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 metabolites. Many structurally related C_{21} furanoterpenes have been isolated from several marine sponge genera, in which the linear C_{21} furanoterpene untenospongion 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.* More recently, untenospongion C (1) was isolated from the S. E. Queensland marine sponge *Coscinoderma mathewsi.* These structural elucidation of 1 was carried out by spectroscopic studies as well as in comparison with untenospongion B (2), 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). We have recently reported the enantioselective synthesis of the linear furanoesterterpene (-)-idiadione (4), isolated from marine sponge *Spongia idia*, in which we assigned (S)-configuration to the chiral center C(11). 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.

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% H₂O₂, Ph₂Se₂ and 70% t-BuOOH), 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 BF₃·Et₂O 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.

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

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

The ylid \textbf{ii} was prepared from 3-furylmethyltriphenylphosphonium bromide with \textit{n}-BuLi in THF according to the Katsumura procedure\cite{13}, and resulting THF solution of \textbf{ii} was reacted with \textbf{15} to give bisfurano compound \textbf{16} as a mixture of \textit{E-16a} and \textit{Z-isomer 16b} in ratio of 1.1 and 1.\cite{11} However, no effect was obtained on attempted Wittig-Schlosser method, providing a mixture of \textbf{16a} and \textbf{16b} in a ratio of 1.5 and 1. Finally, the mixture of \textbf{16a,b} was then hydrolyzed with HgCl\textsubscript{2} and CaCO\textsubscript{3} in aqueous MeCN, followed by separation of the resulting mixture by preparative TLC (silica gel) to afford (-)-untenospongin C (\textbf{1}), [\alpha]_D\textsuperscript{22} -9.46 (c 0.31, CHCl\textsubscript{3}) \{lit.;\cite{2} [\alpha]_D\textsuperscript{22} -9.3 (c 1.0, CHCl\textsubscript{3})\} as the major
product (35% yield) and 4Z-isomer of 1, [α]_D^{22} -8.58 (c 0.83, CHCl_3) 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 (-)-untenospongins 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.

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REFERENCES AND NOTES

11. Assignment of geometry and the ratio were obtained from ^1H-NMR studies.
14. Spectral data of compound 9: a colorless oil. [α]_D^{22}+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); ^13C-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. [α]_D^{22}+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, $J = 6.6$ 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 (-)-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. 4Z-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.