constant $K_{t/c}$ for captopril on protonation state of the carboxylic acid and thiol groups is due mainly to differences in rate constants for cis to trans interconversion for the (CO_2^-, SH) and (CO_2^-, S^-) forms. Using rate constants determined in this study, the average lifetimes of the cis and trans conformations are calculated to be approximately 185 and 270 s, respectively, at physiological pH. When the kinetics and equilibria for the binding of captopril by angiotensin converting enzyme have been characterized, these results will be useful for determining if cis to trans interconversion is rate limiting in the binding of captopril by angiotensin converting enzyme.

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A Highly Selective Synthesis of Monodisperse Oligo(ethylene glycols)

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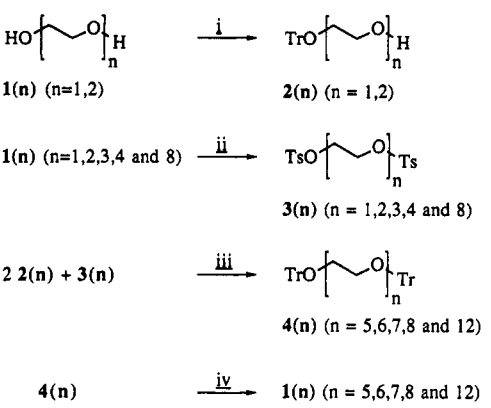
Although oligo(ethylene glycols) [$H[-OCH_2CH_2]_n-OH$, **1**(***n***); cf. Scheme I] have found widespread application as synthons for crown ether-type derivatives,[1] surfactants,[2] ion-conducting materials,[3] and new materials,[4] the published synthetic methods for commercially unavailable or expensive representatives **1**(***n***) ($n > 4$) are hampered by laborious procedures.[5] Depending on the oligomer, either vacuum distillation or preparative gel permeation chromatography has to be applied for the isolation and purification of the compounds. Since we required easy access to monodisperse **1**(***n***) with n up to 12 for our material research program, we were prompted to address this problem.

We here report a highly selective synthesis, which lacks laborious purification procedures and is very convenient for the preparation of the higher representatives as well. It is based on the quantitative chain extension of α,ω-ditosylated oligo(ethylene glycols) **3**(***n***) (n = 1, 2, 3, and 4) with 2 equiv of the sodium salt of monotritylated mono- or diethylene glycol **2**(***n***) (n = 1 or 2). Hydrogenolysis of the α,ω-ditrityl endcapped homologues **4**(***n***) furnishes the chain-extended monodisperse oligo(ethylene glycols) (Scheme I).

Scheme I[a]



[a] (i) TrCl, C_5H_5N; (ii) TsCl, KOH, CH_2Cl_2; (iii) NaH, THF; (iv) H_2(g), Pd/C, CH_2Cl_2.

Results and Discussion

Pivotal to the approach is our finding of a convenient access to monoprotected ethylene **2**(**1**) and diethylene glycol **2**(**2**), respectively. This was achieved on an 1 molar scale by solvolysis of trityl chloride in a 10-fold excess of glycol **1**(**1**) or **1**(**2**) in the presence of pyridine. The compounds **2**(***n***) (n = 1, 2) were separated from the excess glycol, which can be used again, by extraction with toluene and purified by recrystallization (yield > 75%).

Quantitative chain extension of α,ω-ditosylates **3**(***n***) to the appropriate α,ω-ditritylated oligo(ethylene glycols) **4**(***n***) was achieved by reaction of 2 equiv of the sodium salt of **2**(***n***) (n = 1, 2) with **3**(***n***) (n = 1, 2, 3, 4, and 8 (vide infra), respectively) (Scheme I).

Compounds **3**(***n***) were obtained via an improved procedure involving the addition of small portions of freshly powdered potassium hydroxide to a solution of the appropriate **1**(***n***) (n = 1, 2, 3, 4, and 8) and *p*-toluenesulfonyl chloride in dichloromethane while maintaining the temperature between 0 and 5 °C. The α,ω-ditosylated oligo(ethylene glycols) **3**(***n***) (n = 1, 2, 3, 4, and 8, respectively) were isolated (95–99%) (cf. Experimental Section and ref 6a) without purification.

Following this approach, **4**(***n***) with n = 5, 6, 7, 8, and 12 (vide infra) were conveniently prepared. However, **4**(**5**) could only be prepared by reaction of 2 equiv of the sodium salt of **2**(**1**) with tosylate **3**(**3**). The other approach, i.e. coupling of 2 equiv of the sodium salt of **2**(**2**) with tosylate **3**(**1**), was unsuccessful. ^{1}H NMR spectroscopy revealed that competitive β-elimination[7] occurring with **3**(**1**) thwarted the desired chain extension reaction. In contrast, **4**(**6**) could be prepared in two ways, either from 2 equiv of the sodium salt of **2**(**1**) and **3**(**4**) or from the sodium salt of **2**(**2**) and **3**(**2**). Compounds **4**(**7**) and **4**(**8**) were synthesized by coupling of 2 equiv of the sodium salt of **2**(**2**) with α,ω-ditosylates **3**(**3**) and **3**(**4**), respectively.

Compounds **4**(***n***) were quantitatively converted into the corresponding monodisperse oligo(ethylene glycols) **1**(***n***) (n = 5, 6, 7, 8, and 12) by hydrogenolysis in the presence of 10% palladium on carbon in dichloromethane. The

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products were characterized by capillary gas chromatography, ^1H-, ^{13}C-NMR, and IR spectroscopy, and mass spectrometry (cf. Experimental Section).

The generality of our approach was confirmed by the preparation of the higher homologue 1(12). Thus, α,ω-ditosylation of 1(8) and coupling of the ditosylate 3(8) with 2 equiv of the sodium salt of 2(2), followed by the hydrogenolysis of 4(12) yields monodisperse 1(12).

Experimental Section

All reagents were purchased from Janssen Chimica. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone. Toluene was dried on powdered KOH and filtered before use. The ethylene glycols 1(*n*) were dried on activated 4-Å molecular sieves. Pyridine was freshly distilled from KOH powder. All reactions were carried out under a nitrogen atmosphere. NMR spectra were recorded on a Bruker AC 300 spectrometer (^1H: 300 MHz; ^{13}C: 75 MHz) using the solvent ($CDCl_3$: ^1H, 7.26 ppm; ^{13}C, 77.00 ppm) or TMS (0.00 ppm) as internal standard. IR spectra were measured on a Perkin-Elmer 283 spectrophotometer. Mass spectra were measured with a JEOL JMS-AX505W mass spectrometer and reported (*m/e*; % fragment). DSC curves were determined on a Perkin-Elmer DSC II. Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus and are uncorrected. Elemental analyses were carried out by Dornis u. Kolbe, Microanalytical Laboratory, Mülheim a.d. Ruhr 1, Germany. It should be noted that the oligo (ethylene glycols) 1(*n*) and their derivatives 3(*n*) and 4(*n*) are highly hygroscopic; consequently, they have to be handled with care in order to prevent absorption of moisture especially during prolonged storage. Absorption of moisture was assessed with isothermal thermogravimetry (temperature 100 °C, nitrogen atmosphere) using a Perkin-Elmer TGS-2 with an autobalance AR-2.

General Procedure for Monotritylation of Monoethylene 1(1) and Diethylene Glycol 1(2). A 3-L three-necked flask equipped with mechanical stirrer, thermometer, and nitrogen inlet is charged with either ethylene glycol [1(1), 620.6 g, 10.00 mol] or diethylene glycol [1(2), 1062 g, 10.00 mol] and pyridine (119 g, 1.50 mol). The solution is heated at 45 °C, and triphenylmethyl chloride (278.8 g, 1.00 mol) is added under vigorous stirring. After additional stirring for 16 h, the reaction mixture, which contains a white precipitate, is extracted with toluene at 40 °C. The combined toluene extract is concentrated under reduced pressure. The solid residue is dissolved in boiling CH_2Cl_2 (500 mL) from which the desired product crystallizes upon slowly cooling to −15 °C. The crude product is filtrated and recrystallized by dissolving it in boiling EtOAc, followed by addition of *n*-hexane and slowly cooling to −25 °C [1 g of 2(1), 1 mL EtOAc/1 mL hexane; 1 g of 2(2), 2 mL EtOAc/1 mL hexane].

4,4,4-Triphenyl-3-oxabutanol 2(1): 227.37 g (75%) of a white crystalline solid; mp 103.8–104.4 °C; TLC (silica, $CHCl_3$) R_f = 0.1; ^1H-NMR δ 7.48–7.42 (m, 6 H), 7.34–7.20 (m, 9 H), 3.77–3.71 (A of AA'MM'X, *J*(AX) = 6.2 Hz, 2 H), 3.28–3.25 (M of AA'MM'X, 2 H), 1.98 (X of AA'MM'X, *J*(AX) = 6.2 Hz, 1 H, disappeared upon addition of ^2H_2O); ^{13}C-NMR δ 143.91, 128.64, 127.83, 127.06, 86.64, 64.81, 62.33; IR (KBr) 3350 (br), 3060, 2955, 2915, 2870, 1450, 1093, 1060 cm^{-1}; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] 304 (7, $[M]^{\cdot+}$) and 243 (100, $[(C_6H_5)_3C]^+$). Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62, O, 10.51. Found C, 82.94; H, 6.68; O, 10.39.

7,7,7-Triphenyl-3,6-dioxaheptanol 2(2): 267.34 g (77%) of a white crystalline solid; mp 112.7–114.5 °C; TLC (silica, $CHCl_3$) R_f = 0.1; ^1H-NMR δ 7.48–7.42 (m, 6 H), 7.32–7.18 (m, 9 H), 3.76–3.71 (A of AA'MM'X, *J*(AX) = 5.9 Hz, 2 H), 3.69–3.65 (A of AA'XX', 2 H), 3.63–3.59 (M of AA'MM'X, 2 H), 3.28–3.25 (X of AA'XX', 2 H), 2.13 (X of AA'MM'X, *J*(AX) = 5.9 Hz, 1 H, disappeared upon addition of ^2H_2O); ^{13}C-NMR δ 144.01, 128.68, 127.77, 126.97, 86.68, 72.26, 70.60, 63.34, 61.86; IR (KBr) 3350 (br), 3060, 2955, 2915, 2870, 1450, 1093, 1060 cm^{-1}; FABMS (Xe; matrix: *m*-nitrobenzyl alcohol) 371 (3, $[M + Na]^+$), 349 (1.5, $[M + H]^+$), 348 (3, $[M]^{\cdot+}$), 243 (100, $[(C_6H_5)_3C]^+$). Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94; O, 13.77. Found: C, 79.24; H, 7.05; O, 13.68.

General Procedure for α,ω-Ditosylation of Ethylene Glycols 1(*n*). A 2-L three-necked flask equipped with mechanical stirrer, thermometer, and nitrogen inlet is charged with the appropriate glycol 1(*n*) (0.50 mol), *p*-toluenesulfonyl chloride (194.5 g, 1.02 mmol), and CH_2Cl_2 (500 mL). The homogeneous mixture is cooled to 0 °C with a CO_2 (s)–acetone bath. Freshly powdered KOH (225 g, 4 mol) is added in small amounts under vigorous stirring while maintaining the reaction temperature below 5 °C (exothermic reaction). The mixture is stirred for 3 h at 0 °C after which CH_2Cl_2 (500 mL) and ice–water (600 mL) are added. The organic phase is separated, and the aqueous phase is extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layer is washed with water (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Spectral characterization (^1H and ^{13}C NMR and IR) revealed that the products were pure. For 3(*n*) (*n* = 1, 2, 3, 4, and 8), the analytical data were in agreement with previously reported results.[6] They could be used in the chain extension reactions without further purification!

1,2-Bis(tosyloxy)ethane 3(1): The product solidified during the reaction; therefore an additional quantity of CH_2Cl_2 (1200 mL) is used in the workup procedure: 177.31 g (96%) of a white crystalline solid; mp 124.5–126.5 °C (lit.[6a] 124–127 °C).

1,5-Bis(tosyloxy)-3-oxapentane 3(2): 203.89 g (98%) of a white crystalline solid; mp 87.0–87.5 °C (lit.[6a] 87.0–87.5 °C).

1,8-Bis(tosyloxy)-3,6-dioxaoctane 3(3): 226.81 g (99%) of a white crystalline solid; mp 80–81 °C (lit.[6a] 80–81 °C).

1,11-Bis(tosyloxy)-3,6,9-trioxaundecane 3(4): 245.94 g (98%) of a clear colorless oil.[6a]

1,24-Bis(tosyloxy)-3,6,9,12,15,18,21-heptaoxatetracosane 3(8): 34.42 g (95%) of a clear colorless oil;[6b] ^1H-NMR δ 7.80–7.75 (A of AA'XX', 4 H), 7.35–7.29 (X of AA'XX', 4 H), 4.16–4.11 (A of AA'XX', 4 H), 3.68–3.64 (X of AA'XX', 4 H), 3.62 (s, 12 H), 3.60 (s, 4 H), 3.56 (s, 8 H), 2.41 (s, 6 H); ^{13}C-NMR δ 144.72, 132.94, 129.75, 127.89, 70.65, 70.52, 70.47, 70.42, 69.18, 68.59, 21.56; IR (NaCl) 3040, 2860 (br), 1440, 1350, 1140–1090 (br) cm^{-1}.

General Procedure for Chain Extension of α,ω-Ditosylated Ethylene Glycols 3(*n*) with Monotritylated Ethylene Glycols 2(*n*) (*n* = 1, 2). A 3-L one-necked flask equipped with a nitrogen inlet is charged with NaH (0.50 mol) and THF (800 mL). The appropriate 2(*n*) with *n* = 1 or 2 (0.40 mol) is added to the magnetically stirred suspension. After stirring for 24 h, the reaction vessel is cooled to 0 °C in an ice-bath and the appropriate 3(*n*) (0.20 mol) dissolved in THF (800 mL) is added dropwise in 1 h; it should be stipulated that an accurate stoichiometry is important. Afterwards the mixture is stirred for an additional 96 h, and the course of the reaction is followed by ^1H-NMR spectroscopy after workup of analytical samples. Upon completion, the solvent is removed under reduced pressure, dry CH_2Cl_2 (500 mL) is added, and the mixture is poured into a stirred mixture of CH_2Cl_2 (500 mL) and ice–water (1000 mL). The organic phase is separated, and the aqueous layer is extracted with CH_2Cl_2 (3 × 250 mL). The combined organic phase is washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The acid-sensitive 4(*n*) were obtained in essentially quantitative yield.

1,1,1,18,18,18-Hexaphenyl-2,5,8,11,14,17-hexaoxaoctadecane 4(5): 140.97 g (96%) of a clear viscous oil. Anal. Calcd for $C_{48}H_{50}O_6$: C, 79.75; H, 6.97; O, 13.28. Found: C, 79.68; H, 6.95; O, 13.28.

1,1,1,21,21,21-Hexaphenyl-2,5,8,11,14,17,20-heptaoxaheneicosane 4(6): 149.27 g (97%) of a clear viscous oil. Anal. Calcd for $C_{50}H_{54}O_7$: C, 78.30; H, 7.10; O, 14.60. Found: C, 78.12; H, 7.12; O, 14.65.

1,1,1,24,24,24-Hexaphenyl-2,5,8,11,14,17,20,23-octaoxatetracosane 4(7): 155.44 g (96%) of a clear viscous oil. Anal. Calcd for $C_{52}H_{58}O_8$: C, 77.01; H, 7.21; O, 15.78. Found: C, 77.29; H, 6.99; O, 15.85.

1,1,1,27,27,27-Hexaphenyl-2,5,8,11,14,17,20,23,26-nonaoxaheptacosane 4(8): 163.02 g (95%) of a clear viscous oil; ^1H-NMR δ 7.48–7.42 (m, 12 H), 7.32–7.17 (m, 18 H), 3.68–3.60 (m, which contains A of AA'XX', 28 H) and 3.26–3.21 (X of AA'XX', 4 H); ^{13}C-NMR δ 144.10, 128.68, 127.70, 126.86, 86.49, 70.75, 70.67, 70.64, 70.58, 70.53, 63.30; IR (NaCl) 3058, 2960–2840, 1490, 1450, 1160–1040 (br) cm^{-1}; FABMS (Xe; matrix; *m*-nitrobenzyl alcohol) 884 (2.5, $[M + K]^+$), 877 (11, $[M + Na]^+$), 855 (2, $[M + H]^+$), 243 (100, $[(C_6H_5)_3C]^+$). Anal. Calcd for $C_{54}H_{62}O_9$: C, 75.85; H, 7.31; O, 16.84. Found: C, 75.74; H, 7.19; O, 16.84.

1,1,1,39,39,39-Hexaphenyl-2,5,8,11,14,17,20,23,26,29,32,35,38-tridecaoxanonatriacontane 4(12): 0.025 molar scale (16.97 g of 3(8)); 25.3 g (98%) of a clear viscous oil; ^{1}H-NMR δ 7.48–7.42 (m, 12 H), 7.32–7.17 (m, 18 H), 3.68–3.60 (m, which contains A of AA'XX', 44 H), 3.26–3.21 (X of AA'XX', 4 H); ^{13}C-NMR δ 144.12, 128.70, 127.72, 126.87, 86.51, 70.72, 70.64, 70.61, 70.52, 70.51, 63.32; IR (NaCl) 3058, 2960–2840, 1490, 1450, 1160–1040 (br) cm^{-1}; FABMS (Xe; matrix: *m*-nitrobenzyl alcohol) 1069 (6, $[M + K]^+$), 1053 (21, $[M + Na]^+$), 1048 (5, $[M + NH_4]^+$), 1031 (1, $[M + H]^+$), 243 (100, $[(C_6H_5)_3C]^+$). Anal. Calcd for $C_{62}H_{78}O_{13}$: C, 72.21; H, 7.62; O, 20.17. Found: C, 72.19; H, 7.63; O, 20.16.

General Procedure for Deprotection of α,ω-Dititylated Ethylene Glycols 4(*n*). A high pressure glass flask is charged with the appropriate **4(*n*)** (0.10 mol), dry CH_2Cl_2 (250 mL), and 10% palladium on carbon (1.5 g). Hydrogenolysis is carried out at 25 °C under 4 atm hydrogen pressure in a Parr apparatus for 4 days. With thin-layer chromatography the course of the reaction is followed [TLC (silica, $CHCl_3$); R_f **4(n)** and **2(n)** 0.05–0.15 [for $n > 4$); R_f triphenylmethane 0.9; R_f **1(n)** 0–0.05]. Upon completion of the reaction, the catalyst is filtered and washed with CH_2Cl_2 (50 mL), and the combined filtrate is concentrated under reduced pressure. The residue is dissolved in boiling MeOH (300 mL). Upon cooling the solution to −25 °C, the sideproduct triphenylmethane crystallizes and is filtered. After concentration of the filtrate, the remaining oily product is stirred with dry hexane (4 × 100 mL) to remove last traces of triphenylmethane. The purity of the oligo(ethylene glycols) was assessed with capillary gas chromatography after trimethylsilylation of the hydroxyl end groups[8] [column 30 m × 0.309 mm, Durabond-5; injector temperature 350 °C, FID detector temperature 250 °C, temperature program 175 °C to 350 °C, rate of 25 °C min^{-1}; carrier gas N_2, flow 1.5 mL min^{-1}].

3,6,9,12-Tetraoxatetradecane-1,15-diol 1(5): 22.98 g (96%) of a clear colorless oil.[5b]

3,6,9,12,15-Pentaoxaheptadecane-1,17-diol 1(6): 26.77 g (95%) of a clear colorless oil.[5d]

3,6,9,12,15,18-Hexaoxaeicosane-1,20-diol 1(7): 31.03 g (95%) of a clear colorless oil.[5d]

3,6,9,12,15,18,21-Heptaoxatricosane-1,23-diol 1(8): 36.06 g (97%) of a clear colorless oil;[5b] ^{1}H-NMR δ 3.72–3.66 (A of AA'MM'X, J(AX) = 6.1 Hz, 4 H), 3.64–3.61 (m, 24 H), 3.59–3.54 (M of AA'MM'X, 4 H), 2.92–2.87 (X of AA'MM'X, J(AX) = 6.1 Hz, 2 H, disappeared upon addition of ^2H_2O); ^{13}C-NMR δ 72.50, 70.54, 70.50, 70.48, 70.27, 61.62; IR (NaCl) 3600–3100 (br), 3000–2800 (br), 1450, 1160–1000 (br) cm^{-1}; FABMS (Xe, no matrix used) 393 (33, $[M + Na]^+$), 371 (32, $[M + H]^+$), 221 (2, $[H(OC_2H_4)_5]^+$), 177 (12, $[H(OC_2H_4)_4]^+$), 133 (39, $[H(OC_2H_4)_3]^+$), 89 (75, $[H(OC_2H_4)_n]^+$), and 45 (100, $[HOC_2H_4]^+$).

3,6,9,12,15,18,21,24,27,30,33-Undecaoxapentatriacontane-1,35-diol 1(12): 0.02 molar scale, 10.59 g (97%) of a waxy solid; mp 21.2 °C, maximum of DSC curve; ^{1}H-NMR δ 3.67–3.62 (A of AA'XX', 4 H), 3.62–3.56 (m, 40 H), 3.56–3.51 (X of AA'XX', 4 H), 2.89 (bs, 2 H, disappeared upon addition of ^2H_2O); ^{13}C-NMR δ 72.36, 70.41, 70.37, 70.14, 61.45; IR (NaCl) 3600–3100 (br), 3000–2800 (br), 1450, 1160–1000 (br) cm^{-1}; FABMS (Xe, matrix: glycerol) 1093 (0.2, $[2M - H]^+$), 569 (2.5, $[M + Na]^+$), 547 (45, $[M + H]^+$), 265 (2, $[H(OC_2H_4)_6]^+$), 221 (4, $[H(OC_2H_4)_5]^+$), 177 (15, $[H(OC_2H_4)_4]^+$), 133 (42, $[H(OC_2H_4)_3]^+$), 89 (77, $[H(OC_2H_4)_2]^+$), 45 (100, $[HOC_2H_4]^+$). Anal. Calcd for $C_{24}H_{50}O_{13}$: C, 52.73; H, 9.23. Found: C, 53.14; H, 9.23.

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Supplementary Material Available: Physical data for **1(*n*)** (n = 5, 6, and 7), **3(*n*)** (n = 1, 2, 3, and 4), and **4(*n*)** (n = 5, 6, and 7) and ^{1}H-NMR spectra of compounds **1(*n*)** (n = 5, 6, 7, 8, and 12) (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Theoneberine: The First Brominated Benzyltetrahydroprotoberberine Alkaloid from the Okinawan Marine Sponge *Theonella* sp.

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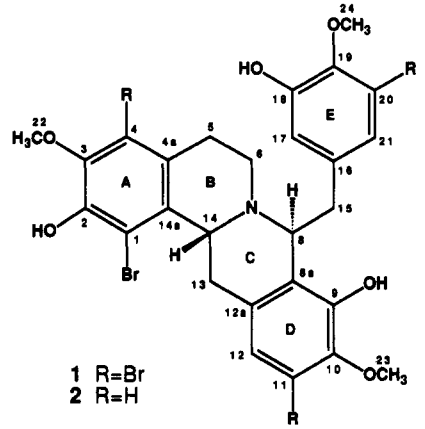
Among a number of tyrosine-derived alkaloids isolated from a variety of marine organisms,[2] several isoquinoline alkaloids have been obtained from marine sponges,[3] starfish,[4] and tunicates.[5] Recent studies have demonstrated that marine sponges of the genus *Theonella* are a rich source of unique bioactive natural products, most of which, however, belong to peptides[6] or polyoxygenated metabolites.[7] During our investigations on bioactive substances from Okinawan marine organisms,[8] we further examined extracts of the *Theonella* sponge of a different collection, resulting in isolation of a novel tetrahydroprotoberberine alkaloid, theoneberine (1). In this paper we describe the isolation and structure elucidation of 1.



The sponge *Theonella* sp. was collected off Ie Island, Okinawa, and kept frozen until used. The methanol ex-

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