Biomimetic Synthesis of Theonellin Isocyanide

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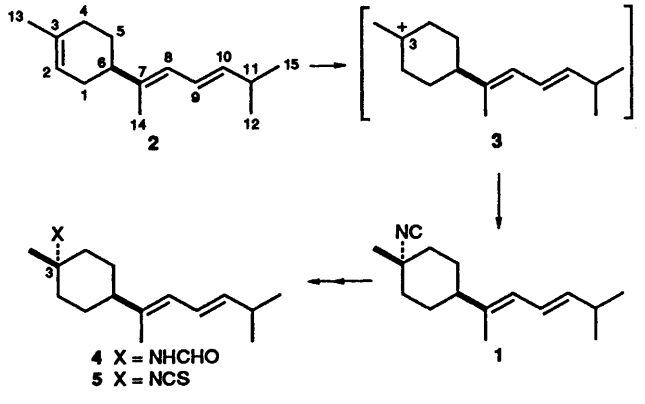
A marine sesquiterpene of the theonellin class has been synthesized for the first time. Direct amination of the theonelline carbon framework **2** in a biomimetic fashion, a crucial step, was achieved by employing a triflic acid-promoted Ritter-type reaction at low temperature (−78 °C).

Scheuer's laboratory reported the isolation and characterization of theonellin isocyanide **1** from a nudibranch, *Phyllidia* sp., from Sri Lanka.[1] The distinctive parts of this molecule, a bisabolene class sesquiterpene with a plane of symmetry in its structure, are an *E,E* conjugated diene system and a nitrogen substituent at C-3.[1]

Theonellin isocyanide **1** appears to be biogenetically related to theonellin **2**, theonellin formamide **4** and theonellin isothiocyanate **5** which were isolated from a sponge, *Theonella* cf. *swinhoei* by Nakamura.[2] It was reasoned that regiospecific protonation of theonelline **2** would produce a carbonium ion-like intermediate **3**, which upon capture by an ambident cyanide nucleophile (Ritter reaction) would provide theonellin isocyanide **1** (Scheme 1).[3] Further transformation of **1** would

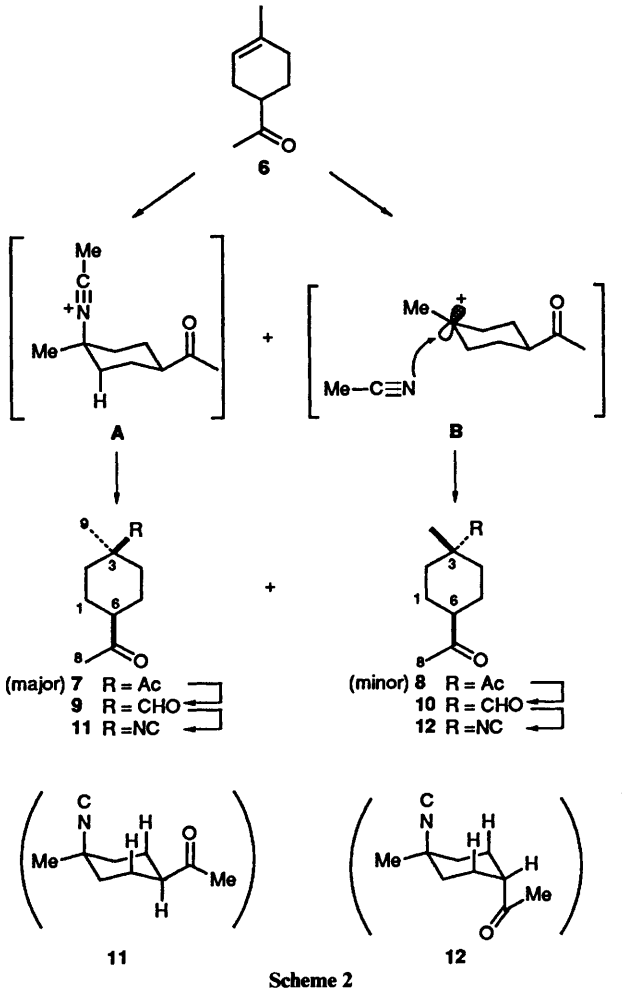


Scheme 1

then yield theonellin formamide **4** and theonellin isothiocyanate **5**.[4]

Initially, for the synthesis of theonellin isocyanide **1**, we chose 4-acetyl-1-methylcyclohex-1-ene **6** as the model compound and explored the Ritter reaction for the introduction of the nitrogen substituent (Scheme 2).[5] Reaction of **6** with concentrated sulfuric acid in acetonitrile at 0 °C followed by hydrolysis with aqueous sodium hydrogen carbonate provided a mixture of the amides **7** and **8** in a 7:3 ratio.

We assumed that the stereochemistry of the major isomer was **7** with the nitrogen substituent axially orientated, the reaction mechanism of the Ritter reaction being thought to involve *trans*-antiparallel electrophilic addition of H^+ and MeCN to the olefinic bond of **6** through a conformation where the acetyl group is equatorially orientated. This reaction path will give an intermediate **A** which is successively hydrolysed to yield the major isomer **7**. A minor isomer **8** may be derived from the carbonium ion intermediate **B** which was attacked by MeCN from the less hindered side.



Scheme 2

The stereochemistry of **8** was confirmed by its conversion into the known 1-acetyl-4-isocyano-4-methylcyclohexane **12** which has been derived by the degradation studies of theonellin isocyanide **1** by Scheuer.[1] The mixture of **7** and **8** upon treatment with triethyloxonium tetrafluoroborate followed by hydrolysis with acetic acid in aqueous tetrahydrofuran provided the corresponding amines. These amines, upon reaction with acetic formic anhydride, furnished a mixture of formamides **9** and **10**. Dehydration of these formamides with tetrabromomethane, triphenylphosphine and diisopropylethylamine in dichloromethane at −20 °C (modification of Ziehn's procedure)[7] afforded a mixture of the isocyanides **11** and **12**, which was easily separated by silica-gel chromatography. The isocyanide **11** was independently prepared from pure **7** by identical procedures. The ^1H NMR spectra of the isocyanide **12** derived from **8** showed 6-H (δ_H 2.59, 1 H, qn, *J* 5) which was in good agreement with that reported by Scheuer (δ_H 2.59, 1 H,

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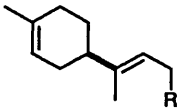
sept, J 5), and this result confirms the stereochemistry of **7** and **8**.

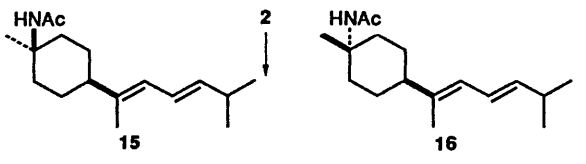
In addition, close study of the 500 MHz ^{1}H NMR spectra support the conformational assignments of the isocyanides **11** and **12**: 6-H of the isocyanide **11** (δ_H 2.24, tt, J 13, 4) is axial, because of its large $J_{1,6}$ value (13 Hz); if the ring is chair, the conformation must be as shown in Scheme 2. The 6-H signal for the isocyanide **12** (δ_H 2.59, quintet, J 5), was small, $J_{1,6}$ (5 Hz) compared with that of **11** and is only compatible with an equatorial proton, thus bringing the acetyl group into an axial orientation. The chemical shift of the isocyanide **12** (δ_H 2.59) compared with that of the isomer **11** (δ_H 2.24) supports this assignment of 6-H stereochemistry. If we assume that the ring of **12** is chair, the methyl group of **12** is now equatorial (see Scheme 2). The energetic cost of allowing the acetyl group to take up an axial conformation is reduced by the absence of 1,3-diaxial interactions at the methyl group.

We next turned our attention to the preparation of theonellin **2**. The allyl alcohol **13** was prepared by Delay and Ohlof's procedure from the cyclohexene **6** in two steps as a mixture of the Z and E isomers (1:5).[8] This allyl alcohol **13** was further transformed into the allyl sulfone **14** in 78% yield by conversion into the allyl bromide (phosphorus tribromide and pyridine in ether) followed by the reaction with sodium benzenesulfinate in dimethylformamide (DMF). Recrystallization provided the E allyl sulfone **14** in pure form. Construction of the diene moiety of theonelline **2** was accomplished in 88% overall yield by the following Julia *trans*-olefination procedures:[9] (i) treatment of **14** with butyllithium followed by isobutyraldehyde at −78 °C, (ii) acetylation of the resulting hydroxy sulfone with acetic anhydride and pyridine and (iii) treatment of this acetoxy sulfone with sodium amalgam (5%) and sodium hydrogen phosphate in methanol.[10] The product ratio of E:Z was *ca.* 83:17. This stereoisomeric mixture could not be separated at this stage and was used in the next reaction.



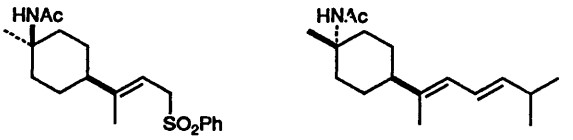
13 R = OH
14 R = SO_2Ph

With theonelline **2** to hand, attention was next directed to its amination. Theonellin **2** was treated with conc. H_2SO_4 in acetonitrile at 0 °C followed by aqueous $NaHCO_3$ to furnish **15** and **16** in 33% yield in the ratio 4.3:1. The low yield of this step may be a result of the competitive reaction of the diene moiety with conc. H_2SO_4. A more regiospecific reaction and milder conditions were sought. This was realized by treatment of theonelline **2** with trifluoromethanesulfonic acid (triflic acid, 1.5 equiv.) and MeCN (8 equiv.) in CH_2Cl_2 at −78 °C for 2 h followed by hydrolysis with aqueous $NaHCO_3$ to yield a 65:35 mixture of **15** and **16** in 63% yield (60% conversion of the starting material). Use of a limited amount of MeCN was crucial for the selectivity of this reaction. Indeed, the reaction of **2** with triflic acid in a 2:1 mixture of CH_2Cl_2 and MeCN gave a 93:7 mixture of 15:16 indicating that the *trans* addition mechanism predominates. Using a limited amount of MeCN may enforce the formation of the carbonium ion. This isomeric mixture was easily separated by silica gel chromatography to provide homogeneous **16**.



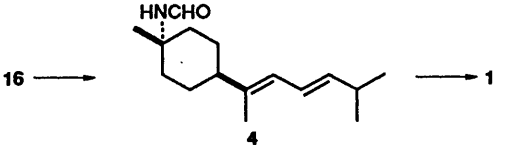
15 **16**

A higher yielding and more practical approach from **14** to **16** was pursued. Reaction of **15** with triflic acid and MeCN in CH_2Cl_2 provided **17** and **18** in 98% combined yield in the ratio 51:49. The resulting allyl sulfone **18** was transformed into **16** in 98% yield through a similar Julia *trans* olefination procedure as previously described.



17 **18**

Treatment of **16** with $Et_3O^+BF_4^-$ followed by hydrolysis with AcOH in aqueous THF afforded the corresponding amine. This, upon treatment with AcOCHO, furnished theonellin formamide **4** as crystals in 88% overall yield from **16**. Finally, the formamide **4** was smoothly converted into theonellin isocyanide **1** in 89% yield using Baldwin's procedure (trifluoromethanesulfonic anhydride and diisopropylethylamine at −78 °C for 3 min).[11] The yield for this reaction was low with a prolonged reaction time (20–30 min).



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Spectral data for compounds **1**, **2** and **4** were in good agreement with those reported in the literature and those kindly provided by Professor P. J. Scheuer and Dr. H. Nakamura.

The method developed here should be widely applicable to the elaboration of a wide variety of terpenes with nitrogen substituents. The one drawback of this sequence is the generally moderate selectivity observed during the Ritter reaction stage due to the carbonium ion intermediate. Efforts are presently underway to develop alternative and more efficient approaches to terpenes with nitrogen substituents.

Experimental

General Details.—M.p.s were determined on an oil bath apparatus and are uncorrected. IR spectra were recorded using a Shimadzu IR-420 IR spectrometer for chloroform solution unless otherwise stated. ^{1}H NMR spectra were determined using a JEOL FX-200 spectrometer operating at 200 MHz unless otherwise stated. Other spectrometers used were JEOL EX 270 and JEOL JNM-GX 500. ^{13}C NMR spectra were determined using the JEOL-90 instrument, operating at 22.50 MHz unless otherwise stated; the JEOL EX270 instrument operating at 67.80 MHz was also used. Dilute solution in deuteriochloroform were used throughout unless stated otherwise, with tetramethylsilane as the internal standard. All J values are in Hz. High-resolution mass spectra were recorded on a JMS-DX 705L instrument by S. Kitamura (Nagoya University).

N,N-Dimethylformamide was dried over molecular sieves 4A. Pyridine was dried over potassium hydroxide. All reactions were carried out under argon. All organic solutions from work-up procedures were dried by brief exposure to anhydrous sodium sulfate. Column chromatography were performed on silica gel supplied by E. Merck (Art 7734) and Fuji Davison (BW-820 MH). Preparative TLC were made on plates prepared

with a 2 mm layer of silica gel PF254 obtained from E. Merck (Art 7747).

4-Acetamido-1-acetyl-4-methylcyclohexane **7**.—To a solution of conc. sulfuric acid (20 cm^3, 0.38 mol) in acetonitrile (400 cm^3) cooled to 0 °C was added 4-acetyl-1-methylcyclohexene **6** (20 cm^3, 0.137 mol) dropwise. After being stirred for 3.5 h, the reaction mixture was poured into aqueous sodium hydrogen carbonate (100 g of sodium hydrogen carbonate and 500 cm^3 of water). The aqueous phase was extracted with ethyl acetate. The organic extracts were combined, dried and evaporated under reduced pressure to afford crude product (19.97 g). This was purified by recrystallization from ethyl acetate at −20 °C to afford the major product **7** as pure crystals (5.65 g). Further crystallization provided a mixture **7** and **8** as crystals (5.88 g). The combined yield was 43% (11.53 g); m.p. 122 °C (from ethyl acetate–hexane) (Found: C, 66.9; H, 9.8; N, 7.1. $C_{11}H_{19}NO_2$ requires C, 66.97; H, 9.71; N, 7.10%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH), 1700 (COMe) and 1660 (CON); δ_H(270 MHz; $CDCl_3$) 1.38 (3 H, s, 3-Me), 1.94 (3 H, s, COMe) and 2.16 (3 H, s, 6-H).

1-Acetyl-4-formamido-4-methylcyclohexane **9** *and* **10**.—To a solution of a mixture of **7** and **8** (587 mg, 2.98 mmol) dissolved in dichloromethane (12 cm^3) was added sodium carbonate (2 g) followed by a solution of triethyloxonium tetrafluoroborate (*ca.* 1 mol dm^{-3} in dichloromethane, 6 cm^3). After being stirred at room temperature for 4 h, the reaction mixture was poured into water. The aqueous layer was extracted with dichloromethane (×2), and the combined extracts were dried and concentrated under reduced pressure. The resulting crude imino ether (0.69 g) was dissolved in a mixture of tetrahydrofuran (14 cm^3), water (1.5 cm^3) and acetic acid (1.5 cm^3) and the solution stored at room temperature overnight; it was then evaporated to remove tetrahydrofuran. Water (*ca.* 10 cm^3) was added to the residue, and the solution was neutralized with sodium carbonate (4.0 g). The aqueous solution was extracted with dichloromethane. The combined extracts were dried and concentrated under reduced pressure to afford crude amine (0.41 g); which was immediately dissolved in dichloromethane (6 cm^3), and treated with acetic formic anhydride (1.1 cm^3). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure. Chromatography of the residue on silica gel with ethyl acetate–hexane (1:3 followed by 3:1) provided a mixture of the formamides **9** and **10** (323 mg, 60%).

1-Acetyl-4-isocyano-4-methylcyclohexane **11** *and* **12**.—A solution of a mixture of the formamides **9** and **10** (285 mg, 1.45 mmol), tetrabromomethane (1.233 g, 3.7 mmol) and diisopropylethylamine (1.3 cm^3, 7.48 mmol) dissolved in dichloromethane (15 cm^3) was cooled to −20 °C. To this solution was added a solution of triphenylphosphine (918 mg, 3.5 mmol) in dichloromethane (*ca.* 2 cm^3) dropwise. After the mixture had been stirred at −20 °C for 55 min, the reaction was quenched by addition of water. The aqueous layer was extracted with ether, and the combined extracts were washed with 1 mol dm^{-3} HCl, saturated aqueous sodium hydrogen carbonate and brine, dried and concentrated under reduced pressure to afford crude product (1.928 g). This was purified by silica gel chromatography with ether–hexane (1:10 followed by 1:3) to afford the isocyanides **12** (148 mg) and **11** (40 mg combined yield 72%). *1-Acetyl-4-isocyano-4-methylcyclohexane* **11**. $\nu_{max}(CHCl_3)/cm^{-1}$ 2080 (NC) and 1690 (CO); δ_H(200 MHz; $CDCl_3$) 1.45 (3 H, t, *J* 2, 3-Me), 2.17 (3 H, s, COMe); (500 MHz; $CDCl_3$) 1.4 (2 H, m), 1.45 (3 H, t), 1.77 (2 H, qd, *J* 13, 4), 1.90 (2 H, br dd, *J* 13, 4), 2.01 (2 H, br d, *J* 13), 2.17 (3 H, s) and 2.24 (1 H, tt, *J* 13, 4); δ_C(67.80 MHz, $CDCl_3$) 23.8, 27.7, 29.9, 37.4, 49.9 and 57.4 (t, *J* 5, 3-C), 154.8 (t, *J* 5, NC) and 210.3 (CO) (Found: M^+, 165.1161. $C_{10}H_{15}NO$ requires *M*, 165.1154).

1-Acetyl-4-isocyano-4-methylcyclohexane **12**. $\nu_{max}(CHCl_3)/cm^{-1}$ 2080 (NC) and 1690 (CO) (lit.,[1] 2980, 2950, 2870, 2130, 1705, 1335 and 1135); δ_H(200 MHz; $CDCl_3$) 1.40 (3 H, t, *J* 2, 3-Me), 2.16 (3 H, s, COMe) and 2.59 (1 H, qn, *J* 5, 6-H); (500 MHz; $CDCl_3$) 1.40 (3 H, t), 1.65 (2 H, m), 1.78 (2 H, tt, *J* 13, 5), 1.8–2.0 (4 H), 2.16 (3 H, s), 2.59 (1 H, qn, *J* 5) [lit.,[1] 300 MHz, $CDCl_3$, 1.38 (3 H, s), 1.96–1.5 (unresolved), 2.15 (3 H, s), 2.59 (1 H, sept, *J* 5)]; δ_C(67.80 MHz, $CDCl_3$) 22.7, 28.0, 28.1, 35.5, 46.4, 57.3 (t, *J* 5, 3-C), 153.9 (t, *J* 4, NC) and 210.5 (CO) (Found: M^+, 165.1165. $C_{10}H_{15}NO$ requires *M*, 165.1154).

(E)-*Allyl Sulphone* **14**.—To a solution of the allyl alcohol **13** (19.0 g., 0.114 mol) and pyridine (3 cm^3) dissolved in ether (400 cm^3) cooled to 0 °C was added phosphorus tribromide (11.5 cm^3, 0.063 mol) dropwise. After being stirred at 0 °C for 20 min, the reaction mixture was poured into water. The separated organic phase was successively washed with water, saturated aqueous sodium hydrogen carbonate and brine, dried and concentrated under reduced pressure to yield the allyl bromide (22.09 g, 85%). This allyl bromide was immediately dissolved in DMF (400 cm^3), and treated with sodium benzenesulfinate (30 g, 0.15 mol) at room temperature. The reaction mixture was heated at 70 °C for 2 h, and then poured into water (800 cm^3). The aqueous phase was extracted with ether (×3). The combined extracts were washed with water and brine, dried and concentrated under reduced pressure to provide the allyl sulfone (25.66 g, 78%). Recrystallization from ether–hexane gave the pure (*E*)-allyl sulfone **14** (17.51 g, 53%), m.p. 84 °C (from ether–hexane) (Found: C, 70.3; H, 7.8; $C_{17}H_{22}SO_2$ requires C, 70.31; H, 7.64%); δ_H(270 MHz; $CDCl_3$) 1.26 (3 H, s, Me), 1.64 (3 H, s, Me), 3.82 (2 H, d, *J* 8, CH_2SO_2), 5.22 (1 H, t, *J* 8, C=CH), 5.35 (1 H, br s, C=CH), 7.4–8.0 (5 H, Ph).

Theonelline **2**.—To a solution of the allyl sulfone **14** (3.0 g, 10.34 mmol) dissolved in tetrahydrofuran (90 cm^3) cooled to −78 °C was added butyllithium (1.6 mol dm^{-3} solution in hexane; 9.0 cm^3, 14.4 mmol). After the mixture had been stirred at −78 °C for 20 min, isobutyraldehyde (2.4 cm^3, 26.4 mmol) was introduced and stirring continued for a further 15 min; acetic anhydride (6 cm^3) was then added. After being stirred for 5 min, the reaction mixture was warmed to room temperature and pyridine (18 cm^3) was added to it. After being left overnight, the reaction mixture was poured into water and the aqueous layer separated; this was then extracted with ether. The combined extracts were washed with 1 mol dm^{-3} HCl, saturated aqueous sodium hydrogen carbonate and brine, dried and concentrated under reduced pressure. The resulting residue was passed through a short column of silica gel with ether–hexane (1:1) as eluent to afford the acetoxy sulfone (4.53 g). This, dissolved in methanol (140 cm^3), was treated with Na_2HPO_4 (4.5 g) followed by sodium amalgam (15 g) at 0 °C. Additional sodium amalgam (24.99 g) was added until TLC analysis showed the absence of starting material. The reaction mixture was diluted with water (200 cm^3) and extracted with hexane. The combined extracts were washed with water and brine, dried and concentrated under reduced pressure. The resulting residue was passed through a short column of silica gel (*ca.* 12 g) with hexane as eluent to afford theonelline (1.84 g, 88%). HPLC analysis of this product showed the *trans-cis* ratio to be 83:17.

This mixture of theonelline **2** and its *cis* isomer were inseparable at this point and, accordingly, only major NMR signals corresponding to theonelline **2** are described; δ_H(200 MHz; $CDCl_3$) 1.01 (6 H, d, *J* 7, 15-Me), 1.65 (3 H, s, 3-Me), 1.73 (3 H, s, 7-Me), 2.35 (1 H, 11-H), 5.57 (1 H, dd, *J* 15, 7, 10-H), 5.39 (1 H, brs), 5.83 (1 H, d, *J* 10, 8-H), 6.24 (1 H, ddd, *J* 15, 10, 1, 9-H) [lit.,[2] 1.02 (6 H, d, *J* 6.6), 1.72 (3 H, d, *J* 1), 2.34 (1 H, octet, *J* 6.6), 5.54 (1 H, dd, *J* 15, 6.6), 5.80 (1 H, br d, *J* 11) and 6.24 (1 H, ddq, *J* 15, 11, 1)]; δ_C(50.20 MHz, $CDCl_3$) 14.6 (14-C), 22.6 (11-Me),

23.5 (13-C), 27.8 (5-C), 30.6 (1-C or 4-C), 30.7 (1-C or 4-C), 31.4 (11-C), 43.1 (6-C), 120.8 (2-C), 123.3 (8-C or 9-C), 123.6 (8-C or 9-C), 133.5 (3-C), 139.8 (10-C) and 140.5 (7-C) (lit.,[2] 14.7, 22.7, 23.5, 28.0, 30.7, 30.8, 31.4, 43.2, 120.9, 123.4, 123.9, 133.6, 139.8 and 140.5).

Theonellin acetamide **15** *and* **16**.—To a solution of theonelline **2** (108 mg, 0.36 mmol) in a mixture of acetonitrile (0.20 cm^3, 4.3 mmol) and dichloromethane (5 cm^3) cooled to −78 °C was added trifluoromethanesulfonic acid (0.07 cm^3, 0.79 mmol). After being stirred at −78 °C for 2 h, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate. The aqueous phase was separated and extracted with dichloromethane and the combined extracts were dried and concentrated under reduced pressure to afford a residue. HPLC analysis of this crude product revealed the ratio of compounds **15**:**16** to be 65:35. Purification by silica gel chromatography with ether–hexane (1:50) followed by ethyl acetate–hexane (1:1) as eluent provided theonelline **2** (65 mg), and a mixture of **15** and **16** (53 mg, 63% yield based on theonelline used).

A solution of theonelline **2** (73 mg, 0.36 mmol) in a mixture of acetonitrile (1 cm^3) and dichloromethane (2 cm^3) cooled to −78 °C was treated with trifluoromethanesulfonic acid (0.04 cm^3, 0.45 mmol) for 3 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and the aqueous phase separated and extracted with dichloromethane. The combined extracts were dried and concentrated under reduced pressure to afford a residue. HPLC analysis of this crude product revealed the ratio of compounds **15** and **16** to be 93:7. Purification by silica gel chromatography with ether–hexane (1:50) followed by ethyl acetate-hexane (1:1) as eluent provided theonelline **2** (12 mg, 16% recovered), and a mixture of compounds **15** and **16** (44 mg, 73% yield based on theonellin used).

Acetamides **17** *and* **18**.—To a solution of acetonitrile (9 cm^3, 192 mmol) and trifluoromethanesulfonic acid (17.0 g, 192 mmol) in dichloromethane (260 cm^3) cooled to −78 °C was added a solution of the allyl sulfone **14** (8.0 g, 27.6 mmol) in dichloromethane (40 cm^3). After being stirred at −78 °C for 2 h, the reaction mixture was poured into aqueous sodium hydrogen carbonate. The aqueous layer was separated, and extracted with dichloromethane and the organic phase was dried and concentrated under reduced pressure to afford a crude mixture of the allyl sulfone **14** and the acetamides **17** and **18**. The product ratio of compounds **17** and **18** was found to be 51:49 by HPLC analysis. Purification by silica gel chromatography provided the allyl sulfone **14** (1.03 g), **18** and its isomer **17** (8.21 g). Yield based on consumed starting material was 98%.

Acetamide **18**. M.p. 120 °C (from ethyl acetate–hexane) (Found: C, 65.35; H, 7.8; N, 4.0. $C_{19}H_{27}NSO_3$ requires C, 65.30; H, 7.79; N, 4.01%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH), 1650 (CONH) and 1500 (CONH); δ_H(200 MHz; $CDCl_3$) 1.21 (3 H, s, 3-Me), 1.35 (3 H, s, 7-Me), 1.91 (3 H, s, COMe), 3.81 (2 H, d, *J* 8, CH_2SO_2), 5.21 (1 H, t, *J* 8, C=CH), 5.29 (1 H, br s, C=CH) and 7.4–7.9 (5 H, Ph).

Acetamide **17**. M.p. 118 °C (from ethyl acetate–hexane) (Found: C, 65.2; H, 7.8; N, 4.0. $C_{19}H_{27}NO_3S$ requires C, 65.30; H, 7.79; N, 4.01%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (NH), 1670 (CONH) and 1510 (CONH); δ_H(200 MHz; $CDCl_3$) 1.25 (3 H, s, 3-Me), 1.34 (3 H, s, 7-Me), 1.96 (3 H, s, COMe), 2.2–2.3 (2 H), 3.81 (2 H, d, *J* 8, CH_2SO_2), 5.21 (1 H, t, *J* 8, C=CH), 5.2 (1 H, br s, C=CH) and 7.4–7.9 (5 H, Ph).

Theonellin acetamide **16**.—The procedure described here was similar to that used for the theonellin **2**. Thus, allyl sulfone (a 12:88 mixture of **17** and **18**; 3.56 g, 10.2 mmol) in tetrahydrofuran (180 cm^3) was treated with butyllithium (19.0 cm^3, 25.3 mmol) at −78 °C to give, after 20 min at this temperature, a yellow precipitate. The reaction mixture was warmed to −20 °C, and stirring was continued for 20 min. The solution was recooled to −78 °C, and isobutyraldehyde (4.6 cm^3, 50.7 mmol) was introduced. After 20 min at −78 °C, the reaction was quenched by addition of saturated aqueous ammonium chloride. The separated aqueous layer was extracted with ethyl acetate and the combined extracts were dried, and concentrated under reduced pressure. The resulting residue was dissolved in a mixture of acetic anhydride (20 cm^3) and pyridine (40 cm^3). After the mixture had been stirred at room temperature overnight, the solvent was evaporated under reduced pressure. The resulting residue was passed through a short column of silica gel with ethyl acetate–hexane (2:1) as eluent to afford crude acetoxy sulfone (7.02 g). This, in methanol (80 cm^3), was treated with disodium hydrogen phosphate (3 g) followed by sodium amalgam (15.9 g) at 0 °C. Additional sodium amalgam (17.3 g) was added. The reaction mixture was diluted with water (200 cm^3) and extracted with ether. Following work-up as described before, the resulting residue (3.37 g) was purified by silica gel chromatography (silica gel 100 g) with ethyl acetyl–hexane (1:10 followed by 1:1) to give the following column fractions; theonellin acetamide derived from **17** (139 mg, oil), a 1:1 mixture of **17** and **18** (777 mg) and theonellin acetamide **16** (1.70 g). The total yield was 98% (2.62 g). Recrystallization from ethyl acetate–hexane provided an analytically pure crystalline sample of **16**. *Theonellin acetamide* **16**. M.p. 103 °C (from ether–hexane); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH), 1650 (CONH) and 1500 (CONH); δ_H(200 MHz; $CDCl_3$) 1.01 (6 H, d, *J* 7, 12, 15-Me), 1.39 (3 H, s, 3-Me), 1.72 (3 H, d, *J* 1, 7-Me), 1.92 (3 H, s, COMe), 2.33 (1 H, sept, *J* 7, 11-H), 5.26 (1 H, br s, 2-H), 5.58 (1 H, dd, *J* 15, 7, 10-H), 5.81 (1 H, d, *J* 11, 8-H) and 6.22 (1 H, ddd, *J* 15, 11, 1, 9-H) (Found: M^+, 263.2266. $C_{17}H_{29}NO$ requires *M*, 263.2249).

Theonellin formamide **4**.—The procedure used was similar to that used for the production of 1-acetyl-4-formamido-4-methylcyclohexane **9** and **10**. Theonellin acetamide **16** (1.47 g, 5.59 mmol) in dichloromethane (80 cm^3) was treated with triethyloxonium tetrafluoroborate (1 mol dm^3 solution in dichloromethane, freshly prepared; 14 cm^3) and sodium carbonate (5.0 g), and the reaction mixture was stirred at room temperature for 1.5 h. Work-up as described before gave the crude imino ether (1.6 g). This, together with acetic acid (6 cm^3), water (6 cm^3) and tetrahydrofuran (60 cm^3) was stirred at room temperature overnight. Solvent was evaporated, and water was removed azeotropically with ethanol (× 3) to afford the amine (2.37 g). This, in dichloromethane (50 cm^3), was treated with acetic formic anhydride (4 cm^3) for 40 min at room temperature. Solvent was removed under reduced pressure, and the resulting oil was passed through a short column of silica gel with ethyl acetate as eluent to afford the formamide **4** (1.46 g); this afforded crystals (877 mg) from ether–hexane. Purification of the residue from mother liquor by preparative TLC provided further formamide **4** (317 mg); total yield was 88% from theonellin acetamide **16**. NMR analysis of **4** proved to be extremely difficult, because it exists as 1:1 mixture of two rotational isomers; m.p. 92 °C (from ether–hexane) (Found: C, 76.95; H, 10.9; N, 5.6. $C_{16}H_{27}N$ requires C, 77.04; H, 10.92; N, 5.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1670 (NHCHO) (lit.,[1] 1685).

Theonellin isocyanide **1**.—A solution of theonellin formamide **4** (80 mg, 0.32 mmol) and diisopropylethyl amine (0.37 cm^3, 2.13 mmol) dissolved in dichloromethane (6 cm^3) was cooled to −78 °C, and triflic anhydride (0.10 cm^3, 0.60 mmol) was added dropwise. After being stirred at −78 °C for 3 min, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate. The aqueous layer was separated and extracted with

ether and the combined extracts were washed with 1 mol dm^{-3} HCl, saturated aqueous sodium hydrogen carbonate and brine, dried and concentrated under reduced pressure. Purification of the resulting residue by silica gel chromatography using ether–hexane (1:200 followed by 1:25) as eluent provided theonellin isocyanide **1** (66 mg, 89%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2120 (NC), 1460, 1370 and 1120 (lit.,[1]; neat, 3040, 2970, 2950, 2880, 2130, 1470, 1385, 1128, 965); δ_H(200 MHz; $CDCl_3$) 1.01 (6 H, d, *J* 7, 11-Me), 1.43 (3 H, br s, 3-Me), 1.72 (3 H, s, 7-Me), 2.35 (1 H, 6-H), 5.60 (1 H, dd, *J* 15, 7, 10-H), 5.80 (1 H, d, *J* 10, 8-H), 6.21 (1 H, dd, *J* 15, 10, 9-H) {lit.,[1] 0.99 (d, *J* 6.8), 1.42 (t, *J* 2), 1.7 (br s), 2.33 (mult, *J* 6.8, 1), 5.58 (dd, *J* 15, 6.8), 5.79 (d, *J* 10.8), 6.2 (dd, *J* 15, 10.8, 1)}; δ_C(67.80 MHz, $CDCl_3$) 15.2, 22.5 (12, 15-C), 25.1, 26.4, 31.4, 38.2 (t, *J* 5), 44.8, 56.7, 123.4, 123.8, 138.6, 140.6 and 152.2 (br t, *J* 4), {lit.,[1]; 15.1 (14-C), 22.4 (12, 15-C), 26.3 (1, 5-C), 31.5 (11-C), 38.1 (2, 4-C), 44.6 (6-C), 56.6 (t, coupled to ^{14}N, 3-C), 123.3, 123.7 (8, 9-C), 138.4 (7-C), 140.5 (10-C) and 152.2 (coupled to ^{14}N, 16-C); Data collected from the spectrum provided by Scheuer; 15.2, 22.5, 25.1, 26.4, 31.4, 38.2, 44.7, 56.6, 123.4, 123.8, 138.6, 140.7 and 152.2} (Found: M^+, 231.1970. $C_{16}H_{25}N$ requires *M*, 231.1987) (lit.,[1] HRMS: *m/z* 231.1975. Calc. for $C_{16}H_{25}N$; 231.1987).

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