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Toward the Macrocidins: Macrocyclization via Williamson Etherification of a Phenolate

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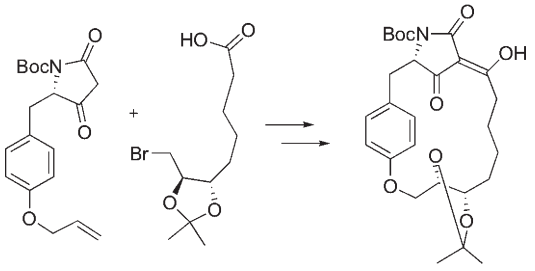


The synthesis of macrocyclic 3-acyltetramic acids which are immediate precursors of the fungal herbicide macrocidin A (**1**) is reported. The crucial closure of the macrocycle was achieved in excellent yield by an unprecedented Williamson etherification of an ω-bromo phenolate generated in situ by a Pd-mediated *O*-deallylation.

The macrocyclic 3-acyltetramic acids macrocidin A (**1**) and B (**2**) (Figure 1) were extracted in 2003 by a Dow AgroSciences group from field isolates of the pathogenic fungus *Phoma macrostoma* Montagne dwelling on diseased Canada thistles.[1] They were found to induce chlorosis and bleaching when tested postemergence on various greenhouse-grown broadleaf weeds. Tetramic acids (i.e., pyrrolidine-2,4-diones) are a common structural motif found in over 150 natural products many of which exhibit distinct biological activities.[2] While this substance class in general has been receiving growing attention over the last 20 years,[3] macrocyclic derivatives are still few and far between. Due to

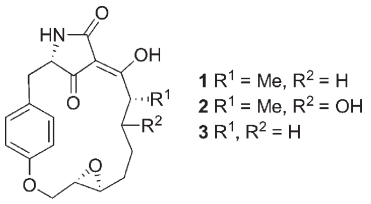
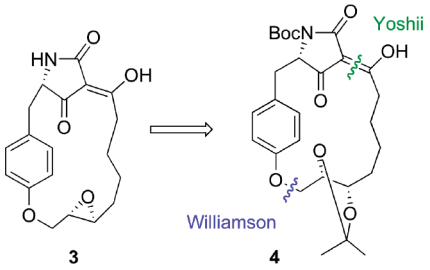


FIGURE 1. Macrocidins A (**1**) and B (**2**) and nor-macrocidin A (**3**).

their complexity, they were also rarely chosen as synthetic targets.[4] The macrocidins are molecules worthy of synthesis given their potential as a template for herbicide design.

Recently, Pfaltz et al. published the first total synthesis of **1** using a macrolactamization followed by a Lacey−Dieckmann cyclization to install the pyrrolidine ring.[5] The only other reported attempt at a synthesis of **1** foundered on the epoxidation of the alkene introduced by a ring-closing metathesis (RCM) reaction.[6]

SCHEME 1. Retrosynthesis of Nor-macrocidin A (3)



Herein, we describe an alternative approach toward the core structure of the macrocidin family. We chose a simplified nor-macrocidin A (**3**) that features the most critical structural hallmarks of **1**, namely the formal 18-membered ring, the epoxide, and the three stereogenic centers. The synthesis is based on the 3-acylation of a tyrosine-derived tetramic acid according to a protocol by Yoshii[7] followed by an intramolecular Williamson etherification (Scheme 1). The latter was inspired by Ley's synthesis of rapamycin which, to the best of our knowledge, comprises the only other example of a similar nondiaryl macroetherification.[8] The epoxide would be generated[10] at a later stage from the deprotected *syn*-diol[9] group of **4** designated to be introduced as part of the carboxylic acid required for the Yoshii acylation.

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(2) For recent examples, see: (a) Wangun, H. V. K.; Dahse, H.-M.; Hertweck, C. *J. Nat. Prod.* **2007**, *70*, 1800–1803. (b) Lang, G.; Cole, A. L. J.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2006**, *69*, 151–153. (c) Ratnayake, A. S.; Davis, R. A.; Harper, M. K.; Veltri, C. A.; Andjelic, C. D.; Barrows, L. R.; Ireland, C. M. *J. Nat. Prod.* **2005**, *68*, 104–107. (d) Wang, C.-Y.; Wang, B.-G.; Wiryowidagdo, S.; Wray, V.; van Soest, R.; Steube, K. G.; Guan, H.-S.; Proksch, P.; Ebel, R. *J. Nat. Prod.* **2003**, *66*, 51–56. (e) Schmidt, K.; Riese, U.; Li, Z.; Hamburger, M. *J. Nat. Prod.* **2003**, *66*, 378–383.

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(4) For recent examples, see: (a) Cramer, N.; Buchweitz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem.—Eur. J.* **2006**, *12*, 2488–2503. (b) Henderson, J. A.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8499–8501.

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(7) (a) Hori, K.; Arai, M.; Nomura, K.; Yoshii, E. *Chem. Pharm. Bull.* **1987**, *35*, 4368–4371.

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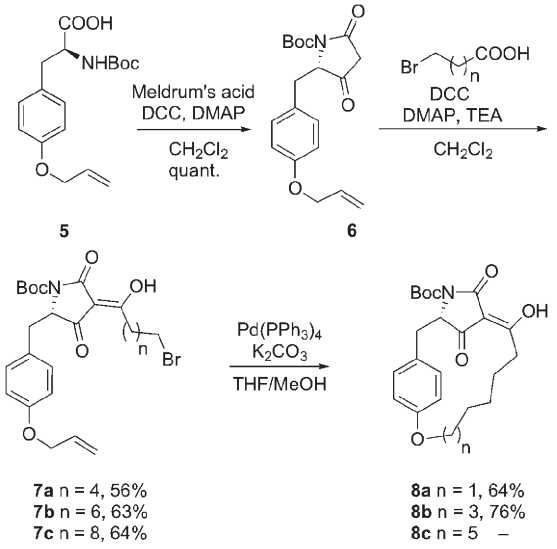
SCHEME 2. Synthesis of Surrogate Tetramic Acids 8

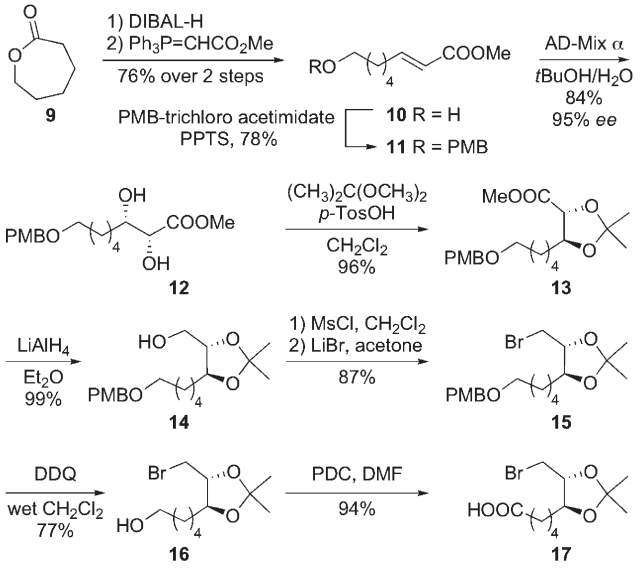


The feasibility of a Williamson etherification for macrocyclization was demonstrated by the synthesis of simplified derivatives **8** lacking the epoxide group (Scheme 2).

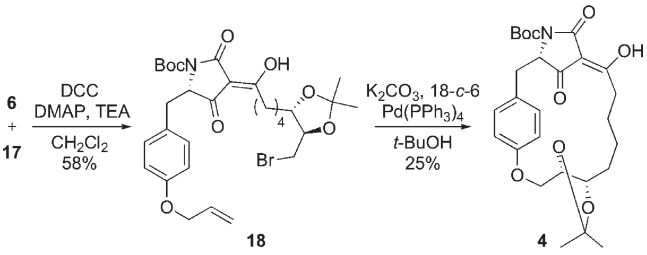
Commercially available bisprotected tyrosine **5** was quantitatively converted with Meldrum's acid to the corresponding tetramic acid **6** according to a known general procedure.[11] 3-Acylation of **6** with ω-bromo acids of different chain length afforded 3-acyltetramic acids **7** in fair yields.[7] These were deallylated under mild basic conditions and in the presence of a catalytic amount of $Pd(PPh_3)_4$.[12] Gratifyingly, the so-formed phenolate intermediate underwent ring-closing etherification right away, leaving 16- and 18-membered macrocycles **8a** and **8b** in very good yields. Control experiments with previously deallylated **7b** (obtained by applying the same protocol as above, but at room temperature) in the absence of $Pd(PPh_3)_4$ failed, which suggests that the catalyst is requisite for the entire two-step sequence. We assume that the phenolate remains coordinated to Pd until released concomitantly with the base-induced elimination of the allyl ligand. Since the rotational freedom of the 3-acyl residue is restricted by the other ligands (Ph_3P, allyl) on Pd, the likelihood of an intramolecular S_N-reaction between phenolate and bromide is increased. Although the analogous 20-membered macrolactam **8c** could not be prepared in this way, this is the first macrocyclizing Williamson reaction that shows signs of generality. It is the more valuable from a practical viewpoint, since alternative methods affording large rings, such as RCM or lactonization/lactamization, require high-dilution conditions as a rule.[13]

For the synthesis of nor-macrocidin A (**3**), the acetonide-bearing ω-bromo acid **17** had to be prepared (Scheme 3). Methyl (*E*)-8-hydroxy-oct-2-enoate **10** was obtained by reduction of ε-caprolactone **9** and subsequent Wittig alkenation of the resulting lactol applying slightly modified literature pro-

SCHEME 3. Synthesis of Enantiopure Acid 17



SCHEME 4. Synthesis of Nor-macrocidin A Precursor (4)



cedures.[14] Protection of the alcohol as *p*-methoxybenzyl ether **11**[15] and AD-mix α dihydroxylation gave **12** as its 2*R*,3*S* enantiomer with 95% ee.[16] Formation of acetonide **13** and reduction of its ester moiety to leave alcohol **14** both proceeded with excellent yields. A two-step conversion of the alcohol into the bromide **15** via the mesylate was necessary since all other standard methods failed.[17] PMB-cleavage with DDQ[18] liberated alcohol **16**, which in turn was oxidized with PDC[19] to afford acid **17** in very good yield. Its reaction with tetramic acid **6** under Yoshii[7] conditions led to 3-acyltetramic acid **18** in ca. 60% yield (Scheme 4), which we expected to be amenable to cyclization under conditions as applied for the synthesis of **8**.[12] However, with K_2CO_3 as a base **18** was only deallylated and no etherification of the phenol product took place. Employing Cs_2CO_3 instead led to reductive dehalogenation of **18** as to NMR spectra. Palladium-catalyzed reductions of halides are quite rare and only known for aromatic systems. In these rare cases, reduction takes place under basic conditions with

(11) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177–1182.

(12) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.-H.; Thayumanavan, S. *J. Org. Chem.* **2003**, *68*, 1146–1149.

(13) For recent examples, see: Kiyota, H., Ed. *Topics in Heterocyclic Chemistry: Marine Natural Products 5*; Springer-Verlag: Berlin, Heidelberg, 2006; pp 189−254.

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(15) (a) Wessel, H. P.; Iversen, T.; Bundel, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2250. (b) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139–4142.

(16) According to chiral HPLC, when compared to a racemic sample prepared using $KMnO_4$.

(17) Such as: PBr_3/pyridine; CBr_4/PPh_3; Br_2/PPh_3.

(18) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.

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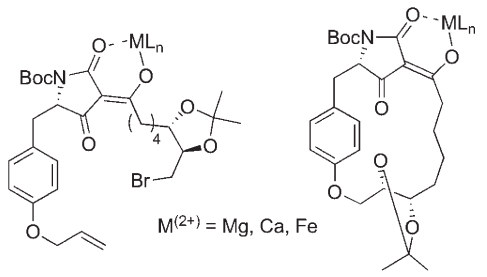

FIGURE 2. Assumed metal chelate complexes of 3-acyltetramic acids.

methanol acting as the reductant.[20] To preclude such a mechanism, we henceforth used *tert*-butyl alcohol, which is not readily oxidized.

The use of *tert*-butyl alcohol, K_2CO_3, and 18-crown-6 completely suppressed dehalogenation, while the macrocyclization still worked nicely (Scheme 4). However, the purification of tetramic acid **4** proved rather tedious and intricate owing to the compound's properties. Like most 3-acyltetramic acids, it showed a high affinity toward silica gel and a pronounced tendency for metal chelate formation.[21] We assume the formation of mixed metal chelates during column chromatography on commercial silica gel containing trace amounts of metal impurities, e.g., Mg^{2+}, Ca^{2+}, and Fe^{2+} (Figure 2). These complexes not only hamper any chromatographic purification but also cause significant signal broadening in NMR spectra.

After extensive optimization testing a vast number of solvent systems and common purification techniques, reversed-phase column chromatography (Merck, LiChroprep RP18) gave **4** in modest yield and still as mixed metal complexes. The metals were removed by extraction with Na_2EDTA solution (0.05 M, pH ~4.7) to finally yield the pure tetramic acid **4**.

In summary, we have developed a new Pd-mediated one-pot macrocyclization of *p*-(ω-bromoalkyl)phenyl allyl ethers proceeding under mildly basic conditions. It comprises a tandem deallylation−Williamson-type etherification. As exemplified for the 18-membered ring system of the macrocidin family, it works well at least for the synthesis of large rings with extended planar, rigid segments. A thorough assessment of the scope of this reaction and the role of palladium in its mechanism is already under way as is an optimization of the workup of the macrocidin precursor **4**.

Experimental Section

***N*-Boc-(5*S*)-[4-(allyloxy)benzyl]pyrrolidine-2,4-dione (6).** Boc-allyl-L-tyrosine (3.21 g, 10.0 mmol) was dissolved in anhyd CH_2Cl_2 (40 mL), and Meldrum's acid (1.59 g, 11.0 mmol), DCC (2.46 g, 12.0 mmol), and DMAP (2.44 g, 20.0 mmol) were added successively. After being stirred at room temperature for 2.5 h, the precipitated DHU was removed by filtration and washed with CH_2Cl_2 (2 × 20 mL), and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (120 mL) and washed with 2 M HCl (3 × 40 mL) and brine (40 mL), the organic layer was heated under reflux for 1 h, and the solvent was removed under reduced pressure. Tetramic acid **6** was obtained as a white amorphous foam (3.45 g, 10.0 mmol, quant), pure by NMR and elemental analysis: R_f 0.38 (cyclohexane/ethanol 2:1); $[\alpha]^{26}_D$ 75 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, MeOD-d_4 only enol form is observed) δ 1.60 (s, 9 H), 3.09 (dd, *J* = 14.0 Hz, 2.6 Hz, 1 H), 3.41 (dd, *J* = 14.0 Hz, 5.2 Hz, 1 H), 4.47 (ddd, *J* = 5.2 Hz, 1.6 Hz, 1.5 Hz, 2 H), 4.64 (dd, *J* = 5.2 Hz, 2.6 Hz, 1 H), 5.22 (ddt, *J* = 10.6 Hz, 1.6 Hz, 1.5 Hz, 1 H), 5.36 (ddt, *J* = 17.3 Hz, 1.6 Hz, 1.5 Hz, 1 H), 6.03 (ddt, *J* = 17.3 Hz, 10.6 Hz, 5.2 Hz, 1 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 6.97 (d, *J* = 8.7 Hz, 2 H), enolic proton not observed; ^{13}C NMR (75 MHz, MeOD-d_4 only enol form is observed) δ 28.5 (CH_3), 35.0 (CH_2), 62.5 (CH), 69.7 (CH_2), 83.6 (C^q), 96.4 (CH), 115.3 (CH), 117.4 (CH_2), 127.5 (C^q), 131.8 (CH), 135.0 (CH), 150.9 (C^q), 159.2 (C^q), 173.3 (C^q), 178.1 (C^q); IR (ATR) ν_{max} 3166, 1754, 1610, 1511, 1362, 1150, 1077 cm^{-1}; *m*/*z* (EI) 345 (4) [M^+]. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.77; H, 6.79; N, 4.43.

***N*-Boc-(5*S*)-3-(6-bromooctanoyl)-5-[4-(allyloxy)benzyl]pyrrolidine-2,4-dione (7b).** A solution of **6** (345 mg, 1.0 mmol) in anhyd CH_2Cl_2 (10 mL) was treated at 0 °C with DAMP (41 mg, 0.33 mmol), 8-bromooctanoic acid (245 mg, 1.1 mmol), and DCC (250 mg, 1.2 mmol) and stirred at room temperature for 1.5 h. Anhydrous NEt_3 (0.15 mL, 1.1 mmol) was added, and the reaction mixture was stirred under reflux for 24 h and then allowed to reach room temperature. Precipitated DHU was removed by filtration and washed with diethyl ether (2 × 30 mL), and the combined filtrates were washed with aq $KHCO_3$ (30 mL 10%) and 2 M HCl (2 × 30 mL). Drying over Na_2SO_4, removal of the solvent under reduced pressure, and column chromatography of the residue on silica gel (cyclohexane/ethyl acetate 3:1 to cyclohexane/ethanol 1:2) yielded an unidentified salt of the title compound. It was dissolved in ethyl acetate (30 mL), and the resulting solution was washed with aq Na_2EDTA (30 mL, 0.05M). Drying over Na_2SO_4 and removal of the solvent under reduced pressure yielded **7b** as viscous orange oil (345 mg, 0.63 mmol, 63%): R_f 0.29 (cyclohexane/ethanol 4:1); $[\alpha]^{25}_D$ −17 (*c* 1.0, $CHCl_3$); mp 80 °C (potassium salt); ^{1}H NMR (300 MHz, MeOD-d_4) δ 1.13−1.82 (m, 10 H), 1.62 (s, 9 H), 2.74 (t, *J* = 7.4 Hz, 2 H), 3.17 (dd, *J* = 13.9 Hz, 2.6 Hz, 1 H), 3.36 (dd, *J* = 13.9 Hz, 5.2 Hz, 1 H), 3.43 (t, *J* = 6.7 Hz, 2 H), 4.46 (ddd, *J* = 5.2 Hz, 1.7 Hz, 1.5 Hz, 2 H), 4.56 (dd, *J* = 5.2 Hz, 2.6 Hz, 1 H), 5.22 (ddt, *J* = 10.5 Hz, 1.5 Hz, 1.5 Hz, 1 H), 5.35 (ddt, *J* = 17.3 Hz, 1.7 Hz, 1.5 Hz, 1 H), 6.01 (ddt, *J* = 17.3 Hz, 10.5 Hz, 5.2 Hz, 1 H), 6.76 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 26.7 (CH_2), 28.6 (CH_3), 29.0, 29.5, 30.0, 34.0, 34.7, 34.8, 35.9 (CH_2), 65.0 (CH), 69.8 (CH_2), 84.9, 105.4 (C^q), 115.7 (CH), 117.6 (CH_2), 127.5 (C^q), 132.0, 134.9 (CH), 150.8, 159.3, 177.5, 195.2, 195.3 (C^q); IR (ATR) ν_{max} 1713, 1609, 1510, 1301, 1246, 1148 cm^{-1}; *m*/*z* (EI) 451 (10), 449 (4) [M − Boc]$^+$. Anal. Calcd for $C_{27}H_{35}BrKNO_6$: C, 55.10; H, 5.99; N, 2.38. Found: C, 55.10; H, 6.10; N, 2.72.

(*S*)-7-Hydroxy-4-aza-15-oxa-5,21-dioxo-4-*tert*-butoxycarbonyltricyclo[14.2.2.1^{3,6}]hencosa-1(19),6,16(20),17-tetraene (8b). A solution of the potassium salt of **7b** (295 mg, 0.50 mmol, obtained by dissolving **7b** in ethyl acetate followed by washing with aq $KHCO_3$ and drying over Na_2SO_4) in a mixture of anhyd THF/methanol 5:1 (60 mL) was treated first with $Pd(PPh_3)_4$ (26 mg, 25 μmol, 5 mol %) and 5 min later with K_2CO_3 (208 mg, 1.50 mmol). The resulting mixture was heated under reflux for 27 h, the volatiles were removed under reduced pressure, and the residue thus obtained was dissolved in CH_2Cl_2 (50 mL) with addition of 2 M HCl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuum. Column chromatography on silica (cyclohexane/ethyl acetate 1:1 to cyclohexane/ethanol 1:1) yielded an unidentified salt of the title compound which was dissolved in ethyl acetate (30 mL) and washed with aq Na_2EDTA (30 mL, 0.05M). Drying over Na_2SO_4 and removal of the solvent under reduced pressure afforded compound **8b** as a viscous yellow oil (165 mg, 0.38 mmol, 76%): R_f 0.36 (cyclohexane/ethanol 2:1);

(20) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619–1620.
(21) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Morisaki, N.; Hashimoto, Y. *Chem. Pharm. Bull.* **2001**, *49*, 206–212.

$[\alpha]^{25}_D$ −5 (*c* 1.0, MeOH). Two isomers were visible in the NMR spectra; * denotes signals of the major one: ^{1}H NMR (300 MHz, MeOD-d_4) δ 0.75−1.57 (m, 12 H), 1.62, 1.64* (s, 9 H), 2.24 (br. s, 1 H), 3.11 (dd, J = 14.1 Hz, 3.1 Hz, 1 H), 3.43 (dd, J = 14.1 Hz, 4.1 Hz, 1 H), 4.18 (t, J = 5.4 Hz, 2 H), 4.66 (dd, J = 4.1 Hz, 3.1 Hz, 1 H), 6.57−7.01 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 23.7*, 24.7, 25.4*, 25.7, 26.2*, 26.6, 26.9*, 27.6*, 27.8 (10 × CH_2), 28.1, 28.2* (2 × CH_3), 32.4, 33.4* (2 × CH_2), 34.5, 34.9* (2 × CH_2), 61.4, 62.3* (2 × CH_2), 65.5, 67.1* (2 × CH_2), 83.4*, 84.3 (2 × C^q), 103.0, 105.8* (2 × C^q), 115.7, 116.6 (2 × br. CH), 125.3*, 126.4 (2 × C^q), 130.6, 130.9 (2 × br CH), 148.8, 149.7* (2 × C^q), 155.9, 156.7* (2 × C^q), 164.4*, 173.8 (C^q), 191.6, 191.9, 195.9*, 197.8* (4 × C^q); IR (ATR) ν_{max} 1608, 1509, 1347, 1300, 1247, 1146, 1024 cm^{-1}; *m*/*z* (EI) 429 (25) [M$^+$]; HRMS (EI) calcd for [M − Boc] 329.1627, found 329.1630.

***N*-Boc-(5*S*)-3-[5-[(4*S*,5*R*)-5-bromomethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-hydroxypent-1-ylidene]-5-[4-(allyloxy)benzyl]-pyrrolidine-2,4-dione (18).** To an ice-cooled solution of **6** (421 mg, 1.22 mmol) in anhyd CH_2Cl_2 (25 mL) were successively added DMAP (49 mg, 0.40 mmol), DCC (301 mg, 1.46 mmol), and **17** (397 mg, 1.34 mmol, dissolved in 5 mL anhyd CH_2Cl_2). The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. The mixture was cooled to 0 °C, anhyd NEt_3 (0.19 mL, 1.34 mmol) was added, and stirring was continued at this temperature for a further 30 min. Finally, the reaction was heated under reflux for 19 h. Workup analogous to that of **7b** yielded the compound **18** as a bright yellow amorphous solid (445 mg, 0.71 mmol, 58%): R_f 0.53 (cyclohexane/ethanol 3:1) 0.27 (RP-C18, H_2O/MeCN 2:1); $[\alpha]^{26}_D$ −22 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, MeOD-d_4) δ 1.05−2.03 (m, 6 H), 1.37 (s, 6 H,), 1.61 (s, 9 H), 2.66−2.82 (m, 2 H), 3.17 (br. d, J = 13.6 Hz, 1 H), 3.35 (dd, J = 13.6 Hz, 4.0 Hz, 1 H), 3.48 (dd, J = 11.0 Hz, 4.9 Hz, 1 H), 3.54 (dd, J = 11.0 Hz, 4.4 Hz, 1 H), 3.83 (br. s, 2 H), 4.45 (d, J = 4.7 Hz, 2 H), 4.50 (br. s, 1 H), 5.21 (d, J = 10.4 Hz, 1 H), 5.35 (d, J = 17.2 Hz, 1 H), 6.01 (ddt, J = 17.2 Hz, 10.5 Hz, 4.7 Hz, 1 H), 6.76 (d, J = 7.9 Hz, 2 H), 6.91 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 26.3, 26.6, 26.8 (CH_2), 27.5, 28.0, 28.6 (CH_3), 33.4, 34.3 (CH_2), 36.2 (CH_2), 64.5 (CH), 69.7 (CH_2), 81.0, 81.4 (CH), 84.3, 104.3, 110.2 (C^q), 115.3 (CH), 117.5 (CH_2), 128.4 (C^q), 132.0, 135.0 (CH), 151.9, 158.9, 170.7, 194.3, 197.6 (br. C^q); IR (ATR) ν_{max} 1626, 1510, 1366, 1300, 1244, 1151 cm^{-1}; *m*/*z* (EI) 623 (3), 621 (2) [M$^+$], 523 (6), 521 (6) [M − Boc]$^+$; HRMS (ESI) calcd for $C_{30}H_{39}BrNO_8^-$ 620.1865, found 620.1877

Macrocyclic Tetramic Acid 4. To a solution of **18** (125 mg, 0.20 mmol) in anhyd *t*-BuOH (24 mL), K_2CO_3 (83 mg, 0.60 mmol) were added 18-crown-6 (53 mg, 0.20 mmol) and Pd(PPh_3)$_4$ (11 mg, 10 μmol, 5 mol %). The resulting mixture was stirred under reflux for 3 d, diethyl ether (80 mL) was added, and the organic layer was washed with saturated aq NH_4Cl (3 × 30 mL), dried over Na_2SO_4, and concentrated in vacuum. The residue thus obtained was submitted to column chromatography on Lichroprep RP-18 affording an unidentified salt of the title compound which was dissolved in ethyl acetate (30 mL) and washed with aq Na_2EDTA (2 × 20 mL; 0.05 M). After being dried over Na_2SO_4, the solution was concentrated under reduced pressure to leave tetramic acid **4** as a yellowish oil (25 mg, 50 μmol, 25%): R_f (RP-C18) 0.43 (H_2O/MeCN 3:1); $[\alpha]^{24}_D$ −14 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, MeOD-d_4) δ 1.06−1.20 (m, 1 H), 1.27−1.67 (m, 6 H), 1.36, 1.39 (s, 3 H), 1.80−1.90 (m, 1 H), 3.13 (dd, J = 14.0 Hz, 2.9 Hz, 1 H), 3.43 (dd, J = 14.0 Hz, 4.4 Hz, 1 H), 3.73−3.81 (m, 1 H), 3.90−3.98 (m, 1 H), 4.26−4.31 (m, 2 H), 4.62−4.68 (m, 1 H), 6.58−7.01 (m, 4 H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 24.2 (CH_2), 26.0, 26.7 (CH_3), 27.2, 27.7 (CH_2), 28.4 (CH_3), 34.7, 35.8 (CH_2), 63.9 (CH), 68.9 (CH_2), 78.3, 79.1 (CH), 84.7 (C^q), 106.7, 109.4 (C^q), 116.1 (CH), 127.9 (C^q), 131.8 (br. CH), 150.9, 158.7, 177.4 (C^q), 195.6, 196.7 (br. C^q); IR (ATR) ν_{max} 3338, 1770, 1708, 1649, 1610, 1254, 1150 cm^{-1}; *m*/*z* (ESI-TOF, negative mode) 500 [M − H]$^-$, 400 [M − Boc]$^-$, 297; HRMS (ESI) calcd for $C_{27}H_{34}NO_8^-$ 500.2284, found 500.2259.

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Supporting Information Available: Detailed experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.