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SYNTHESIS OF PROTECTED L,L-CYCLOTRYPTOPHYLTYROSINE, A KEY UNIT OF TRYPTORUBIN A

Ryohei Nokura, Mayu Senda, Haruhiko Fukaya, and Yukio Hitotsuyanagi*

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan; E-mail: yukioh@toyaku.ac.jp

Abstract – A protected form of L,L-cyclotryptophyltyrosine, a key structure of the bicyclic hexapeptide tryptorubin A isolated from *Streptomyces* sp. CLI2509, was synthesized. Treatment of Boc-L-Trp-3-borono-L-Tyr(Me)-OMe, obtained from the coupling reaction of Boc-L-Trp-OH and H_2N-3-iodo-L-Tyr(Me)-OMe and the subsequent borylation of iodide, with $Cu(OAc)_2$, pyridine, and 4 Å molecular sieves in dichloromethane at 30 °C for 48 h at a concentration of 0.001 M gave protected L,L-cyclotryptophyltyrosine in 58% yield. The structure of obtained protected L,L-cyclotryptophyltyrosine was confirmed by X-ray crystallography, revealing the presence of a pyramidal indole nitrogen atom.

Tryptorubin A (**1**) is a bicyclic hexapeptide isolated from *Streptomyces* sp. CLI2509, a bacterial symbiont of the bracket fungus *Hymenochaete rubiginosa*,[1] and the first characterized member of a new family of ribosomally synthesized and post-translationally modified peptides (Figure 1).[2] Its structure was determined by NMR and MS measurements, including ^{13}C–^{13}C COSY and ^{15}N HMBC analyses of isotope-

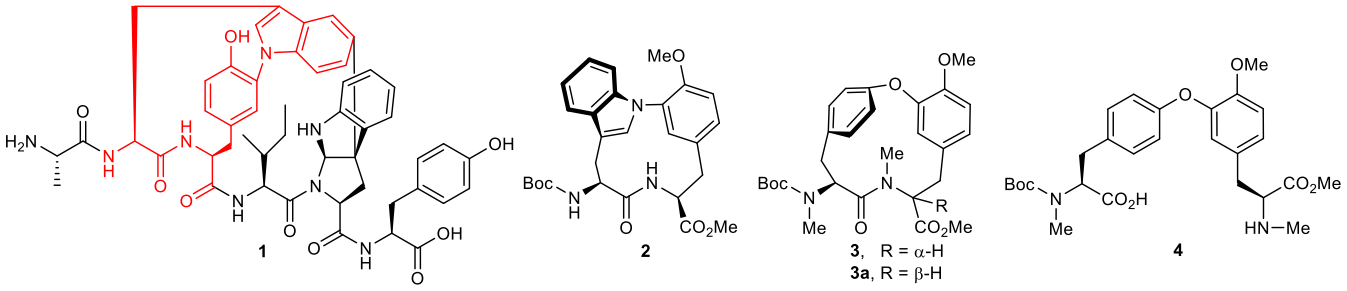
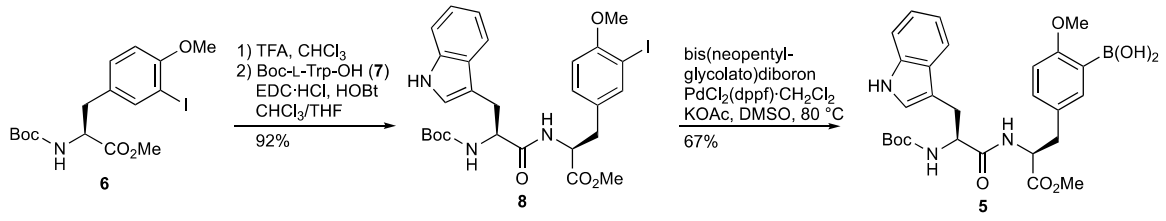


Figure 1. Structures of tryptorubin A (**1**) and protected L,L-cyclotryptophyltyrosine **2**, L,L-*N*,*N*′-dimethylcycloisodityrosine **3**, L,D-*N*,*N*′-dimethylcycloisodityrosine **3a**, and L,L-*N*,*N*′-dimethylisodityrosine **4**

enriched materials, degradation, and computer modeling,[1] and established by total synthesis.[3] Peptide **1** has unique structural features including linkages of heteroaromatic rings between side chains of amino acids, providing a rigid bicyclic globular structure. The most striking structural feature of peptide **1** is the presence of a strained L,L-cyclotryptophyltyrosine moiety where the indolyl nitrogen atom of tryptophyltyrosine is connected to the ε carbon atom of the tyrosine.[4] In this study, we synthesized the L,L-cyclotryptophyltyrosine moiety of tryptorubin A, using the intramolecular Chan-Lam coupling reaction[5] of the protected tryptophyl-boronotyrosine dipeptide, and analyzed its structure by X-ray crystallography.

Prior to synthesizing protected L,L-cyclotryptophyltyrosine **2**, the reported methods for preparing structurally related 14-membered protected L,L-*N*,*N*′-dimethylcycloisodityrosine **3** were considered. Several procedures for synthesizing peptide **3** have previously been reported[6] as it is a component of important natural products including RA-series antitumor peptides[7] and bouvardin.[8] Peptide **3** was not obtained by peptide bond formation from the protected form of L,L-*N*,*N*′-dimethylisodityrosine **4**,[9] and more simplified substrates could also not cyclize into a 14-membered ring.[10] Moreover, owing to its highly strained structure, protected L,L-*N*,*N*′-dimethylcycloisodityrosine **3** is prone to epimerize at the C-terminal amino acid under basic conditions to afford the energetically more stable L-D form **3a**.[6d,e] Owing to their strained structures, such property of **3** may also be true of **2**. Thus, in the synthesis of peptide **2**, we deemed that the connection between the indolyl nitrogen atom and the carbon atom at the ε position of tyrosine should be made after they are linked to form the dipeptide, and the subsequent formation of the C–N bond between those positions would be realized by using the intramolecular Chan-Lam coupling reaction.

Dipeptide precursor **5** for the coupling reaction to furnish **2** was prepared as shown in Scheme 1. Boc-3-iodo-L-Tyr(Me)-OMe (**6**)[6i] was treated with TFA in $CHCl_3$, and the obtained amine was coupled with Boc-L-tryptophan (**7**) using EDC·HCl and 1-hydroxybenzotriazole (HOBt) in $CHCl_3$/THF to afford **8** in 92% yield from **6**. Peptide **8** was borylated with bis(neopentylglycolato)diboron, $PdCl_2(dppf)\cdot CH_2Cl_2$, and KOAc in DMSO at 80 °C under an argon atmosphere to give **5** in 67% yield.



Scheme 1. Synthesis of boronodipeptide **5**

Peptide **5** was subjected to cyclization to search for suitable reaction conditions for producing **2** (Table 1). When 0.001 M of **5** was mixed with 2.5 equivalents of $Cu(OAc)_2$ and 5 equivalents of pyridine, 4-(dimethylamino)pyridine (DMAP),[6i] or triethylamine in dichloromethane, and the reaction mixture was

stirred at 30 °C for 48 h, cyclized product **2** was obtained in 3%, 32%, or 7% yields, respectively, accompanied by uncyclized deborylation product **9** and acetate **10** (entries 1–3). The structure of **2** was confirmed by X-ray crystallography (Figure 2).[11] Among the amines, DMAP gave the highest yield, and pyridine and triethylamine appeared to be less suitable for substrate **5**, producing significant amounts of deborylation product **9** in 71% and 80% yields, respectively, which are similar to the results obtained in the synthesis of cycloisodityrosine.[6i] However, the yield of **2** rose to 35% when 1,000 equivalents of

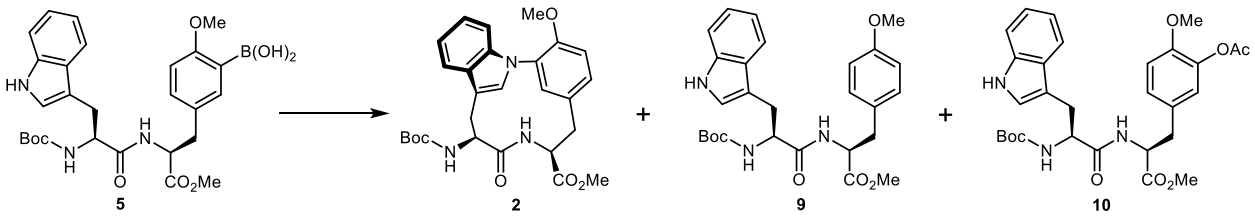


Table 1. Cyclization of **5**[a]

Entry	$Cu(OAc)_2$ (eq)	Pyridine (eq)	DMAP (eq)	Et_3N (eq)	Yield of **2** (%)	Yield of **9** (%)	Yield of **10** (%)
1	2.5	5			3	71	24
2	2.5		5		32	19	19
3	2.5			5	7	80	3
4	2.5	1000			35	20	16
5	2.5	1500			54	6	18
6	2.5	2000			58	11	24
7	2.5	2500			45	5	20
8	3	2000			55	5	17

[a] Reactions were carried out at 30 °C for 48 h. The concentration of **5** is 0.001 M relative to CH_2Cl_2.

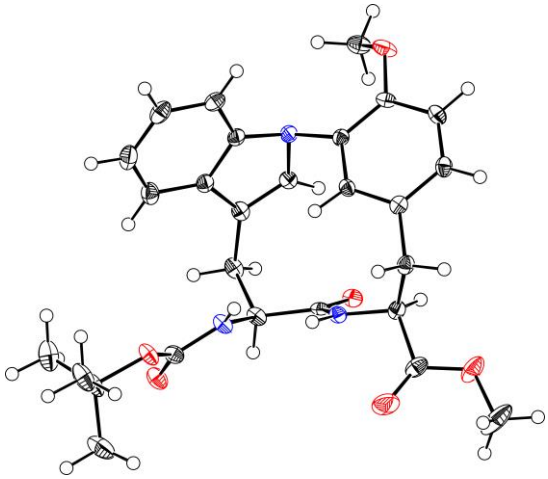


Figure 2. X-ray crystal structure of **2**

pyridine was employed in the reaction (entry 4). In addition, the use of 1,500 or 2,000 equivalents of pyridine further enhanced the yield of **2** up to 54% or 58%, respectively, whereas the use of 2,500 equivalents of pyridine did not improve the yield of **2**, affording a 45% yield (entries 5–7). The use of three equivalents of $Cu(OAc)_2$ and 2,000 equivalents of pyridine did not enhance the yield, affording **2** in 55% yield (entry 8). Employing large amounts of pyridine in this reaction is superior to the use of DMAP because pyridine is less basic than DMAP and can be readily removed from the reaction mixture by evaporation under reduced pressure.

The X-ray crystallography of **2** indicated its unique structural feature, namely, its indole nitrogen atom has a pyramidal form, with angle sums around the indole nitrogen of 331.39(53), 329.12(55), and 329.47(56)° in its hexagonal crystal form. In the ^{1}H NMR spectrum of **2** in CD_3OD, the H-2 signal of tyrosine was observed at δ 5.97 ppm as a doublet with J = 2.0 Hz. This chemical shift value is fairly upfield compared to the shifts of H-5 (δ 7.03 ppm) and H-6 (δ 7.05 ppm) signals of the tyrosine moiety. In the crystal structure of **2**, the H-2 proton of tyrosine was located at the upward part of the pyrrole ring in indole. Supposing that the crystal structure of **2** was almost the same as the solution structure of **2**, this signal was observed as an upfield shifted resonance due to the anisotropic effect from the pyrrole ring in the indole nucleus.

In conclusion, we have found an effective method of preparing a protected form of L,L-cyclotryptophyltyrosine **2**, the key structure of bicyclic hexapeptide tryptorubin A **1**, which involves the intramolecular Chan-Lam coupling reaction of the protected L-tryptophyl-3-borono-L-tyrosine using large amounts of pyridine in an efficient manner. The X-ray crystallography of **2** confirmed its structure and indicated that its indole nitrogen atom could not adopt a planar structure but exhibits a pyramidal form due to its highly strained nature.

EXPERIMENTAL

General

The melting point was determined on a Yanaco MP-3 apparatus and recorded uncorrected. Optical rotations were measured on a JASCO P-1030 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-410 spectrometer. NMR spectra were recorded on a Bruker AVANCE III HD 500 spectrometer at 300 K. The ^{1}H chemical shifts in $CDCl_3$ or CD_3OD were referenced to the residual $CHCl_3$ (δ 7.26 ppm) or CD_2HOD (δ 3.31 ppm) resonance, respectively, and the ^{13}C chemical shifts, to the solvent resonance (δ 77.03 or 49.0 ppm). Mass spectra were obtained with a Waters Xevo G2-XS QTof spectrometer. Preparative HPLC was carried out on a Shimadzu LC-6AD pump unit equipped with an SPD-10A UV detector (λ = 254 nm) and a Wakosil-II 5C18 HG column (5 μm, 20 mm × 250 mm) eluted with a solvent mixture at the flow rate of 10 mL/min.

Boc-L-Trp-3-iodo-L-Tyr(Me)-OMe (8). To a solution of **6** (167 mg, 0.384 mmol) in $CHCl_3$ (3 mL) was added TFA (3 mL) at 0 °C, and the reaction mixture was stirred at this temperature for 30 min and then at room temperature for 1 h. Volatiles were removed under reduced pressure, and the residue was transferred to an InertSep PSA cartridge column (1 g/6 mL) and eluted with MeOH (10 mL). After evaporation under reduced pressure, the residue was dissolved in $CHCl_3$ (3 mL) to prepare an amine solution. Boc-L-Trp-OH (117 mg, 0.384 mmol) and HOBt·H_2O (61.8 mg, 0.404 mmol) were dissolved in 2:1 $CHCl_3$/THF (4.5 mL), to which was added EDC·HCl (77.4 mg, 0.404 mmol) at 0 °C. After stirring at 0 °C for 20 min, the amine solution was added to the reaction mixture, followed by stirring at 0 °C for 5 h and then at room temperature for 15 h. Next, 15:1 $CHCl_3$/MeOH (60 mL) was added to the reaction mixture, followed by washing sequentially with H_2O (3 mL) and saturated aqueous NaCl (3 mL), drying over Na_2SO_4, and filtering, after which the solvent was removed under reduced pressure. The residue was separated by HPLC (45:55 H_2O/MeCN) to give **8** (219 mg, 92%) as a white foam.

$[\alpha]^{25}_D$ −21.9 (*c* = 0.11, MeOH). IR (film) ν_{max} 3405, 3336, 3006, 2976, 2934, 1739, 1696, 1667, 1491, 1457, 1438, 1366, 1279, 1255, 1216, 1166, 1049, 1019, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (9H, s), 2.83 (2H, d, *J* = 5.7 Hz), 3.15 (1H, dd, *J* = 14.6, 6.9 Hz), 3.34 (1H, brd, *J* = 11.4 Hz), 3.63 (3H, s), 3.81 (3H, s), 4.43 (1H, brs), 4.69 (1H, brm), 5.08 (1H, brs), 6.25 (1H, brd, *J* = 6.2 Hz), 6.52 (1H, d, *J* = 8.4 Hz), 6.72 (1H, dd, *J* = 8.4, 2.0 Hz), 7.04 (1H, brs), 7.13 (1H, ddd, *J* = 7.9, 7.2, 1.0 Hz), 7.19 (1H, ddd, *J* = 8.1, 7.2, 1.1 Hz), 7.24 (1H, d, *J* = 2.0 Hz), 7.36 (1H, d, *J* = 8.1 Hz), 7.66 (1H, d, *J* = 7.9 Hz), 8.12 (1H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1 (CH_2), 28.3 (CH_3, 3C), 36.5 (CH_2), 52.3 (CH_3), 53.1 (CH), 55.2 (CH), 56.3 (CH_3), 80.2 (C), 85.8 (C), 110.6 (C), 110.7 (CH), 111.3 (CH), 119.0 (CH), 119.9 (CH), 122.4 (CH), 123.3 (CH), 127.5 (C), 129.8 (C), 130.3 (CH), 136.3 (C), 140.0 (CH), 155.4 (C), 157.2 (C), 171.15 (C), 171.24 (C). HR-ESI-MS *m/z* 644.1235 ($[M+Na]^+$, calcd for $C_{27}H_{32}N_3O_6NaI$, 644.1233).

Boc-L-Trp-3-borono-L-Tyr(Me)-OMe (5). Compound **8** (218 mg, 0.351 mmol), bis(neopentyl-glycolato)diboron (159 mg, 0.704 mmol), KOAc (104 mg, 1.06 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (43.1 mg, 0.0528 mmol) were dissolved in DMSO (2 mL), and the reaction mixture was stirred at 80 °C under an argon atmosphere for 20 h. After cooling to room temperature, H_2O (8 mL) was added, and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with saturated aqueous NaCl (2 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure, and the residue was passed through an InertSep PSA cartridge column (1 g/6 mL) by eluting with EtOAc (10 mL). The solvent was removed under reduced pressure, and the residue was separated by HPLC (60:40 H_2O/MeCN) to afford **5** (127 mg, 67%) as a colorless gummy solid.

$[\alpha]^{25}_D$ −16.9 (*c* = 0.15, MeOH). IR (film) ν_{max} 3404, 3347, 3009, 2979, 1740, 1694, 1668, 1607, 1493, 1421, 1367, 1338, 1238, 1165, 1048, 756 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 1.36 (9H, s), 2.89 (1H, dd, *J* =

13.8, 7.5 Hz), 2.92–3.06 (2H, overlapped), 3.16 (1H, dd, *J* = 14.7, 5.7 Hz), 3.62 (3H, s), 3.76 (3H, s), 4.34 (1H, app t, *J* = 6.3 Hz), 4.62 (1H, app t, *J* = 6.2 Hz), 6.80 (1H, brd, *J* = 8.2 Hz), 6.92 (1H, brs), 6.98–7.11 (4H, overlapped), 7.32 (1H, d, *J* = 8.1 Hz), 7.57 (1H, brd, *J* = 7.8 Hz). ^{13}C NMR (125 MHz, CD_3OD) *δ* 28.6 (CH_3, 3C), 29.1 (CH_2), 37.6 (CH_2), 52.6 (CH_3), 55.1 (CH), 55.7 (CH_3), 56.8 (CH), 80.7 (C), 110.88 (C), 110.93 (CH), 112.3 (CH), 119.4 (CH), 119.8 (CH), 122.4 (CH), 124.1 (C), 124.6 (CH), 128.9 (C), 129.5 (C), 132.4 (CH), 134.9 (CH), 138.1 (C), 157.5 (C), 161.9 (C), 173.0 (C), 174.4 (C). HR-ESI-MS *m/z* 562.2341 ($[M+Na]^+$, calcd for $C_{27}H_{34}N_3O_8NaB$, 562.2337).

Cyclization of 5. To a solution of **5** (23.9 mg, 0.0443 mmol) in CH_2Cl_2 (44 mL) were added pyridine (7.1 mL, 88 mmol) and powdered 4 Å molecular sieves (240 mg), and the mixture was stirred at 30 °C for 30 min. Copper(II) acetate (20.1 mg, 0.111 mmol) was added to the mixture, and the mixture was stirred at 30 °C for 48 h. The reaction mixture was filtered through a Celite pad, and the filtrate was passed through an InertSep CBA cartridge column (1 g/6 mL) using 1:1 $CHCl_3$/EtOAc (20 mL). The solvent was evaporated off, and the residue was separated by HPLC (50:50 H_2O/MeCN) to afford **2** (12.7 mg, 58%), **9** (2.4 mg, 11%), and **10** (6.0 mg, 24%).

2: colorless needles, mp 212−214 °C. $[\alpha]^{25}_D$ +237 (*c* = 0.097, MeOH). IR (film) ν_{max} 3353, 3009, 2979, 2930, 1738, 1717, 1638, 1509, 1261, 1245, 1161, 753 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *δ* 1.54 (9H, s), 2.67 (1H, brt, *J* = 12.5 Hz), 2.79 (1H, brd, *J* = 14.3 Hz), 3.05 (1H, brd, *J* = 14.1 Hz), 3.38 (1H, app d, *J* = 14.1 Hz), 3.68 (3H, s), 4.03 (3H, s), 4.33 (1H, dd, *J* = 11.6, 1.9 Hz), 4.68 (1H, brs), 5.97 (1H, d, *J* = 2.0 Hz), 6.44 (1H, s), 7.03 (1H, d, *J* = 8.5 Hz), 7.05 (1H, dd, *J* = 8.5, 2.0 Hz), 7.23–7.31 (2H, overlapped), 7.36 (1H, app dd, *J* = 7.3, 1.5 Hz), 7.59 (1H, br d, *J* = 6.6 Hz). ^{13}C NMR (125 MHz, CD_3OD) *δ* 27.7 (CH_2), 28.7 (CH_3, 3C), 34.6 (CH_2), 53.0 (CH_3), 55.9 (CH), 57.4 (CH_3), 59.7 (CH), 81.6 (C), 115.3 (CH), 116.9 (CH), 118.8 (C), 120.6 (CH), 123.8 (CH), 125.4 (CH), 129.6 (CH), 131.0 (CH), 132.1 (C), 132.2 (C), 136.1 (C), 147.0 (CH), 151.6 (C), 154.3 (C), 157.0 (C), 172.7 (C), 172.8 (C). HR-ESI-MS *m/z* 494.2289 ($[M+H]^+$, calcd for $C_{27}H_{32}N_3O_6$, 494.2291).

9: colorless amorphous solid. $[\alpha]^{25}_D$ −17.6 (*c* = 0.17, MeOH). IR (film) ν_{max} 3337, 3006, 2978, 2953, 2933, 1740, 1697, 1667, 1513, 1367, 1249, 1175, 1034, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.43 (9H, s), 2.84–2.92 (2H, m), 3.13 (1H, dd, *J* = 14.6, 7.1 Hz), 3.32 (1H, brd, *J* = 11.4 Hz), 3.62 (3H, s), 3.74 (3H, s), 4.44 (1H, brs), 4.69 (1H, brm), 5.11 (1H, brs), 6.18 (1H, brs), 6.64 (2H, app d, *J* = 8.7 Hz), 6.69 (2H, app d, *J* = 8.7 Hz), 7.01 (1H, brs), 7.13 (1H, ddd, *J* = 7.9, 7.0, 1.0 Hz), 7.20 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz), 7.35 (1H, app d, *J* = 8.1 Hz), 7.66 (1H, d, *J* = 7.9 Hz), 8.16 (1H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 28.3 (CH_2), 28.3 (CH_3, 3C), 37.0 (CH_2), 52.2 (CH_3), 53.3 (CH), 55.1 (CH), 55.2 (CH_3), 80.1 (C), 110.6 (C), 111.2 (CH), 113.9 (CH, 2C), 118.9 (CH), 119.8 (CH), 122.3 (CH), 123.4 (CH), 127.5 (C, 2C), 130.2 (CH, 2C), 136.2

(C), 155.4 (C), 158.6 (C), 171.1 (C), 171.4 (C). HR-ESI-MS *m/z* 518.2266 ([M+Na]$^+$, calcd for $C_{27}H_{33}N_3O_6Na$, 518.2267).

10: colorless amorphous solid. $[\alpha]^{25}_D$ −8.1 (*c* = 0.14, MeOH). IR (film) ν_{max} 3362, 3008, 2979, 2934, 1745, 1700, 1669, 1514, 1367, 1269, 1211, 1167, 1126, 1026, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (9H, s), 2.31 (3H, s), 2.92 (2H, brs), 3.09 (1H, brm), 3.31 (1H, brm), 3.66 (3H, s), 3.79 (3H, s), 4.45 (1H, brs), 4.78 (1H, m), 5.22 (1H, brs), 6.19 (1H, brs), 6.60–6.66 (3H, overlapped), 6.83 (1H, brs), 7.11 (1H, ddd, *J* = 7.9, 7.1, 1.1 Hz), 7.17 (1H, ddd, *J* = 7.9, 7.1, 1.2 Hz), 7.30 (1H, app d, *J* = 7.9 Hz), 7.69 (1H, brd, *J* = 6.8 Hz), 8.40 (1H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7 (CH_3), 28.2 (CH_2), 28.3 (CH_3, 3C), 36.7 (CH_2), 52.3 (CH_3), 52.8 (CH), 55.1 (CH), 55.9 (CH_3), 80.0 (C), 110.1 (C), 111.2 (CH), 112.4 (CH), 118.8 (CH), 119.6 (CH), 122.0 (CH), 123.5 (CH), 123.6 (CH), 127.5 (C and CH, 2C), 128.1 (C), 136.2 (C), 139.5 (C), 150.0 (C), 155.5 (C), 169.4 (C), 171.35 (C), 171.44 (C). HR-ESI-MS *m/z* 576.2323 ([M+Na]$^+$, calcd for $C_{29}H_{35}N_3O_8Na$, 576.2322).

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11. Crystallographic data (excluding structure factors) for the structure **2** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2259610. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).