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

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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 1992¹ 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.



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 silvlation, 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 NaBH₄, protection of the primary alcohol as the MOM ether and ozonolysis followed by reductive workup 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, NaBH₄, MeOH, room temp., 97%; ii, MOMCl, Prⁱ₂NEt, 4-DMAP, room temp. 94%; iii, O₃, CH₂Cl₂, -78 °C then NaBH₄, 0 °C, 93%; iv, *p*-TsCl, Et₃N, 4-DMAP, CH₂Cl₂, room temp. 100%; v, Nal, acetone, reflux, 92%; vi, HC=CCH₂OTBS, BuLi, HMPA, THF, -78 °C, 91%; vii, Bu₄NF, THF, room temp., 87%; viii, LiAlH₄, THF, 0 °C; ix, Ac₂O, pyridine, room temp., 79% for 2 steps; x, Swern oxidation, CH₂Cl₂, -78 °C; xi, NH₂OH·HCl, AcONa, MeOH, room temp., 91% for 2 steps; xii, 7% aq. NaOCl, CH₂Cl₂, room temp., 93%; xiii, LiOH·H₂O, THF, H₂O, room temp.; xiv, H₂ (2 kg cm⁻²), Raney Ni, (MeO)₃B, MeOH, H₂O, room temp.; xv, *p*-TsOH, CH₂Cl₂, room temp., 81% for 3 steps; xvi, *c* HCl, MeOH, 60 °C, 97%; xvii, Ph₃P, CBr₄, CH₂Cl₂, 0 °C, 95% for 2 steps

ether produced 10, $[\alpha]_D$ +3.33 (*c* 2.10, CHCl₃), in 68% overall yield from 8.

Reduction of 10 with LiAlH₄, 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 cycloaddition⁵ and complete the skeletal assembly of the left-hand segment. Oxidation of 11 with 7% aqueous NaOCl⁶ 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 4Hcyclohexa[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 hydrotelluride⁸ 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 19.9 The crude intermediate was immediately reduced with lithium in ammonia at $-78 \,^{\circ}$ C to give 1, $[\alpha]_{D} - 9.6 (c \, 0.50, \text{CHCl}_{3})$, in 27% overall yield based on 15. ¹H and ¹³C NMR, and mass spectral data as well as the TLC properties of synthetic 1 were indistinguishable



Scheme 3 Reagents and conditions: i, $Ph_3P=CHCO_2Et$, benzene, reflux, 100%; ii, Te, NaBH₄, EtOH, 0 °C, 72%; iii, LiAlH₄, THF, room temp., 84%; iv, Swem oxidation, CH_2Cl_2 , -78 °C; v, $Ph_3P=C(Me)CO_2Et$, benzene, 70 °C, 86% for 2 steps; vi, Bu¹₂AlH, CH₂Cl₂, -78 °C, 92%; vii, Ph_3P , CCl₄, CH₂Cl₂, reflux, 95%; viii, **15**, BuLi, HMPA, THF, -78 °C then add **18**; ix, Li, liq. NH₃, -78 °C, 27% for 2 steps

from those of the natural product except for the sign of the optical rotation, $[\alpha]_D$ +5 (c 0.88, CHCl₃).¹

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Footnotes

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[‡] 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.

 $\begin{aligned} & \text{[Selected spectroscopic data for 19, Pale yellow oil; [$\alpha]_D$ $-1.58 (c 0.63, chloroform); δ_H (200 MHz, CDCl_3) 1.52 (3 H, s), 1.61 (3 H, br s), 1.76 (4 H, m), 2.28 (2 H, m), 2.44 (4 H, m), 2.85 (2 H, s), 5.43 (1 H, br t), 6.17 (1 H, d, J 2.0 Hz), 6.28 (1 H, br s), 7.21 (1 H, br s), 7.26 (1 H, br s) and 7.33 (1 H, t, J 1.7 Hz); δ_C (100 MHz, CDCl_3) 162, 20.8, 22.4, 24.8, 27.2, 28.4, 28.7, 32.1, 39.7, 77.9, 87.2, 110.3, 111.1, 115.9, 124.8, 124.8, 124.8, 131.2, 138.9, 140.8, 142.5 and 152.7; MS m/z (EI) 294 (M^+); HRMS (EI) calcd for C_{21}H_{24}O_2 308.1776. found: m/z 308.1752. \end{aligned}$

|| 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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