

First Total Synthesis of Symbioramide, a Novel Ca^{2+} -ATPase
Activator from *Symbiodinium* sp.

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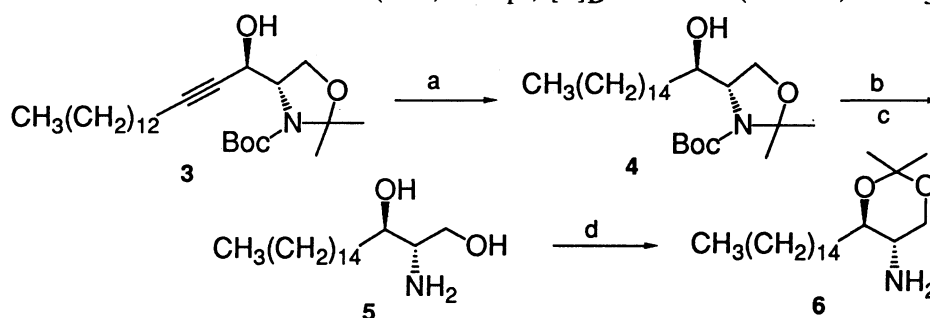
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The first total synthesis of symbioramide (**1**) is described and
simultaneously established the complete stereostructure of **1** to be
(2*S*,3*R*,2'*R*,3'*E*)-*N*-(2'-hydroxy-3'-octadecenoyl)-dihydrosphingosine.

Considerable interest has recently been focused on the bioactive ceramides which are the important constituents of sphingolipids distributed widely in biological membranes.¹⁾ Symbioramide **1**, a novel ceramide, obtained from the cultured dinoflagellate *Symbiodinium* sp., isolated from the inside of gill cells of the Okinawa bivalve *Fragum* sp., is the first example of SR Ca^{2+} -ATPase activator of marine origin and also exhibits antileukemic activity.²⁾

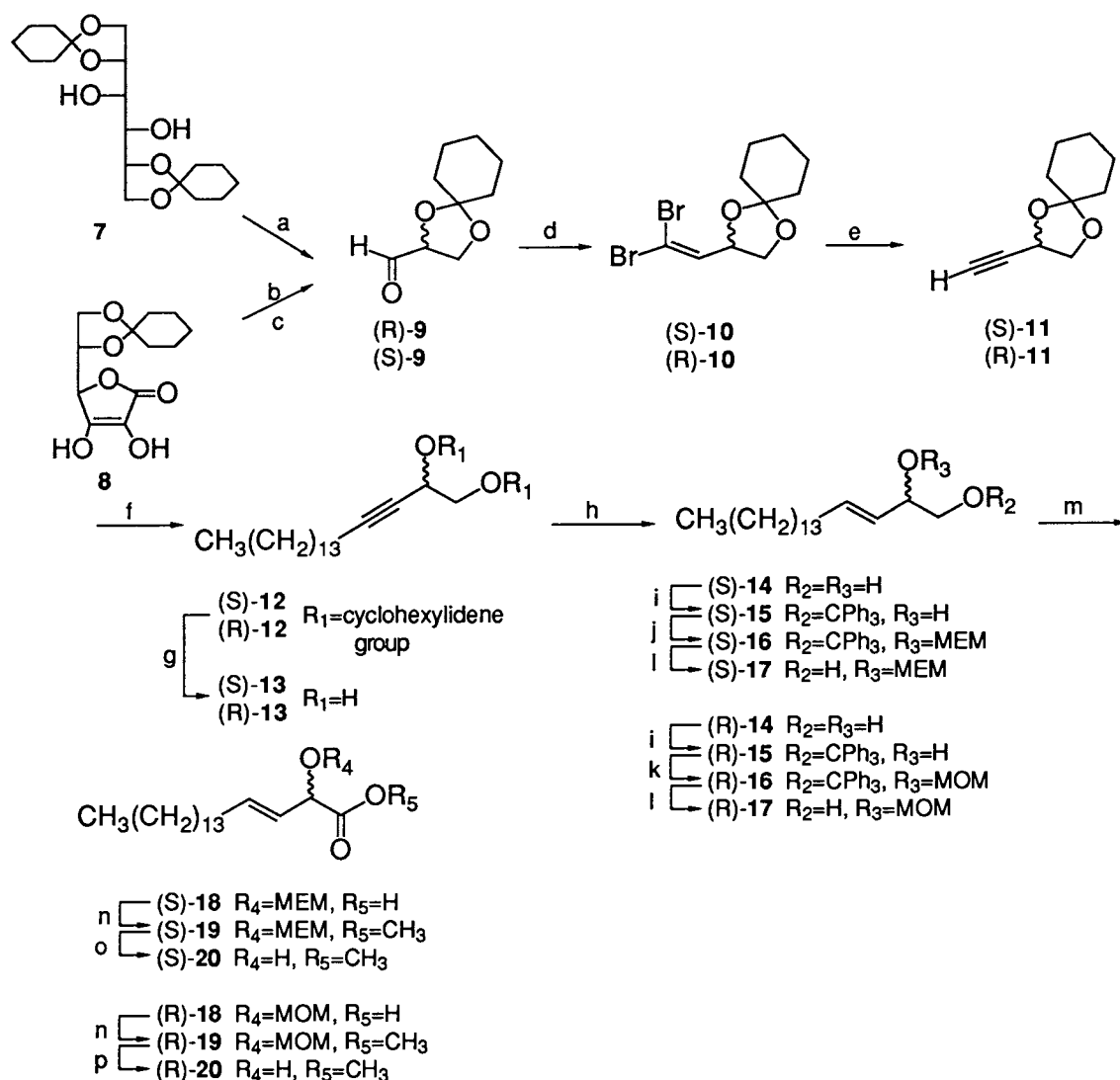
In connection with our synthetic studies on sphingolipids,³⁾ this compound attracted our attention both as a synthetic target and as its biological interest. In addition, a total synthesis of **1** would firmly establish the chemical structure of this compound, especially regarding the stereochemistry of the 2'-hydroxyl group. We now wish to report the first total synthesis of **1**.

D-Erythro-dihydrosphingosine **5** was readily prepared by catalytic hydrogenation of **3** ($[\alpha]_{\text{D}}^{21} -41.3^\circ$ (*c* 2.685, CHCl_3)), obtained from L-serine,⁴⁾ followed by deprotection, which without isolation was converted to the acetone **6** (80%, 4 steps, $[\alpha]_{\text{D}}^{22} +29.5^\circ$ (*c* 1.178, CHCl_3)) (Scheme 1).



Scheme 1. a) H_2 , PtO_2 , AcOEt , room temp, 1 h; b) TsOH , MeOH , room temp, 4 h; c) Ac_2O , AcOEt , room temp, 25 min; d) CSA , $(\text{CH}_3\text{O})_2\text{C}(\text{CH}_3)_2$, reflux, 1 h.

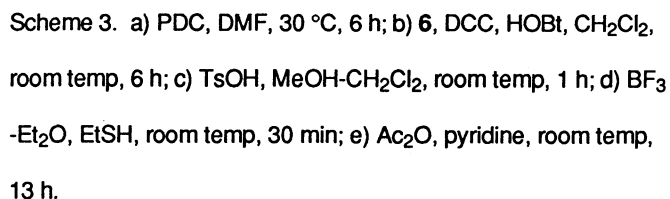
Our effort was then concentrated on the synthesis of the unusual fatty acid methyl ester (*S*)-**20** and (*R*)-**20**, starting with readily accessible aldehyde (*R*)-**9** and L-ascorbic acid derivative **8**, respectively (Scheme 2). To this goal, the enantiomerically pure aldehyde (*R*)-**9**, obtained by NaIO_4 oxidation of dicyclohexylidene-D-mannitol **7**,⁵⁾ was converted into the corresponding



Scheme 2. a) NaIO_4 , $n\text{-Bu}_4\text{NBr}$, $\text{Et}_2\text{O-H}_2\text{O}$, room temp, 3 h; b) LiAlH_4 , THF, reflux, 2 h; c) NaIO_4 , THF- H_2O , 0 °C, 2 h; d) Ph_3P , CBr_4 , CH_2Cl_2 , 0 °C, 20 min; e) $n\text{-BuLi}$, THF, -78 °C, 1 h, then 0 °C, 1 h; f) (i) $n\text{-BuLi}$, THF, -78 °C, then 0 °C, 1 h, (ii) $\text{CH}_3(\text{CH}_2)_{13}\text{OTs}$, THF-HMPA, -78 °C, then room temp, 2 h; g) dHCl , EtOH, reflux, 4 h; h) LiAlH_4 , $\text{CH}_3\text{O}(\text{CH}_2)_2\text{OCH}_3$, reflux, 3 h; i) Ph_3CCl , DMAP, pyridine, 100 °C, 2 h; j) MEMCl , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , room temp, 18 h; k) MOMCl , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , reflux, 30 min; l) TsOH , $\text{MeOH-CH}_2\text{Cl}_2$, room temp, 40 min; m) PDC , DMF, 40-50 °C, 3 h; n) CH_3I , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , room temp, 15 h; o) ZnBr_2 , CH_2Cl_2 , reflux, 8 h; p) $\text{BF}_3\text{-Et}_2\text{O}$, EtSH, room temp, 40 min.

olefin (S)-10 ($[\alpha]_{\text{D}}^{23} -5.23^\circ$ (c 0.968, CHCl_3)). Treatment of (S)-10 with $n\text{-BuLi}$ provided the alkyne (S)-11 ($[\alpha]_{\text{D}}^{24} +39.3^\circ$ (c 0.890, CHCl_3)) which was alkylated to afford (S)-12 (47%, 2 steps,

Finally, the coupling reaction of (R)-18 with 6 led to the formation of the amide 21. Deprotection of the acetonide and the alcohol function was achieved selectively by treatment with TsOH-MeOH followed by BF₃-Et₂O-EtSH to give symbioramide 1 (24% from (R)-17, mp 112-113 °C (benzene/acetone), [α]_D¹⁹ +2.65° (c 0.378, CHCl₃)). Acetylation of 1 gave the triacetate 2 (97%, mp 75-78 °C) (Scheme 3). The spectral data (IR, NMR, mass) of synthetic 1 and 2 were identical with those of natural product and its triacetate, respectively (Table 1).²⁾



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Table 1. Spectral data for **1**, **2**, and (R)-**20**

1: IR (KBr): ν [cm⁻¹] = 3300, 1640, 1530, 1460, and 1060. ¹H NMR (500 MHz, CDCl₃): δ = 7.02 (d, J=7.69 Hz, 1H; NH, exch.), 5.90 (dt, J=14.3, 7.0 Hz, 1H; H-4'), 5.56 (dd, J=15.3, 7.3 Hz, 1H; H-3'), 4.53 (dd, J=7.15, 3.58 Hz, 1H; H-2'), 4.03 (dt, J=11.6, 3.58 Hz, 1H; H-1), 3.83-3.76 (m, 3H; H'-1, H-2, and H-3), 3.15 (d, J=3.3 Hz, 1H; OH-2', exch.), 2.64 (br.s, 1H; OH-1, exch.), 2.51 (d, J=6.04 Hz, 1H; OH-3, exch.), 2.08 (q like, 2H; H₂-5'), 1.55-1.50 (m, 2H; H₂-4), 1.41-1.36 (m, 2H; H₂-6'), 1.31-1.26 (m, 48H), 0.88 (t, J=6.88 Hz, 6H; H₃-18 and H₃-18'). EIMS: m/z 581 (M^+ , 1.23%), 328 (40.22), 253 (45.87), 43 (100). (Found: C, 74.51; H, 12.29; N, 2.36. C₃₆H₇₁O₄N requires C, 74.30; H, 12.30; N, 2.41%)

2: IR (KBr): ν [cm⁻¹] = 3300, 1730, 1660, 1540, 1460, and 1030. ¹H NMR (500 MHz, CDCl₃): δ = 6.52 (d, J=8.8 Hz, 1H; NH), 5.90 (dt, J=14.6, 7.0 Hz, 1H; H-4'), 5.52 (dd, J=15.4, 7.15 Hz, 1H; H-3'), 5.49 (d, J=7.15 Hz, 1H; H-2'), 4.90 (dt, J=8.25, 4.95 Hz, 1H; H-3), 4.38-4.33 (m, 1H; H-2), 4.31 (dd, J=11.27, 6.87 Hz, 1H; H-1), 4.04 (dd, J=11.27, 3.29 Hz, 1H; H'-1), 2.18 (s, 3H; Ac), 2.07 (s, 3H; Ac), 2.04 (s, 3H; Ac), 2.08-2.04 (m, 2H; H₂-5'), 1.62-1.57 (m, 2H; H₂-4), 1.39-1.35 (m, 2H; H₂-6'), 1.31-1.25 (m, 48H), 0.88 (t like, 6H; H₃-18 and H₃-18'). EIMS: m/z 708 (M^+ , 1.00%), 707 (M^+ -H, 2.29), 648 (M^+ -AcOH, 19.69), 370 (100).

(R)-**20**: IR (KBr): ν [cm⁻¹] = 3350, 1760, 1470, and 970. ¹H NMR (500 MHz, CDCl₃): δ = 5.88 (dt, J=15.4, 6.87 Hz, 1H; H-4), 5.50 (dd, J=15.4, 6.33 Hz, 1H; H-3), 4.61 (t, J=6.05 Hz, 1H; H-2), 3.80 (s, 3H; CO₂Me), 2.83 (d, J=5.77 Hz, 1H; OH, exch.), 2.06 (q like, 2H; H₂-5), 1.40-1.37 (m, 2H; H₂-6), 1.31-1.26 (m, 22H), 0.88 (t, J=6.88 Hz, 3H; H₃-18). EIMS: m/z 312 (M^+ , 0.86%), 253 (M^+ -CO₂Me, 100).

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- 7) The low $[\alpha]_D$ value ($[\alpha]_D^{28} -16^\circ$ (c 1, CHCl₃)) of **20** obtained from **12**) may due to the partial epimerization at C-2' or the impurity.

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