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SYNTHESIS OF (-)-UNTENOSPONGIN C, A C₂₁ FURANOTERPENE ISOLATED FROM THE OKINAWAN SPONGE *HIPPOSPONGIA* SP.

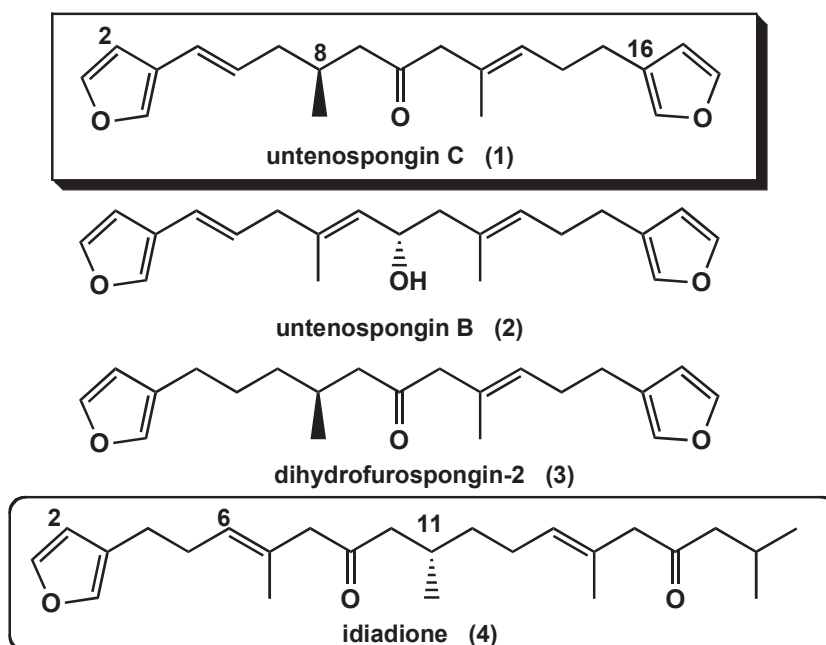
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Abstract – Starting with (*R*)-(+)-citronellol (**5**), the first enantioselective synthesis of (-)-untenospongine C (**1**), a C₂₁ furanoterpene isolated from a marine sponge *Hippospongia* sp., has been achieved, the present synthesis indicating the absolute configuration of **1** as *S*.

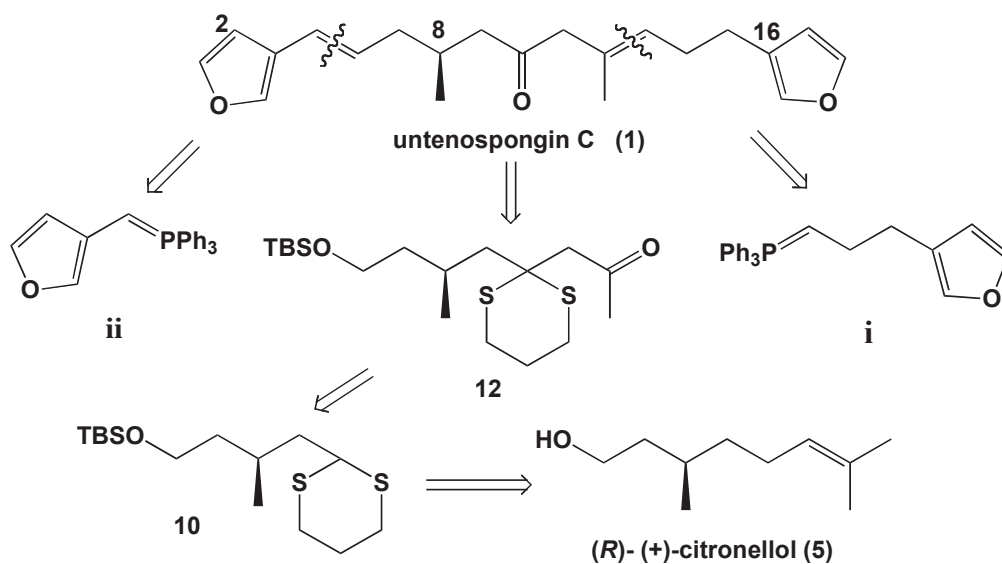
It is well-known that marine sponges are generally the source of unique and biologically active metabolites.¹ Many structurally related C₂₁ furanoterpenes have been isolated from several marine sponge genera, in which the linear C₂₁ furanoterpene untenospongine C (**1**), possessing cytotoxicity against murine lymphoma L1210 cell *in vitro* with the IC₅₀ value of 3.8 μg/ml, was isolated from the Okinawan marine sponge *Hippospongia* sp. in 1993 by Kobayashi *et al.*² More recently, untenospongine C (**1**) was isolated from the S. E. Queensland marine sponge *Coscinoderma mathewsi*.³ These structural elucidation of **1** was carried out by spectroscopic studies as well as in comparison with untenospongine B (**2**),⁴ and the absolute configuration at C(8) was assigned as *S* by use of regio-selective catalytic hydrogenation of **1**



to afford dihydrofurospingin-2 (**3**).⁵

We have recently reported the enantioselective synthesis of the linear furanosesterterpene (-)-idiadione (**4**),⁶ isolated from marine sponge *Spongia idia*, in which we assigned (*S*)-configuration to the chiral center C(11).⁷ As part of synthetic study on marine natural product, the present paper describes the first enantioselective total synthesis of (*S*)-(-)-untenospongins C (**1**) utilizing (*R*)-(+)-citronellol (**5**) as chiral source.

As shown in the retrosynthetic disconnection in Scheme 1, the target molecule **1** could be constructed through the assembly of the three fragments, i.e., two phosphonium ylids **i** and **ii**, and chiral methyl ketone **12**, which could be obtainable from **5**, and act as the precursor necessary for stepwise Wittig reactions in the reaction pathway.

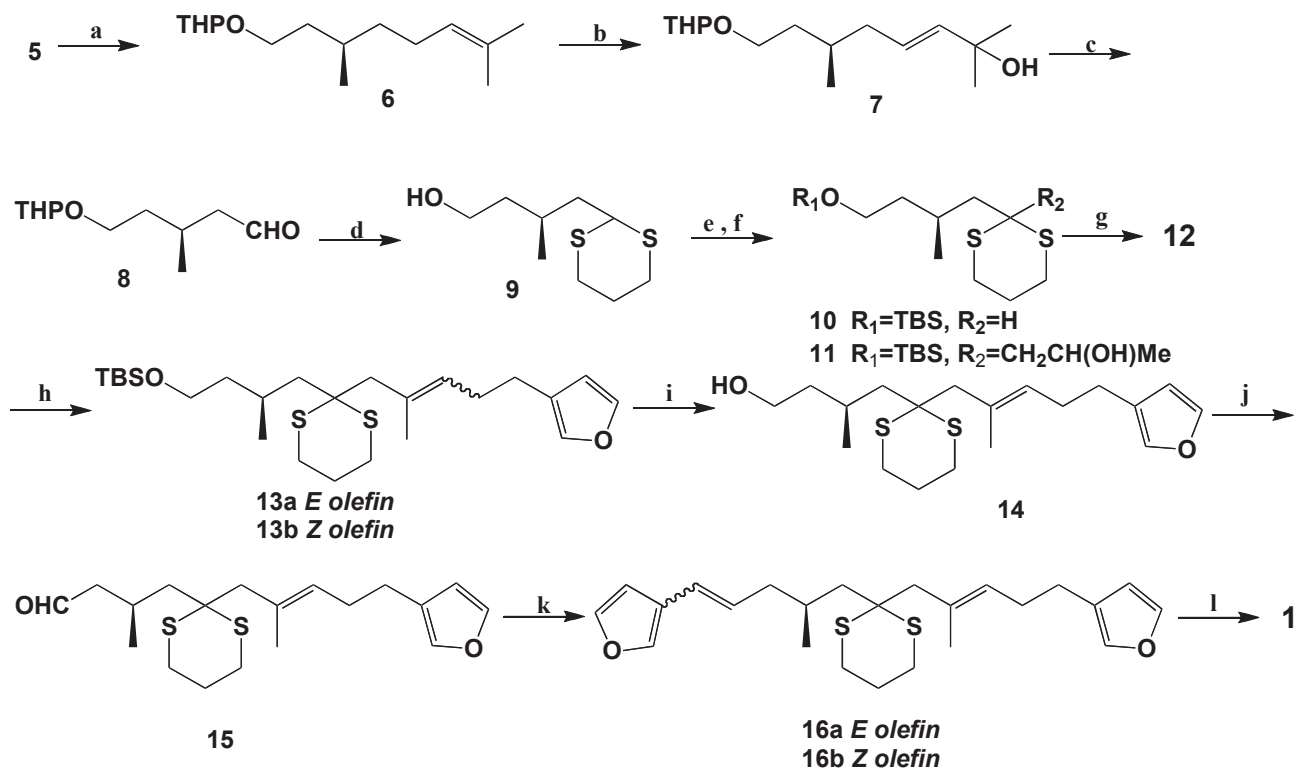


To prepare methylketone **12**, our synthesis started with protection of the hydroxy group in (*R*)-(+)-citronellol (**5**) (98%*ee*) by treatment with DHP in the presence of PPTS to give THP ether **6** in quantitative yield (Scheme 2). Using Sharpless oxidation procedure (30% H_2O_2 , Ph_2Se_2 and 70% *t*-BuOOH),⁸ **6** was converted to allylic alcohol **7** in high yield. Ozonolysis of **7** yielded unstable aldehyde **8** with four carbon loss. Without purification, **8** was then reacted with 1,3-propanedithiol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to afford 1,3-dithiane **9** with concomitant deprotection in 66% yield from **7**. Resulting hydroxy group in **9** was reprotected as the more stable TBS ether, thus providing ether **10**.

The lithium salt, prepared from **10** with *n*-BuLi, was treated with propylene oxide to give alcohol **11**, from which desired methyl ketone **12** was successfully obtained using Swern oxidation.⁹

With key synthetic intermediate **12** in hand, introduction of two kinds of furyl moieties in **12** was examined next. Treatment of [3-(3'-furyl)propyl]triphenylphosphonium bromide with *n*-BuLi in THF led

to the ylide **i** as a yellow THF solution,¹⁰ followed by addition of **12** at 0 °C furnished 31% yield of *E*-**13a** and *Z*-olefin **13b** (ratio: 4.8:1).¹¹ Fortunately, Wittig-Schlosser procedure¹² *via* reconstruction of the betain intermediate was modified successfully for the ratio of **13a** and **13b** to 18.3 : 1 (31% yield).



Scheme 2. Reagents and conditions: (a) DHP, PPTS, CH₂Cl₂, quant.; (b) Ph₂Se₂, H₂O₂, MgSO₄, *t*-BuOOH, CH₂Cl₂, 83%; (c) O₃, NaHCO₃, Me₂S, CH₂Cl₂/MeOH; (d) 1,3-dithiane, BF₃-Et₂O, CHCl₃, 66%; (e) TBSCl, imidazole, DMF, quant.; (f) *n*-BuLi, propyleneoxide, THF, 80%; (g) DMSO TFAA, Et₃N, CH₂Cl₂, 88%; (h) [3-(3'-furyl)propyl] triphenylphosphonium bromide, *n*-BuLi, THF, 31%; (i) TBAF, THF, 94%; (j) DMSO, TFAA, Et₃N, CH₂Cl₂, 58%; (k) 3-furylmethyltriphenylphosphonium bromide, *n*-BuLi, THF 83%; (l) HgCl₂, CaCO₃, MeCN/H₂O, 35%

The mixture **13a,b** was easily separable by preparative TLC (silica gel). Deprotection of TBS group in **13a** with TBAF, followed by Swern oxidation of the resulting alcohol **14** provided aldehyde **15** in 55% yield from **13a**.

The ylide **ii** was prepared from 3-furylmethyltriphenylphosphonium bromide with *n*-BuLi in THF according to the Katsumura procedure,¹³ and resulting THF solution of **ii** was reacted with **15** to give bisfurano compound **16** as a mixture of *E*-**16a** and *Z*-isomer **16b** in ratio of 1.1 and 1.¹¹ However, no effect was obtained on attempted Wittig-Schlosser method, providing a mixture of **16a** and **16b** in a ratio of 1.5 and 1. Finally, the mixture of **16a, b** was then hydrolyzed with HgCl₂ and CaCO₃ in aqueous MeCN, followed by separation of the resulting mixture by preparative TLC (silica gel) to afford (-)-untenospongin C (**1**), [α]_D²² -9.46 (c 0.31, CHCl₃) {lit.,² [α]_D²² -9.3 (c 1.0, CHCl₃)} as the major

product (35% yield) and 4Z-isomer of **1**, $[\alpha]_D^{22} -8.58$ (c 0.83, CHCl₃) as minor product (22% yield). The IR, ¹H and ¹³C NMR of synthetic **1** were identical with those of an authentic sample.

In conclusion, we have accomplished the enantioselective total synthesis of (-)-untenospongic acid (**1**) in an optically active form from (R)-(+)-citronellol (**5**). The present study also supports the absolute stereostructure of **1** by a synthetic means.

ACKNOWLEDGEMENTS

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14. Spectral data of compound **9**: a colorless oil. $[\alpha]_D^{24} +12.2$ (c 0.98, CHCl₃); IR (CHCl₃) cm⁻¹: 3620, 3455, 2905, 1415; ¹H-NMR (CDCl₃, 300 MHz): δ 0.96 (d, *J* = 6.6 Hz, 3H), 1.40~1.94 (m, 9H), 2.1~2.2 (m, 1H), 2.79~2.91 (m, 2H), 4.12 (t, *J* = 7.8 Hz, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 19.4, 26.0, 26.4, 30.3, 30.4, 39.2, 42.4, 45.3, 60.6. **12**: a colorless oil. $[\alpha]_D^{24} +0.67$ (c 1.06, CHCl₃); IR (CHCl₃) cm⁻¹: 2956, 2857, 1717, 1471; ¹H-NMR (CDCl₃, 300 MHz): δ -0.06 (s, 6H), 0.78 (s, 9H),

1.4 (m, 1H), 1.56 (m, 1H), 1.8~2.0 (m, 5H), 2.2 (d, $J = 6.6$ Hz, 3H), 2.8 (m, 4H), 3.02 (s, 2H), 3.53 (m, 2H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ -5.3, 18.3, 21.6, 24.8, 25.9, 26.5, 26.6, 32.2, 41.5, 45.8, 50.4, 50.8, 61.1, 204.5. **14**: a colorless oil. $[\alpha]_{\text{D}}^{24} +8.53$ (c 0.55, CHCl_3); IR (CHCl_3) cm^{-1} : 3618, 2931, 1500, 1440; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.04 (d, $J = 6.6$ Hz, 3H), 1.50 (m, 2H), 1.69 (m, 1H), 1.80 (s, 3H), 1.85~2.10 (m, 6H), 2.31 (t, $J = 7.5$ Hz, 2H), 2.46 (t, $J = 7.5$ Hz, 2H), 2.70 (s, 2H), 2.72~3.0 (m, 4H), 3.70 (m, 2H), 5.30 (t, $J = 5.7$ Hz, 1H); 6.30 (s, 1H), 7.28 (s, 1H), 7.34 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 18.5, 22.7, 24.7, 24.9, 26.1, 26.6, 28.5, 41.7, 46.3, 49.7, 54.1, 60.8, 61.1, 110.9, 124.6, 130.5, 131.5, 138.8, 142.5.

Compound **1** (-)-Untenospongins C: a colorless oil. IR (CHCl_3) cm^{-1} : 3027, 1708, 1502, 1456; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.91 (d, $J = 5.7$ Hz, 3H), 1.58 (s, 3H), 2.05~2.46 (m, 9H), 3.02 (s, 2H), 5.26 (t, $J = 6.6$ Hz, 1H), 5.85 (dt, $J = 15.3, 7.3$ Hz, 1H), 6.20 (d, $J = 15.3$ Hz, 1H), 6.27 (s, 1H), 6.50 (s, 1H); 7.21 (s, 1H), 7.35 (s, 3H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 16.5, 19.9, 24.7, 28.5, 29.2, 40.2, 48.1, 54.5, 107.4, 110.9, 121.1, 124.2, 124.5, 128.1, 128.9, 129.6, 138.8, 139.5, 142.6, 143.3, 209.3. 4Z-isomer of **1**: a colorless oil. IR (CHCl_3) cm^{-1} : 3029, 1709, 1500; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.93 (d, $J = 6.0$ Hz, 3H), 1.59 (s, 3H), 2.05~2.50 (m, 9H), 3.01 (s, 2H), 5.26 (t, $J = 6.0$ Hz, 1H), 5.85 (dt, $J = 11.7, 6.0$ Hz, 1H), 6.20 (d, $J = 11.7$ Hz, 1H), 6.28 (s, 1H), 6.47 (s, 1H), 7.21 (s, 1H), 7.34 (s, 1H), 7.36 (s, 1H), 7.39 (s, 1H), 7.44 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 16.5, 19.9, 24.6, 28.4, 29.4, 35.9, 48.2, 54.5, 110.9, 110.9, 120.0, 122.4, 124.5, 129.6, 129.6, 138.8, 140.9, 140.9, 142.6, 142.6, 209.2.