*trans*), 103.7/103.8 (MeO-*Ar*H, s-*cis*/s-*trans*), 115.4/116.0 (MeO-*Ar-ipso*, s-*cis*/s-*trans*), 120.1 (TBSO-*Ar*H), 129.4/130.4 (MeO-*Ar*H, s-*cis*/s-*trans*), 130.2 (TBSO-ArH), 130.6 (TBSO-Ar-*ipso*), 154.3 (Ar-OTBS), 158.0/158.7 (Ar-OMe, s-*cis*/s-*trans*), 160.7/161.1 (Ar-OMe, s-*cis*/s-*trans*), 167.1/172.0 (N*C*OCH$_2$, s-*cis*/s-*trans*), 170.5/170.9 (CO_2CH_3, s-*cis*/s-*trans*), 196.1 (*C*OCH$_2$Br) ppm. HRMS (ESI+): calcd. for $C_{29}H_{41}NO_7SiBr$ $[M + H]^+$ 622.1830; found 622.1823.

General Method for the Synthesis of *N*-Protected Tetramic Acids 14a–e: $(EtO)_2P(O)H$ (66 μL, 0.52 mmol) was added to a suspension of *t*BuOK (96 mg, 0.86 mmol) in THF (1 mL) at room temperature. After stirring for 20 min, the mixture was cooled to 0 °C and a solution of bromoacetoacetamide **11a** (107 mg, 0.172 mmol) in THF (1 mL) was added quickly. The mixture was stirred at 0 °C for 30 min before the aldehyde was added [0.258 mmol of (2*E*,4*E*)-2,4-hexadienal, (2*E*,4*E*,6*E*)-2,4,6-octatrienal,[16] hexanal or *p*-anisaldehyde]. After further stirring for 30 min at 0 °C, the reaction was quenched by adding a saturated solution of NH_4Cl and the pH was adjusted to 3–4 with a 2 M solution of citric acid. Extraction with diethyl ether (3 × 10 mL) and evaporation of volatiles gave yellow crude products **13a**–**d**. Desilylation then proceeded by treatment with a 10 M solution of KF (100 μL) in methanol (1 mL)

for 1 h at room temperature. After quenching the reaction with a saturated solution of NH_4Cl and adjusting to pH 3–4 with a 2 M solution of citric acid, the mixture was extracted with CH_2Cl_2 (3×10 mL). Evaporation to dryness gave crude *N*-protected tetramic acids **14a**–**d**, which were purified by filtration through Sephadex LH20 (methanol).

(*S*)-1-(2,4-Dimethoxybenzyl)-5-(4-hydroxybenzyl)-3-[(2*E*,4*E*,6*E*)-1-hydroxyocta-2,4,6-trienylidene]pyrrolidine-2,4-dione (14a): Yellow resin [29 mg, 35% from **11a** and (2*E*,4*E*)-2,4-hexadienal]; R_f = 0.2 (CH_2Cl_2/MeOH, 98:2). $[\alpha]_D^{20}$ = –17 (c = 0.1, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 230 (24900), 278 (12500), 392 (35000) nm. IR (film on NaCl): $\tilde{\nu}$ = 3350, 2931, 2840, 1735, 1697, 1612, 1554, 1508, 1454, 1292, 1242, 1207, 1157, 1041, 1010 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (d, J = 6.8 Hz, 3 H, 8′-H), 3.07 (dd, J = 14.6, 5.0 Hz, 1 H, 5-CH_2), 3.15 (dd, J = 14.6, 5.5 Hz, 1 H, 5-CH_2), 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.80–3.87 (m, 1 H, 5-H), 4.23 (d, J = 14.7 Hz, 1 H, 1-CH_2), 5.02 (d, J = 14.7 Hz, 1 H, 1-CH_2), 6.00 (dq, J = 15.1, 6.7 Hz, 1 H, 7′-H), 6.14–6.40 (m, 2 H, 4′-H, 6′-H), 6.42–6.47 (m, 2 H, 1-ArH), 6.61 (dd, J = 15.0, 10.9 Hz, 1 H, 5′-H), 6.66 (d, J = 8.5 Hz, 2 H, 5-ArH), 6.94 (d, J = 8.4 Hz, 2 H, 5-ArH), 7.09 (d, J = 15.1 Hz, 1 H, 2′-H), 7.12 (d, J = 8.9 Hz, 1 H, 1-ArH), 7.42 (dd, J = 15.1, 11.3 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (C-8′), 33.9 (5-CH_2), 38.4 (1-CH_2), 55.4 (OCH_3), 65.1 (C-5), 98.5 (1-C-ArH), 100.7 (C-3), 104.5 (1-C-ArH), 115.3 (5-C-ArH), 116.2 (1-C-*ipso*), 120.5 (C-2′), 127.0 (5-C-*ipso*), 128.9 (C-4′), 130.7 (5-C-ArH), 131.4 (1-C-ArH), 131.7 (C-6′), 136.7 (C-7′), 143.3 (C-5′), 144.7 (C-3′), 154.7 (5-C-ArO), 158.6 (1-C-ArO), 160.9 (1-C-ArO), 172.9 (C-2), 173.7 (C-1′), 194.6 (C-4) ppm. HRMS (ESI+): calcd. for $C_{28}H_{30}NO_6$ [M + H]$^+$ 476.2067; found 476.2074.

(*S*)-1-(2,4-Dimethoxybenzyl)-5-(4-hydroxybenzyl)-3-[(2*E*,4*E*,6*E*,8*E*)-1-hydroxydeca-2,4,6,8-tetraenylidene]pyrrolidine-2,4-dione (14b): Red-orange resin [23 mg, 7% from **11a** and (2*E*,4*E*,6*E*)-2,4,6-octatrienal]; R_f = 0.2 (CH_2Cl_2/MeOH, 98:2). $[\alpha]_D^{20}$ = –19 (c = 0.1, $CHCl_3$). IR (film on NaCl): $\tilde{\nu}$ = 3333, 3020, 2935, 2839, 1616, 1573, 1539, 1508, 1454, 1361, 1265, 1230, 1207, 1157, 1111, 1033, 1010, 987, 925, 887, 821, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (d, J = 6.7 Hz, 3 H, 10′-H), 3.10 (m, 2 H, 5-CH_2), 3.80 (s, 6 H, OCH_3), 3.82 (dd, J = 8.6, 4.4 Hz, 1 H, 5-H), 4.23 (d, J = 14.7 Hz, 1 H, 1-CH_2), 5.02 (d, J = 14.7 Hz, 1 H, 1-CH_2), 5.84–5.98 (m, 1 H, 9′-H), 6.11–6.45 (m, 4 H, 4′-H, 6′-H, 7′-H, 8′-H), 6.45–6.48 (m, 2 H, 1-ArH), 6.60–6.72 (m, 3 H, 5′-H, 5-ArH), 6.95 (d, J = 8.3 Hz, 2 H, 5-ArH), 7.09 (d, J = 15.2 Hz, 1 H, 2′-H), 7.13 (d, J = 8.9 Hz, 1 H, 1-ArH), 7.44 (dd, J = 15.2, 11.4 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (C-10′), 33.9 (5-CH_2), 38.4 (1-CH_2), 55.4 (OCH_3), 65.1 (C-5), 98.5 (1-C-ArH), 100.7 (C-3), 104.5 (1-C-ArH), 115.3 (5-C-ArH), 116.2 (1-C-*ipso*), 120.6 (C-2′), 126.9 (5-C-*ipso*), 129.8/130.4/131.4/131.7/134.2 (1-C-ArH, C-4′, C-6′, C-8′, C-9′) 130.7 (5-C-ArH), 138.8 (C-7′), 143.3 (C-5′), 146.1 (C-3′), 154.8 (5-C-ArO), 158.6 (1-C-ArO), 160.9 (1-C-ArO), 172.8 (C-2), 173.7 (C-1′), 194.6 (C-4) ppm. HRMS (ESI+): calcd. for $C_{30}H_{32}NO_6$ [M + H]$^+$ 502.2224; found 502.2218.

(*S*)-1-(2,4-Dimethoxybenzyl)-5-(4-hydroxybenzyl)-3-[(2*E*)-1-hydroxy-3-(4-methoxyphenyl)prop-2-enylidene]pyrrolidine-2,4-dione (14d): Yellow solid [30 mg, 34% from **11a** and *p*-anisaldehyde]; m.p. 113–114 °C; R_f = 0.6 (CH_2Cl_2/MeOH, 96:4). $[\alpha]_D^{20}$ = –11 (c = 0.1, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 231 (24200), 401 (35300) nm. IR (film on NaCl): $\tilde{\nu}$ = 3333, 3063, 3001, 2931, 2839, 1620, 1597, 1581, 1566, 1508, 1454, 1419, 1292, 1257, 1207, 1172, 1134, 1111, 1030, 979, 929, 887, 825, 783, 732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08 (dd, J = 14.4, 4.6 Hz, 1 H, 5-CH_2), 3.15 (dd, J = 14.4, 3.8 Hz, 1 H, 5-CH_2), 3.80 (s, 6 H, OCH_3), 3.84–3.90 (m, 4 H, 5-H, OCH_3), 4.24 (d, J = 14.6 Hz, 1 H, 1-CH_2), 5.04 (d, J = 14.6 Hz, 1 H, 1-CH_2), 6.43–6.48 (m, 2 H, 1-ArH), 6.67 (d, J = 8.3 Hz, 2 H, 5-ArH), 6.91 (d, J = 8.7 Hz, 2 H, 3-ArH), 6.97 (d, J = 8.3 Hz, 2 H, 5-ArH), 7.14 (d, J = 8.9 Hz, 1 H, 1-ArH), 7.55–7.60 (m, 1 H, 3-ArH), 7.75 (d, J = 15.9 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.9 (5-CH_2), 38.4 (1-CH_2), 55.4 (OCH_3), 65.1 (C-5), 98.5 (1-C-ArH), 100.7 (C-3), 104.5 (1-C-ArH), 114.5/115.3 (3-C-ArH, 5-C-ArH), 115.7 (C-2′), 116.2 (1-C-*ipso*), 126.9/127.5 (3-C-*ipso*, 5-C-*ipso*), 130.7/130.8 (3-C-ArH, 5-C-ArH), 131.4 (1-C-ArH), 143.9 (C-3′), 154.9 (5-C-ArO), 158.6 (1-C-ArO), 160.8 (1-C-ArO), 162.1 (3-C-ArO), 173.4 (C-2), 173.8 (C-1′), 194.8 (C-4) ppm. HRMS (ESI+): calcd. for $C_{30}H_{29}NO_7$ [M + H]$^+$ 516.2016; found 516.2031.

General Method for *N*-Deprotection: The DMB-protected tetramic acids were stirred in CH_2Cl_2/TFA (4:1, 1 mL, for 0.05 mmol) at room temperature for 1 h. Cyclohexane was then added and the solvents were evaporated. After two successive evaporations in the presence of cyclohexane, the crude product was purified by filtration through Sephadex LH20 (methanol).

(*S*)-5-(4-Hydroxybenzyl)-3-[(2*E*,4*E*,6*E*)-1-hydroxyocta-2,4,6-trienylidene]pyrrolidine-2,4-dione (5): Yellow solid [11 mg, 90% from 18 mg of **14a**]; m.p. 172–173 °C; R_f = 0.3 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{20}$ = –9 (c = 0.1, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 231 (19800), 282 (15000), 358 (16000) nm. IR (film on NaCl): $\tilde{\nu}$ = 3280, 3063, 3020, 2924, 2854, 1643, 1612, 1597, 1550, 1516, 1431, 1375, 1246, 1203, 1168, 1103, 1037, 1006, 983 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (d, J = 6.7 Hz, 3 H, 8′-H), 2.57–2.72 (m, 1 H, 5-CH_2), 3.21 (dd, J = 14.0, 3.4 Hz, 1 H, 5-CH_2), 3.94–4.01 (m, 1 H, 5-H), 6.00–6.12 (m, 1 H, 7′-H), 6.19–6.32 (m, 1 H, 6′-H), 6.40 (dd, J = 14.6, 11.6 Hz, 2 H, 4′-H), 6.68 (dd, J = 14.9, 11.0 Hz, 1 H, 5′-H), 6.78 (d, J = 8.1 Hz, 2 H, 5-ArH), 7.06 (d, J = 8.1 Hz, 2 H, 5-ArH), 7.18 (d, J = 15.1 Hz, 1 H, 2′-H), 7.54 (dd, J = 15.1, 11.4 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (C-8′), 37.5 (5-CH_2), 63.5 (C-5), 99.6 (C-3), 115.8 (5-C-ArH), 120.3 (C-2′), 128.3 (5-C-*ipso*), 128.8 (C-4′), 130.3 (5-C-ArH), 131.7 (C-6′), 137.4 (C-7′), 144.2 (C-5′), 145.9 (C-3′), 155.0 (5-C-ArO), 174.8 (C-2), 175.4 (C-1′), 194.1 (C-4) ppm. HRMS (ESI$^+$): calcd. for $C_{19}H_{20}NO_4$ [M + H]$^+$ 326.1386; found 326.1395.

(*S*)-5-(4-Hydroxybenzyl)-3-[(2*E*,4*E*,6*E*,8*E*)-1-hydroxydeca-2,4,6,8-tetraenylidene]pyrrolidine-2,4-dione (6): Red-orange resin [8 mg, 72% from 16 mg of **14b**]; R_f = 0.3 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{20}$ = –35 (c = 0.05, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 230 (30900), 281 (22400), 378 (34300) nm. IR (film on NaCl): $\tilde{\nu}$ = 3390, 3020, 2920, 2855, 1651, 1616, 1573, 1539, 1516, 1427, 1230, 1172, 1010, 984, 895, 817, 756 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.82 (d, J = 6.7 Hz, 3 H, 10′-H), 2.84–2.90 (m, 1 H, 5-CH_2), 2.99 (dd, J = 14.1, 4.4 Hz, 1 H, 5-CH_2), 4.07 (br. s, 1 H, 5-H), 5.90–5.99 (m, 1 H, 9′-H), 6.13–6.36 (m, 2 H, 6′-H, 8′-H), 6.42–6.55 (m, 2 H, 4′-H, 7′-H), 6.66 (d, J = 8.4 Hz, 2 H, 5-ArH), 6.77–6.82 (m, 1 H, 5′-H), 6.98 (d, J = 8.4 Hz, 2 H, 5-ArH), 7.08 (d, J = 15.2 Hz, 1 H, 2′-H), 7.53 (dd, J = 15.2, 11.4 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, assignments on the basis of HSQC and HMBC correlations): δ = 18.6 (C-10′), 37.5 (5-CH_2), 64.0 (C-5), 116.0 (5-C-ArH), 120.9 (C-2′), 127.7 (5-C-*ipso*), 131.0 (C-6′), 131.3 (C-7′), 131.7 (5-C-ArH), 133.0 (C-8′), 135.1 (C-9′), 140.7 (C-4′), 145.4 (C-5′), 146.2 (C-3′), 157.2 (5-C-ArO), 174.9 (C-2, C-1′), 197.0 (C-4) [C-3 not assigned] ppm. HRMS (ESI+): calcd. for $C_{21}H_{22}NO_4$ [M + H]$^+$ 352.1543; found 352.1555.

(*S*)-5-(4-Hydroxybenzyl)-3-[(2*E*)-1-hydroxyocta-2-enylidene]pyrrolidine-2,4-dione (15): Intermediate **14c** was first obtained according to the general method described above as a pale yellow resin (25 mg, 31% from **11a** and of hexanal). It was then deprotected to

give compound **15** as pale yellow resin (17 mg, 99% yield). Data for **14c**: R_f = 0.2 (CH_2Cl_2/MeOH, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3 H, 8′-H), 1.24–1.39 (m, 4 H, 6′-H, 7′-H), 1.41–1.52 (m, 2 H, 5′-H), 2.28 (q, J = 6.6 Hz, 2 H, 4′-H), 3.07–3.13 (m, 2 H, 5-CH_2), 3.80 (s, 6 H, OCH_3), 3.81–3.87 (m, 1 H, 5-H), 4.23 (d, J = 14.6 Hz, 1 H, 1-CH_2), 5.03 (d, J = 14.6 Hz, 1 H, 1-CH_2), 6.43–6.48 (m, 2 H, 1-ArH), 6.66 (d, J = 8.4 Hz, 2 H, 5-ArH), 6.95 (d, J = 8.4 Hz, 2 H, 5-ArH), 7.00–7.22 (m, 3 H, 2′-H, 3′-H, 1-ArH) ppm. Data for **15**: R_f = 0.3 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{20}$ = –3 (c = 0.2, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 234 (75600), 321 (98000) nm. IR (film on NaCl): $\tilde{\nu}$ = 3294, 3020, 2955, 2928, 2858, 1643, 1573, 1516, 1438, 1361, 1300, 1261, 1207, 1172, 1107, 1033, 987, 929, 895, 868, 817, 756, 725 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 0.93 (t, J = 6.8 Hz, 3 H, 8′-H), 1.32–1.39 (m, 4 H, 6′-H, 7′-H), 1.48–1.55 (m, 2 H, 5′-H), 2.32 (q, J = 7.5 Hz, 2 H, 4′-H), 2.87 (dd, J = 8.1, 6.0 Hz, 1 H 5-CH_2), 2.99 (dd, J = 14.1, 4.4 Hz, 1 H, 5-CH_2), 4.03–4.09 (m, 1 H, 5-H), 6.66 (d, J = 8.5 Hz, 2 H, 5-ArH), 6.98 (d, J = 8.5 Hz, 2 H, 5-ArH), 7.06 (d, J = 15.7 Hz, 1 H, 2′-H), 7.16 (dt, J = 15.7, 6.6 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 14.3 (C-8′), 23.5 (C-7′), 28.9 (C-5′), 32.5 (C-6′), 34.1 (C-4′), 37.6 (5-CH_2), 69.0 (C-5), 103.6 (C-3), 116.1 (5-C-ArH), 122.2 (C-3′), 127.7 (5-C-*ipso*), 131.8 (5-C-ArH), 151.7 (C-2′), 157.3 (5-C-ArO), 175.4 (C-2), 187.5 (C-1′), 197.6 (C-4), [C-3, C-4 and C-1′ were assigned on the basis of HMBC correlations] ppm. HRMS (ESI+): calcd. for $C_{19}H_{24}NO_4$ [M + H]$^+$ 330.1699; found 330.1696.

(*S*)-5-(4-Hydroxybenzyl)-3-[(2*E*)-1-hydroxy-3-(4-methoxyphenyl)-prop-2-enylidene]pyrrolidine-2,4-dione (16): Yellow solid [11 mg, 83% from 19 mg of **14d**]; m.p. 215–216 °C; R_f = 0.3 (CH_2Cl_2/MeOH, 95:4). $[\alpha]_D^{20}$ = –7 (c = 0.1, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 232 (18600), 248 (15200), 393 (40500) nm. IR (film on NaCl): $\tilde{\nu}$ = 3333, 3186, 2924, 2854, 1651, 1627, 1558, 1512, 1419, 1246, 1168, 1103, 1022, 976, 933, 871, 810, 717 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 2.93 (dd, J = 14.0, 8.2 Hz, 1 H, 5-CH_2), 3.12 (dd, J = 14.0, 5.0 Hz, 1 H, 5-CH_2), 3.84 (s, 3 H, OCH_3), 4.65 (dd, J = 8.2, 5.0 Hz, 1 H, 5-H), 6.69 (d, J = 8.4 Hz, 2 H, 5-ArH), 6.71 (d, J = 16.1 Hz, 1 H, 2′-H), 6.97 (d, J = 8.7 Hz, 2 H, 5-ArH), 7.06 (d, J = 8.4 Hz, 2 H, 3-ArH), 7.57 (d, J = 8.1 Hz, 2 H, 3-ArH), 7.61 (d, J = 16.1 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 37.6 (5-CH_2), 55.5 (C-5), 55.9 (OCH_3), 100.7 (C-3, weak), 115.5–116.2 (3-C-ArH, 5-C-ArH), 124.1 (C-2′), 128.3–128.9 (3-C-*ipso*, 5-C-*ipso*), 131.3–131.6 (3-C-ArH, 5-C-ArH), 146.1 (C-3′), 157.3 (5-C-ArO), 163.6 (3-C-ArO), 169.2 (C-2), 174.6 (C-1′), 195.8 (C-4) ppm. HRMS (ESI+): calcd. for $C_{21}H_{19}NO_5$ [M + H]$^+$ 366.1335; found 366.1342.

***N*-Acetoacetyl-L-tyrosine Methyl Ester (17):** A solution of diketene (600 μL, 7.8 mmol) in CH_2Cl_2 (6 mL) was added at 0 °C to a solution of L-tyrosine methyl ester hydrochloride (1.5 g, 6.48 mmol) and NEt_3 (1.2 mL, 8.42 mmol) in CH_2Cl_2 (15 mL). After 2 h stirring at room temperature, the mixture was neutralized with a 5% aqueous HCl solution (20 mL) and extracted with CH_2Cl_2 (30 mL). The organic extract was washed with brine (20 mL) and dried with Na_2SO_4 before evaporation. Purification by silica gel chromatography (CH_2Cl_2/MeOH, 99:1) afforded 1.42 g of acetoacetamide **17** as a colorless resin (78% yield). R_f = 0.4 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{20}$ = +20 (c = 0.3, MeOH). IR (film on NaCl): $\tilde{\nu}$ = 3317, 1716, 1651, 1516, 1438, 1361, 1222, 1172, 1118 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3 H, COCH, 2′-H), 2.98 (dd, J = 14.0, 6.9 Hz, 1 H, ArCH_2), 3.10 (dd, J = 14.0, 5.5 Hz, 1 H, ArCH_2), 3.38 (s, 2 H, $COCH_2CO$), 3.74 (s, 3 H, CO_2CH_3), 4.84 (m, 1 H, CHN), 5.30 (s, 1 H, OH), 6.73 (d, J = 8.4 Hz, 2 H, ArH), 6.99 (d, J = 8.4 Hz, 2 H, ArH), 7.41 (d, J = 7.4 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, C_5D_5N): δ = 30.0 ($COCH_3$), 36.5 (ArCH_2), 49.3 ($COCH_2CO$), 52.0 (CO_2CH_3), 53.6 (CHN), 115.3 (C-ArH), 126.5 (C-*ipso*), 130.0 (C-ArH), 155.5 (C-ArO), 166.3 (NHCO), 171.7 (CO_2CH_3), 203.8 ($COCH_3$) ppm. HRMS (ESI+): calcd. for $C_{14}H_{18}NO_5$ [M + H]$^+$ 280.1179; found 280.1178.

(*S*)-5-(4-Hydroxybenzyl)-3-[1-hydroxyethylidene]pyrrolidine-2,4-dione (7): To a solution of acetoacetamide **17** (134 mg, 0.48 mmol) in THF (5 mL) was added *t*BuOK (234 mg, 1.92 mmol) at 0 °C. The resulting mixture was stirred for 15 h at room temperature. Quenching with 1 M HCl (3 mL) was followed by extraction with AcOEt (3 × 5 mL). The organic extracts were combined and washed with water (10 mL) and brine (10 mL) and dried with $MgSO_4$ before evaporation. Purification by silica gel chromatography (CH_2Cl_2/MeOH, 1:0→8:2) gave compound **7** as a white solid (81 mg, 68%). M.p. 185–186 °C; R_f = 0.3 (CH_2Cl_2/MeOH, 8:2). $[\alpha]_D^{20}$ = +34 (c = 0.3, $CHCl_3$). UV/Vis (MeOH): λ (ε, L mol^{-1} cm^{-1}) = 228 (11800), 278 (3700) nm. IR (film on NaCl): $\tilde{\nu}$ = 3317, 3070, 3024, 2962, 2932, 1710, 1647, 1516, 1446, 1361, 1230, 1172, 1114 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 2.22 (s, 3 H, 2′-H), 3.31 (dd, J = 14.0, 7.9 Hz, 1 H, 5-CH_2), 3.54 (dd, J = 14.0, 5.2 Hz, 1 H, 5-CH_2), 5.46–5.38 (m, 1 H, 5-H), 7.08 (d, J = 8.4 Hz, 2 H, ArH), 7.37 (d, J = 8.4 Hz, 2 H, ArH), 9.29 (d, J = 8.2 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, C_5D_5N): δ = 29.9 (C-2′), 37.7 (5-CH_2), 55.1 (C-5), 91.8 (C-3, weak), 116.3 (C-ArH), 128.4 (C-*ipso*), 131.1 (C-ArH), 157.8 (C-ArO), 166.8 (C-2), 174.7 (C-4), 203.0 (C-4) ppm. HRMS (ESI+): calcd. for $C_{13}H_{14}NO_4$ [M + H]$^+$ 248.0917; found 248.0926.

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