A highly convergent enantioselective total synthesis of marine natural product, furanoterpene

Toshikazu Bando and Kozo Shishido*†

Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

The enantioselective total convergent synthesis of marine furanoterpene 1 is achieved and the absolute configuration of the only existing quaternary stereogenic centre is found to be *S*.

The structurally unique C_{21} furanoterpene **1**, isolated by Kobayashi and co-workers from an Arabian Sea sponge *Fasciospongia cavernosa* in 1992[1] along with a presumed biogenetic precursor 12,13-didehydrofurospongin-1 **2**,‡ contains a 4*H*-cyclohexa[*b*]furan moiety and a 3-monosubstituted furan group connected by a heptadienyl carbon tether. The absolute configuration of the quaternary stereogenic centre (C_{13}) remains to be determined. Because of the structural and biogenetic similarity between **1** and the marine sesterterpene hippospongin[2a] (Okinonellin A[2b]), which inhibits the growth of the Gram-positive bacterium *Bacillus Subtillis*, the cell division of starfish embryos and exhibits antispasmodic activity, the development of an efficient and enantioselective synthesis of **1** has significant value.

We now report a highly convergent and enantioselective total synthesis of **1**, thereby establishing its absolute stereochemistry, based on the fused furan construction methodology recently developed in our laboratories.[3]

The synthetic strategy required the preparation of the configurationally defined enantiopure left-hand segment (C_{11}–C_{21}) **3** and the right-hand segment (C_1–C_{10}) **4**, combining the two fragments through an acetylenic alkylation to provide a penultimate intermediate **5**, and concluding with a reduction of the triple bond to give **1**, Scheme 1.

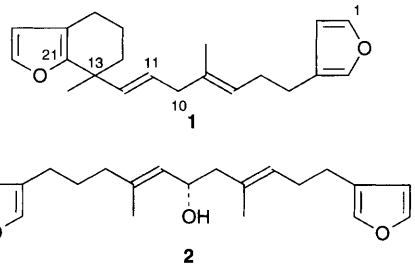
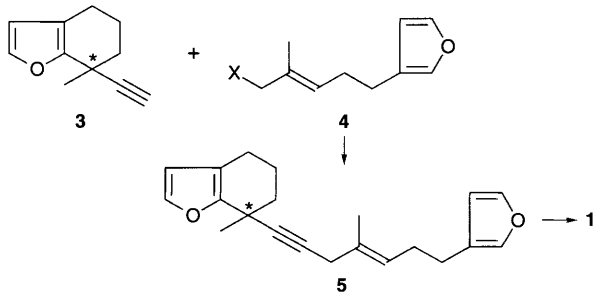
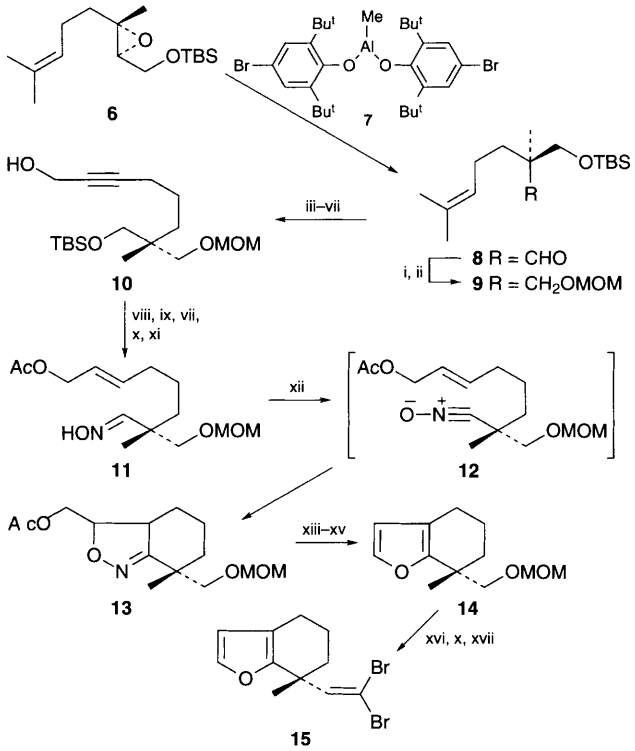


Fig. 1



Scheme 1

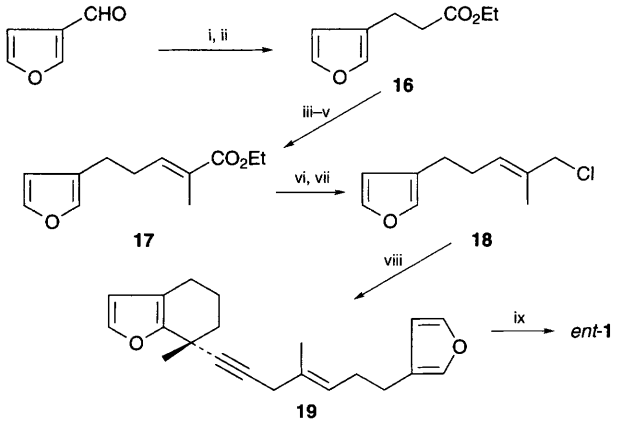
The synthesis of the optically active furan **15**, the precursor of **3**, is summarized in Scheme 2. A key element of the approach involves the introduction of chirality at an early stage into the quaternary stereogenic centre at the future C_{13} employing the organoaluminum-promoted rearrangement developed by Yamamoto.[4] Thus, treatment of the optically active epoxy silyl ether **6**, derived from the Sharpless asymmetric epoxidation of geraniol using L-(+)-diethyl tartrate followed by silylation, with methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) **7** provided the (*S*)-aldehyde **8** in 97% yield and 95% ee. Reduction of **8** with $NaBH_4$, protection of the primary alcohol as the MOM ether and ozonolysis followed by reductive work-up of the resulting **9** afforded the alcohol which was then converted into the corresponding iodide. Alkylation of the lithium acetylide of the protected prop-2-ynyl alcohol with the iodide and subsequent selective removal of the primary TBS



Scheme 2 *Reagents and conditions*: i, $NaBH_4$, MeOH, room temp., 97%; ii, MOMCl, Pr^i_2NEt, 4-DMAP, room temp. 94%; iii, O_3, CH_2Cl_2, −78 °C then $NaBH_4$, 0 °C, 93%; iv, *p*-TsCl, Et_3N, 4-DMAP, CH_2Cl_2, room temp. 100%; v, NaI, acetone, reflux, 92%; vi, $HC{\equiv}CCH_2OTBS$, BuLi, HMPA, THF, −78 °C, 91%; vii, Bu_4NF, THF, room temp., 87%; viii, $LiAlH_4$, THF, 0 °C; ix, Ac_2O, pyridine, room temp., 79% for 2 steps; x, Swern oxidation, CH_2Cl_2, −78 °C; xi, $NH_2OH{\cdot}HCl$, AcONa, MeOH, room temp., 91% for 2 steps; xii, 7% aq. NaOCl, CH_2Cl_2, room temp., 93%; xiii, $LiOH{\cdot}H_2O$, THF, H_2O, room temp.; xiv, H_2 (2 kg cm^{-2}), Raney Ni, $(MeO)_3B$, MeOH, H_2O, room temp.; xv, *p*-TsOH, CH_2Cl_2, room temp., 81% for 3 steps; xvi, *c* HCl, MeOH, 60 °C, 97%; xvii, Ph_3P, CBr_4, CH_2Cl_2, 0 °C, 95% for 2 steps

ether produced **10**, $[\alpha]_D$ +3.33 (*c* 2.10, $CHCl_3$), in 68% overall yield from **8**.

Reduction of **10** with $LiAlH_4$, followed by acetylation of the resulting *trans*-allyl alcohol and desilylation produced the neopentyl alcohol, which led to the formation of oxime **11** by Swern oxidation and subsequent condensation of the aldehyde and hydroxylamine. The stage was now set to explore the crucial construction of the bicyclic fused furan moiety *via* an intramolecular [3 + 2] dipolar cycloaddition[5] and complete the skeletal assembly of the left-hand segment. Oxidation of **11** with 7% aqueous NaOCl[6] gave, *via* the nitrile oxide **12**, isoxazoline **13**,§ which was sequentially hydrolysed, exposed to reductive hydrolysis conditions,[7] and briefly treated with a catalytic amount of toluene-*p*-sulfonic acid to afford 4*H*-cyclohexa[*b*]furan **14** in 75% overall yield from **11**. One carbon elongation was then achieved by successive acid hydrolysis, Swern oxidation and dibromoalkenation to give **15**, the precursor of the left-hand segment. Allyl chloride **18** was readily prepared from 3-furaldehyde as summarized in Scheme 3. Wittig alkenation and subsequent chemoselective reduction of the double bond with sodium hydrotelluride[8] furnished **16**, which was smoothly transformed, *via* **17**, into **18** as shown in Scheme 3. The total synthesis of **1** was efficiently completed from the optically active fused furan part **15** and allyl chloride **18**. Treatment of dibromide **15** with BuLi in THF–HMPA at −78 °C, followed by addition of **18** at the same temperature yielded the coupled ene-yne **19**.¶ The crude intermediate was immediately reduced with lithium in ammonia at −78 °C to give **1**, $[\alpha]_D$ −9.6 (*c* 0.50, $CHCl_3$),‖ in 27% overall yield based on **15**. ^1H and ^{13}C NMR, and mass spectral data as well as the TLC properties of synthetic **1** were indistinguishable from those of the natural product except for the sign of the optical rotation, $[\alpha]_D$ +5 (*c* 0.88, $CHCl_3$).[1]



Scheme 3 *Reagents and conditions*: i, $Ph_3P{=}CHCO_2Et$, benzene, reflux, 100%; ii, Te, $NaBH_4$, EtOH, 0 °C, 72%; iii, $LiAlH_4$, THF, room temp., 84%; iv, Swern oxidation, CH_2Cl_2, −78 °C; v, $Ph_3P{=}C(Me)CO_2Et$, benzene, 70 °C, 86% for 2 steps; vi, Bu^i_2AlH, CH_2Cl_2, −78 °C, 92%; vii, Ph_3P, CCl_4, CH_2Cl_2, reflux, 95%; viii, **15**, BuLi, HMPA, THF, −78 °C then add **18**; ix, Li, liq. NH_3, −78 °C, 27% for 2 steps

This investigation was financially supported by a Grant-in-Aid for Scientific Research (No. 04671295) from the Ministry of Education, Science and Culture, Japan. We are grateful to Dr Masaru Kobayashi (Hokkaido University) for providing a sample and ^1H NMR spectra of natural product **1**. Professor Hisashi Yamamoto (Nagoya University) for providing valuable information about the use of the organoaluminum-promoted rearrangement and Professor Nagao Kobayashi (Tohoku University) for his helpful discussions about CD spectra.

Footnotes

† E-mail: shishido@ph.tokushima-u.ac.jp

‡ Based on the chemical conversion of **2** into **1** by acid, Kobayashi and Sarma suggest that at least a portion of **1** may be an artefact formed from **2** during the isolation process.

§ This was obtained as an inseparable 1 : 1 mixture of two diastereoisomers.

¶ *Selected spectroscopic data* for **19**, Pale yellow oil; $[\alpha]_D$ −1.58 (*c* 0.63, chloroform); δ_H (200 MHz, $CDCl_3$) 1.52 (3 H, s), 1.61 (3 H, br s), 1.76 (4 H, m), 2.28 (2 H, m), 2.44 (4 H, m), 2.85 (2 H, s), 5.43 (1 H, br t), 6.17 (1 H, d, *J* 2.0 Hz), 6.28 (1 H, br s), 7.21 (1 H, br s), 7.26 (1 H, br s) and 7.33 (1 H, t, *J* 1.7 Hz); δ_C (100 MHz, $CDCl_3$) 16.2, 20.8, 22.4, 24.8, 27.2, 28.4, 28.7, 32.1, 39.7, 77.9, 87.2, 110.3, 111.1, 115.9, 124.8, 124.8, 124.8, 131.2, 138.9, 140.8, 142.5 and 152.7; MS *m/z* (EI) 294 (M^+); HRMS (EI) calcd for $C_{21}H_{24}O_2$ 308.1776. found: *m/z* 308.1752.

‖ The CD spectra of synthetic and natural **1** displayed a positive Cotton effect at 222 nm ($\Delta\varepsilon$ = +6.7) and a negative one at 222 nm ($\Delta\varepsilon$ = −2.1), respectively. These results and the value of optical rotations indicated that a partial racemization has taken place in the natural product.

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Received, 2nd April 1996; Com. 6/02300B