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Total Synthesis of the C37-C45 F-Ring Fragment of Spongistatins

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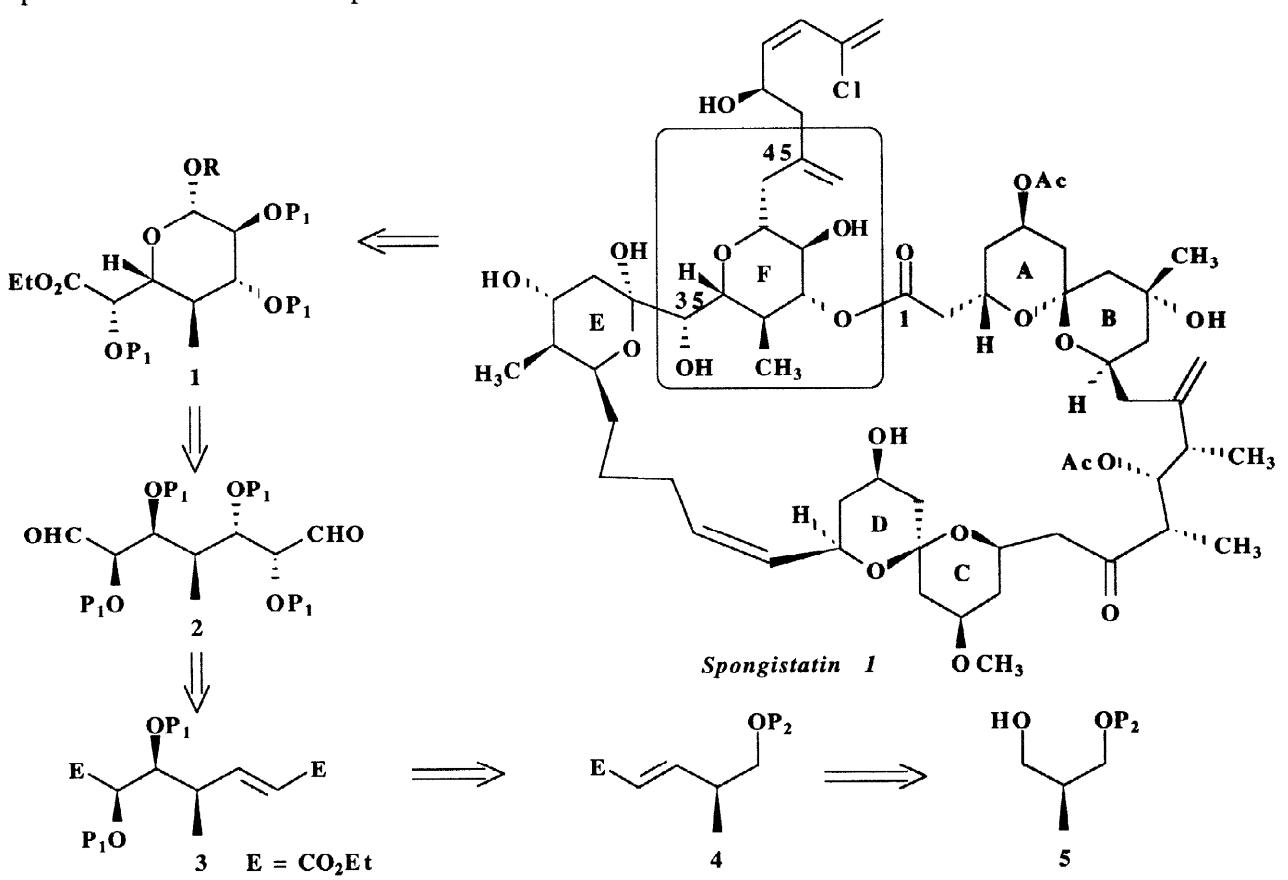
Abstract : The highly substituted F ring of Spongistatins was synthesized from (*R*)-(+)-3-benzyloxy-2-methylpropan-1-ol (**5**), using two sequential Sharpless dihydroxylations as key-steps. A 4-deoxy-4-methyl-D-*threo*-L-*gluco*heptopyranose derivative was obtained and could be used to generate the corresponding allyl ß-C-glycoside. © 1998 Elsevier Science Ltd. All rights reserved.

Following the recent isolation and structural elucidation of Spongistatins,[1] which displayed remarkable growth inhibitory activity against several chemoresistant cancer cells,[2] many research groups have been focused on the development of a synthetic route to these marine macrolides. Due to their very low natural abundance, the design of a total synthesis of these compounds is required for further biological evaluation and medicinal exploitation of their antimitotic potential.

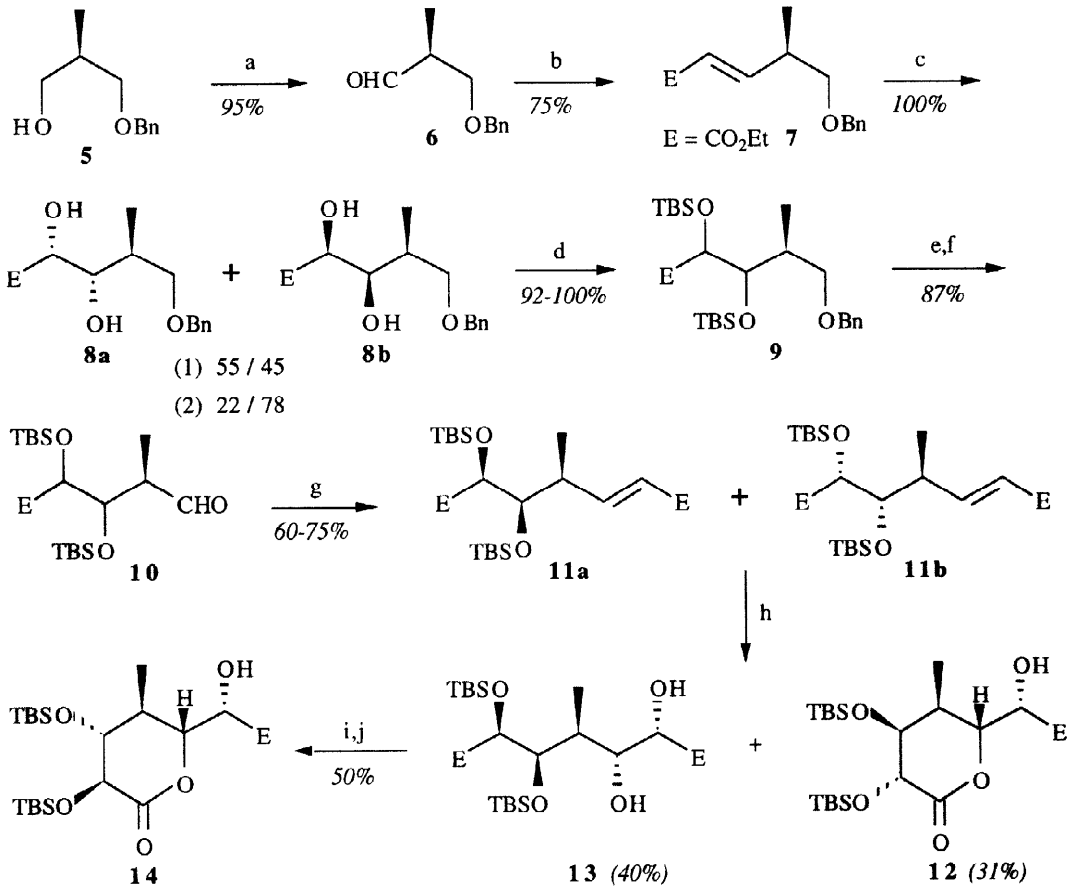


Scheme 1

PII: S0040-4039(97)10817-6

Spongistatins consist of 42-membered macrocyclic lactones (Scheme 1), possessing complex structural features such as two spiroacetal units (AB and CD), ulose and C-pyranoside rings (E and F) and triene side chains.

Seminal achievements were reported on the synthesis of the spiroacetal subunits[3] and more recently, Paterson[4] described the construction of the highly functionalized C_{36}-C_{46} fragment. In this paper, we wish to present a new stereocontrolled approach to a 4-deoxy-4-methyl-D-*threo*-L-*gluco*heptopyranose derivative that constitute the C_{37}-C_{45} fragment of Spongistatins, containing the F ring. Our retrosynthetic analysis was based on the selective cyclization of tetraol **2** which should lead to the hemiacetal **1** with all equatorial substituents. The linear precursor **2** should be obtained by two sequential and stereoselective dihydroxylations, the monoprotected diol **5** being the precursor for this two directional chain elongation. Our synthesis of the F pyranoside fragment is summarized in Scheme 2.



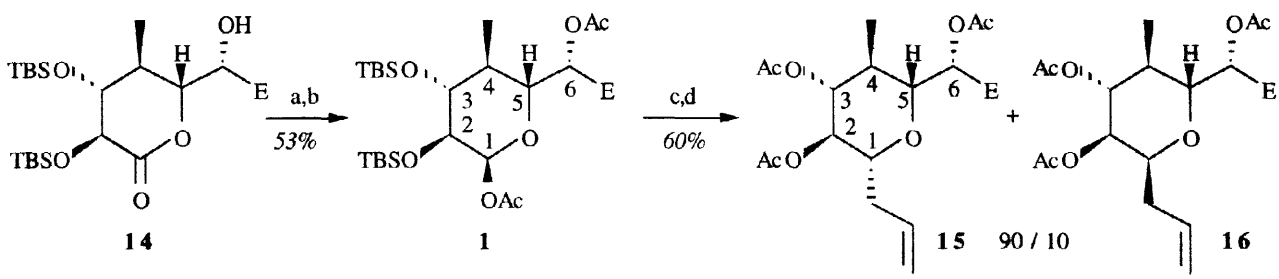
(a) PCC 1.5 eq, CH_2Cl_2, RT, 5h; (b) $(EtO)_2P(O)CH_2CO_2Et$ 1.6 eq, NaH 1.5 eq, THF, -78°C, 10 min; (c) (1) OsO_4 1.5%, NMO 1.5 eq, 0°C-->RT, 10h; (2) $K_2OsO_2(OH)_4$ 1%, $(DHQD)_2PHAL$ 5%, $K_3Fe(CN)_6$ 3 eq, K_2CO_3 3 eq, $MeSO_2NH_2$ 1 eq, ^tBuOH / H_2O (1/1), RT, 24h; (d) TDBMSOTf 3 eq, 2,6-lutidine 5 eq, CH_2Cl_2, 0°C-->RT; (e) H_2, Pd/C, MeOH, RT; (f) Dess-Martin periodinane 1.8 eq, CH_2Cl_2, RT, 3h; (g) $(EtO)_2P(O)CH_2CO_2Et$ 1.8 eq, NaH 1.7 eq, THF, -78°C, 5 min; (h) OsO_4 6% NMO 2.2 eq, acetone / H_2O, RT, 18h; (i) HF(aq) / MeCN (5 / 95), 10h; TBDMSOTf 4 eq; 2,6-lutidine 6 eq, CH_2Cl_2, 0°C-->RT.

Scheme 2

The starting (*R*)-(+)-3-benzyloxy-2-methylpropan-1-ol **5** was prepared by enzymatic resolution, as reported by Santaniello[5] with 90% ee. After quantitative oxidation of the primary alcohol, a Wittig-Horner reaction with triethylphosphonoacetate provided the α,ß-unsaturated ester **7** in 75% yield.

Treatment with a catalytic amount of OsO_4 in the presence of NMO[6] afforded a 55 : 45 mixture of diols **8a** and **8b**. When using an enriched AD-mix-ß,[7] it was then possible to get the *syn* compound with a selectivity of **8a** / **8b** = 22 : 78.[8] These diols, which could not be separated by chromatography, were protected as *tert*-butyldimethylsilyl ethers in high yield (92-100%). Sequential hydrogenolysis of the terminal benzyl ether and oxidation of the resulting primary alcohol with Dess-Martin periodinane[9], gave crude aldehyde **10** which did not need any purification. Conversion to the unsaturated ethyl esters **11a** and **11b** was carried out by means of a second Wittig-Horner olefination with 60 to 75% yield. This mixture was submitted to Sharpless dihydroxylation which took place with almost complete *anti* diastereoselectivity with respect to the methyl group. Moreover, we found out that the tetrol with all hydroxyl groups *anti* with respect to the methyl group underwent *in situ* cyclization into lactone **12**, whereas the other diastereoisomer **13** remained open, allowing an easy separation of the two isomers. After desilylation, using aqueous HF in acetonitrile, the open tetrol cyclized to give aldonolactone **14**, after reprotection. Two-dimentional NMR experiments (NOESY, COSY45) confirmed the relative configuration of **14**[10] to be the one required in the F subunit of Spongistatin 1. The enantiomeric excess at that stage, determined after conversion to Mosher's ester,[11] was of 91%. Treatment with DIBAL-H reduced the lactone selectively, and the resulting hemiacetal was bis-acetylated (89% yield) to give our targeted pyranoside **1**.[12]

In the presence of one equivalent of TMSOTf and acetic anhydride, the two silyl protective groups were replaced by acetates leaving us with participating group for the ß-C-glycosidation. Treatment of this crude reaction mixture with allyltrimethylsilane and more TMSOTf as the Lewis acid promotor,[13] gave a 9:1 mixture of ß-C-pyranoside **15**[14] and α-C-pyranoside **16** (60% yield). Interestingly and expectedly, the allyl α-C-pyranoside of 1 was obtained by direct treatment with allyltrimethylsilane and TMSOTf.



14 **1** **15** 90 / 10 **16**

(a) DIBAL-H 3 eq, -78°C, CH_2Cl_2, 30 min; (b) Ac_2O / pyridine (1/1), DMAP cat, RT, 8h; (c) TMSOTf 1 eq, Ac_2O 2 eq, MeCN, -20°C, 1h; (d) TMSOTf 3 eq, $AllylSiMe_3$ 4eq, MeCN, 0°C, 5h.

Scheme 3

In conclusion, the total synthesis of the protected 4-deoxy-4-methyl-D-*threo*-L-*gluco*pyranouronate **1** was achieved in 12 steps from chiral diol **5**. C-glycosidation of **1** was successful and should allow one to use it in the construction of Spongistatins. Our approach features several steps which do not need any purification of the crude materials and that can be carried out on large quantities. Further studies are underway to complete the synthesis of the diene side chain and to build the ulose ring from the terminal ester of **1** or **15**.

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References and notes

1. (a) Pettit, G.R.; Cichacz, Z.A.; Gao, F.; Herald, C.L.; Boyd, M.R.; Schmidt, J.M.; Hooper, J.N.A. *J. Org. Chem.* **1993**, *58*, 1302-1304; (b) Pettit, G.R.; Cichacz, Z.A.; Gao, F.; Herald, C.L.; Boyd, M.R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166-1168; (c) Pettit, G.R.; Herald, C.L.; Cichacz, Z.A.; Gao, F.; Schmidt, J.M.; Boyd, M.R.; Christie, N.D.; Boettner, F.E. *Ibid.* **1993**, 1805-1807; (d) Pettit, G.R.; Cichacz, Z.A.; Gao, F.; Herald, C.L.; Boyd, M.R.; Schmidt, J.M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605-1606; (e) Pettit, G.R. *Pure Appl. Chem.* **1994**, 2271-2281. See also the altohyrtin macrolides, e.g. : Kobayashi, M.; Aoki, S.; Gato, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 2142.
2. (a) Bai, R.; Cichacz, Z.A.; Herald, C.L.; Pettit, G.R.; Hamel, E. *Mol. Pharmacol.* **1993**, *44*, 757-766; (b) Bai, R.; Taylor, G.F.; Cichacz, Z.A.; Herald, C.L.; Keppler, J.A.; Pettit, G.R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714-9721; (c) Bai, R.; Taylor, G.F.; Schmidt, J.M.; Williams, M.D.; Kepler, J.A.; Pettit, G.R.; Hamel, E. *Mol. Pharmacol.* **1995**, *47*, 965-976.
3. (a) Paterson, I.; Oballa, R.M.; Norcross, R.D. *Tetrahedron Lett.* **1996**, *37*, 8581-8584; (b) Claffey, M.M.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 7646-7647; (c) Hayes, C.J.; Heathcock, C.H. *Ibid.* **1997**, *62*, 2678-2679; (d) Paquette, L.A.; Zuev, D. *Tetrahedron Lett.* **1997**, *38*, 5115-5118; (e) Paquette, L.A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119-5122; (f) Paterson, I.; Oballa, R.M. *Ibid* **1997**, *38*, 8241-8244. See also Dunkel, R.; Mentzel, M.; Hoffmann, H.R.M. *Tetrahedron* **1997**, *53*, 14929-14936.
4. Paterson, I.; Keown, L.E. *Tetrahedron Lett.* **1997**, *38*, 5727-5730.
5. Grisenti, P.; Ferraboschi, P; Manzocchi, A.; Santaniello, E. *Tetrahedron* **1992**, *48*, 3827-3834.
6. Park, C.Y.; Kim, B.M. *Tetrahedron Lett.* **1991**, *32*, 1003-1006.
7. (a) Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, 57, 2768-2771; (b) Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-2547.
8. Using AD-mixtures prepared with other chiral ligands ($(DHQ)_2PHAL$, $(DHQD)_2PYR$) resulted in a loss of selectivity.
9. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
10. Data for **14** : ^1H NMR δ ($CDCl_3$, 400 MHz) 4.89 (1H, dd, J = 10.6 Hz, J = 2.2 Hz, H-C(5)); 4.32 (1H, dd, J = 8.0 Hz, J = 2.2 Hz, H-C(6)); 4.29-4.17 (2H, m, CH_2(OEt)); 4.04 (1H, d, J = 3.7 Hz, H-C(2)); 3.73 (1H, dd, J = 3.7 Hz, J = 2.4 Hz, H-C(3)); 2.97 (1H, d, J = 8.0 Hz, OH), 2.28-2.23 (1H, m, H-C(4)); 1.29 (3H, t, J = 7.2 Hz, CH_3(OEt)); 1.13 (3H, d, J = 7.2 Hz, CH_3-C(4)); 0.93, 0.91 (18H, 2s, CH_3(*t*-Bu)); 0.17, 0.15, 0.08, 0.07 (12H, 4s, $2Me_2Si$)). ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 171.9, 169.1, 82.4, 74.4, 71.5, 69.9, 62.3, 28.0, 25.6, 25.5, 17.9, 14.1, 13.4, -4.6, -4,9, -5.0, -5.4. Elemental analysis for $C_{22}H_{44}O_7Si_2$. Calc : C, 55.46; H, 9.24. Found : C, 55.55; H, 9.31. $[\alpha]_D^{25}$ = 21 (c = 0.4, MeOH).
11. Ward, D.E.; Rhee, C.K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166.
12. Data for **1** : ^1H NMR δ ($CDCl_3$, 400 MHz) 5.83 (1H, d, J = 2.0 Hz, H-C(1)); 5.23 (1H, d, J = 2.3 Hz, H-C(6)); 4.29-4.17 (2H, m, CH_2(OEt)); 4.19 (1H, dd, J = 11.1 Hz, J = 2.3 Hz, H-C(5)); 3.68 (1H, dd, J = 8.7 Hz, J = 8.1 Hz, H-C(3)); 3.60 (1H, dd, J = 8.1 Hz, J = 2.0 Hz, H-C(2)); 2.26-2.21 (1H, m, H-C(4)); 2.19, 2.07 (6H, 2s, $2CH_3CO$); 1.28 (3H, t, J = 7.1 Hz, CH_3(OEt)); 0.94, 0.93 (18H, 2s, CH_3(*t*-Bu)); 0.83 (3H, d, J = 7.0 Hz, CH_3-C(4)); 0.11, 0.10, 0.09, 0.06 (12H, 4s, $2Me_2Si$).^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 170.4, 169.4, 91.7, 75.2, 75.0, 71.3, 70.0, 61.7, 29.8, 25.7, 25.6, 21.1, 20.5, 18.1, 18.0, 14.0, 12.6, -4.4, -4.5, -4.9, -5.0.
13. (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383-2386; (b) Panek, J.S.; Sparks, M.A. *J. Org. Chem.* **1989**, *54*, 2034-2038.
14. An intense correlation between H-C(1) and H-C(5) was observed in NOESY experiment, confirming the β configuration of the major C-glycoside. Data for **15** : ^1H NMR δ ($CDCl_3$, 400 MHz) 5.73 (1H, m, CH=); 5.28 (1H, d, J = 2.7 Hz, H- C(6)); 5.11-5.06 (3H, m, CH_2= and H-C(3)); 4.74 (1H, dd, J = 8.0 Hz, J = 8.6 Hz, H-C(2)); 4.31-4.17 (2H, m, CH_2(OEt)); 4.22 (1H, dd, J = 7.0 Hz, J = 2.7 Hz, H-C(5)); 4.05 (1H, m, H-C(1)); 2.61-2.53 (1H, m, CH_2(All)); 2.43-2.27 (2H, m, CH_2(All) and H-C(4)); 2.27, 2.16, 2.10 (9H, 3s, $3CH_3CO$); 1.31 (3H, t, J = 7.1 Hz, CH_3(OEt)); 0.91 (3H, d, J = 7.0 Hz, CH_3-C(4)). ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 170.4, 169.8, 169.6, 167.9, 133.7, 117.3, 75.3, 72.1, 71.4, 70.7, 68.9, 61.9, 34.0, 30.4, 21.1, 20.9, 20.6, 14.1, 12.3. MS (IC / NH3) : 418 $(M + NH_4)^+$; 401 $(M + H)^+$.