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# SYNTHESIS OF (-)-UNTENOSPONGIN C, A $C_{21}$ FURANOTERPENE ISOLATED FROM THE OKINAWAN SPONGE *HIPPOSPONGIA* SP.

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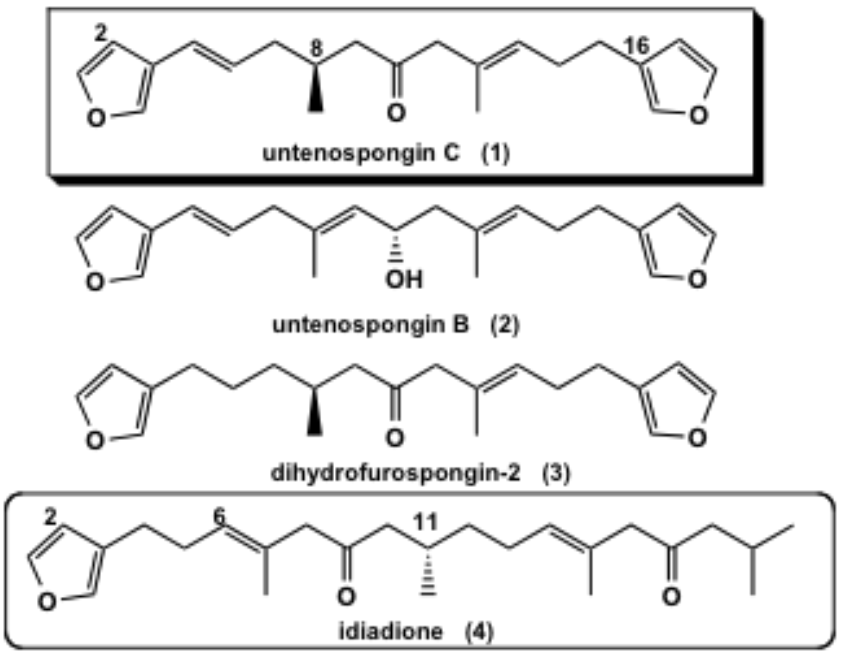
**Abstract** – Starting with (*R*)-(+)-citronellol (**5**), the first enantioselective synthesis of (-)-untenospongin C (**1**), a $C_{21}$ furanoterpene isolated from a marine sponge *Hippospongia* sp., has been achieved, the present synthesis indicating the absolute configuration of **1** as *S*.

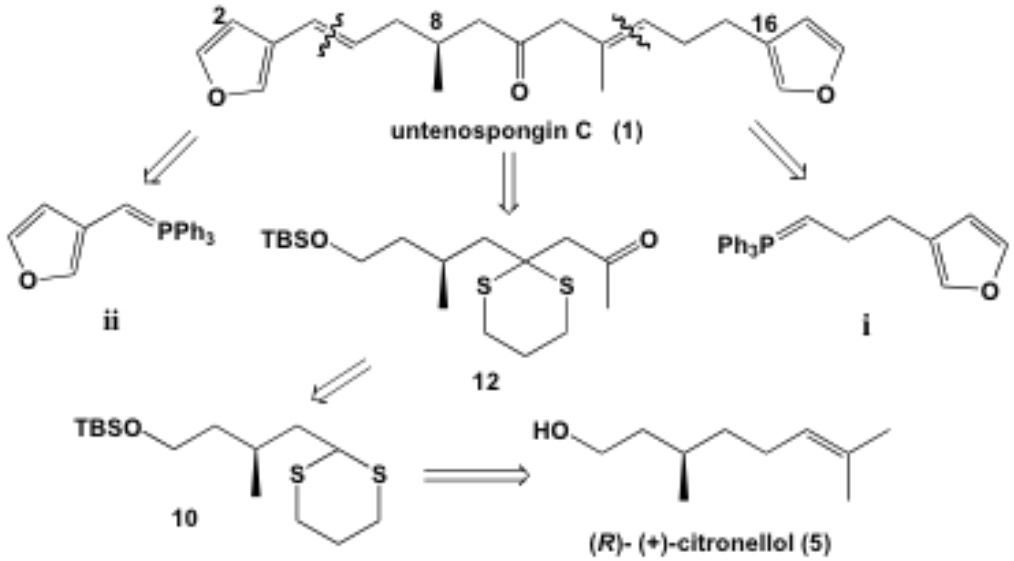
It is well-known that marine sponges are generally the source of unique and biologically active methabolites.[1] Many structurally related $C_{21}$ furanoterpenes have been isolated from several marine sponge genera, in which the linear $C_{21}$ furanoterpene untenospongin C (**1**), possessing cytotoxicity against murine lymphoma L1210 cell *in vitro* with the $IC_{50}$ value of 3.8 μg/ml, was isolated from the Okinawan marine sponge *Hippospongia* sp. in 1993 by Kobayashi *et al*.[2] More recently, untenospongin 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 untenospongin 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 dihydrofurospongin-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*)-(-)-untenospongin 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.



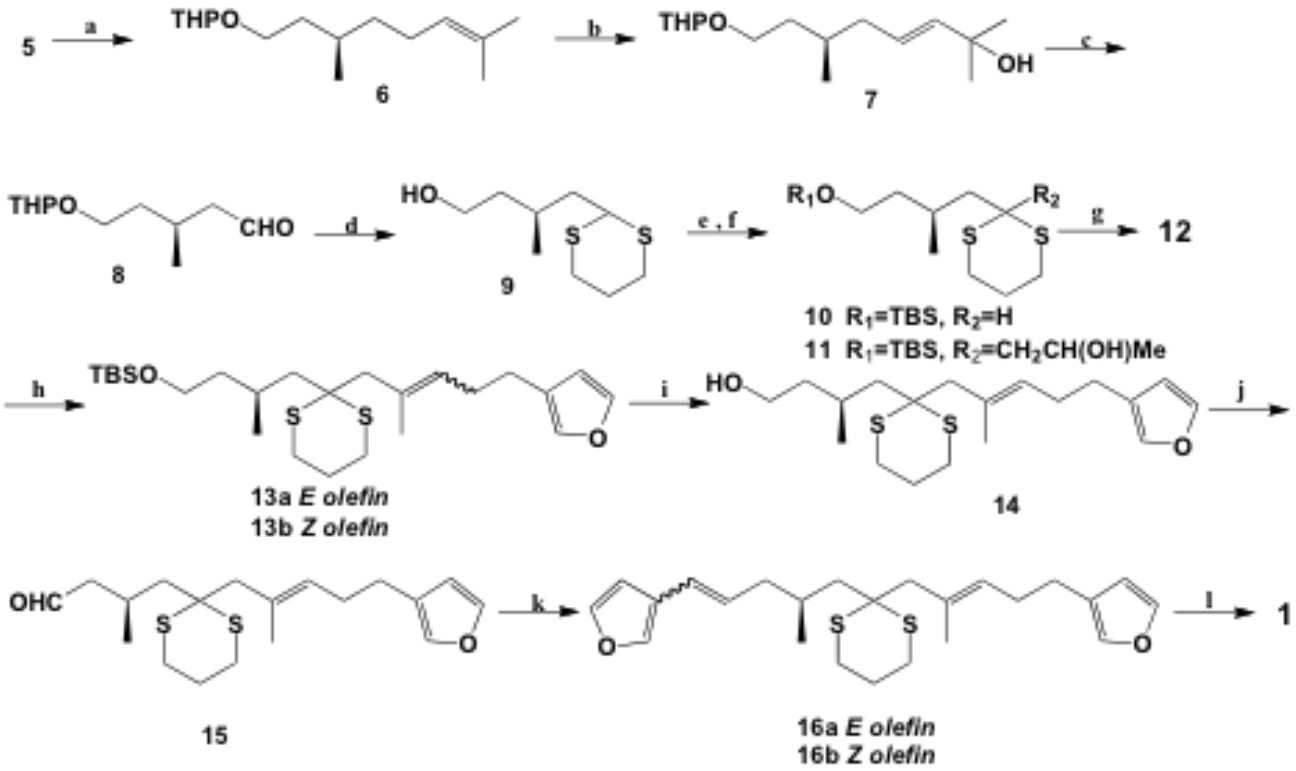

Scheme 1.

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 $BF_3 \cdot Et_2O$ 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 procedure[12] *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, $CH_2Cl_2$, quant.; (b) $Ph_2Se_2$, $H_2O_2$, $MgSO_4$, *t*-BuOOH, $CH_2Cl_2$, 83%; (c) $O_3$, $NaHCO_3$, $Me_2S$, $CH_2Cl_2$/MeOH; (d) 1,3-dithiane, $BF_3$-$Et_2O$, $CHCl_3$,66%; (e) TBSCl, imidazole, DMF, quant.; (f) *n*-BuLi, propyleneoxide, THF, 80%; (g) DMSO TFAA, $Et_3N$, $CH_2Cl_2$, 88%; (h) [3-(3'-furyl)propyl]triphenylphosphonium bromide, *n*-BuLi, THF, 31%; (i) TBAF,THF, 94%; (j) DMSO, TFAA, $Et_3N$, $CH_2Cl_2$, 58%; (k) 3-furylmetyltriphenylphosphonium bromide, *n*-BuLi, THF 83%; (l) $HgCl_2$, $CaCO_3$, MeCN/$H_2O$, 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 ylid **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 $HgCl_2$ and $CaCO_3$ in aqueous MeCN, followed by separation of the resulting mixture by preparative TLC (silica gel) to afford (-)-untenospongin C (**1**), $[\alpha]_D^{22}$ -9.46 (c 0.31, $CHCl_3$) {lit.,[2] $[\alpha]_D^{22}$ -9.3 (c 1.0, $CHCl_3$)} as the major product (35% yield) and 4*Z*-isomer of

**1**, $[\alpha]_D^{22}$ -8.58 (c 0.83, $CHCl_3$) as minor product (22% yield). The IR, $^1H$ and $^{13}C$ NMR of synthetic **1** were identical with those of an authentic sample.

In conclusion, we have accomplished the enantioselective total synthesis of (-)-untenospongin C (**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, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 3620, 3455, 2905, 1415; $^1H$-NMR ($CDCl_3$, 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); $^{13}C$-NMR ($CDCl_3$, 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, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 2956, 2857, 1717, 1471; $^1H$-NMR ($CDCl_3$, 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. $[\alpha]_D^{24}$ +8.53 (c 0.55, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 3618, 2931, 1500, 1440; $^1$H-NMR ($CDCl_3$, 300 MHz): δ 1.04 (d, *J* = 6.6Hz, 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** (-)-Untenospongin C: a colorless oil. IR ($CHCl_3$) $cm^{-1}$: 3027, 1708, 1502, 1456; $^1$H-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 ($CDCl_3$, 75MHz): 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. 4*Z*-isomer of **1**: a colorless oil. IR ($CHCl_3$) $cm^{-1}$: 3029, 1709, 1500; $^1$H-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 ($CDCl_3$, 75MHz): 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.