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

Yoshihiro Noda,* Shuji Ugajin, Akihiko Yamanaka, and Natsuki Mamiya

Department of Chemical Biology and Applied Chemistry, College of Engineering
Nihon University. Tamura-machi Koriyama Fukushima, 963-8642, Japan
e-mail:noda@chem.ce.nihon-u.ac.jp

Abstract – Starting with (R)-(+-)citronellol (5), the first enantioselective synthesis of (-)-utenospongin 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. 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. More recently, untenospongin 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 untenospongin 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).\textsuperscript{5}

We have recently reported the enantioselective synthesis of the linear furanosesterpene (-)-idiadione (4),\textsuperscript{6} isolated from marine sponge \textit{Spongia idia}, in which we assigned (S)-configuration to the chiral center C(11).\textsuperscript{2} As part of synthetic study on marine natural product, the present paper describes the first enantioselective total synthesis of (S)-(−)-untenospongien 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.

\begin{center}
\includegraphics[width=\textwidth]{scheme1.png}
\end{center}

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\textsubscript{2}O\textsubscript{2}, Ph\textsubscript{2}Se\textsubscript{2} and 70% t-BuOOH),\textsuperscript{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\textsubscript{3}·Et\textsubscript{2}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.\textsuperscript{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,\textsuperscript{10} followed by addition of 12 at 0 °C furnished 31% yield of E-13a and Z-olefin 13b (ratio: 4.8:1).\textsuperscript{11} Fortunately, Wittig-Schlosser procedure\textsuperscript{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](image)

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,\textsuperscript{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.\textsuperscript{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\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 (1), [\(\alpha\)]\textsubscript{D}\textsuperscript{22} -9.46 (c 0.31, CHCl\textsubscript{3}) \{lit.,\textsuperscript{2} [\(\alpha\)]\textsubscript{D}\textsuperscript{22} -9.3 (c 1.0, CHCl\textsubscript{3})\} as the major product (35% yield) and 4Z-isomer of...
I, $[\alpha]_D^{22} -8.58$ (c 0.83, CHCl$_3$) as minor product (22% yield). The IR, $^1$H and $^{13}$C NMR of synthetic I 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 I by a synthetic means.

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REFERENCES AND NOTES

11. Assignment of geometry and the ratio were obtained from $^1$H-NMR studies.
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; $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 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): $\delta$ 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; $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ -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): $\delta$ -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): $\delta$ 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): $\delta$ 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 (-)-Untenospongion C: a colorless oil. IR (CHCl$_3$) cm$^{-1}$: 3027, 1708, 1502, 1456; $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 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): $\delta$ 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 I: a colorless oil. IR (CHCl$_3$) cm$^{-1}$: 3029, 1709, 1500; $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 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): $\delta$ 16.5, 19.9, 24.6, 28.4, 29.4, 35.9, 48.2, 54.5, 110.9, 120.0, 122.4, 124.5, 129.6, 129.6 138.8, 140.9, 140.9, 142.6, 142.6, 209.2.